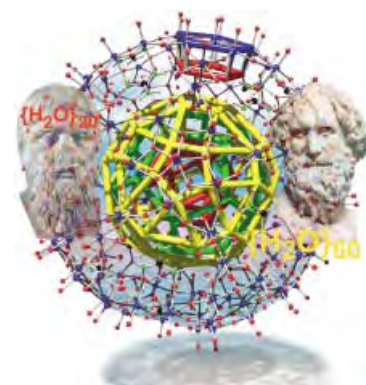


COVER PICTURE

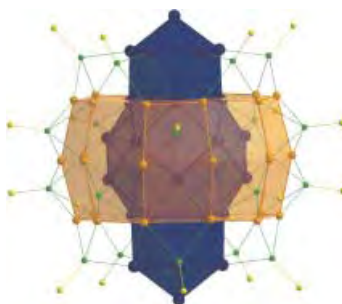
The cover picture shows a novel hierarchic endohedral clusterization of H_2O molecules in the form of a dodecahedron ($(\text{H}_2\text{O})_{20}$, red), a further “mounted” dodecahedron (green), and a rhombicosidodecahedron ($(\text{H}_2\text{O})_{60}$, yellow). The shell/host (Mo atoms blue, O red) is built up by 12 pentagonal $\{(\text{Mo})\text{Mo}_3\}$ type building blocks (one is highlighted as a blue ring), which are connected by 30 Mo^{V}_2 linkers with the consequence that 20 nanosized Mo_9O_9 pores/rings of classical crown ether quality are formed in which 20 guanidinium cations are encapsulated (C black, N green). The Mo^{V}_2 type linkers are stabilized by $\text{PO}_2\text{H}_2^-/\text{SO}_4^{2-}$ ligands (P/S purple). As the clusterization in the cavity takes place after filling the receptors/pores at the cluster surface with guests, a process is modeled by which a cell converts an extracellular molecular signal into a response. The representative red ring below the blue ring is marked out by the 60 H_2O ligands coordinated to the pentagonal Mo units, which altogether form a rhombicosidodecahedron (not shown completely). As the geometric forms described are those of Platonic and Archimedean solids Plato and Archimedes feel involved. Further details are reported by A. Müller et al. on p. 3756 ff.



REVIEWS

Contents

How metallic are gallium and aluminum clusters? To answer this question detailed information about the structures and physical properties of as many metalloid cluster compounds as possible must be collected—not an easy task as the synthesis of these compounds is anything but easy. Like elemental gallium the clusters of gallium form a variety of different structures, these in fact bear a complicated resemblance to each other and to the elemental forms. By way of introduction the picture shows the $[\text{Ga}_{84}\{\text{N}(\text{SiMe}_3)_2\}_{20}]^{4-}$ cluster, one of the largest metalloid clusters structurally characterized to date.



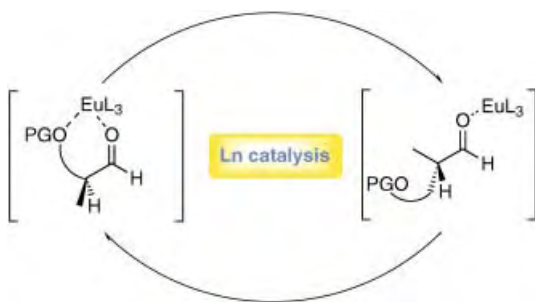
A. Schnepf, H. Schnöckel* .. 3533–3554

Metalloid Aluminum and Gallium
Clusters: Element Modifications on the
Molecular Scale?

Keywords: aluminum • cluster
compounds • gallium • metal–metal
interactions • structure elucidation

Angew. Chem. **2002**, 114, 3683–3704

High coordination numbers and fast ligand association and dissociation: Lanthanide complexes are ideal candidates for use as homogeneous catalysts in many organic reactions, for example, the aldol addition, which can either occur via a chelate or a nonchelate intermediate (see scheme; PG = protecting group).



Angew. Chem. **2002**, *114*, 3705–3722

K. Mikami,* M. Terada,
H. Matsuzawa 3555–3572

“Asymmetric” Catalysis by Lanthanide Complexes

Keywords: asymmetric catalysis • enantioselectivity • coordination chemistry • lanthanides • Lewis acids

MINIREVIEW

Gold is more “relativistic” than any other element before fermium. One consequence is the large electronegativity of Au, which qualitatively explains the stability of (solid or liquid) cesium auride, Cs^+Au^- (see picture), and other systems with Au^- ions. The structure and bonding of the recently discovered $\text{CsAu} \cdot \text{NH}_3$ is discussed. Other ammoniates and some future possibilities are outlined.



Angew. Chem. **2002**, *114*, 3723–3728

P. Pyykkö * 3573–3578

Relativity, Gold, Closed-Shell Interactions, and $\text{CsAu} \cdot \text{NH}_3$

Keywords: cesium • closed-shell interactions • computer chemistry • gold • relativistic effects

VIPs

The following communications are “Very Important Papers” in the opinion of two referees. They will be published shortly (those marked with a diamond will be published in the next issue). Short summaries of these articles can be found on the *Angewandte Chemie* homepage at the address <http://www.angewandte.org>

Syntheses and Crystal Structures of the New Ag-S Clusters
[$\text{Ag}_{70}\text{S}_{16}(\text{SPh})_{34}(\text{PhCO}_2)_4(\text{triphos})_4$] and [$\text{Ag}_{188}\text{S}_{94}(\text{PR}_3)_{30}$]

X.-J. Wang, T. Langetepe,
C. Persau, B.-S. Kang,
G. M. Sheldrick, D. Fenske* ◆

Ethane and Ethylidene Dicarboxylates from the Ruthenium(II)-Catalyzed Disproportionative Addition of Carboxylic Acids to Ethene

T. Funaioli,* F. Marchetti,
G. Fachinetti* ◆

Cell-Free Biosynthesis of Fluoroacetate and 4-Fluorothreonine in *Streptomyces cattleya*

C. Schaffrath, S. L. Cobb,
D. O'Hagan* ◆

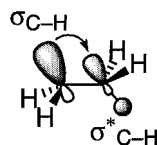
Selective Measurements of a Nitroxide–Nitroxide Distance of 5 nm and a Nitroxide–Copper Distance of 2.5 nm in a Terpyridine-Based Copper(II) Complex by Pulse EPR Spectroscopy

E. Narr, A. Godt, G. Jeschke* ◆

A Synthesis Route to Enantiomerically Pure Jasmonoids

M. Ernst, G. Helmchen*

When will we accept the quantum nature of chemistry? A critical view on how we teach the origin of rotational barriers (see picture) emphasizes the importance of continuously updating what we teach our students.



P. R. Schreiner* 3579–3582

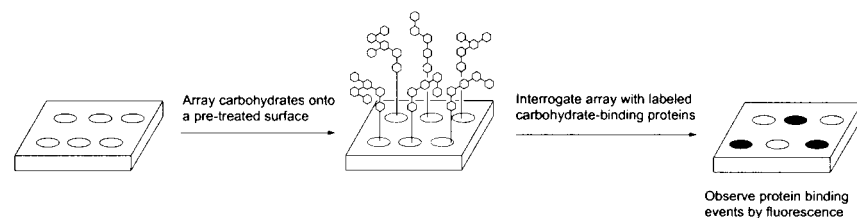
Teaching the Right Reasons: Lessons from the Mistaken Origin of the Rotational Barrier in Ethane

Keywords: alkanes • computations • conformational analysis • hyperconjugation • rotational barriers

Angew. Chem. **2002**, *114*, 3729–3732

HIGHLIGHTS

Rapid identification of carbohydrate-binding events that leads to a better understanding of signaling processes is being achieved through the development of carbohydrate microarrays. In the example shown, array carbohydrates are first immobilized on a pretreated surface and then interrogated with fluorescently labeled carbohydrate-binding proteins; the binding event can then be observed by fluorescence spectroscopy.



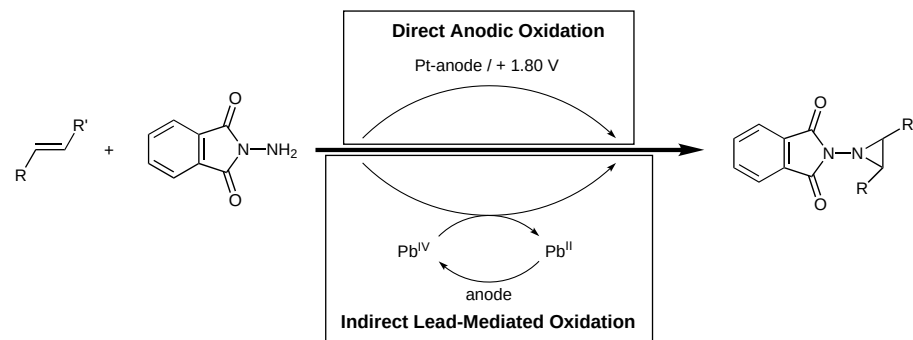
K. R. Love, P. H. Seeberger* 3583–3586

Carbohydrate Arrays as Tools for Glycomics

Keywords: carbohydrates • microarrays • monolayers • oligosaccharides • self-assembly

Angew. Chem. **2002**, *114*, 3733–3736

Less lead is good, no lead is better still: Environmentally friendly aziridinations of alkenes can be conducted under either indirect lead-mediated or direct metal-free electrochemical potential-controlled oxidation conditions using suitable hydrazine derivatives. In economic and ecological terms, the method represents another important step in electroorganic synthesis towards future methods that avoid the production of toxic waste.



G. Hilt* 3586–3588

Direct Electrochemical Aziridination of Alkenes under Metal-Free Conditions

Keywords: alkenes • electrochemistry • heterocycles • lead • oxidations

Angew. Chem. **2002**, *114*, 3737–3740

CORRESPONDENCE

Not the definitive work but rather contributions to a body of literature have recently been portrayed in a Highlight in *Angewandte Chemie* according to the author of this Correspondence. Herein, misrepresentations and omissions with regard to the literature on microwave chemistry are addressed.

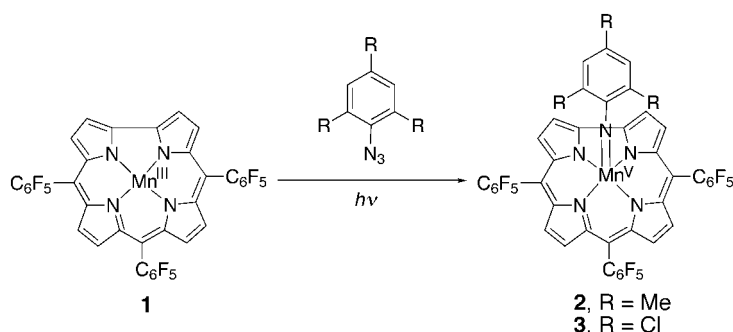
C. R. Strauss* 3589–3591

Microwave-Assisted Reactions in Organic Synthesis—Are There Any Nonthermal Microwave Effects?

Keywords: correspondence • microwave chemistry • synthetic methods

Angew. Chem. **2002**, *114*, 3741–3743

At last, terminal imido complexes of manganese(v), the postulated intermediates in aziridination and amination reactions, have been prepared. The structurally well-defined (imido)manganese(v) corroles, **2** and **3**, are easily synthesized from manganese(III) corroles with organic azides under photolysis conditions and react with electron-rich nucleophiles such as organic phosphanes.



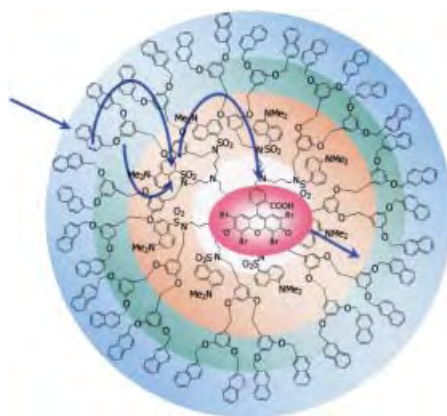
Angew. Chem. **2002**, *114*, 3744–3747

R. A. Eikey, S. I. Khan,
M. M. Abu-Omar* 3592–3595

The Elusive Terminal Imido of
Manganese(v)

Keywords: azides • corroles •
manganese • multiple bonds • photolysis

An eosin molecule encapsulated into the dendrimer shown in the picture collects electronic energy from all 64 chromophoric units of the dendrimer, which comprises three different types of chromophore. Efficient intramolecular (within the dendrimer) and intermolecular (dendrimer-host → eosin-guest) energy-transfer processes by a Förster type mechanism, as suggested by the strong overlap between the emission and absorption spectra of the relevant donor and acceptor units.



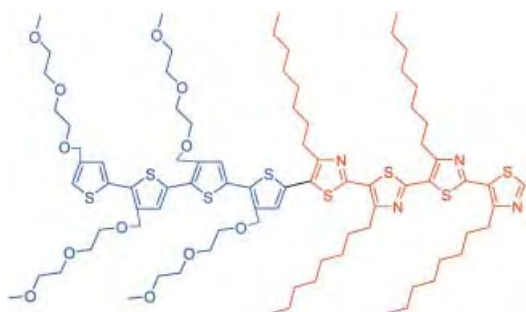
Angew. Chem. **2002**, *114*, 3747–3750

U. Hahn, M. Gorka, F. Vögtle,*
V. Vicinelli, P. Ceroni, M. Maestri,*
V. Balzani* 3595–3598

Light-Harvesting Dendrimers: Efficient
Intra- and Intermolecular Energy-
Transfer Processes in a Species
Containing 65 Chromophoric Groups of
Four Different Types

Keywords: chromophores • dendrimers •
energy transfer • eosin • fluorescence

A diodelike rectifying effect was observed in Langmuir–Blodgett monolayers of a p-n junction molecule, the amphiphilic π -conjugated diblock oligomer shown. A reference molecule without the p-n junction feature shows nonrectifying behavior.

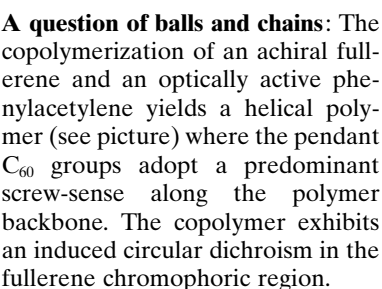


Angew. Chem. **2002**, *114*, 3750–3753

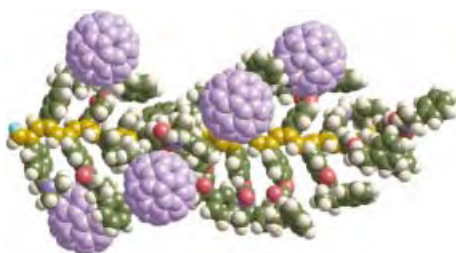
M.-K. Ng, L. Yu* 3598–3601

Synthesis of Amphiphilic Conjugated
Diblock Oligomers as Molecular Diodes

Keywords: electronic devices •
Langmuir–Blodgett films • polymers •
scanning probe microscopy



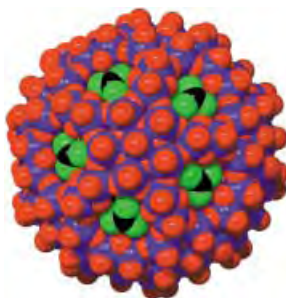
Responsive sensing clusters: By linking {(Mo)Mo₃} type building units with different spacers, spherical clusters (nanosponges) having 20 different nano-sized and tunable Mo_nO_m pores/macrocycles of the type and quality of the classical crown ethers of supramolecular chemistry are formed (see picture of an [Mo₃O₉]-type host with guanidinium ion [(NH₂)₃C]⁺ guests; Mo blue, O red, N green, C black). This property allows the development of a novel spherical-surface and nanoporous-cluster chemistry with the possibility of the formation of extended cluster networks (solid-state structures), as well as a modeling of cell responses to extracellular signal molecules.



A Helical Array of Pendant Fullerenes on an Optically Active Polyphenylacetylene

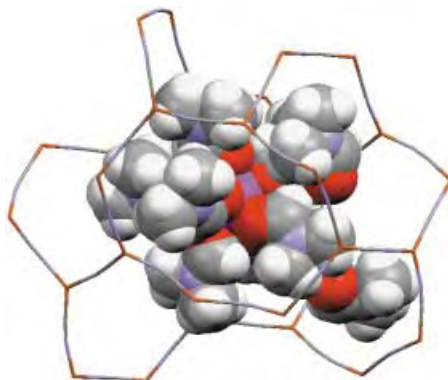
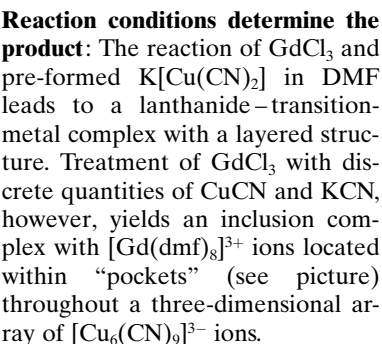
Keywords: chirality • circular dichroism • fullerenes • helical structures • polymerization

Reaction conditions determine the product: The reaction of GdCl_3 and pre-formed $\text{K}[\text{Cu}(\text{CN})_2]$ in DMF leads to a lanthanide-transition-metal complex with a layered structure. Treatment of GdCl_3 with discrete quantities of CuCN and KCN , however, yields an inclusion complex with $[\text{Gd}(\text{dmf})_8]^{3+}$ ions located within “pockets” (see picture) throughout a three-dimensional array of $[\text{Cu}_6(\text{CN})_6]^{3-}$ ions.



Changeable Pore Sizes Allowing Effective and Specific Recognition by a Molybdenum-Oxide Based “Nanosponge”: En Route to Sphere-Surface and Nanoporous-Cluster Chemistry

Keywords: host–guest systems • molecular recognition • nanostructures • polyoxometalates • topology



An Inclusion Complex with $[\text{Gd}(\text{dmf})_8]^{3+}$ Ions Encapsulated in Pockets of an Anionic Array of $[\{\text{Cu}_6(\text{CN})_9\}^{3-}]_\infty$ Units; A Cyanide-Bridged Cu–Gd Layer Structure

Keywords: copper • cyanides • gadolinium • inclusion compounds • layered compounds

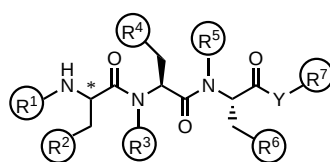
The figure shows two chemical structures. Structure 1 (left) is a cobalt atom (Co) coordinated by a cyanide ligand (C≡N) and a dimethylglycine (DMG) ligand. The cobalt atom is also coordinated by two nitrogen atoms from a protein ligand (B₁₂ antibody) and two water molecules (H₂O). Structure 2 (right) shows the cobalt atom coordinated by a cyanide ligand and a dimethylglycine ligand, with the protein ligand (B₁₂ antibody) and water molecules. The structures are labeled 1 and 2.

An Antibody that Reconstitutes the “Base-On” Form of B₁₂ Coenzymes

Keywords: antibodies • cofactors • molecular recognition • vitamin B12



Potent mono- and bisubstrate inhibitors of the enzyme protein farnesyltransferase are furnished by a structurally broadly varied compound library derived from the natural product peptidocinnamin E (see picture), by a six-to-nine-step solid-phase peptide synthesis. One inhibitor was identified as inducing apoptosis in H-Ras-transformed tumor cells.



M. Thutewohl, L. Kissau, B. Popkirova, I.-M. Karaguni, T. Nowak, M. Bate, J. Kuhlmann, O. Müller, H. Waldmann * 3616–3620

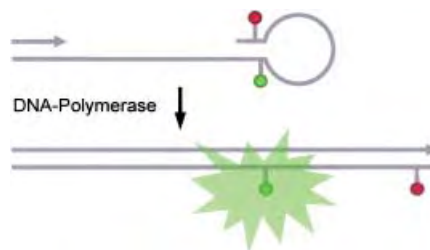
Solid-Phase Synthesis and Biological Evaluation of a Peptidocinnamin E Library

Keywords: apoptosis • combinatorial chemistry • farnesyltransferase inhibitors • peptidocinnamin E • solid-phase synthesis

Angew. Chem. **2002**, *114*, 3768–3772



An assay for real-time monitoring of DNA synthesis by DNA polymerases is presented. With the opening of a dual dye-labeled probe, triggered by the progressing enzymatic DNA synthesis, a fluorescent signal is generated (see scheme), enabling the high-throughput quantitative characterization of inhibitors and monitoring of the DNA polymerase reaction in cell lysates.



D. Summerer, A. Marx * 3620–3622

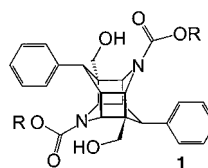
A Molecular Beacon for Quantitative Monitoring of the DNA Polymerase Reaction in Real-Time

Keywords: DNA polymerases • enzyme assay • enzyme inhibitors • high-throughput screening • reporter systems

Angew. Chem. **2002**, *114*, 3778–3780



More is not always better: Until now it was considered that modulators of P-glycoprotein-associated multidrug resistance in cancer treatment showed greater inhibitory activity with an increasing number of moieties that could participate in hydrogen bonds. This theory has been questioned for the first time with a new class of symmetrical inhibitors **1** based on hydroxymethyl-3,9-diazatetraasteranes.



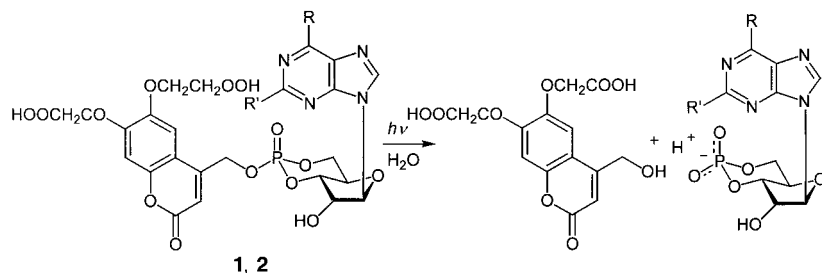
A. Hilgeroth,* J. Molnár, E. De Clercq 3623–3625

Using Molecular Symmetry to Form New Drugs: Hydroxymethyl-Substituted 3,9-Diazatetraasteranes as the First Class of Symmetric MDR Modulators

Keywords: cage compounds • MDR modulators • medicinal chemistry • photochemistry • structure–activity relationships

Angew. Chem. **2002**, *114*, 3772–3775

The linear correlation between the increase of fluorescence and the extent of photolysis upon flash photolysis of bis(carboxymethoxy)coumarinylmethyl-caged cAMP (**1**, R = H, R' = NH₂) and cGMP (**2**, R = NH₂, R' = OH) allows the visualization and quantification of the release process of the cyclic nucleotides within cells.



1, 2

V. Hagen,* S. Frings, J. Bendig, D. Lorenz, B. Wiesner, U. B. Kaupp 3625–3628

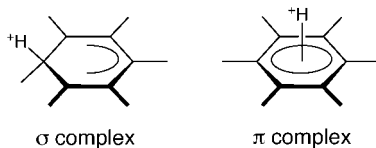
Fluorescence Spectroscopic Quantification of the Release of Cyclic Nucleotides from Photocleavable [Bis(carboxymethoxy)coumarin-4-yl]methyl Esters inside Cells

Keywords: fluorescence • ion channels • nucleotides • photolysis • signal transduction

Angew. Chem. **2002**, *114*, 3775–3777

Structure of gas-phase arenium ions:

The long-standing controversy about the geometry of protonated benzene is unambiguously solved by IR spectroscopy. The first high-resolution gas-phase spectrum of an arenium ion shows that the σ complex (not the π complex; see picture) is the most stable structure of $C_6H_7^+$.



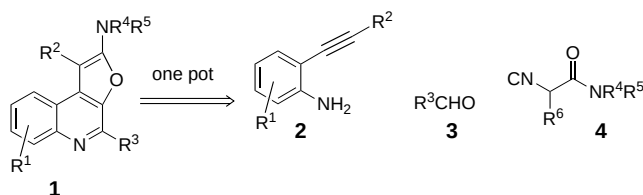
N. Solcà, O. Dopfer* 3628–3631

Protonated Benzene: IR Spectrum and Structure of $C_6H_7^+$

Keywords: arenium ions • aromatic substitution • carbocations • IR spectroscopy • reactive intermediates

Angew. Chem. 2002, 114, 3781–3784

Five bonds form in one pot, from three well-designed yet readily accessible substrates. Simply mixing an *ortho*-alkynyl aniline **2**, an aldehyde **3**, and ammonium chloride **4** in toluene at room temperature, followed by addition of an isocyanacetamide **4** and heating to reflux, provides the polysubstituted furo[2,3-*c*]quinoline **1** in good to excellent yield.



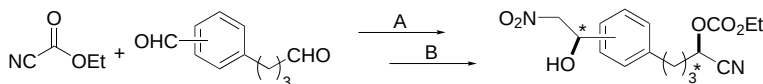
Angew. Chem. 2002, 114, 3785–3787

A. Fayol, J. Zhu* 3633–3635

Synthesis of Furoquinolines by a Multicomponent Domino Process

Keywords: cycloaddition • multicomponent reactions • nitrogen heterocycles • synthetic methods

Two catalysts in one! Catalyst tuning with achiral additives effectively constructed and reconstructed a chiral environment around the catalyst $[YLi_3\{\text{tris}(\text{binaphthoxide})\}]$, which enabled tandem asymmetric catalysis from achiral substrates using a single catalyst component in one pot (see scheme: A = cyanation reaction, B = nitroaldol reaction).



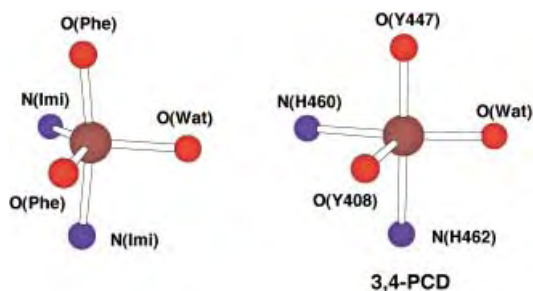
Angew. Chem. 2002, 114, 3788–3790

J. Tian, N. Yamagiwa, S. Matsunaga, M. Shibasaki* 3636–3638

An Asymmetric Cyanation Reaction and Sequential Asymmetric Cyanation–Nitroaldol Reaction Using a $[YLi_3\{\text{tris}(\text{binaphthoxide})\}]$ Single Catalyst Component: Catalyst Tuning with Achiral Additives

Keywords: asymmetric catalysis • asymmetric synthesis • cyanation • multicomponent reactions • yttrium

The spectral characteristics as well as the active-site structure of protocatechuate 3,4-dioxygenase (3,4-PCD) have now been mimicked with a ferric aqua complex containing a sterically hindered salen ligand. The coordination sphere of this distorted trigonal-bipyramidal complex (see structures, left; Imi = imino, Phe = phenolate, Wat = water) is the same as that of 3,4-PCD (right; Tyr408, Tyr447, His460, His462).



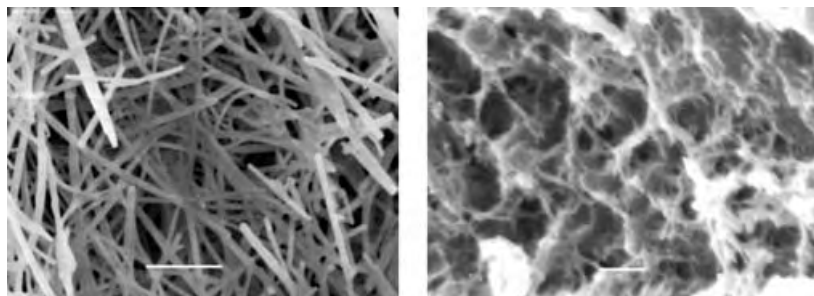
Angew. Chem. 2002, 114, 3790–3793

H. Fujii,* Y. Funahashi 3638–3641

A Trigonal-Bipyramidal Ferric Aqua Complex with a Sterically Hindered Salen Ligand as a Model for the Active Site of Protocatechuate 3,4-Dioxygenase

Keywords: bioinorganic chemistry • enzyme models • iron • metalloenzymes • schiff bases

A crystallographic mismatch branching mechanism, rather than molecular self-assembly, controls the architecture of the crystalline structure. Self-organized functional materials with a 3D fibrous network structure (see scanning electron micrographs; right) have been constructed from needlelike crystals of lanosterol: dihydrolanosterol and diisooctylphthalate (left) by using an ethylene/vinyl acetate copolymer as a branching creator.



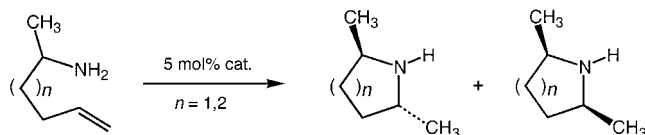
Angew. Chem. **2002**, *114*, 3793–3797

X. Y. Liu,* P. D. Sawant 3641–3645

Micro/Nanoengineering of the Self-Organized Three-Dimensional Fibrous Structure of Functional Materials

Keywords: copolymers • crystal growth • nanostructures • networks • soft materials

Modification of the metal center in the complexes $[\text{Ln}\{\text{N}(\text{TMS})_2\}_3]$ ($\text{Ln} = \text{Y}, \text{Nd}$; $\text{TMS} = \text{trimethylsilyl}$) is readily achieved by amine elimination in the presence of sterically hindered chelating diamines to provide complexes with substantially augmented catalytic activities and improved stereoselectivities in intramolecular alkene hydroamination (see scheme).



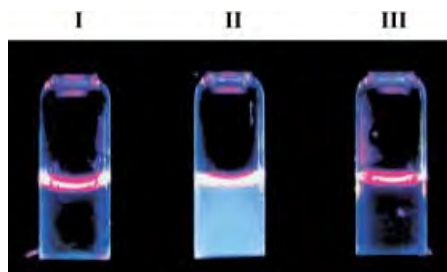
Angew. Chem. **2002**, *114*, 3797–3799

Y. K. Kim, T. Livinghouse* . 3645–3647

Exceptional Rate Enhancements and Improved Diastereoselectivities through Chelating Diamide Coordination in Intramolecular Alkene Hydroaminations Catalyzed by Yttrium and Neodymium Amido Complexes

Keywords: amino alkenes • cyclization • hydroamination • nitrogen heterocycles • rare-earth metals

In the living cell is where the authors hope to elucidate the structure of RNA by using their bispyrene-conjugated 2'-O-methyloligoribonucleotide (OMUp2-I) fluorescence probe, to detect the hybridization with complementary RNA. The picture shows irradiated I) single-stranded OMUp2-I, II) hybrid of OMUp2-I with oligoRNA, and III) OMUp2-I and oligoDNA.



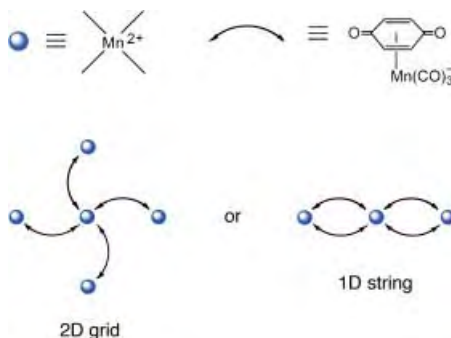
Angew. Chem. **2002**, *114*, 3800–3802

A. Mahara, R. Iwase, T. Sakamoto, K. Yamana, T. Yamaoka, A. Murakami* 3648–3650

Bispyrene-Conjugated 2'-O-Methyloligoribonucleotide as a Highly Specific RNA-Recognition Probe

Keywords: antisense agents • fluorescent probes • FRET • RNA recognition

The concentration of metal ions influences the structural characteristics of self-assembled coordination polymers constructed from Mn^{2+} ions and $[(\eta^4\text{-benzoquinone})\text{Mn}(\text{CO})_3]^-$ ions. At very low metal-ion concentrations, 1D “string” formations are obtained (see picture), while at higher concentrations, 2D “grid” networks are formed.



Angew. Chem. **2002**, *114*, 3802–3805

M. Oh, G. B. Carpenter, D. A. Sweigart* 3650–3653

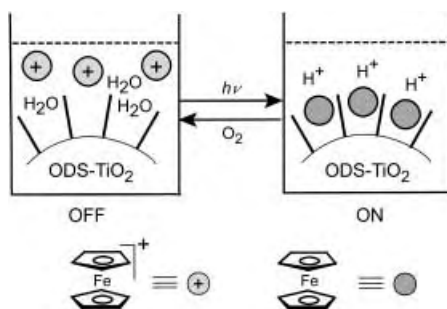
Self-Assembly Using Organometallic Ligands as Spacers in the Controlled Formation of Isomeric 1D and 2D Supramolecular Quinonoid Networks

Keywords: manganese • polymers • quinones • self-assembly • supramolecular chemistry



Reduction by near-UV light and oxidation by atmospheric oxygen drives the self-reversing photoredox system consisting of a solution of ferrocenium tetrafluoroborate containing a suspension of TiO_2 particles coated with octadecyltrichlorosilane (ODS, see scheme). Reduction of the ferrocenium ions decolorizes the blue solution while the white ODS- TiO_2 particles become yellowish beige. Subsequent oxidation in air regenerates the blue solution and white particles.

Angew. Chem. **2002**, *114*, 3805–3808

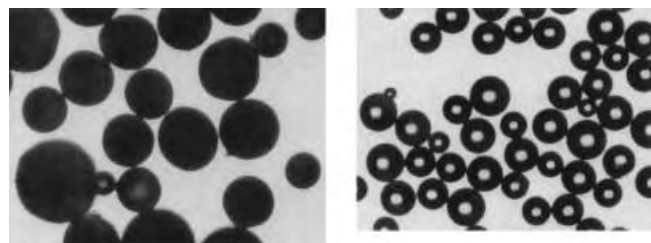


M. Muraoka, S. L. Gillett,
T. W. Bell * 3653–3656

Reversible Photoinsertion of Ferrocene into a Hydrophobic Semiconductor Surface: A Chemionic Switch

Keywords: metallocenes • photochemistry • redox chemistry • semiconductors • surface chemistry

Both macroporous and gel-type high-quality spherical particulate styrene–divinylbenzene resins (see representative optical micrograph) can be synthesized in good yield on a small scale by using an oscillatory baffled reactor. The methodology is tolerant to the use of functional co-monomers.



Angew. Chem. **2002**, *114*, 3808–3811

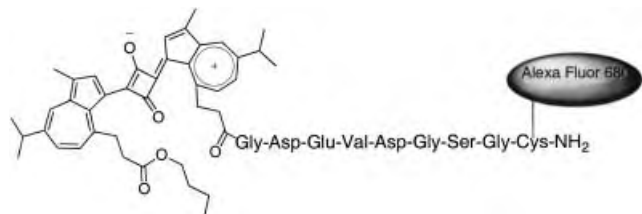
D. C. Sherrington,* A. Lanver,
H.-G. Schmalz, B. Wilson, X.-W. Ni,
S. Yuan 3656–3659

Gram-Scale Synthesis of Suspension-Polymerized Styrene–Divinylbenzene-Based Resins Using an Oscillatory Baffled Reactor

Keywords: cross-linking • polymerization • styrene • synthetic methods



Turning off the light. A fluorescence quencher based on azulene was synthesized which absorbs light in the range of 650 to 800 nm. Since protease sensing was possible with the derivative shown (Alexa Fluor 680 is the fluorochrome), applications in vivo for imaging molecular targets can be expected.



Angew. Chem. **2002**, *114*, 3811–3814

W. Pham, R. Weissleder,
C.-H. Tung * 3659–3662

An Azulene Dimer as a Near-Infrared Quencher

Keywords: azulenes • fluorescence • molecular imaging • proteases • sensors

A pair of seven-membered chelate rings are found in the palladium(IV) complex assembled in only a single step from commercially available $[\text{Pd}_2(\text{dba})_3]$, tetrachloro-1,2-benzoquinone, and norbornene. The structure consists of a C_2 -symmetrical palladSpirocyclic framework and an ether ligand, as confirmed by X-ray analysis of the thf complex (see picture).



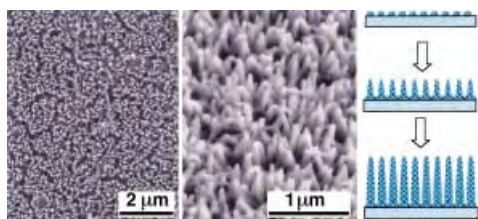
Angew. Chem. **2002**, *114*, 3814–3817

Y. Yamamoto,* T. Ohno,
K. Itoh 3662–3665

Single-Step Assembly of a C_2 -Symmetrical Palladium(IV) Spirocyclic Complex

Keywords: Lewis acids • metallacycles • palladium • quinones • structure elucidation

Controlling growth: Large arrays of oriented conducting polymer nanowires were prepared by controlled nucleation and growth during a stepwise electrochemical deposition process, without the use of porous membrane supports (see scheme and electron micrographs).



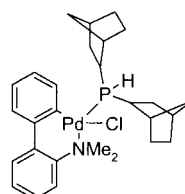
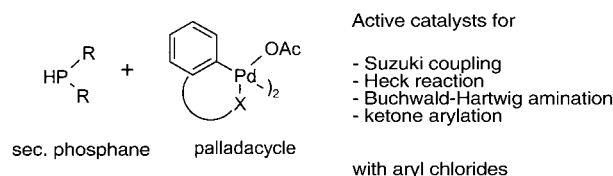
Angew. Chem. **2002**, *114*, 3817–3820

L. Liang, J. Liu,* C. F. Windisch, Jr.,
G. J. Exarhos, Y. Lin 3665–3668

Direct Assembly of Large Arrays of
Oriented Conducting Polymer Nanowires

Keywords: aniline • conducting
materials • electrochemistry •
nanostructures • polymers

 **High yields in important Pd-catalyzed reactions** of aryl chlorides (see scheme) are obtained with complexes consisting of a palladacycle and a secondary phosphane which could be prepared in situ or isolated. The latter were shown to be stable, and easy to handle in air, and the in situ catalysts allow optimization of the catalyst by variation of the two components.



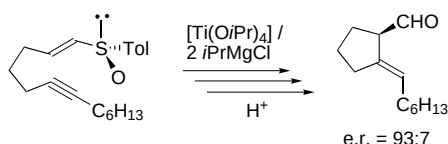
Angew. Chem. **2002**, *114*, 3820–3823

A. Schnyder, A. F. Indolese,* M. Studer,*
H.-U. Blaser 3668–3671

A New Generation of Air Stable, Highly
Active Pd Complexes for C–C and C–N
Coupling Reactions with Aryl Chlorides

Keywords: aryl chlorides • coupling
reactions • homogeneous catalysis •
palladacycles • phosphanes

Reusing the metal: Combination of the sulfoxide-based asymmetric enyne cyclization (Ti^{III} mediated) and the Pummerer reaction (Ti^{IV} mediated) in tandem was effected by a reagent system consisting of a relay of titanium(II) to titanium(IV), which permits a one-pot synthesis of cyclic aldehydes in an optically active form (see scheme; Tol = *p*-tolyl).



Angew. Chem. **2002**, *114*, 3823–3826

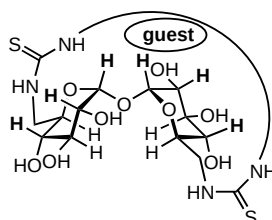
M. Narita, H. Urabe,
F. Sato* 3671–3674

Sulfur-Functionalized Olefins for
Titanacycle Formation: Tandem
Asymmetric Cyclization and the
Pummerer Reaction Based on Sulfoxides
Promoted by Titanium(II)-to-Titanium(IV)
Relay

Keywords: cyclization • metallacycles •
Pummerer reaction • sulfoxides •
synthetic methods • titanium



The “dark side” of cyclodextrins can be observed in cyclotrehalins, a new family of cyclooligosaccharide receptors made from α,α' -trehalose building blocks. A hydrophobic guest included in these hosts is forced to interact with the β face of the D-glucopyranose subunits (see schematic picture).



Angew. Chem. **2002**, *114*, 3826–3828

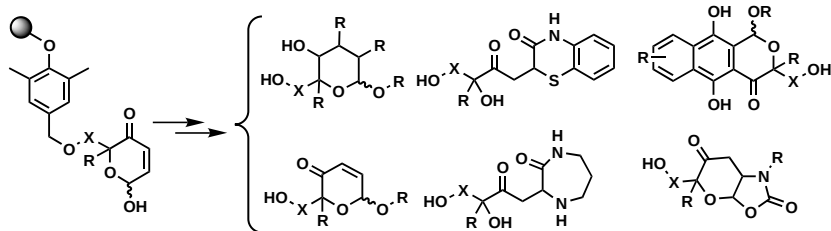
J. M. Benito, J. L. Jiménez Blanco,
C. Ortiz Mellet,*
J. M. García Fernández* 3674–3676

Cyclotrehalins: Cyclooligosaccharide
Receptors Featuring a Hydrophobic
Cavity

Keywords: carbohydrates • host–guest
systems • oligosaccharides • receptors



Antimicrobials, antifungals, anticoccidials, pesticides, and herbicides—druglike scaffolds with potential applications such as these are provided by a combinatorial library containing oxazolidiones, naphthoquinones, thiazinones, and diazepinones which were obtained within a few simple steps from solid-supported 2H-pyran-3(6H)-ones as “polymorphic” key intermediate leads (see scheme).



Angew. Chem. **2002**, *114*, 3829–3832

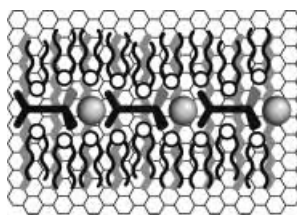
E. A. Couladouros,*

A. T. Strongilos 3677–3680

Generation of Libraries of Pharmacophoric Structures with Increased Complexity and Diversity by Employing Polymorphic Scaffolds

Keywords: combinatorial chemistry • drug design • heterocycles • solid-phase synthesis

Multicomponent self-assembly of transition-metal ions, rigid ditopic metal ion receptors, amphiphiles, and alkanes leads to perfectly straight epitaxially oriented nanostructures on the basal plane of graphite (see schematic representation). The long-chain alkanes act as a templating layer that enables the nanoscopic assemblies to be adsorbed in a predictable manner.



D. G. Kurth,* N. Severin,

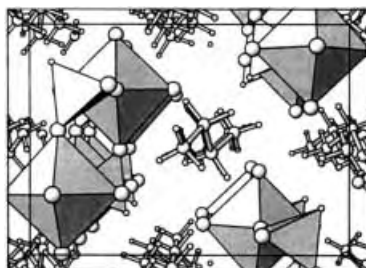
J. P. Rabe * 3681–3683

Perfectly Straight Nanostructures of Metallosupramolecular Coordination-Polyelectrolyte Amphiphile Complexes on Graphite

Keywords: nanostructures • scanning probe microscopy • self-assembly • single-molecule studies • supramolecular chemistry

Angew. Chem. **2002**, *114*, 3833–3835

Mild hydrothermal conditions can be used to synthesize the first inorganic–organic hybrid fluorochromium(III) phosphite. The crystal structure (see unit cell) shows that the material consists of double chains of alternating CrO_3F_3 octahedra and HPO_3 tetrahedra. Furthermore, the magnetic behavior indicates the existence of antiferromagnetic interactions.



S. Fernández, J. L. Mesa,* J. L. Pizarro,

L. Lezama, M. I. Arriortua,

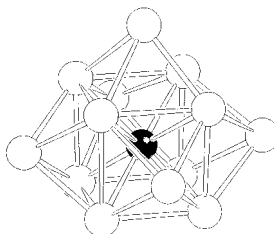
T. Rojo * 3683–3685

$(\text{C}_2\text{H}_{10}\text{N}_2)[\text{Cr}(\text{HPO}_3)\text{F}_3]$: The First Organically Templated Fluorochromium(III) Phosphite

Keywords: chromium • magnetic properties • materials science • template synthesis • UV/Vis spectroscopy

Angew. Chem. **2002**, *114*, 3835–3837

The progressive replacement of Rh with Ni modulates the electronic as well as chemical properties of body-centered $[\text{Rh}_{14-x}\text{Ni}_x(\text{CO})_9(\mu\text{-CO})_{16}]^{n-}$ clusters ($x=0$, $n=4$; $x=1$, $n=5$ (shown here); $x=2$, $n=4$; $x=5$, $n=2$, 3) and prompts multivalence. The complexes obtained are isostructural, but not isoelectronic.



D. Collini, C. Femoni, M. C. Iapalucci,

G. Longoni,* P. H. Svensson,

P. Zanello 3685–3688

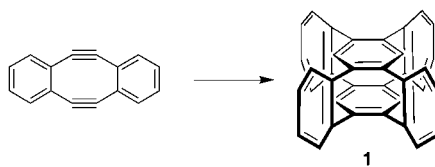
Tuning Electronic Behavior of Carbonyl Metal Clusters by Substitution of Interstitial and Capping Atoms

Keywords: carbonyl complexes • cluster compounds • electrochemistry • nickel • rhodium

Angew. Chem. **2002**, *114*, 3837–3840

**Highly strained but thermally stable:**

Tetrabenzocyclophane **1**, which was obtained in a four-step synthesis by two Diels–Alder addition reactions (see scheme) sublimes at high temperature, rather than decomposing. The distorted aromatic rings are more reactive with tetracyanoethylene than those in [2.2]paracyclophane. Another consequence of heightened strain is a bathochromic shift of the cyclophane band to 330 nm, the longest wavelength absorption for this band to date.



M. Brettreich, M. Bendikov, S. Chaffins, D. F. Perepichka, O. Dautel, H. Duong, R. Helgeson, F. Wudl* 3688–3691

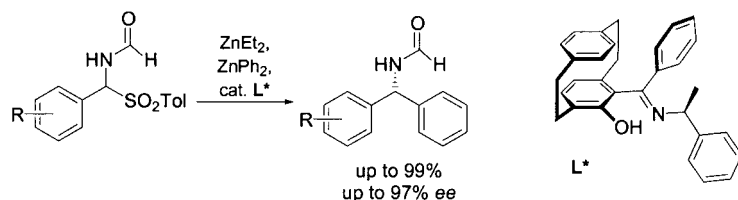
Synthesis, X-ray Structure, and Properties of a Tetrabenzannulated 1,2,4,5-Cyclophane

Keywords: cycloaddition • cyclophanes • density functional calculations • electrochemistry • strained molecules

Angew. Chem. **2002**, *114*, 3840–3843



Both planar and central chirality are not necessary in [2.2]paracyclophane-based N,O-ligands to achieve high enantioselectivity: diarylmethylamines are obtained in excellent yields and enantioselectivities up to 97% *ee* in the enantioselective transfer of a phenyl group from organozinc reagents to imines in the presence of catalytic amounts of ketimine **L*** (see scheme).



N. Hermanns, S. Dahmen, C. Bolm, S. Bräse* 3692–3694

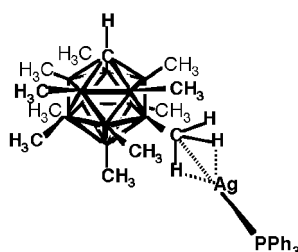
Asymmetric, Catalytic Phenyl Transfer to Imines: Highly Enantioselective Synthesis of Diarylmethylamines

Keywords: cyclophanes • enantioselectivity • homogeneous catalysis • imines • zinc

Angew. Chem. **2002**, *114*, 3844–3846



Both in the solid state and in solution, the complex $[(PPh_3)Ag(HCB_{11}Me_{11})]$ displays significant intermolecular $Ag \cdots H_3C$ interactions. This complex serves as a model for the interaction between a d^{10} metal center and an alkane.



M. J. Ingleson, M. F. Mahon, N. J. Patmore, G. D. Ruggiero, A. S. Weller* 3694–3697

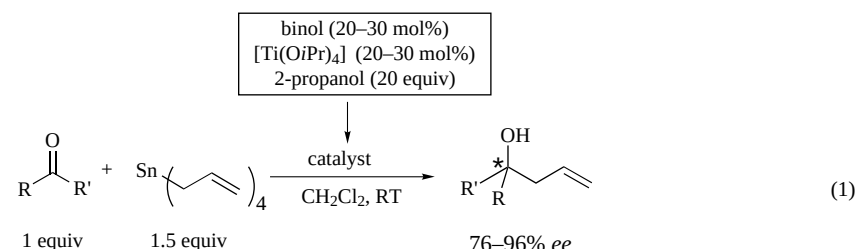
$[(PPh_3)Ag(HCB_{11}Me_{11})]$: A Complex with Intermolecular $Ag \cdots H_3C$ Interactions

Keywords: anions • C–H activation • carboranes • phosphane ligands • silver

Angew. Chem. **2002**, *114*, 3846–3849



Allylation of ketones made easy: commercially available reagents can be used at room temperature to transform ketones into homoallylic alcohols with good to excellent enantioselectivities [Eq. (1)]. This process belongs to a rare class of reactions that catalytically form quaternary stereogenic centers.



K. M. Waltz, J. Gavenonis, P. J. Walsh* 3697–3699

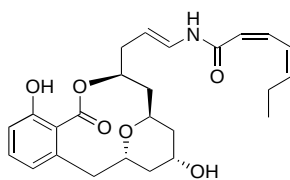
A Simple, Reliable, Catalytic Asymmetric Allylation of Ketones

Keywords: alcohols • allylation • asymmetric catalysis • titanium

Angew. Chem. **2002**, *114*, 3849–3852



Mimicking nature's biosynthetic pathway to polyketides, a two-step procedure involving allylation followed by ozonolysis was applied five times in total for the construction of the carbon skeleton of apicularen A (**1**). Application of the developed synthetic technology also establishes an entry into designed apicularen analogues.

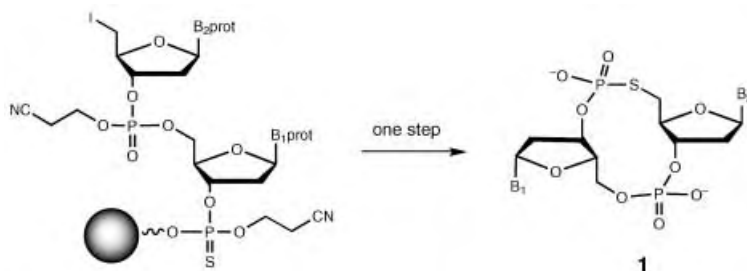


1: apicularen A

Angew. Chem. **2002**, *114*, 3853–3856



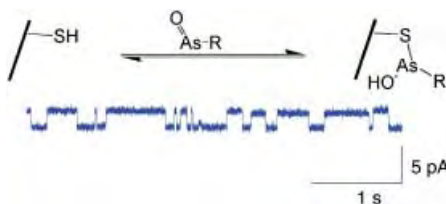
Only one additional step is required to extend oligonucleotide synthesis to generate cyclic oligonucleotides by standard automated phosphoramidite chemistry. After 5'-iodination, cleavage from the solid support yields phosphorothioate-bridged compounds **1**, which are under investigation as potentially bioactive molecules, in 40–80 % yields.



Angew. Chem. **2002**, *114*, 3856–3859



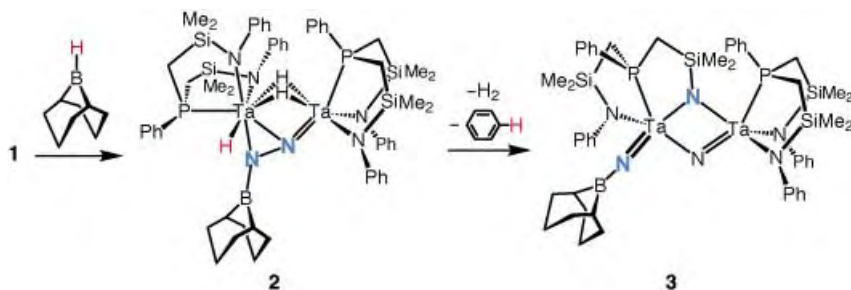
Arsenic, currents, and pores: Reversible covalent-bond-forming reactions are monitored by single-molecule detection. One reactant, a thiol group, is present on the wall of a protein pore, while the second, an organoarsenic(III) compound is in solution (see scheme). The reaction is detected by observing the current flowing through the pore (see trace), which allows the determination of rate constants with microsecond time resolution.



Angew. Chem. **2002**, *114*, 3859–3861



A clean break: Hydroboration of the side-on, end-on N_2 unit of $[(NPN)Ta]_2(\mu-\eta^1:\eta^2-N_2)(\mu-H)_2$ (**1**; $NPN = PhP(CH_2SiMe_2NPh)_2$) by 9-BBN results in the addition of the B–H bond across the Ta– N_2 moiety to generate a N–B bond and a terminal Ta–H unit (**2**). Surprisingly, this species is unstable in solution. Thus, this hydroboration triggers a cascade of reactions that result in N–N bond cleavage and ancillary ligand rearrangement in the formation of the imide–nitride species **3**.



Angew. Chem. **2002**, *114*, 3861–3864



Supporting information on the WWW
(see article for access details).



Accelerated publications

K. C. Nicolaou,* D. W. Kim,
R. Baati 3701–3704

Stereocontrolled Total Synthesis of
Apicularen A and Its $\Delta^{17,18}$ Z Isomer

Keywords: biomimetic synthesis •
macrolides • natural products •
polyketides • total synthesis

M. Smietana, E. T. Kool* ... 3704–3707

Efficient and Simple Solid-Phase
Synthesis of Short Cyclic
Oligodeoxynucleotides Bearing a
Phosphorothioate Linkage

Keywords: cyclization • drug research •
oligonucleotides • solid-phase synthesis

S.-H. Shin, T. Luchian, S. Cheley,
O. Braha, H. Bayley* 3707–3709

Kinetics of a Reversible Covalent-Bond-
Forming Reaction Observed at the Single-
Molecule Level

Keywords: analytical methods • arsenic •
protein structures • single-molecule
studies • sulfur

M. D. Fryzuk,* B. A. MacKay,
S. A. Johnson, B. O. Patrick . 3709–3712

Hydroboration of Coordinated
Dinitrogen: A New Reaction for the N_2
Ligand that Results in Its
Functionalization and Cleavage

Keywords: dinitrogen • hydroboration •
nitrides • nitrogen fixation • tantalum

* Author to whom correspondence should be addressed



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Instruments and Experimentation in the History of Chemistry	Frederic L. Holmes, Trevor H. Levere	<i>G. B. Kauffman</i> 3715



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http://www.restrictionmapper.org/	Virtual Restriction Analysis: Restriction Mapper	<i>S. Brakmann</i> 3718

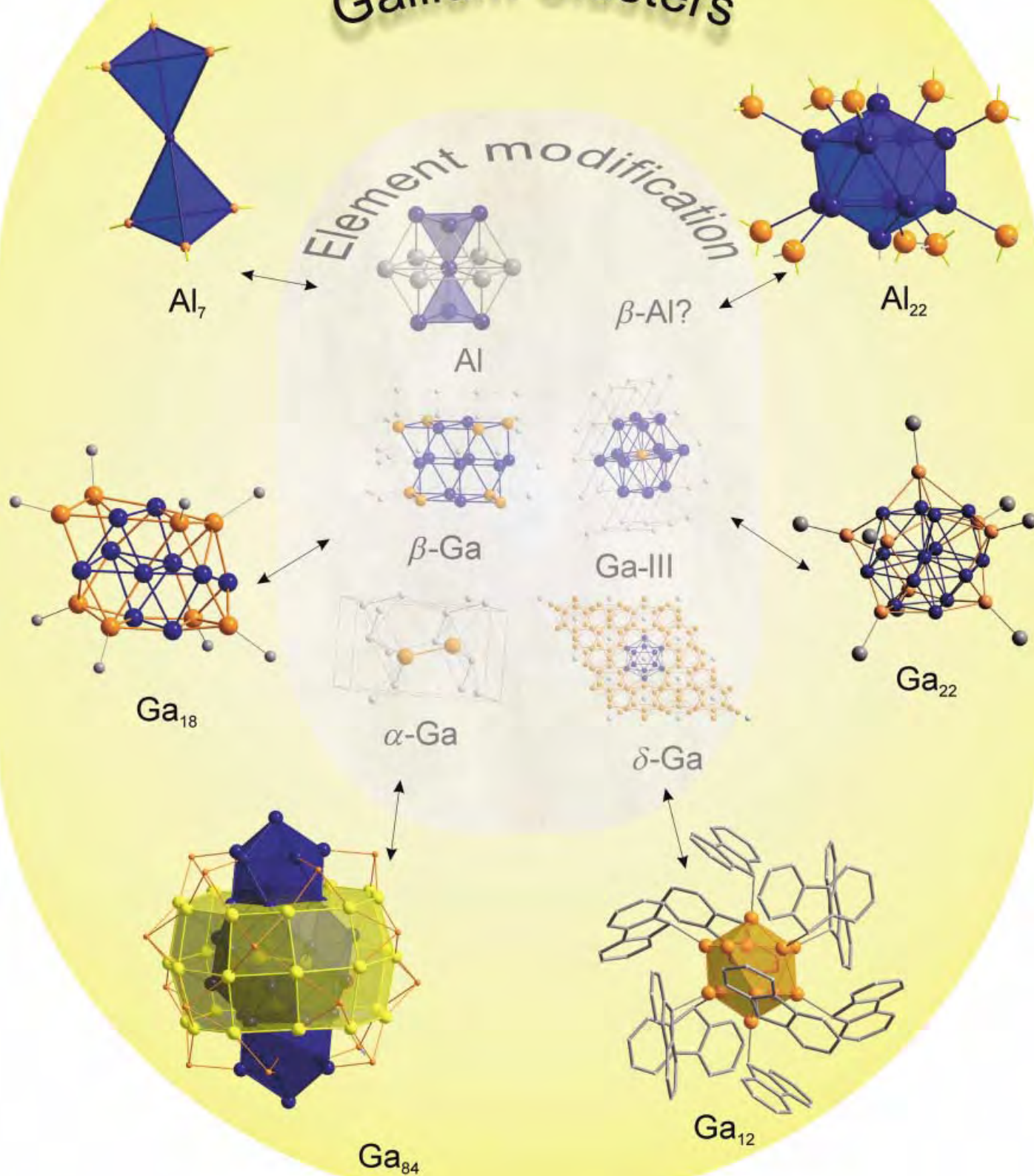
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Metalloid Aluminum and Gallium Clusters



Metalloid Aluminum and Gallium Clusters: Element Modifications on the Molecular Scale?

Andreas Schnepf and Hansgeorg Schnöckel*

Dedicated to Professor Dieter Fenske on the occasion of his 60th birthday

As members of the same group in the periodic table, the industrially significant elements aluminum and gallium exhibit strong similarities in the majority of their compounds. In contrast there are significant differences in the structures of the two elemental forms: Aluminum forms a typical closest-packed metallic structure whereas gallium demonstrates a diversity of molecular bonding principles in its seven structural modifications. It can therefore be expected that differences between Al and Ga compounds will arise when, as for the elemental forms, many metal–metal bonds are formed. To synthesize such cluster compounds, we

have developed the following synthesis procedure: Starting from gaseous monohalides at around 1000 °C, metastable solutions are generated from which the elements ultimately precipitate by means of a disproportionation reaction at room temperature. On the way to the elemental forms, molecular Al and Ga cluster compounds can be obtained by selection of suitable ligands (protecting groups), in which a core of Al or Ga atoms are protected from the formation of the solid element by a ligand shell. Since the arrangement of atoms in such clusters corresponds to that in the elements, we have designated these clusters as metalloid or

elementoid. In accordance with the Greek word εἶδος (ideal, prototype), the atomic arrangement in metalloid clusters represents the prototypic or ideal atomic arrangement in the elements at the molecular level. The largest clusters of this type contain 77 Al or 84 Ga atoms and have diameters of up to two nanometers. They hold the world record with respect to the naked metal-atom core for structurally characterized metalloid clusters.

Keywords: aluminum • cluster compounds • gallium • metal–metal interactions • structure elucidation

1. Introduction

Multi-atom, naked metal clusters are increasingly the subject of investigation by complex physical and quantum-chemical methods, for example, in nanotechnology^[1, 2] because of their special properties in the transitional region between molecular and solid-state chemistry.^[2] The interest in structure of such clusters is vividly illustrated by the 102m high Atomium in Brussels, which represents an Fe₉ section from the structure of solid iron enlarged 150 billion times (Figure 1).

Clearly the creators of the Atomium assumed that an Fe₉ molecule would have the same structure as a section from the solid structure of iron, since they describe their design as an Fe₉ atomic molecule. However, as far as we are aware there is no experimental proof for the existence of such a structure of



Figure 1. The Atomium in Brussels.

a molecular Fe₉ cluster. To obtain information on the arrangement of metal atoms in multiple-atom clusters, chemists have for many years been attempting to synthesize ligand-protected metal-atom clusters to compare their struc-

[*] Prof. Dr. H. Schnöckel, Dr. A. Schnepf
Institut für Anorganische Chemie
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ture and properties with that of the corresponding solid metal.^[2]

We have described such clusters, which contain both ligand-bearing and naked metal atoms that are only bonded to other metal atoms, as *metalloid*,^[3] to express, in accordance with the Greek word εἶδος (ideal, prototype), that the ideal form or the motif of the solid structure can be recognized in the topology of the metal atoms in the cluster. The original limits of the term *metalloid*—used, for example, for the elements silicon and germanium which are metal-like with respect to certain macroscopic properties (e.g. metallic luster)—were extended to include the metalloid clusters, thus accessing an additional structural level, which was only possible through crystal structure analysis.

In general such metalloid clusters contain more direct metal–metal contacts than metal–ligand contacts. This means that metalloid clusters represent a sub-group of the extensive metal-atom cluster group in which, according to the definition of Cotton,^[4] non-metal atoms may also be present.

Until a few years ago, metalloid clusters were known exclusively for the noble transition metals since these could be handled with relative ease (e.g. in aqueous solution). The $[\text{Au}_{55}(\text{PPh}_3)_{12}\text{Cl}_6]$ cluster^[5] is the prototype of this family. Unfortunately no experimental structure data has been determined for this cluster since suitable crystals are not available.

The, at the time, largest metalloid noble-metal clusters to be structurally determined contain 6 naked Pt ($[\text{Pt}_6\text{Ni}_{38}(\text{CO})_{48}\text{H}]^{5-}$),^[6] 11 naked Pd ($[\text{Pd}_{59}(\text{CO})_{32}(\text{PMe}_3)_{21}]$),^[7] and—since 2000—55 naked Pd atoms with no ligand connections ($[\text{Pd}_{145}(\text{CO})_{60}(\text{PEt}_3)_{30}]$; Figure 2).^[8] Therefore it was very surprising when a metalloid cluster with 57 naked aluminum atoms ($[\text{Al}_{77}\text{R}_{20}]^{2-}$, $\text{R} = \text{N}(\text{SiMe}_3)_2$) was prepared and structurally determined in our group about five years ago (Figure 3).^[9] This result was all the more surprising since the synthesis of the first molecular compound

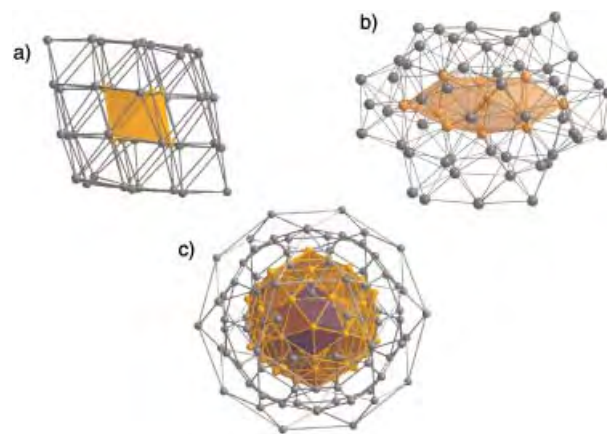


Figure 2. Molecular structure of the metalloid noble-metal clusters a) $[\text{Pt}_6\text{Ni}_{38}(\text{CO})_{48}\text{H}]^{5-}$ b) $[\text{Pd}_{59}(\text{CO})_{32}(\text{PMe}_3)_{21}]$, and c) $[\text{Pd}_{145}(\text{CO})_{60}(\text{PEt}_3)_{30}]$. The naked metal atoms are highlighted in color.

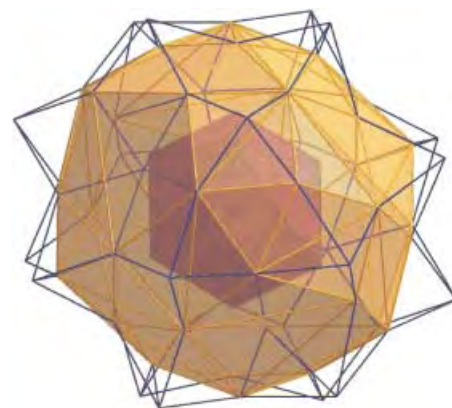


Figure 3. Layered representation of the arrangement of the 77 Al atoms $[1 + 12(\text{red}) + 44(\text{yellow}) + 20(\text{blue})]$ in the metalloid cluster $[\text{Al}_{77}\{\text{N}(\text{SiMe}_3)_2\}_{20}]^{2-}$ (5).

Hansgeorg Schnöckel, born in Marienburg, Western Prussia, studied chemistry at the University of Münster, where he also gained his doctorate under the supervision of H. J. Becher in 1970 on the spectroscopic investigations of boron-containing molecules. Subsequently he undertook matrix investigations of reactive high-temperature molecules, which formed the basis of his Habilitation in 1981. In 1987 he became professor of the University of Münster and in 1989 at the Institute of Inorganic Chemistry at the University of Munich. Since 1993 he has held the chair for analytical chemistry at the University of Karlsruhe. His research interests, that initially concentrated on the spectroscopic and quantum chemical investigations of reactive molecules, have in recent years shifted to synthetic chemistry of aluminum and gallium(i) halides and most recently to the synthesis of metalloid Al and Ga cluster compounds. The synthesis of such cluster units with dimensions on the nanometer scale and the investigation of the geometric and electronic structure by means of experimental and quantum-chemical methods are now central to his research activities with the aim of synthesizing and decomposing metalloid clusters as intermediates on the way from metal atoms to the bulk material.

Andreas Schnepf, born 1968 in Karlsruhe, studied at the University of Karlsruhe, where he received his doctorate in 2000 with studies on polyhedra and metalloid clusters of gallium under the supervision of Professor Schnöckel. He is currently investigating subvalent compounds of the fourth main group of elements at the University of Karlsruhe.



H. Schnöckel



A. Schnepf

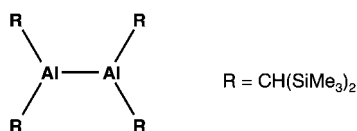


Figure 4. Schematic representation of the first diallane.

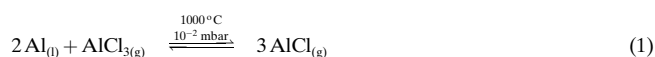
($[\text{Al}_2\{\text{CH}(\text{SiMe}_3)_2\}_4]$; Figure 4) with a 2 electron 2 center (2e2c) aluminum–aluminum bond had only been achieved in 1988.^[10] In this case, and in many others, mainly smaller aluminum and gallium compounds were prepared, usually by traditional synthesis methods^[11–14] (e.g.: dehalogenation reactions: $\text{RMX}_2 + \text{Na}$; or reactions with “GaI” originating from ultrasonic treatment^[15]). Such methods will only be discussed in passing in this review.

We have developed another synthesis variant in which the gaseous monohalides, prepared at around 1000 °C, are subsequently isolated in metastable solutions at –78 °C.^[16, 17] The halogen atoms are substituted by bulky groups and in a parallel disproportionation reaction (e.g. $3\text{AlCl} \rightarrow 2\text{Al} + \text{AlCl}_3$), large Al or Ga clusters are formed. Analogue to the above-mentioned Al_{77} cluster, we have also succeeded recently by such means to synthesize further metalloid aluminum and gallium clusters with diameters on the nanometer scale. In these cases the topology of the metal atoms in the clusters usually reflects that of the metal, or it can be used to give an indication of element modifications yet to be discovered.^[16b,c, 23]

2. Synthesis of Metastable Aluminum- and Gallium-Halide Solutions

2.1. Principles and Experimental Details

The equilibrium between the liquid metal and gaseous mono- and trihalides is described for the example of aluminum [Eq (1)].



The conditions for gallium are almost the same, with the exception that to achieve a comparable ratio of the partial pressures of mono- to trihalide the reaction temperature should be about 100 K lower.

In general, as a result of the increase in entropy, the equilibrium of this endothermic reaction shifts in favor of the gaseous monohalide with increasing temperature and with decreasing total pressure.^[18] The transport of aluminum in the presence of AlCl_3 as described by Klemm et al. and later by Schäfer is also based on the reaction of Equation (1).^[19] The partial-pressure behavior of the gaseous components is solely determined by the thermodynamic data of the mono- and trihalides and the molten metal, which means that it does not matter which halogenation medium is used in the preceding reaction. Thanks to its easy handling and to ensure a continuous stream of gaseous AIX (X = Cl, Br, I) we used a flow of the respective hydrogen-halide gas (e.g. HCl) at about 1000 °C over aluminum [Eq. (2)].



Under these conditions (ca. 10^{-1} mbar total pressure), for example, for the chloride system, there is a more than 20-fold excess of AlCl over AlCl_3 .

To investigate the reactivity of molecular monohalides, we had previously carried out many matrix isolation experiments, which showed that AIX species preferentially oligomerize in solid argon. For example, a ring-shaped structure with D_{2h} point symmetry was inferred from the spectroscopic data for the dimeric species.^[20, 16a] In addition to oligomerization, only the very first reaction and the most recent reaction from the matrix experiments will be mentioned here:

As far back as 1978 we were able to demonstrate the formation of the first threefold coordinate aluminum hydride halide (HAICl_2) from HCl and AlCl ,^[21] and recently we were able elucidate the reaction between AlF and O_2 in solid argon.^[22] AlF was generated at about 1000 °C by passing CF_3H , which was used instead of HF for ease of handling, over molten Al. In addition to an FAIO_2 peroxide with C_{2v} point symmetry, an unexpected $\text{FAI}(\text{O}_2)_2$ species with slightly distorted C_{2v} point symmetry was formed. The formation of such compounds ($\text{FAI}(\text{O}_2)_2$ has a triplet ground state!) is an indication that similar species could also be formed as primary products during the surface oxidation of metallic aluminum.

The positive results from the matrix experiments, which were started about 12 years ago, have enabled us to produce monohalides in gram amounts for synthesis purposes.^[17] Although the experimental realization of this idea has been described many times,^[16, 23] it will be presented briefly here because this experiment forms the basis for all the chemistry to follow. The required co-condensation apparatus is shown in Figure 5. At the center of a vacuum system of about 30-liter

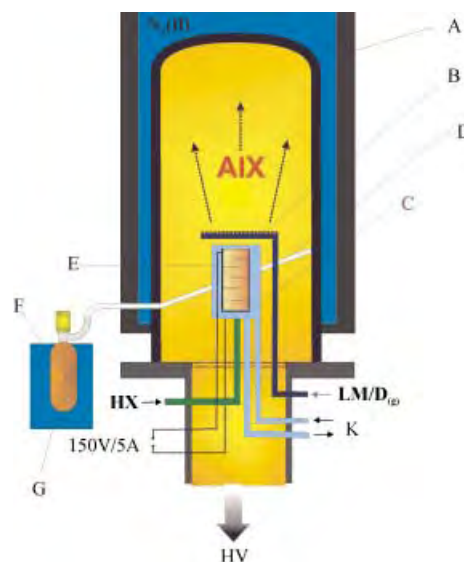


Figure 5. Scheme of the co-condensation apparatus: A = stainless steel vessel (30 L); B = solvent input (LM/D); C = Al in the graphite cell with resistance heating; D = drainage channel; E = cooling shield; F = Schlenk line; G = Dewar with dry ice (–78 °C); K = cooling water; HX = hydrogen halide gas; HV = high vacuum.

volume is a high-temperature reactor which contains molten aluminum at around 1000 °C in several graphite chambers. A flow of hydrogen-halide gas is directed through these reaction

chambers, and the flow is measured by means of the pressure drop in a storage vessel. In general about 40 mmol AlX is synthesized in two hours. After exiting the reactor the gaseous AlX molecules condense, without undergoing further collisions, on the cooled outer walls of the stainless steel vacuum vessel at -196°C . To prevent the aggregation of the AlX species which disproportionate to form aluminum metal, that is, the reverse reaction in Equation (1), when warmed to above -100°C , an excess of a suitable solvent must be co-condensed with the monohalide molecules. We generally use toluene to which a variable amount of a donor component has been added (e.g. NEt_3 , Et_2O , THF). When the solid solvent mixture is melted at about -100°C , deep red solutions are usually obtained which subsequently disproportionate according to Equation (1) in the temperature range -40 to $+50^{\circ}\text{C}$ depending on the halide and the donor and its concentration to the metal and the corresponding trihalide. The metastable AlX and GaX solutions are the starting points for the chemistry described in the following sections.

2.2. Limitations and Advantages of the AlX/GaX Synthesis Method

The limitations of the synthesis method described in Section 2.1 arise from the availability and capabilities of a precision mechanical workshop, since it requires the construction of high-vacuum apparatus in stainless steel involving many vacuum parts, and high- and low-temperature components. The optimization of our apparatus has continued over many years and with new information arising from almost every experiment the apparatus undergoes constant technical improvement. Despite the limitations of the method that mainly arise from the sensitivity and weaknesses of the apparatus, there are many advantages over classical procedures:

- Subvalent halides such as the ring-shaped Al_4X_4 ^[24] and Ga_8X_8 species (Figure 6),^[25] the first Al^I and Ga^I halides to be structurally investigated, are synthesized directly from

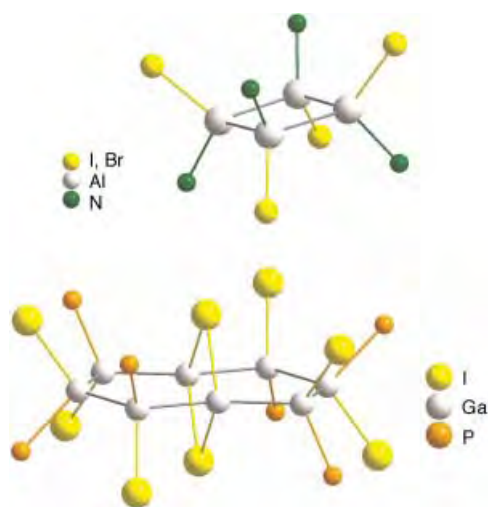


Figure 6. Molecular structures of binary halides $\text{Al}_4\text{X}_4 \cdot 4\text{NEt}_3$ ($\text{X} = \text{I}, \text{Br}$; top) and $\text{Ga}_8\text{I}_8 \cdot (\text{PEt}_3)_6$ (bottom). Of the donor molecules only those atoms directly bonded to the metal atoms are shown.

the above-mentioned primary solutions; this is only possible by this method. The same applies to the first aluminum subhalides with a polyhedral Al framework: $\text{Al}_{22}\text{X}_{20}$ ($\text{X} = \text{Cl},^{[26]} \text{Br}^{[27]}$). These Al_{22} compounds will be described in Section 3.2. Other halides and partially substituted halide compounds are the subject of a recently published review.^[28]

- In the classical reduction of RGaX_2 compounds, for example, with reductants such as alkali metals, temperatures of 50 to 110°C are generally applied which means that only GaR species that contain kinetically stable GaR bonds can be synthesized (e.g. GaCp^* ; ^[29] $\text{Cp}^* = \text{C}_5\text{Me}_5$): Metastable GaX solutions are so reactive that almost every metathesis reaction (e.g. with $\text{LiN}(\text{SiMe}_3)_2$) proceeds at temperatures above -78°C . This means that our method can be used to obtain, for example, the unsubstituted compounds $\text{GaCp}^{[30]}$ and $\text{AlCp}^{[31]}$ ($\text{Cp} = \text{C}_5\text{H}_5$) in solution at low temperatures.
- Disproportionation reactions that proceed even under mild conditions (see above) can give rise to metalloid Al and Ga clusters that contain an increasing number of naked Al or Ga atoms with increasing reaction temperature. When applied to gallium chemistry the trisyl group ($\text{C}(\text{SiMe}_3)_3$) provides some impressive examples. The classical dehalogenation methods of Uhl et al. enabled the first tetrahedral Ga_4R_4 compound ($\text{R} = \text{C}(\text{SiMe}_3)_3$) to be synthesized^[11], we succeeded in synthesizing a Ga_8 compound from a GaBr solution in toluene/THF at lower temperatures^[32] in which tetrahedral Ga_4R_3 groups are connected over a Ga_2 unit (i.e. two naked Ga atoms (see Figure 19). At room temperature the same reaction yields a Ga_{19}R_6 cluster,^[3] that contains 13 naked Ga atoms (see Figure 27), which demonstrates that the disproportionation reaction at this temperature proceeds much further along the path towards generating the metal. Both compounds will be discussed in more detail in Section 4.3.3 and 4.4.3.

3. Aluminum Clusters

3.1. Metalloid Aluminum Compounds

After the first compound with a 2e2c Al–Al bond was synthesized by Uhl (Section 2.2)^[10] and after we had synthesized AlCp^* ,^[33] the first organo–Al^I compound, the objective was to synthesize metalloid aluminum-cluster compounds with as many naked Al atoms, that is, atoms with no attached ligands, as possible. The $\text{N}(\text{SiMe}_3)_2$ ligand proved to be a particularly favorable ligand in this endeavor since it was apparent that the substitution of the halogen atoms ($\text{AlX} + \text{LiR} \rightarrow \text{LiX} + \text{AlR}$) and the disproportionation of the AlX species ($3\text{AlX} \rightarrow 2\text{Al} + \text{AlX}_3$) occur in the same temperature range. Reactions in which substitution is favored tend to the formation of oligomeric AlR species (e.g. $(\text{AlCp}^*)_4$), whereas when substitution is hindered or when there is no suitable substituent the formation of aluminum metal through disproportionation of the AlX species is observed.

In the following section only metalloid aluminum clusters are discussed that are protected by an outer shell of the above-

mentioned $\text{N}(\text{SiMe}_3)_2$ ligand. These clusters therefore contain a naked Al_n core surrounded by $\text{AlN}(\text{SiMe}_3)_2$ groups with strong 2e2c Al–N bonding, in other words bonding between Group III/V elements.

The size of the Al_n cluster core is determined by the reactivity of the AlX solution with respect to disproportionation. Therefore, for a particular halide the size of the resulting cluster can be increased by an increase in temperature: Starting from an AlCl solution, for example, the cluster size progresses from an $[\text{Al}_7\text{R}_6]^-$ (**1**) cluster at -7°C ^[34] through an $[\text{Al}_{12}\text{R}_6]^-$ (**2**) cluster^[35] at room temperature through to an $[\text{Al}_{69}\text{R}_{18}]^{3-}$ (**4**) cluster after warming briefly to 60°C .^[36] When, however, a less reactive AlI solution is used, at room temperature a partially substituted Al_{14} cluster **3** is obtained,^[37] whereas after warming briefly to 60°C the above-mentioned $[\text{Al}_{77}\text{R}_{20}]^{2-}$ (**5**) cluster^[9] forms; in all cases R is the $\text{N}(\text{SiMe}_3)_2$ ligand. The cluster compounds **1–5** are extremely sensitive to moisture and air and may even spontaneously combust after only brief exposure to the atmosphere. Therefore handling these compounds for all physical measurements can be exceptionally difficult (see Section 4.4.6). This behavior contrasts dramatically with that of the metalloid noble-metal clusters (e.g. the Au_{55} ^[5] and Pd_{145} species^[8]), some of which can be handled in aqueous solution and in contact with air. This difference is to be expected: it is comparable to the differences between the noble and the base metals.

All the above-mentioned metalloid Al clusters **1–5** form an Al_n cluster framework, which can be described as a distorted section from the structure of solid aluminum. The geometries of the Al_n frameworks of Al clusters **1–5** are shown in Figure 7 a–e, whereby the distance between the center points of the Al atoms furthest apart increases from 5.46 to 13.35 Å in the series of Figures 7 a → e.

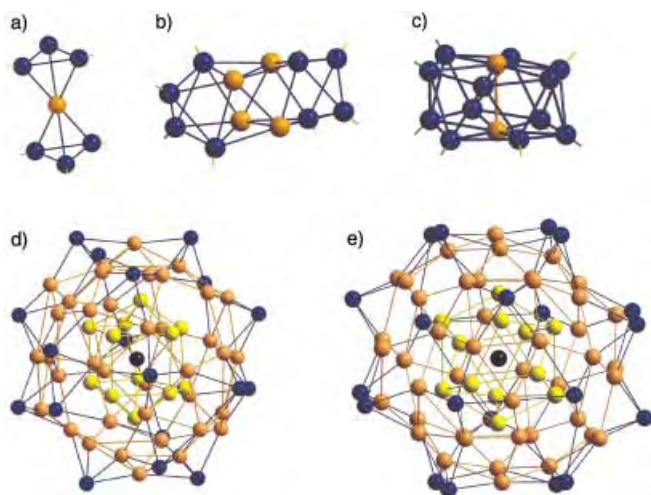


Figure 7. Geometrical arrangement of the Al atoms of the metalloid aluminum clusters: a) $[\text{Al}_7\text{R}_6]^-$ (**1**); b) $[\text{Al}_{12}\text{R}_6]^-$ (**2**); c) $[\text{Al}_{14}\text{R}_6\text{I}_6]^{2-}$ (**3**); d) $[\text{Al}_{69}\text{R}_{18}]^{3-}$ (**4**); e) $[\text{Al}_{77}\text{R}_{20}]^{2-}$ (**5**); R = $\text{N}(\text{SiMe}_3)_2$.

The description of these clusters as molecular nanostructured element modifications therefore appears plausible. This definition is further elucidated in Figure 8 which shows the topological relationship of clusters **1** and **2** to the structure of

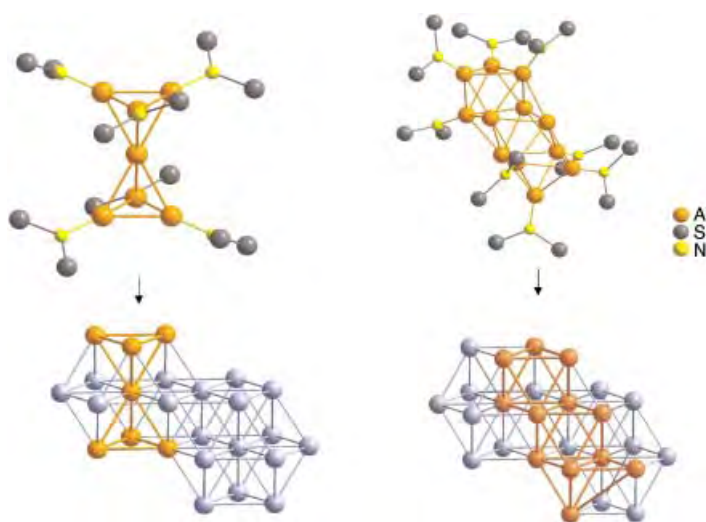


Figure 8. Molecular structures of the metalloid aluminum clusters $[\text{Al}_7\text{R}_6]^-$ (**1**; left) and $[\text{Al}_{12}\text{R}_6]^-$ (**2**; right) and the corresponding sections from the solid-state structure of elemental aluminum. R = $\text{N}(\text{SiMe}_3)_2$.

solid aluminum.^[38] The metallic luster of crystals of clusters **4** and **5** is a further similarity to aluminum.

The relationship of the “wheel-rim-type” structure of the Al_{14} compound **3** to the metal can be demonstrated by a 30° rotation of the two centered Al_6 rings followed by a shift of the six-membered rings towards each other. The other possibility of the formation of an Al_{14} polyhedron with D_{6d} point symmetry by displacement of the naked central atom has been shown to be energetically unfavorable by quantum-chemical calculations: The observed metalloid structure is favored over the anticipated polyhedral structure^[39] described by Wade.^[67]

The principle and the significance of metalloid clusters for the understanding of the formation of metals are made clear by the two largest Al clusters **4** and **5** (Figure 7 d, e) which are almost the same size with 69 and 77 Al atoms and 18 and 20 $\text{N}(\text{SiMe}_3)_2$ groups. In both cases a central Al atom is surrounded by 12 nearest neighbors. Despite the great similarity between the two clusters—the coordination number of the Al atoms decreases from the center to the periphery, the mean Al–Al distance decreases from the center to the periphery indicating that the Al–Al bonds have become more localized and have more molecular character from the inside to the outside—the coordination spheres of the central Al atoms are significantly different: The Al_{13} core of the Al_{69} cluster **4** can be described as distorted D_{5h} (this geometry is often described as decahedral^[40]) whereas the central Al atom in the Al_{77} cluster **5** has been shown to have an icosahedral coordination sphere that is distorted in the direction of a cuboctahedron (Figure 9). Therefore both cases show a different geometry than for the noble-metal clusters: for example, for the Au_{55} cluster a cuboctahedral and icosahedral environment has been postulated and for the Pd_{55} framework of naked Pd atoms at the center of the Pd_{145} cluster an almost undistorted icosahedral Pd_{13} unit has been observed.^[8] This situation demonstrates that for these large metalloid clusters (Al_{69} **4**,^[36] Pd_{145} ,^[8] Al_{77} **5**,^[9] and a larger Ga_{84}

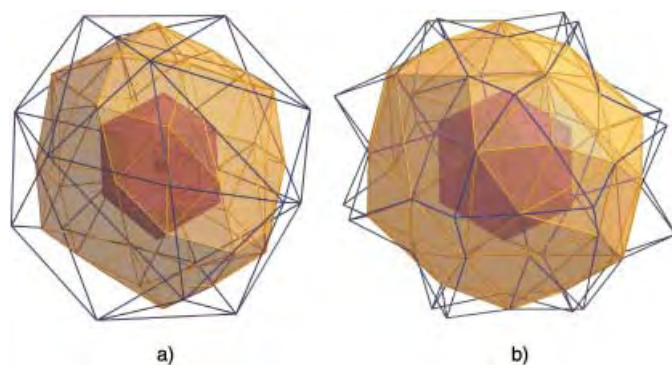


Figure 9. Arrangement of the Al atoms in the metalloid clusters a) $[\text{Al}_{69}\text{R}_{18}]^{3-}$ (**4**) and b) $[\text{Al}_{77}\text{R}_{20}]^{2-}$ (**5**) in a layered representation: **4** 1 + 12(red) + 38(yellow) + 18(blue) Al atoms; **5** 1 + 12(red) + 44(yellow) + 20(blue) Al atoms. $\text{R} = \text{N}(\text{SiMe}_3)_2$.

cluster **10**, which will be described in Section 4.4.6), for which structural data are available, there are significant differences in the centers both amongst the clusters themselves and to the corresponding metals, whereby the Pd_{145} cluster is the most similar with respect to the topology of the metal. However, in all cases the distance of the 12 nearest neighbors from the central atom is shorter than that in the metal, which shows that the bonding has shifted away from predominantly delocalized in the metal in the direction of localized molecular bonding.

We find the significant differences in the Al_{13} center of the Al_{69} cluster and the Al_{77} cluster frameworks of particular interest. Apparently even small changes in the cluster shell, which are probably too small to be observed with common nanoscopic methods (e.g. AFM: atomic force microscopy), lead to changes in the topology of the metal framework at the center which then affect the electronic properties. Unfortunately apart from a preliminary band-structure calculation of the Al_{77} cluster^[41] there have been no detailed investigations that could lead to a deeper understanding of the interactions between the cluster shell and the core. Such investigations, which could make use of the experimental structural data, could serve to model metal-surface reactions, such as the dissolution of aluminum. The structures of **4** and **5** suggest that $\text{Al}^{\text{I}}\text{R}$ units are formed primarily on the surface. According to the observations of **4** and **5**, such primary reactions could also lead to changes in the interior of the metal, even in the nanometer range.

To approach an understanding of the relationship between the structures of the Al_{69} and Al_{77} clusters and that of metallic aluminum, we have compared frameworks of 51 and 57 naked Al atoms from these two clusters with an Al_{55} unit from the metal. To do this, single-point self-consistent-field (SCF) calculations were carried out based on the experimental data from all three species^[36] and the volume enclosing an area of the same electron density ($0.004 \text{ e } \text{\AA}^3$; Figure 10). The results showed that the mean atomic volume (volume of the Al_n cluster framework/number of Al atoms) decreases in the order $\text{Al}_{51}^{3-} > \text{Al}_{57}^{3-} > \text{Al}_{55}^{3-}$. For improved comparability the same charge of $3-$, was specified. Although the Al–Al bonds of the Al_{55} cluster were the longest ($2.86 \text{ \AA}$, as in Al metal) the

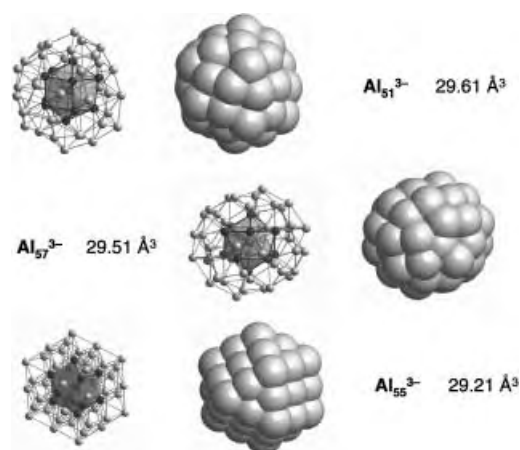


Figure 10. Arrangement of the naked Al atoms in $[\text{Al}_{69}\text{R}_{18}]^{3-}$ (**4**; section of the Al_{51}^{3-} structure) and $[\text{Al}_{77}\text{R}_{20}]^{2-}$ (**5**; Al_{57}^{3-} section), and an Al_{55} section from the solid-state structure of elemental aluminum in ball-and-stick and space-filling representations including the calculated mean atomic volumes for the Al atoms in these three clusters. $\text{R} = \text{N}(\text{SiMe}_3)_2$.

increase in the coordination numbers in the order $\text{Al}_{51}^{3-} < \text{Al}_{57}^{3-} < \text{Al}_{55}^{3-}$ leads to a contraction of the Al_n cluster framework. The stepwise disproportionation of Al^{I} compounds, which always yields Al metal at temperatures above around 60°C , is therefore associated with a contraction of the metal atom framework. This conclusion suggests that a closer investigation of the precipitates with metallic luster that are sometimes observed to form metallic mirrors on the vessel walls after disproportionation would be worthwhile. These could be larger Al clusters with cores of Al atoms that have contracted even further in the direction of the metal.

All previously discussed metalloid Al clusters show that the favored arrangement of Al atoms is a closest packing as in the metal, whereby the observed distortions reflect the adaptation of the cluster core to the AIR “corset”. Since the packing density comes ever closer to that of the metal with increasing cluster size (Figure 10), it is conceivable that there is an alternative pathway during the early stages of cluster formation that could lead to a less compact modification of aluminum. This hypothesis may not be so unlikely since the other Group III metals, boron and gallium (see Section 4), also exist in several modifications. An experimental indication for a hypothetical β -aluminum modification is given by the results discussed in the following Section 3.2.

3.2. Al_{22} Clusters as Intermediates in the Formation of Hypothetical β -Aluminum

Directly after the condensation of AlX species, for example, in the presence of strong donors, the donor-stabilized $\text{Al}_4\text{Br}_4 \cdot 4\text{NEt}_3$ compound^[24] is obtained in which the bonding can be described by means of classical $2e2c$ bonds (see Section 2.2). With weaker donors such as THF, the first polyhedral Al subhalides $\text{Al}_{22}\text{X}_{20} \cdot 12\text{L}$ ($\text{X} = \text{Br}$ (**6**),^[27] Cl (**7**),^[26] $\text{L} = \text{THF}$, tetrahydropyran (THP)) with a unique structure were recently obtained (Figure 11). The icosahedral Al_{12} core of **6** and

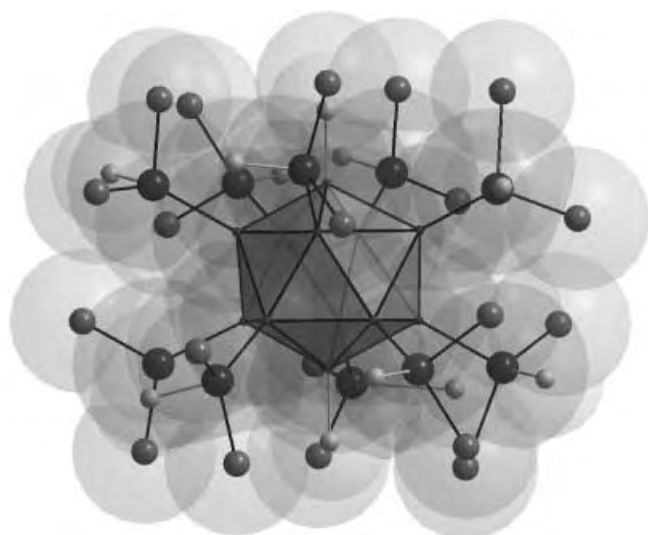


Figure 11. Molecular structure of $\text{Al}_{22}\text{Br}_{20} \cdot 12\text{THF}$ (**6**). Of the THF molecules only the O atoms directly bonded to the Al atoms are shown.

7 is reminiscent of the polyhedral boron subhalides (such as B_4X_4 , B_8X_8 , B_9X_9 , and $\text{B}_{12}\text{X}_{12}^{2-}$),^[42] in which each halogen atom X is directly bonded to a boron atom of the polyhedral framework. In contrast, in the Al_{22} halides **6** and **7**, ten more Al atoms are directly bonded each to an Al atom of the icosahedral Al_{12} framework to present a unique configuration. The outer ten Al atoms are additionally bonded each to two halogen atoms and saturated by a donor molecule. The apex and base atoms in the Al_{12} icosahedron are naked, that is, they are each only shielded by one donor molecule. This type of metal-atom topology is surprising because it has not been observed for any element. It could be expected for boron clusters since, for example, the α -boron modification^[43] in which a network of molecular icosahedral cluster units are to some extent connected by boron–boron bonds. Despite the great sensitivity of these Al_{22} subhalides, it was possible to obtain solid-state ^{27}Al NMR and X-ray photoelectron spectroscopy (XPS) measurements, which showed indeed that three electronically different types of Al atoms are present.^[26, 44]

With respect to the bonding of the Al atoms the structure of these $\text{Al}_{22}\text{X}_{20}$ clusters shows some similarity to bonding in β -rhombohedral boron (which contains a B_{84} unit with a central icosahedral B_{12} framework of which all the boron atoms are connected to B_6 units^[27]). Therefore, ab initio calculations were carried out on the stability of a hypothetical Al modification with the structure of α -boron.^[26] The calculations show that with an expansion of the closest-packed Al atoms in aluminum metal by about 30% a structure analogous to α -boron would be energetically more stable (Figure 12). An expansion of this type would be associated with an energy consumption of about 33 kJ mol^{-1} . As was shown in the discussion of the Al_{69} and Al_{77} clusters (**4** and **5**; Figure 7 d, e), a contraction in the direction of the bulk-metal structure does take place during disproportionation, thus the intermediate existence of a β -Al modification with a larger atom volume cannot be excluded. This hypothesis is supported by model

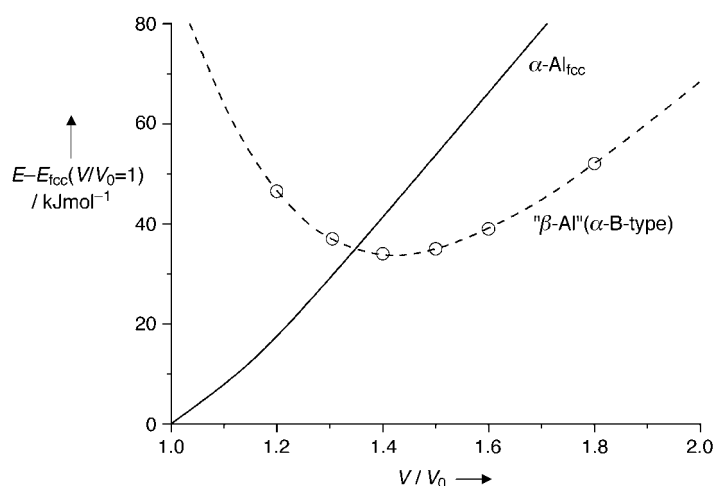


Figure 12. Calculated energy pathway for the real (— α -Al) and hypothetical (--- β -Al) aluminum solid-state modifications during expansion.

calculations that reveal that intermediate compounds analogous to **6** and **7** could be synthesized during disproportionation of $\text{AlCl} \cdot \text{H}_2\text{O}$ to $\text{Al}_{(\text{solid})}$ and AlCl_3 , that could then react further via a hypothetical β -Al modification to the final products $\text{Al}_{(\text{solid})}$ and AlCl_3 (Figure 13).^[26, 27]

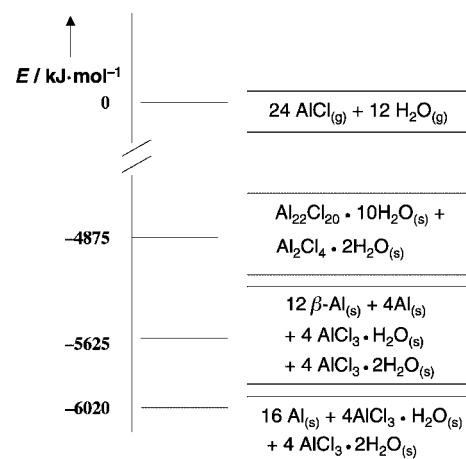


Figure 13. Calculated energy scheme for the modeled disproportionation of AlCl to Al and AlCl_3 in the presence of H_2O as the donor.

For gallium, its wide range of structures containing molecular units will be discussed in Section 4,^[23] the most recent calculations performed in an analogous fashion predict that a previously unknown modification with the α -boron structure could be much easier to obtain since the required energy input during expansion is only about 20% of that required for Al.^[84]

To summarize it can be stated that metalloid Al clusters which form structures with a constant ligand shell ($\text{N}(\text{SiMe}_3)_2$) show a close similarity with the topology of crystalline aluminum. The size of the clusters, which are intermediates on the way to the bulk metal, can be increased by increasing the temperature, however, temperatures above about 60°C lead exclusively to the metal. It is possible that there is

another reaction pathway which would lead initially to a polyhedral $\text{Al}_{22}\text{X}_{20}$ cluster. There are many indications that this cluster can be regarded as an intermediate on the way to a new hypothetical Al modification.

4. Metalloid Gallium Compounds

4.1. The Modifications of the Element

The structurally demonstrated existence of seven modifications for elemental gallium gives rise to the expectation of a larger diversity of metalloid clusters than observed for aluminum, for which only one element modification is known. To classify the topologies of the Ga atoms in all the Ga clusters described below, the most prominent structural features of the seven modifications are described in the following section. In Figure 14 the structural units typical of the normal-pressure modifications α -,^[45] β -,^[46] γ -,^[47] and δ -gallium^[48] and for the high-pressure modifications Ga-II and Ga-III^[49] are shown. Recently under very high pressure a Ga-IV modification was detected which has a fcc packing of the Ga atoms.^[49b]

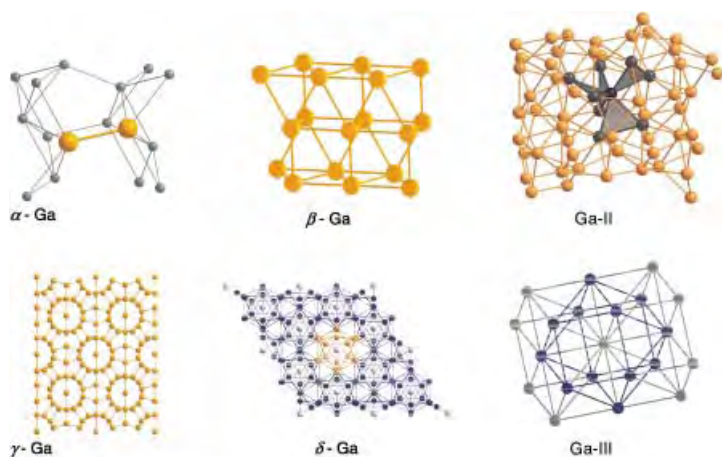


Figure 14. Sections of the normal-pressure solid-state modifications α -, β -, γ -, and δ -gallium and the high-pressure modifications Ga-II and Ga-III.

For α -gallium (coordination number 1+2+2+2) the short Ga–Ga bond of 2.45 Å is characteristic, so that α -gallium is also described as a molecular metal made up of Ga_2 dumbbells. For the low-temperature phases β -, γ -, and δ -gallium the following characteristic units are observed: the ladder structure (coordination number 2+2+2+2) for β -gallium, Ga_7 -rings that stack to form tubes and a centered Ga_n “wire” observed for γ -gallium, and connected Ga_{12} icosahedra for δ -gallium. In all cases pseudomolecular gallium units can be discerned that indicate a degree of covalent bonding, and therefore similarity to the neighboring element boron. In contrast, in the three high-pressure modifications Ga-II, Ga-III, and Ga-IV high coordination numbers and topologies of Ga atoms are observed (Figure 14) that point to analogies with the packing schemes of “true” metals such as the neighboring element aluminum.^[49, 50]

The diversity of bonding options for Ga atoms to each other that are apparent from the different modifications can also be observed in the metalloid clusters. These metalloid clusters could also be described, perhaps more suitably and comprehensively, as *elementoid* clusters since the atomic topologies observed are similar to those found in the bulk element. The special features of gallium in comparison to boron and aluminum in the elemental state, indicate that it would be less than helpful to describe the metal-rich compounds of all three elements on the basis of a single rule even though all three have the same number of valence electrons. The lack of a single ordering principle is a shortcoming, particularly for the gallium clusters, since as a result of their improved synthesis procedures, there is a larger number of them than the corresponding aluminum clusters. A purely formal means of classification for the gallium clusters would be to take, in addition to the oxidation number, the number of gallium atoms to demonstrate analogies to the topologies of the elemental state in the corresponding element modification.^[51]

4.2. Gallium–Gallium Bonds

Before starting the discussion of metalloid gallium clusters with several Ga–Ga bonds, it would be appropriate to make a few basic remarks on gallium–gallium bonding and a critical comment on gallium–gallium triple bonds: A molecular organometallic compound containing the first Ga–Ga 2e2c bond^[52] was synthesized by Uhl et al. at the end of the 1980s (Figure 15a).^[53] To clarify the term metal–metal bond, we

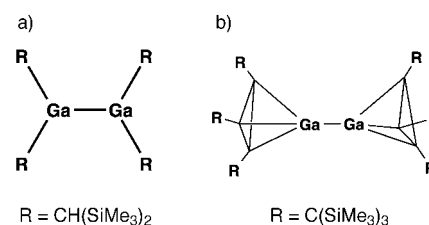


Figure 15. Schematic representation a) of the first digallane and b) $[\text{Ga}_8\text{C}(\text{SiMe}_3)_6]$ (**9**).

have designated the $[\text{Ga}_8\text{R}_6]$ cluster ($\text{R} = \text{C}(\text{SiMe}_3)_3$; Figure 15b, and Figure 19), mentioned in Section 2.2, as a prototypic compound^[32] with a 2e2c metal–metal bond, this is because each of the atoms participating in the Ga–Ga bond does so without bridging atoms and is exclusively bonded to other metal atoms of the same type. With the help of quantum-chemical calculations on the model compounds $[\text{Ga}_2\text{R}_4]$ and $[\text{Ga}_4\text{H}_4]$ and the experimental data for $[\text{Ga}_2\text{R}_4]$ and $[\text{Ga}_4\text{R}_4]$ the strength of the metal–metal bond in $[\text{Ga}_8\text{R}_6]$ can be classified as lying between that of a classical 2e2c bond and a 2e3c bond.^[59] Such bonding found in cluster elements (e.g. in fullerenes and Zintl ions) is currently of intense interest and a review article on this topic has recently appeared.^[54]

Although there are no indications for the existence of Ga–Ga double bonds, a discussion regarding the “Ga–Ga triple bond” has raged for several years.^[55] This was initiated

by a remarkable experimental result in which a compound (**11**) with a $[\text{Ga}_2\text{R}_2]^{2-}$ unit ($\text{R} = 2,6\text{-C}_6\text{H}_3\text{Trip}_2$; $\text{Trip} = 2,4,6\text{-C}_6\text{H}_2\text{iPr}_3$)^[56] and bridging Na^+ ions was investigated structurally and with the aid of quantum-chemical calculations.^[57] As a result of the short Ga–Ga bond length (2.32 Å) the term Ga–Ga triple bond was introduced for this bond. Critical assessments of the interpretation of the bonding in the $[\text{Ga}_2\text{R}_2]^{2-}$ unit were to be anticipated as there are other examples of short Ga–Ga bonds for which it is unlikely that a triple bond is present, for example, a) the Ga–Ga bonds of 2.35 Å in digallane $[\text{GaN}(\text{Dipp})\text{CH}=\text{CH}(\text{Dipp})]_2$ ($\text{Dipp} = 2,6\text{-diisopropylphenyl}$).^[58] b) the Ga_2 dumbbell discussed in Section 4.4.6 ($d(\text{Ga}–\text{Ga}) = 2.35$ Å) in the Ga_{84} cluster **10**, and c) the above-mentioned Ga_2 unit in $\alpha\text{-Ga}$, which despite a coordination number of seven for each Ga atom, exhibits an unexpectedly short bond of 2.45 Å. We also consider the description “triple bond” to be at least misleading since, if the term is used literally, a bond should hold together atoms and therefore a triple bond should be characterized by triple bond strength in comparison to a single bond. Since the bonding strength is graphically illustrated by the restoring forces during bond stretching, the force constant provides a good measure and shows that the Ga–Ga “triple bond” can at best be described as a strong single bond.^[59] It is apparent that the six electrons contributing to the bond strength do so to very different extents. In contrast the force constants for the corresponding bonds with arsenic (the next-but-one neighbor to gallium) yield the anticipated trend, that is, a ratio of 1:1.9:3.1 for the force constants of single, double, and triple bonds in the model compounds As_2H_4 , As_2H_2 , and As_2 .^[59]

In addition to the force constant, there are other indications that the short distance of the Ga–Ga “triple bond” is significantly influenced by the bridging Na^+ ions, so that in **11** we may in fact be dealing with a $[\text{RGaNa}_2\text{GaR}]$ cluster (Figure 16a).^[60] To avoid the use of, in our opinion, a

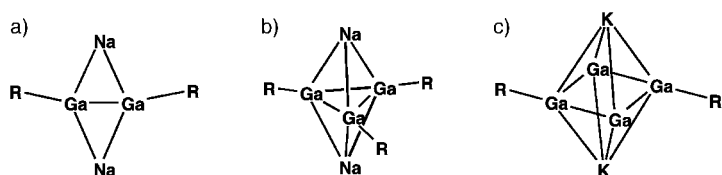


Figure 16. Schematic representation of the compounds a) $[\text{Ga}_2\text{R}_2\text{Na}_2]$ (**11**, $\text{R} = 2,6\text{-C}_6\text{H}_3\text{Trip}_2$) b) $[\text{Ga}_3\text{R}_3\text{Na}_2]$ (**12**, $\text{R} = 2,6\text{-C}_6\text{H}_3\text{Mes}_2$), and c) $[\text{Ga}_4\text{R}_4\text{K}_2]$ (**13**, $\text{R} = 2,6\text{-C}_6\text{H}_3\text{Trip}_2$).

misleading definition of multiple bonds for the heavier main-group elements, we proposed an alternative description: 4e2c bonds instead of double bonds and 6e2c bonds instead of triple bonds.^[60, 61]

4.3. Ga_n Clusters ($n = 4$ to 9)

A central motif in quite a few gallium clusters is the Ga_2 unit (e.g. $[\text{Ga}_6\text{R}_8]^{2-}$ (**8**), $[\text{Ga}_8\text{R}_6]$ (**9**), and $[\text{Ga}_{84}\text{R}_{20}]^{4-}$ (**10**)), which is a defining structural feature for $\alpha\text{-gallium}$ (see Section 4.1). Of note is that in the $[\text{Ga}_2\text{R}_2\text{Na}_2]$ species **11**^[56] (see Section 4.1; Figure 16a), the Ga_2 unit has the oxidation

state 0 which means that the reduction has already proceeded to the elemental state. Therefore this Ga_2 unit (or a $[\text{Ga}_2\text{Na}_2]^{2+}$ cluster) lies on the borderline between the Zintl anions on the one side^[104] and the metalloid gallium clusters with their intermediate oxidation states between +1 and 0 on the other. A similar analysis leads from the $[\text{Ga}_3\text{R}_3\text{Na}_2]$ species (**12**; $\text{R} = 2,6\text{-C}_6\text{H}_3\text{Mes}_2$; $\text{Mes} = 2,4,6\text{-C}_6\text{H}_2\text{Me}_3$)^[62] to the $[\text{Ga}_3\text{Na}_2]^{3+}$ units^[63] or from the $[\text{Ga}_4\text{R}_2\text{K}_2]$ compound (**13**; Figure 16c $\text{R} = 2,6\text{-C}_6\text{H}_3\text{Trip}_2$)^[64] to the $[\text{Ga}_4\text{K}_2]^{2+}$ and $[\text{Ga}_4^0]$ clusters.^[105] Since the Ga–Na and Ga–K bond lengths in all the clusters of this type lie in the ranges anticipated from the sum of the metal radii, an assessment with the help of additional quantum-chemical calculations^[65] should lead to a deeper understanding of the bonding in these Ga clusters that goes beyond the merely descriptive use of the term Ga–Ga multiple bonds.^[60]

4.3.1. Ga_4 and Ga_5 Clusters

$[\text{Ga}_4\text{R}_4]$ species^[11, 66] with a tetrahedral Ga_4 framework represent the starting point in gallium-cluster chemistry. As in the corresponding $[\text{Al}_4\text{R}_4]$ species, these clusters should be designated as pre-closo clusters according to the Wade–Mingos rules^[67, 93] and not metalloid clusters because they contain exclusively ligand-bearing Ga atoms. Despite this, the Ga_4 cluster in the $[\text{Ga}_4\text{R}_2\text{K}_2]$ species **13** (Figure 16c) has interesting bonding with respect to metalloid properties since the formal oxidation state of the Ga atoms is 0. The short Ga–Ga bonds of 2.46 Å and the planarity of the Ga_4 units point to analogies to both $\alpha\text{-gallium}$ ($\text{Ga}–\text{Ga} = 2.45$ Å) and $\beta\text{-gallium}$ with its ladder structure. A $[\text{Ga}_4\text{R}_4\text{Na}_2]$ compound ($\text{R} = \text{Si}t\text{Bu}_3$)^[68] can be described as an intermediate between the tetrahedral $[\text{Ga}_4\text{R}_4]$ cluster and the formally neutral planar Ga_4 unit in $[\text{Ga}_4\text{R}_2\text{K}_2]$, as it contains a butterfly-type Ga_4 framework and the oxidation state 0.5 (Figure 17b). Two other Ga_4 clusters with intermediate oxidation states of +1 and +1.5 have a Ga_4 framework with (distorted) D_{3h} point

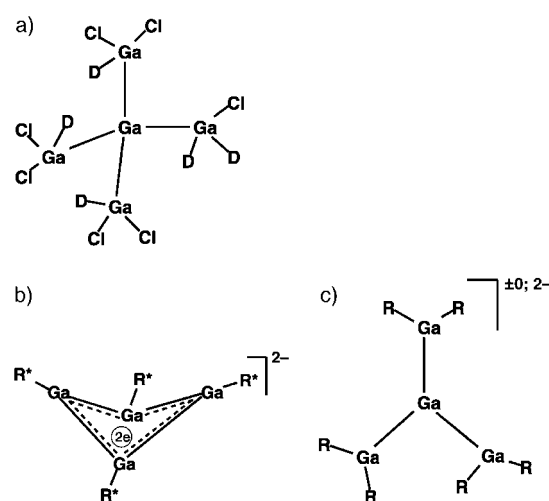


Figure 17. Schematic representation of the compounds a) $[\text{Ga}_5\text{Cl}_7(\text{Et}_2\text{O})_5]$, b) $[\text{Ga}_4(\text{Si}t\text{Bu}_3)_4\text{Na}_2]$, c) $[\text{Ga}(\text{GaR}_2)_3\text{Na}_2]$ (**14**), and $[\text{Ga}(\text{GaR}_2)_3\text{Na}_2]$ (**15**). $\text{R} = \text{Trip}$.

symmetry: $[\text{Ga}(\text{GaR}_2)_3\text{Na}_2]$ (**14**; $\text{R} = \text{Trip}$)^[69] and $[\text{Ga}(\text{GaR}_2)_3]$ (**15**; $\text{R} = \text{Trip}$; Figure 17 c).^[69] The central naked Ga atoms to which the formal oxidation state 0 can be assigned are a step in the direction of metalloid clusters.

A description similar to that of the latter Ga_4 clusters can also be applied to a Ga_5X_7 halide,^[70] in which a naked Ga atom (also formally Ga^0) is surrounded tetrahedrally by four Ga atoms. Three of the surrounding Ga atoms are attached to two halogen atoms whereas the fourth gallium atom is only attached to one halogen atom (Figure 17 a). An analogous Al_5X_7 compound with a similar structure was recently synthesized (a halide transfer leads to the crystalline compound via two ionic species $[\text{Al}_5\text{X}_8]^-$ and $[\text{Al}_5\text{X}_8]^+$).^[71]

4.3.2. Ga_6 Clusters

We recently reported on the $[\text{Ga}_6\text{R}_8]^{2-}$ cluster compound (**8**, $\text{R} = \text{SiPh}_2\text{Me}$; Figure 18)^[72] in which the mean oxidation state of the gallium atoms is +1. After removal of two R[−] groups the formation of an octahedral $[\text{Ga}_6\text{R}_6]$ pre-*closo* unit,

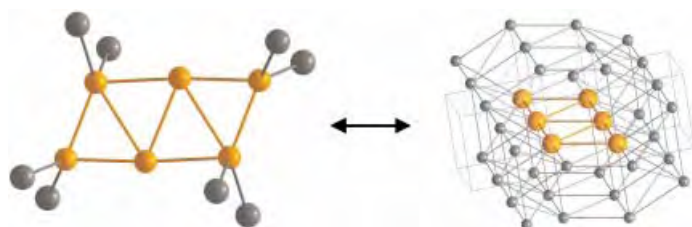


Figure 18. Molecular structure of $[\text{Ga}_6(\text{SiPh}_2\text{Me})_8]^{2-}$ (**8** omitting Ph and Me groups) and the corresponding section from the solid-state structure of β -gallium.

analogue to the tetrahedral $[\text{Ga}_4\text{R}_4]$ cluster mentioned in Section 4.3.1, could be assumed. Model calculations have shown, however, that a rhomboid Ga_6 unit with two naked Ga atoms would be favored over the pre-*closo* cluster.^[72] Similar calculations for the corresponding B_6 and Al_6 compounds—for which the octahedral units are favored—show that the Ga_6 cluster **8** is a special case. The similarity of the arrangement of the gallium atoms in **8** to that in β -gallium shows that, in contrast to aluminum and boron, specific connectivity principles predetermined by the element will be favored. The absence of a Ga_6 compound with an octahedral Ga_6 framework—in $[\text{Ga}_6\text{Cp}_6]^*$ ^[29] the very long Ga–Ga bond lengths (4.07 and 4.17 Å) show that these bonds must be described differently—and that many compounds with octahedral boron (e.g. $\text{B}_6\text{I}_6^{2-}$ ^[73]) or Al_6 frameworks ($[\text{Al}_6\text{R}_6]^-$, $\text{R} = t\text{Bu}$ ^[74]) exist, indicate that the topological similarities in certain element modifications and clusters are a result of the special bonding options available to gallium atoms. The description of the $[\text{Ga}_6\text{R}_8]^{2-}$ cluster **8** as *metalloid*—or in this case preferably as *elementoid* (in relation to β -gallium)—is therefore plausible.

4.3.3. Ga_8 and Ga_9 Clusters

The octameric GaI compound $[\text{Ga}_8\text{I}_6(\text{PET}_3)_6]$ (Figure 6),^[25] the first Ga_8 cluster, has already been mentioned. The oxidation state of the Ga atoms of +1 and the classical 2e2c

Ga–Ga bonds confirm that this cluster cannot be described as metalloid. The Ga_8 cluster $[\text{Ga}_8\text{R}_6]$ (**9**; $\text{R} = \text{C}(\text{SiMe}_3)_3$) is a model compound for a 2e2c metal–metal bond (Section 4.2).^[32] This cluster (Figure 19) can be described as

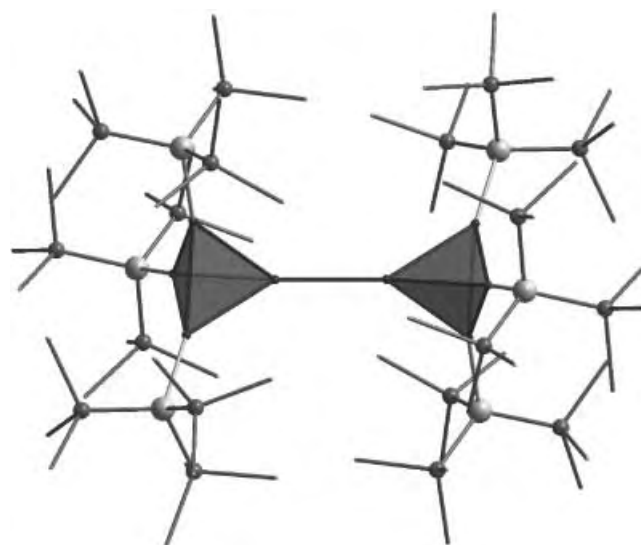


Figure 19. Molecular structure of $[\text{Ga}_8\{\text{C}(\text{SiMe}_3)_3\}_6]$ (**9**).

metalloid for two reasons: firstly the central Ga_2 unit reflects the motif of α -gallium. Secondly the Ga_2 unit with a distance of 2.61 Å between the Ga atoms can be described as a link in the chain of the Ga_n wire in the center of the Ga_7 tubes of γ -gallium (Ga–Ga 2.60 Å; see Figure 14). A $[\text{Ga}_8\text{R}_6]$ cluster (**16**; $\text{R} = \text{supersilyl} = \text{Si}t\text{Bu}_3$) recently synthesized by Wiberg et al. shows a completely different geometry.^[75, 76] The Ga cluster framework in **16** is illustrated together with the that of the analogous $[\text{Ga}_8\text{R}_6\text{Na}_2]$ species **17** ($\text{R} = \text{supersilyl}$) in Figure 20.

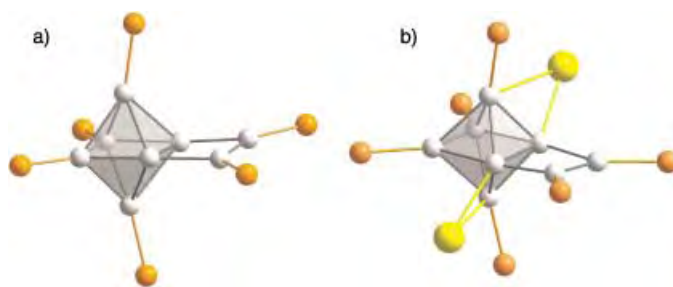


Figure 20. Molecular structures of a) $[\text{Ga}_8\text{R}_6]$ (**16**) and b) $[\text{Ga}_8\text{R}_6]^{2-}$ (**17**) omitting the *t*Bu groups. $\text{R} = \text{Si}t\text{Bu}_3$.

Wiberg et al. showed that the unexpected Ga_8R_6 framework (Ga_6R_4 with linking Ga_2R_2 groups) in **16** can be described with the help of the Wade–Mingos rules as a twofold capped tetrahedrotetragallane (hypo-pre-*closo*-hexagallane; $2n - 2$ cluster electrons) and the $\text{Ga}_8\text{R}_6^{2-}$ unit in **17** ($2n + 2 = 14$ cluster electrons) as a *closo* compound in which the two neighboring R groups can be replaced by the RGaGaR group.^[75] It is also evident that the planar Ga_6 unit in **16** and **17**, in particular because of the presence of two naked Ga atoms, bears a similarity to that in the above-mentioned $[\text{Ga}_6\text{R}_8]^{2-}$ cluster **8** (Figure 18), which is also described as

metalloid. The oxidation state of 0.75 in **16** and 0.5 in **17** in contrast to +1 for **8** shows, however, that reduction has already proceeded extensively in the direction of a three-dimensional connectivity of the gallium atoms as found in elemental gallium (in this case β -gallium). For **17**, the Ga–Na bonds of almost 3.00 Å (also approximately the sum of the metal radii) indicate that the sodium atoms,^[65] have to be included as part of the cluster framework (see discussion in Section 4.2). Such interactions between lithium atoms and a gallium-cluster framework can generally be excluded since in all previous cases the lithium ions are completely screened from the cluster anion by coordinating donor molecules. In Section 4.4 the relationship between the $[\text{Ga}_8\text{R}_6]^-$ clusters **16** and **17**, and the $[\text{Ga}_{10}\text{R}_6]$ and $[\text{Ga}_{18}\text{R}_8]$ clusters **22** and **27** will be discussed.

The dianion $[\text{Ga}_8\text{R}_8]^{2-}$ (**18**; R = fluorenyl) has a square-antiprismatic framework of eight Ga atoms and has eight σ bonds to the fluorenyl ligands (Figure 21).^[77] According to

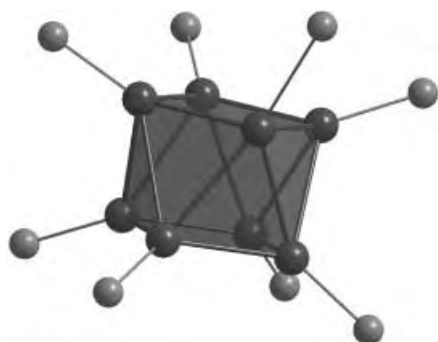


Figure 21. Molecular structure of $[\text{Ga}_8(\text{C}_{13}\text{H}_9)_8]^{2-}$ (**18**). Of the fluorenyl ligands only the C atoms directly bonded to the Ga atoms are shown.

the Wade–Mingos rules, such a cluster with $2n + 2$ framework electrons should form a dodecahedral (Do) *closo* cluster. The square-antiprismatic (SA) form actually observed could also be plausibly explained with the help of DFT calculations on the model compounds $[\text{Ga}_8\text{H}_8]^{2-}$ and $[\text{B}_8\text{H}_8]^{2-}$ (each with Do and SA structures). The results showed that the experimentally determined SA form of $[\text{Ga}_8\text{H}_8]^{2-}$ is indeed the most favorable (8 kJ mol^{−1}), whereas for $[\text{B}_8\text{H}_8]^{2-}$ as anticipated the Do form is energetically favored (62 kJ mol^{−1}). Since the sequence of orbitals for the two $[\text{Ga}_8\text{H}_8]^{2-}$ isomers do not differ much from each other **18** should be described as a *closo* compound despite the basic square-antiprismatic form.^[77] Compound **18** clearly differs from the second compound with fluorenyl as the ligand $[\text{Ga}_{12}\text{R}_{10}]^{2-}$ (**21**; R = fluorenyl), which will be discussed in Section 4.4.1.

The $[\text{Ga}_9\text{R}_9]$ cluster (**19**; R = *t*Bu, Figure 22)^[78] recently synthesized by Uhl et al. can also be described as a threefold capped prism, a pre-*closo* gallane, which demonstrates clearly the analogy to the corresponding $\text{B}_9\text{X}_9^{n-}$ compounds (X = H, halogen; $n = 0–2$).^[79] A mean oxidation state of 0.56 for the Ga atoms in the $[\text{Ga}_9\text{R}_6]^-$ cluster (**20**; R = Si(SiMe₃)₃; Figure 22b)^[80] synthesized in 1997 by Linti from “GaI” points to a metalloid structural element (see Section 4.4.6 for the icosahedral-capped Ga_{84} cluster **10**; δ -Ga; Figure 14). On the

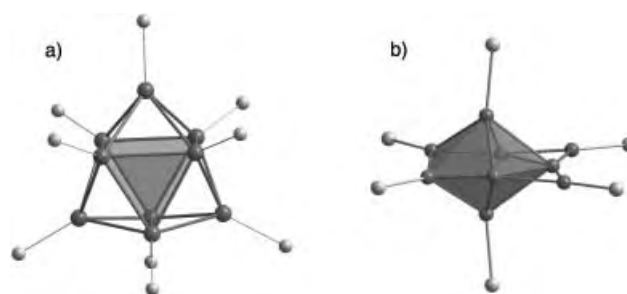


Figure 22. Schematic representation of a) $[\text{Ga}_9\text{tBu}_9]$ (**19**) and b) $[\text{Ga}_9\text{R}_6]^-$ (**20**; R = Si(SiMe₃)₃). Of the ligands only the C or Si atoms directly bonded to the Ga atoms are shown.

other hand this cluster with its $n - 1$ total electron pairs does fit into the Wade–Rudolf–Mingos concept.^[67]

The structural diversity of the Ga_8 and Ga_9 clusters shows the possibilities for variation in the connectivity of Ga atoms and the associated difficulty in describing and classifying the Ga_n clusters. On the other hand this diversity makes the investigation of gallium compounds so interesting since unexpected experimental findings may well form the basis for new bonding concepts. Particularly the larger Ga_n clusters, described in Section 4.4, can be described as molecular intermediates on the way to one of the seven gallium modifications. We will concentrate on this aspect since quantum-chemical calculations (including band-structure calculations) are possible in principle but have previously only helped in understanding the topology in individual cases. First formulations from this analysis method, which can be extended to band-structure investigations of hypothetical element modifications, could be developed to become the basis for a deeper understanding of these clusters as intermediates on the way to three-dimensionally ordered bulk material (see Section 4.4.1^[84]).

4.4. Metalloid Ga_n Clusters ($n = 10–84$)

With an increasing number of Ga atoms and particularly with an increasing number of naked gallium atoms that bear no ligands, it is expected that the atomic configuration in the cluster will approach that of the element modifications, which means that metalloid or—often more appropriate—elementoid Ga clusters with mean oxidation states for the Ga atoms decreasing from +1 to 0 will result. Since there are obviously no strict limits for the total number of gallium atoms in the metalloid topology—Section 4.3 described metalloid partial structures for several smaller Ga clusters—in this section we will start with a Ga_{12} cluster for which the distorted icosahedral Ga_{12} unit is reminiscent of analogous *closo*-type compounds discussed in the Section 4.4.1, such as, **18**.^[77] In Section 4.4.2 a Ga_{10} and a Ga_{13} cluster will be discussed in which the concept of the quantum-chemical calculated packing density and the experimentally accessible density variations in the element modifications, as mentioned for the Al_n clusters, plays a role. The $[\text{Ga}_{13}(\text{GaR})_6]^-$ structure in the Ga_{19} cluster (Section 4.4.3) provides conclusive evidence for a better understanding of the bonding in the gallium-rich

clusters with 18, 22, and 26 Ga atoms (Section 4.4.4 and 4.4.5). Finally in Section 4.4.6 the bonding, structure, and some considerations of the physical properties of the $[\text{Ga}_{84}\text{R}_{20}]^{4-}$ cluster **10** will be given. With respect to the number of naked metal atoms, this cluster is the largest structurally characterized metalloid cluster.

4.4.1. Ga_{12} Clusters

There is no gallium cluster corresponding to the icosahedral $[\text{Al}_{12}\text{R}_{12}]^{2-}$ -cluster ($\text{R} = i\text{Bu}$),^[81] with which Uhl et al. made a significant contribution to the renaissance of aluminum research. However, the $[\text{Ga}_{12}\text{R}_{10}]^{2-}$ cluster (**21**, $\text{R} = \text{fluorenyl}$),^[82] is structurally similar. This cluster is formed together with the above-mentioned $[\text{Ga}_8\text{R}_8]^{2-}$ cluster **18** during the reaction of GaBr with fluorenyl lithium (Figure 23). Quantum-chemical calculations show that, in contrast to the model



Figure 23. Molecular structure of $[\text{Ga}_{12}(\text{C}_{13}\text{H}_9)_{10}]^{2-}$ (**21**).

compound $[\text{Al}_{12}\text{H}_{10}]^{2-}$, the HOMO in a $[\text{Ga}_{12}\text{H}_{10}]^{2-}$ cluster is at a particularly unfavorable level for oxidation to the $[\text{Ga}_{12}\text{H}_{12}]^{2-}$ species so that the absence of a corresponding $[\text{Ga}_{12}\text{R}_{12}]^{2-}$ cluster appears to be plausible. On the other hand for aluminum the metalloid $[\text{Al}_{12}\text{R}_8]^-$ cluster **2** (analogous to $[\text{In}_{12}\text{R}_8]^{[83]}$) exists in which a section from the close packing of metallic aluminum is realized. Apparently the formation of a similar structure for a Ga_{12} cluster is not favorable although the cleavage of two R^- groups from the cluster ($[\text{Ga}_{12}\text{R}_{10}]^{2-} \rightarrow [\text{Ga}_{12}\text{R}_8] + 2\text{R}^-$) should be possible. The absence of a normal-pressure modification with close-packed Ga atoms (in contrast to close-packed elemental structures of aluminum and indium) on the one hand and the realization of the δ -modification for gallium with its connected Ga_{12} icosahedra on the other, makes the formation of an icosahedrally distorted $[\text{Ga}_{12}\text{R}_{10}]^{2-}$ cluster plausible. From this viewpoint the designation metalloid for this cluster is reasonable. The reaction to yield the Ga_{84} cluster **10** (see Section 4.4.6), which also contains icosahedral partial structures with its GaGa_5 caps, also produced other clusters with structural units that were previously typical only for the element boron. The similarity of many Ga cluster compounds to the basic icosahedral framework in α -boron yields the first experimental indications that, in addition to the δ -modification, there

may be a hypothetical modification for gallium that resembles α -boron. The most recent quantum-chemical band-structure calculations from Häussermann et al.,^[84] based on the original work from von Schnering, Nesper, and Parinello et al.,^[50] show that this new phase should be much easier to realize than the β -aluminum phase (postulated in Section 3.2) and that our method of disproportionation under mild conditions (-50 to $+50^\circ\text{C}$) could enable possible experimental access to this new gallium modification.

4.4.2. Ga_{10} and Ga_{13} Clusters

Recently the clusters $[\text{Ga}_{10}\text{R}_6]$ (**23**; $\text{R} = \text{Si}t\text{Bu}_3$), $[\text{Ga}_{10}\text{R}_6]^-$ (**22**; $\text{R} = \text{Si}(\text{SiMe}_3)_3$), and $[\text{Ga}_{13}\text{R}_6]$ (**24**; $\text{R} = \text{Si}t\text{Bu}_3$), were synthesized by Linti and Wiberg et al.^[85] The two Ga_{10} clusters **22** and **23** show differing topologies of the gallium frameworks (Figure 24). In the neutral cluster **22** there are two different

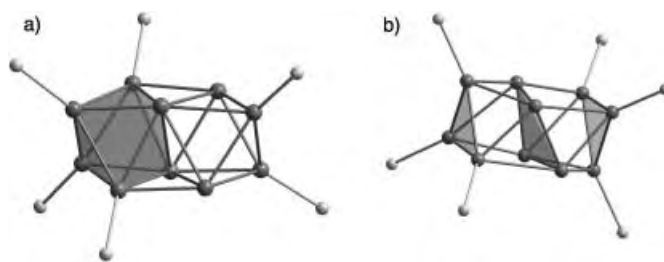


Figure 24. Molecular structures of a) $[\text{Ga}_{10}\text{R}_6]$ (**23**; $\text{R} = \text{Si}t\text{Bu}_3$) and b) $[\text{Ga}_{10}\text{R}_6]^-$ (**22**; $\text{R} = \text{Si}(\text{SiMe}_3)_3$). Of the ligands only the Si atoms directly bonded to the Ga atoms are shown.

octahedra (with two or four ligand-bearing Ga atoms, respectively) connected by a shared edge. In the cluster anion **23** two triangular faces of ligand-bearing Ga atoms— $(\text{GaR})_3$ —are connected over a rhomboid Ga_4 group. Since both Ga_{10} clusters contain the same number of ligands as the Ga_{13} cluster and in the case of **22** and **24** even the same type of ligand ($\text{Si}t\text{Bu}_3$), a detailed comparison of the structures would appear to be appropriate. Unfortunately the structural data for **24** were only rudimentary so that they could not be included in a database. However, we were able recently to synthesize $[\text{Ga}_7(\text{GaR})_6]^-$ (**24'**; $\text{R} = \text{Si}(\text{SiMe}_3)_3$) which is related to **24** and to determine its structure (Figure 25).^[86] The seven naked Ga atoms in **24'** form a cube which is missing a corner. The three complete square faces of the cube are capped with GaR groups. The three incomplete square faces are shielded by a $(\text{GaR})_3$ group, with the center of the Ga_3 group pointing towards the missing corner of the cube. This arrangement is reminiscent of the structure of a SiAl_{14} cluster (Figure 26),^[87] in which a central Si atom is surrounded by a cube of naked Al atoms, the faces of which are each capped by AlR groups ($\text{R} = \text{Cp}^*$).^[88]

To determine the atomic volume of the Ga_n framework of the Ga_{10} and Ga_{13} clusters and thereby trace the progress of the formation of metal, we have carried out single-point SCF calculations, in analogy to the Al clusters (see Section 3.1 and Figure 10), for the anions **23** and **24'**, both containing six hypersilyl ligands ($\text{Si}(\text{SiMe}_3)_3$). As anticipated the atomic volume decreases from the Ga_{10} cluster ($36.9 \text{ \AA}^3$ per Ga atom)

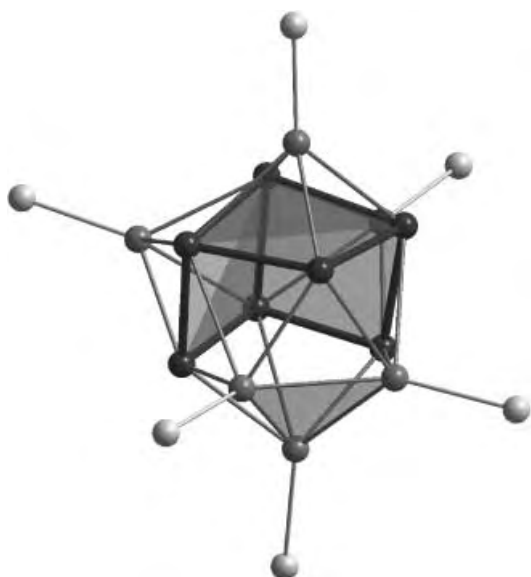


Figure 25. Molecular structure of $[\text{Ga}_{13}\text{R}_6]^-$ (**24'**; $\text{R} = \text{Si}(\text{SiMe}_3)_3$). Of the $\text{Si}(\text{SiMe}_3)_3$ groups, only the Si atoms directly bonded to the Ga atoms are shown.

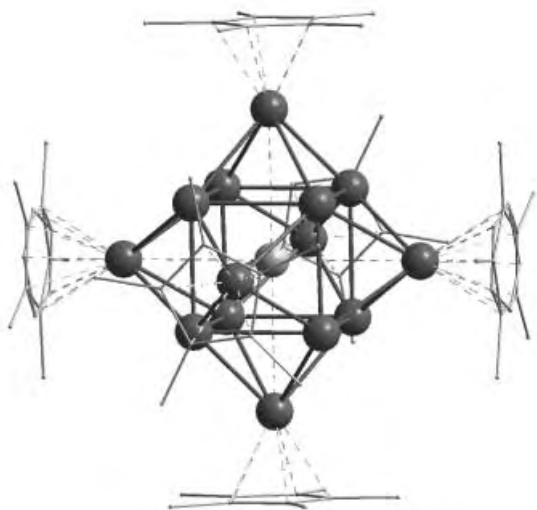


Figure 26. Molecular structure of the metalloid cluster $[\text{SiAl}_8(\text{AlCp}^*)_6]$.

to the Ga_{13} cluster ($35.0 \text{ \AA}^3$ per Ga atom) by around 5%. Since in neither case is there a centered structure, in contrast to $[\text{Ga}_{22}\text{R}_8]$ and $[\text{Ga}_{26}\text{R}_8]^{2-}$ —clusters **26** and **28** (see Section 4.4.4), and since the ratio of the naked to the ligand-bearing Ga atoms is still low (0.66 for **23** and 1.17 for **24'**; in contrast to 1.75 for **26** and 2.2 for **28**) the mean atomic volumes for **23** and **24'** are still about 10% larger than those of the Ga_{22} and Ga_{26} cluster units. Further quantum-chemical calculations are required (e.g. separate calculations for the entire cluster and for the cluster core of naked Ga atoms), to compare, for example, the electronic structure (e.g. the HOMO/LUMO separation) with the results from the band-structure calculations for the real element modifications. To summarize it can be concluded that for **23** and **24'** with the same shell of six GaR groups a larger number of naked gallium atoms in the core of **24'** leads to a higher density and

therefore a closer resemblance to the bulk material. This principle will become more apparent in Section 4.4.4 for clusters with a larger shell of eight GaR groups.

4.4.3. Ga_{19} Clusters

The $[\text{Ga}_{19}\text{R}_6]^-$ cluster (**25**; $\text{R} = \text{C}(\text{SiMe}_3)_3$; Figure 27)^[3] under discussion here is remarkable for many reasons:

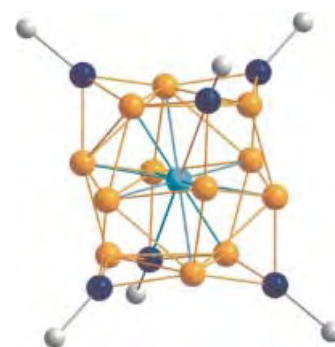


Figure 27. Molecular structure of $[\text{Ga}_{19}\text{R}_6]^-$ (**25**; $\text{R} = \text{C}(\text{SiMe}_3)_3$). Of the $\text{C}(\text{SiMe}_3)_3$ groups, only the C atoms directly bonded to the Ga atoms are shown.

- Cluster **25** is the only metalloid gallium cluster for which a ^{71}Ga NMR spectrum in solution has been obtained.
- **25** is a centered cluster in which the central gallium atom has the coordination number 12 the same as has in “real” metals.
- **25** is the only metalloid gallium cluster and, to our knowledge, the largest metalloid cluster for which MALDI and ESI mass spectra have been obtained,^[89, 90] which provide for the first time experimental evidence about the bonding in such clusters.

The highly symmetrical environment of the central gallium atom enables the observation of the ^{71}Ga NMR signal at $\delta^{71}\text{Ga} = -134 \text{ ppm}$ ^[3] which is the only experimental evidence available for the assignment of calculated NMR spectrum chemical shifts to metalloid clusters: for example, $[\text{Ga}_{13}(\text{GaR})_6]^-$: $\text{R} = \text{H}, \text{CH}_3, \text{C}(\text{SiH}_3)_3$; $\delta^{71}\text{Ga} = -6, -109, -231 \text{ ppm}$. The results obtained show that the shifts calculated by the DFT method for naked Ga clusters—for example $[\text{Ga}_{13}]^-$ (I_h): $\delta^{71}\text{Ga} = -603$ ^[3] and $[\text{Ga}_{13}]^-$ (D_{5h}): $\delta^{71}\text{Ga} = -455$ ^[89]—differ drastically from those of ligand-shielded Ga clusters,^[1, 3] and that conclusions from the results obtained for naked metal clusters can only be applied to ligand-shielded metalloid clusters to a very limited extent.

Application of the Jellium model to the cluster core of 13 gallium atoms gives rise, with 40 electrons, to the expectation of particularly high stability and therefore the observation of the $[\text{Ga}_{13}]^-$ ion in the mass spectrometric (MALDI) investigation as by far the most intensive peak was not surprising.^[89] Investigations currently being performed with the ESIMS method have yielded the first indications^[90] that collisions with inert-gas molecules remove sequentially the six GaR groups from **25** to finally result in the stable $[\text{Ga}_{13}]^-$ cluster as also observed in the MALDI experiments. The stability of this cluster anion is made more obvious by the

calculated value for the electron affinity of the neutral $[\text{Ga}_{13}]$ cluster. The value of 3.35 eV^[89] corresponds approximately to that of the fluorine atom (3.45 eV). The stability of the $[\text{Ga}_{13}]^-$ cluster ion, which clearly illustrates the electron deficiency in clusters of the elements of the third main group and which is confirmed by the formation of Ga_n Zintl ions^[104] also illustrates the difficulties that can be anticipated for any investigation on the reactivity of such Ga_{13} anions in the gas phase. In addition the great sensitivity of the $[\text{Ga}_{19}\text{R}_6]^-$ solution demands a large experimental effort to transfer the educt without it decomposing to the mass spectrometer and then to use the $[\text{Ga}_{13}]^-$ species obtained after fragmentation for further reactions in the gas phase. To summarize it can be stated that **25** represents a stroke of luck for the assessment of the bonding in Ga_n clusters, since it is possible for the first time to show unambiguously by experiment that GaR groups and not R^- groups can be designated as the shell of this cluster, and that for the first time for a central metal atom in a cluster an experimental value for the chemical shift in the NMR spectrum can be obtained.

4.4.4. Ga_{18} , Ga_{22} , and Ga_{26} Clusters

After two neutral compounds with the composition $[\text{Ga}_{22}\text{R}_8]$ ($\text{R} = \text{Si}(\text{SiMe}_3)_3$,^[91] $\text{Ge}(\text{SiMe}_3)_3$ ^[92]) had been obtained, we recently succeeded in synthesizing another representative of this type with supersilyl ligands, $[\text{Ga}_{22}(\text{Si}t\text{Bu}_3)_8]$ (**26**; Figure 28b).^[93] Slight modification of the synthesis conditions

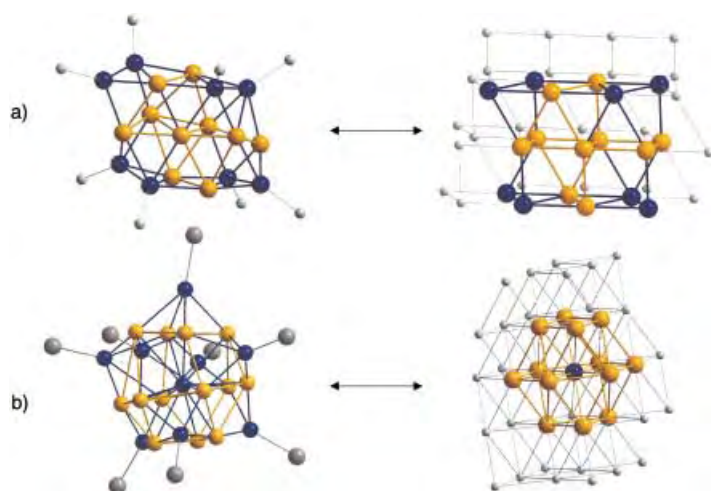


Figure 28. Molecular structures of a) $[\text{Ga}_{18}(\text{Si}t\text{Bu}_3)_8]$ (**27**) and b) $[\text{Ga}_{22}(\text{Si}t\text{Bu}_3)_8]$ (**26**, of the $\text{Si}t\text{Bu}_3$ groups, only the Si atoms directly bonded to the Ga atoms are shown) and corresponding sections from the solid-state structures of β -gallium and Ga-III.

enabled a further neutral cluster to be obtained; the $[\text{Ga}_{18}\text{R}_8]$ cluster (**27**; $\text{R} = \text{Si}t\text{Bu}_3$; Figure 28a).^[93] Analogous to the results for the Ga_{10} , Ga_{13} , and Ga_{19} clusters, **27** and **26** can be described as $[\text{Ga}_{10}(\text{GaR})_8]$ and $[\text{Ga}_{14}(\text{GaR})_8]$, which means that inside a cage of eight GaR groups are either 10 or 14 naked Ga atoms. For **26** a higher packing density and a smaller mean atomic volume is to be expected than for **27**. The above-mentioned single-point SCF calculations indeed

showed that the mean atomic volume decreases from **27** to **26** by about 5%. As a result of the topological similarity of **27** to β -gallium and that of **26** to high-pressure modification gallium-(III) (Figure 28) it is not surprising that the experimentally determined density increases by about 5% between these two gallium modifications. Although in **26** and **27** there are a different number of naked metal atoms they are surrounded by the same number and type of ligands, thus making such comparisons plausible.

Since the supersilyl group ($\text{Si}t\text{Bu}_3$) is obviously somewhat bulkier than the hypersilyl group ($\text{Si}(\text{SiMe}_3)_3$), eight $\text{GaSi}t\text{Bu}_3$ groups lead to a cluster pair with 18 or 22 gallium atoms, whereas eight $\text{GaSi}(\text{SiMe}_3)_3$ ligands lead to a pair with 22 or 26 gallium atoms. The latter type of compound $[\text{Ga}_{18}(\text{GaR})_8]^{2-}$ (**28**) was synthesized by Linti and Rodig from “GaI” in the form of black crystals that show metal luster in reflected light (Figure 29).^[94] The cluster core in **28** is

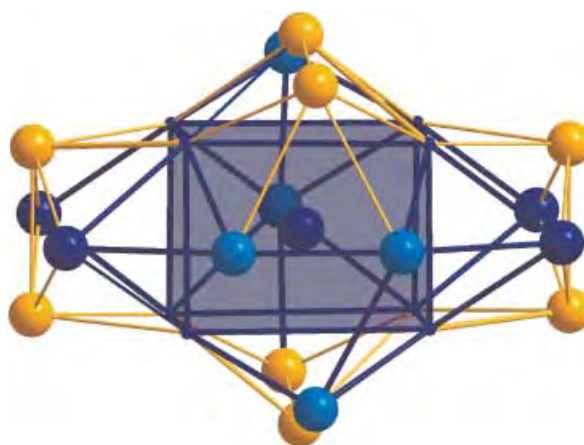


Figure 29. Arrangement of the 26 Ga atoms in $[\text{Ga}_{26}\text{R}_8]^{2-}$ (**28**; $\text{R} = \text{Si}(\text{SiMe}_3)_3$). The first coordination sphere around the central Ga atom is shown as a polyhedral representation and the Ga atoms attached to a ligand are orange.

particularly reminiscent of the high-pressure modification Ga-III with its 4+8 coordination. The Ga_{18} unit in **28** can be described as follows: A central gallium atom is surrounded by a pseudo cuboctahedron of 13 gallium atoms (8+3+2). The remaining four naked gallium atoms are part of two Ga_4R_2 units that are located over two Ga_4 faces of the Ga_{14} core.

To analyze the bonding situation, for most of the cluster compounds described here, physical measurements (e.g. UV/Vis, conductivity etc.) are required in addition to the successful structure investigation. As the investigations discussed later on in Section 4.4.6 the largest metalloid gallium cluster $[\text{Ga}_{84}\text{R}_{20}]^{4-}$ (**10**; $\text{R} = \text{N}(\text{SiMe}_3)_2$) shows, many surprises could be expected that could help to understand the special bonding in metalloid clusters as intermediates on the way to the bulk phase. Unfortunately, apart from the cluster compounds **10** (Ga_{84}) and **25** (Ga_{19}), great difficulties are to be expected because of a) the extreme sensitivity to air and moisture, b) the small crystal dimensions, and c) the reproducible but not yet optimized syntheses, resulting in insufficient yield.

4.4.5. Other Ga_{22} Clusters

Since it was possible to obtain the Ga_{22} cluster discussed in Section 4.4.4 with three different ligands, it is apparent that this electronic configuration is particularly stable. We assigned this to, amongst other factors, the closed Jellium configuration with 58 electrons ($14 \times 3 + 8 \times 2$).^[91] Recently we were able to isolate another Ga_{22} compound for which this stability criterion also applies, but in which despite the same mean oxidation state of the gallium atoms a different arrangement of the 22 gallium atoms is observed: The use of “slender” $N(SiMe_3)_2$ ligands means that ten instead of eight ligands can fit in the outer shell so that a $[Ga_{22}R_{10}]^{2-}$ cluster ($R = N(SiMe_3)_2$) **29** results. The shell construction $GaGa_{11}-(GaR)_{10}$ of **29** can be seen in Figure 30.^[95]

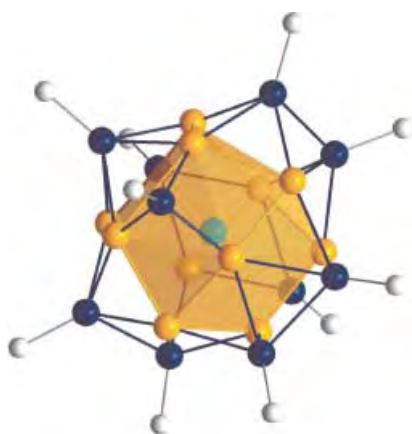


Figure 30. Molecular structure of $[Ga_{22}R_{10}]^{2-}$ (**29**; $R = N(SiMe_3)_2$; only the N atoms directly bonded to the Ga atoms are shown). The first coordination sphere around the central Ga atom is shown in a polyhedral representation.

Single-point calculations for the Ga_{22} cluster cores of **29** and **26** show that in the transition from **29** to **26** the atomic volume in the Ga_{22} unit decreases by 2%. We have interpreted this shrinkage in volume to mean that **29** can be considered an intermediate on the way from the β -modification (2+6 coordination) to the high-pressure Ga-III modification (4+8 coordination). This “phase transition” of a Ga_{22} unit is associated with an energy increase of 9 kJ (calculated from single-point SCF calculations). Analogously it was also determined that the high-pressure fcc gallium phase Ga-IV, is only a few kJ higher in energy, than the β -gallium modification.^[50] Further calculations and experiments (e.g. UV/Vis spectra) are required to understand the relationship between such “nanostructured” phase transitions at the molecular level and true phase transitions in the bulk phase.

In addition the significance of the bulkiness of the ligands for the structure of the Ga_{22} clusters **29** and **26** and for the electronic properties of a cluster becomes clear. A hypothetical $[Ga_{22}R_9]^-$ cluster, which could result from the $[Ga_{19}R_6]^-$ cluster **25** discussed in Section 4.4.3 by the addition of three GaR groups, should stabilize, depending on the bulkiness of the ligand, by elimination of a R^- group (large ligand) or by addition of another R^- ligand (small ligand) to yield $[Ga_{22}R_8]$ or $[Ga_{22}R_{10}]^{2-}$; clusters analogous to **26** and **29** (Figure 31).

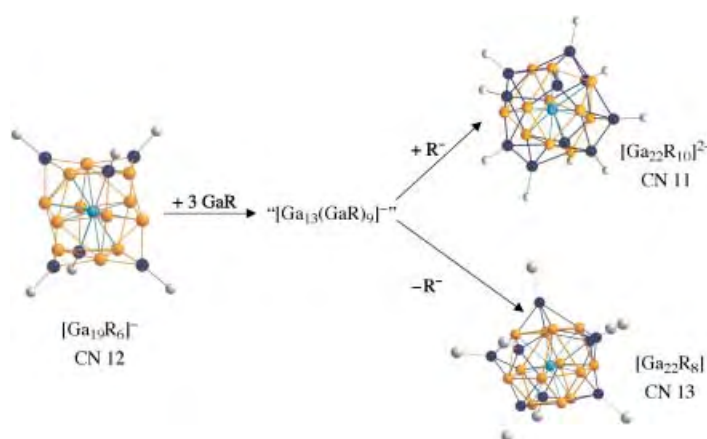


Figure 31. Variation of the coordination sphere around the central Ga atom arising from the differing steric demands of the ligands $C(SiMe_3)_3$, SiR_3 , $N(SiMe_3)_2$ in the clusters **25**, **26**, and **29**.

The structure of the cluster **29** came as a surprise to us. We had long expected a further variant of a Ga_{22} cluster with a topology analogous to the $Al_{22}X_{20}$ species **6** and **7** (Section 3.2). Unfortunately despite a great deal of effort we have not been able to synthesize the analogous Ga_{22} halide. There are, however, the first indications that such a species is formed in an important primary step to the $[Ga_{84}R_{20}]^{4-}$ cluster discussed in Section 4.4.6. Recently, we succeeded in isolating a partially substituted $[Ga_{22}R_{10}Br_{10+n}]$ cluster (**30**; $n = 0-2$; $R = N(SiMe_3)_2$, Figure 32).^[96] The data acquisition during the

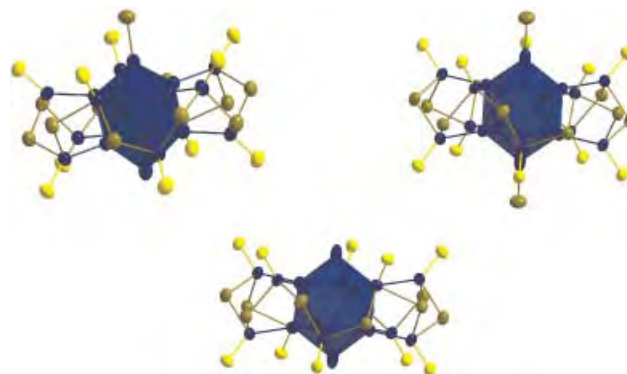


Figure 32. Preliminary molecular structure of **30** (of the $N(SiMe_3)_2$ groups only the N atoms directly bonded to the Ga atoms are shown). The central Ga_{12} icosahedron is emphasized by a polyhedral representation.

X-ray diffraction experiment and the subsequent structure analysis proved to be extremely complex for this compound, since the unit cell ($a = 40.5$; $b = 38.5$; $c = 58.8$ Å, $\alpha = \beta = \gamma = 90^\circ$) is very large. Therefore, we had to perform the X-ray diffraction experiment with the help of synchrotron radiation, and the acquired data is currently under analysis. Preliminary structure data and the graphical representations enable us to conclude that this partially substituted Ga_{22} halide is indeed an intermediate to the Ga_{84} cluster **10**. In addition, this preliminary result could be seen as an indication that a primary Ga_{22} halide analogue to the $Al_{22}X_{20}$ cluster should exist. Its existence and facile disproportionation could provide access to a modification analogous to α -boron (see Section 4.4.1).^[84]

4.4.6. Ga_{84} Clusters

Under similar reaction conditions used for the synthesis of the $[\text{Al}_{77}\text{R}_{20}]^{2-}$ cluster **5** (Section 3.2), the Ga_{84} cluster $[\text{Ga}_{84}(\text{N}(\text{SiMe}_3)_2)_{20}]^{4-}$ (**10**),^[97] is obtained from a metastable GaBr solution and $\text{LiN}(\text{SiMe}_3)_2$. The molecular structure of **10** is illustrated in a similar fashion to that of **5** in Figure 33.

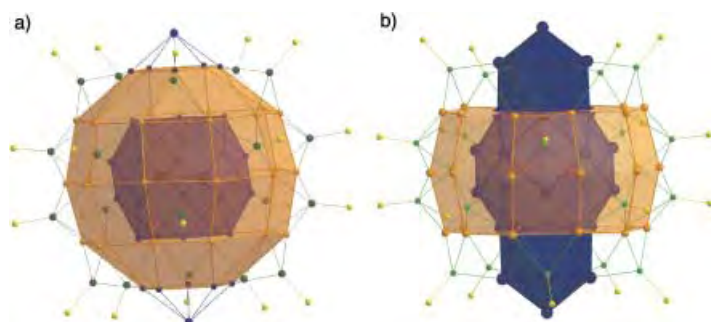


Figure 33. Molecular structure of $[\text{Ga}_{84}\text{R}_{20}]^{4-}$ (**10**; $\text{R} = \text{N}(\text{SiMe}_3)_2$ only the N atoms (yellow) directly bonded to the Ga atoms are shown). a) Layered representation analogous to the representation of the Al_{77} cluster **5** (see Figure 9b). b) Representation corresponding to the relationship of the bond lengths within the Ga_{84} cluster.

With respect to the naked metal atoms, this is the largest metalloid cluster that has ever been structurally determined by diffraction methods. The Ga_2 unit in the center of the 64 naked Ga atoms is unique in this field of chemistry (Figure 33b). The Ga_2 unit ($d(\text{Ga}-\text{Ga}) = 2.35 \text{ \AA}$), which contains a bond that is almost as short as the so-called triple Ga–Ga bond ($2.32 \text{ \AA}$) discussed in Section 4.2 and resembles the Ga_2 dumbbell unit of α -gallium. The Ga_2 unit is surrounded by a Ga_{32} shell in the form of a football with icosahedral caps (see δ -gallium (Figure 14) and $[\text{Ga}_{22}\text{R}_{10}\text{X}_{10}]$ (**30**; Figure 32). The apex and base atoms of this Ga_{32} unit are naked and are oriented towards each other in the crystal in an unusual fashion. The $\text{Ga}_2\text{Ga}_{32}$ unit is surrounded by a “belt” of 30 Ga atoms that are also naked. Finally the entire Ga_{64} framework is protected by 20 GaR groups.

The high pseudosymmetry of the cluster molecule **10**, clearly shown in Figure 34, which resembles the approximate five- and tenfold symmetry of quasicrystals, points to molecular bonding such as that found in the fullerenes. A relationship to the recently published cadmium–gallium phases can also be perceived.^[98] On the other hand the spherical layered construction (Figure 33) shows the analogy to metalloid clusters (e.g. $[\text{Al}_{77}\text{R}_{20}]^{2-}$ (**5**)), so that the bonding in **10** can be described as intermediate between the two extremes.

The arrangement of the Ga_{84} cluster in the crystal is clearly illustrated in Figure 35. The Ga_{84} clusters are lined up in “tubes”. The distance between two cluster molecules that is, between the naked base and apex of gallium atoms of two clusters, is 1.3 nm, whereby two parallel oriented toluene molecules bridge the intermediate space. Although four-point measurements for electrical conductivity in the temperature range 350 to 2 K have been carried out, the mechanism of electron conductivity—**10** is a semiconductor at room temperature with a small band gap of 0.03 eV; below 7 K **10** becomes—

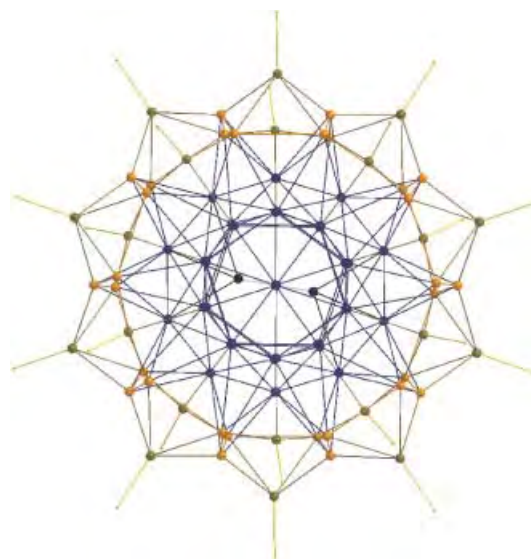


Figure 34. View of the molecular structure of **10** (of the $\text{N}(\text{SiMe}_3)_2$ groups only the N atoms directly bonded to the Ga atoms are shown) along the axis through the two naked Ga atoms.

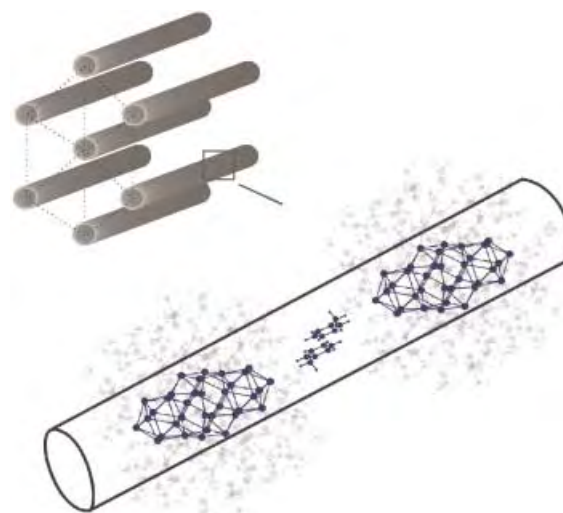


Figure 35. Molecular structure of **10** (of the $\text{N}(\text{SiMe}_3)_2$ groups only the N atoms directly bonded to the Ga atoms are shown) and arrangement of the clusters in the crystal and the two bridging toluene molecule per cluster.

superconducting at least in some ranges—cannot be conclusively explained.^[99] This question is currently the subject of quantum-chemical and experimental investigations. In addition we hope with the help of synchrotron radiation to clarify the question of the possible rotation of the central Ga_2 unit and finally for the very first time for a metalloid cluster determine the electron-density distribution by experimental methods. The prerequisites for such fundamental investigations are fulfilled, since excellent crystals of **10** can be obtained in good yields.

5. Conclusions, Summary, and Outlook

Ligand-free naked metalloid clusters, for example, in molecular beams, present the first step to understanding of

the size dependence of the physical properties of metals, from nanoparticles through to the bulk phase. Quantum-chemical calculations have proven useful to supplement such investigations particularly in questions of topology.^[1, 100] To obtain experimental details of the structure and to determine the physical properties of structurally known metal-atom clusters, such clusters must be protected by ligands and be available in crystalline form. With the help of such metalloid clusters it should be possible to obtain first insights into the elementary processes of dissolution and precipitation of metals from solution. To clarify such fundamental questions, however, detailed information on many metalloid clusters with different numbers of naked metal atoms in the cluster core is imperative.

The geometric structure of the M_xL_y cluster framework is the primary property according to which such clusters should be classified. Further physical data on compounds with nanostructured metalloid clusters can only be reliably interpreted when a uniform and known arrangement of the metal atoms in the cluster framework is present. Therefore, crystalline compounds of metalloid clusters are the primary prerequisite for all investigations. The next step depends on being able to isolate the individual structurally determined cluster units from the crystal lattice and then determine the physical properties of the single clusters in question. This long-term objective has been partially achieved in the gas-phase investigation of a structurally determined $[Ga_{19}R_6]^-$ cluster (**25**; $R = C(SiMe_3)_3$) in the FT mass spectrometer. Further investigations, for example, with force microscopic methods on Al and Ga clusters are currently underway.

It is amazing that such investigations have been carried out for the first time on the difficult to synthesize and difficult to handle (many compounds ignite spontaneously in air) metalloid clusters of base metals such as Al and Ga since worldwide the main emphasis of all activity in the metal atom cluster field is on the metalloid clusters of the precious metals (e.g. Au, Pt, Pd). This is understandable since these can be synthesized without great effort (e.g. in aqueous solution) and can usually be handled without the need for inert-gas techniques. The Au_{55} cluster compound^[5] synthesized for the first time by Schmidt is certainly the most prominent representative of the metalloid precious-metal clusters. This Au_{55} cluster is being applied in almost all areas of chemical research concerned with functional nanostructures although there is still no detailed structural information obtained from a crystal-structure analysis. The few structure determinations on larger noble-metal clusters (see Figure 2) and all other experimental results indicate that in these cluster cores essentially the structure formed is that known from the bulk phase. This means that such precious-metal clusters can with high probability be regarded as metal particles on the nanometer scale.^[101] This finding appears to be plausible since the metal–ligand interactions (e.g. Au–Cl, Au–P, Au–CO) are weaker than the metal–metal interactions in the cluster core. Changes in the ligand sphere should therefore—in contrast to the metalloid clusters of base metals—cause only minor changes in the metal atom framework.

The lack of suitable crystals of almost all metalloid noble-metal clusters on the one hand and the formation of crystals

with dimensions of $1 \times 1 \times 0.5$ mm, for example, for the Ga_{84} cluster compound **10**, on the other depends apparently on different mechanisms of formation and ultimately also on the different bonding types in the two types of clusters: the noble-metal clusters are synthesized by the reduction (e.g. with BH_4^- ; B_2H_6) of a noble metal salt, for example AuX_3 or PdX_2 , in the presence of suitable complex builders, such as CO, PR_3 . This reaction proceeds essentially spontaneously to the elementary noble metal since the activation barriers for the growth of the metalloid cluster as an intermediate are apparently very small. Fortunately there is a certain reaction step for some systems with a higher activation threshold which hinders further growth of the particular cluster species. This feature is possibly at work in the synthesis of the Au_{55} cluster so that spontaneous reaction together with very low solubility leads to the formation of tiny crystalline particles. Detailed quantum-chemical calculations could help to understand this reaction better and then possibly to influence it so that cluster growth is slowed down (e.g. by means of stronger metal–ligand bonds), to obtain larger crystals.

Apparently the method that we have developed for the disproportionation of metastable Al^I and Ga^I solutions is more suitable for the formation of crystalline compounds since the reaction conditions (temperature, donor, solvent) can be selected to influence the reactivity so that defined clusters can be isolated. The activation thresholds for the individual stages of cluster growth are very probably higher in this case than for the formation of the noble-metal clusters. This interpretation appears plausible since for the metalloid Al and Ga clusters discussed here the ligands are attached to a particular metal atom of the cluster framework by strong $2e2c$ bonds, which means that the formation and cleavage of such bonds, some of which are stronger than the metal–metal interactions in the cluster,^[90] are associated with much higher activation thresholds than is known to be the case for ligand–noble-metal interactions. The first experimental evidence for the gas-phase reaction of a metalloid cluster ($[Ga_{19}R_6]^-$ (**25**)) indeed indicates that the GaR bonds are stronger than the Ga–Ga interactions so that a naked Ga_{13}^- cluster ion is generated in a unique fashion by the successive cleavage of GaR units.^[90] Such investigations also yield the first evidence for the mechanism of dissolution of a base metal, which apparently proceeds by a different route than for the noble metals, since, for example, the Al–X bonds on the periphery of an Al_n cluster are stronger than the corresponding Au–X bonds in Au clusters.

Compared to this single piece of experimental evidence for the mechanism of dissolution of a metal, there is a multitude of aluminum and gallium clusters that can be considered as intermediates between the monohalides or their substitution products and the metal. The diversity of the clusters obtained with, in some cases, the same ligand framework enables, for the first time, an overall analysis: The drastic changes in bond lengths and coordination numbers from the cluster core to the periphery show clearly that these clusters cannot be regarded as small metal particles. For example, the two clusters of almost the same size with 69 and 77 aluminum atoms (**4** and **5**) show that small changes in the number of ligands (the ligand is identical) lead to significant changes in the cluster core. This

result means that small changes on a metal surface of dimensions of up to several nanometers could also result in geometric and electronic changes in the interior of the metal.

The diversity of observed cluster structures clearly illustrates another aspect: they generally reflect the connectivity principles that are present in the elements. Aluminum clusters predominantly show topologies of Al atoms that reflect close packing whereas gallium clusters show very different structures of the Ga frameworks corresponding to the diversity of the observed element modifications. With Ga clusters, variation of the number of ligands for the same number of total gallium atoms even allows a pseudo-nanostructured phase transition to be simulated; from $[\text{Ga}_{22}\text{R}_{10}]^{2-}$ (**29**; $\text{R} = \text{N}(\text{SiMe}_3)_2$) to $[\text{Ga}_{22}\text{R}_8]$ (**26**; $\text{R} = \text{Si}t\text{Bu}_3$). On the other hand the same ligand shell can be used to generate different packing densities in the core of the cluster: $[\text{Ga}_{18}\text{R}_8]$ (**27**; $\text{R} = \text{Si}t\text{Bu}_3$) and $[\text{Ga}_{22}\text{R}_8]$ (**26**; $\text{R} = \text{Si}t\text{Bu}_3$), so that topologies of Ga atoms result that resemble a particular normal-pressure or high-pressure modification of elemental gallium. The few results obtained so far already show that through the choice of the reaction conditions and the ligand, the cluster size and the arrangement of atoms in the cluster core can in principle be tailored, which means that nanostructured element modifications may be attainable in the long-term. It could even be possible with the help of the methods developed here to synthesize elemental modifications previously known only hypothetically. For example, it is conceivable that the icosahedral subhalides (such as $\text{Al}_{22}\text{X}_{20}$ $\text{X} = \text{Cl}, \text{Br}$, **6** and **7**) could be linked together as building units in an analogous fashion to the linkage of fullerenes or Zintl anions,^[54, 102] so that ultimately nanostructured aluminum clusters with icosahedral building units could be obtained, for example, directly by 2e2c Al–Al bonding after cleavage of Al_2X_4 (this halide has already been shown to exist during disproportionation^[16a]).

Between aluminum and gallium, and also the neighboring element boron, there are great differences in the formation of clusters despite the presence of the same number of valence electrons. These differences are already obvious in the many connectivity possibilities for the atoms in the elemental forms themselves, which means that the element modifications already show that the bonding in compounds of these elements would be difficult to evaluate according to a single principle (e.g. Wade–Mingos).^[67] Despite this, established rules for boron clusters can be applied to the smaller metalloid Al and Ga clusters with certain additional assumptions, as recent DFT calculations have shown.^[100] In addition we have started to develop counting rules for smaller Ga and Al metalloid clusters,^[103] that, however, will probably not be transferable to the larger clusters. Therefore, the first assignment principle, presented here, for the larger metalloid clusters incorporates the structures of the elements in the various modifications, which means that the metalloid or elementoid clusters are described as nanostructured element modifications.

The development of the synthesis concept described here for metalloid clusters should ultimately be capable of extension to element combinations and therefore molecular nanostructured alloys as several results on metalloid SiAl and

SiGa clusters have shown.^[87, 89] Such mixed clusters resemble the Zintl-type compounds.^[104, 105]

Many experimental and quantum-chemical investigations are required before the final objective of a deeper understanding between the ever-increasing size of molecular cluster units and the bulk phase can be approached. It is therefore important that as many intermediates are investigated in detail with the nanoscopic methods now available. Since investigations on such sensitive samples as the Al and Ga clusters described here are associated with a large experimental effort, it cannot be expected that results will emerge quickly from the investigations currently in progress.

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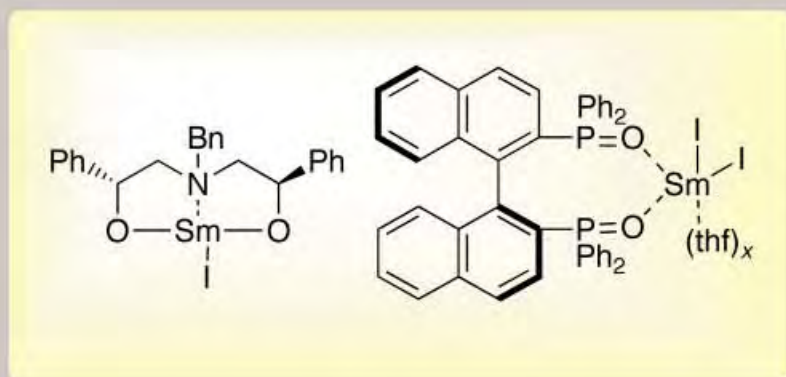
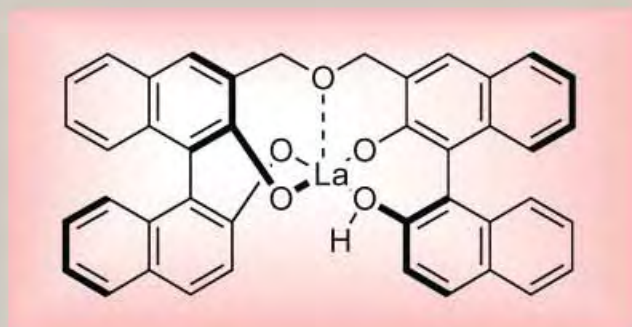
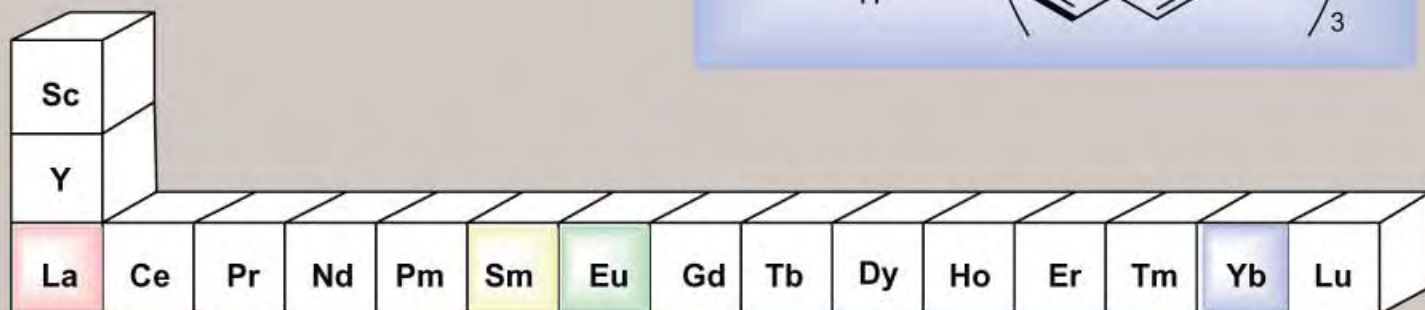
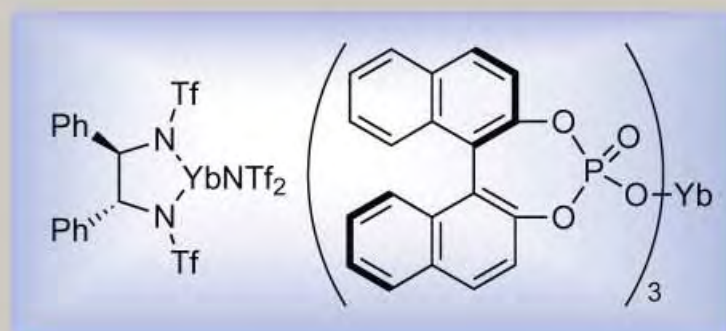
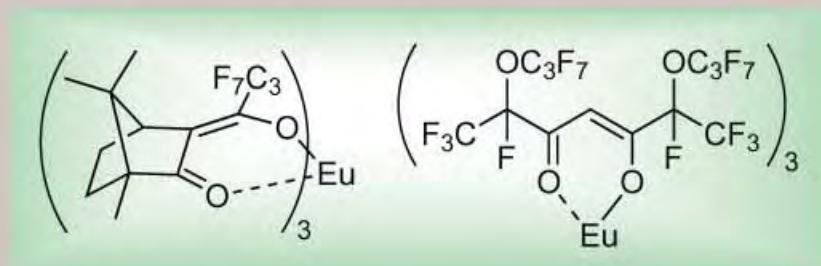
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Asymmetric Catalysis by Lanthanide Complexes



“Asymmetric” Catalysis by Lanthanide Complexes

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Catalysis with lanthanide (Ln) complexes has been underestimated for long time, although Ln^{III} complexes have great advantages as Lewis acid catalysts for “asymmetric” carbon–carbon bond-forming reactions. Lanthanide complexes are highly active in ligand-substitution reactions, especially with hard ligands. The association with substrates and dissociation of products are achieved fast enough for

high catalyst efficiency. The asymmetric catalysis of organic reactions can be greatly advanced by the use of Ln complexes with chiral ligands such as binaphthol (binol). Ln^{II} complexes are good reducing agents, which can be used in a wide variety of synthetically important reactions; when chiral ligands are used, many of these reactions are highly stereoselective. In the context of “green chemistry”, the de-

velopment of asymmetric Ln catalysts, and their recyclable use, is of increasing importance. This review gives an overview of the most recent developments in catalysis with lanthanide(II) and lanthanide(III) complexes.

Keywords: asymmetric catalysis • enantioselectivity • coordination chemistry • lanthanides • Lewis acids

1. Introduction

“Asymmetric” catalysis of organic reactions is an important subject in modern science and technology.^[1] Regarding the unique coordination chemistry of the f-block elements (“lanthanide” complexes),^[2] particularly high coordination numbers are an advantage as organic reactions can be promoted catalytically rather than stoichiometrically.^[3] The following characteristics are typical of lanthanide complexes: 1) The lanthanide cations, generally in the oxidation states +2–+4, have an extended Xe-core electronic configuration; they have 5s²5p⁶ outer-shell electrons and 4f^{*n*} deep-lying electrons (*n* = 1–14; Table 1). 2) The inert 4f shell lies inactive, deep in the interior of the cation and is well-shielded by the filled 5s² and 5p⁶ orbitals. The character of these f-block elements is in sharp contrast to that of d-block elements, in which the outer d orbital is filled sequentially. Ln³⁺ ions are commonly thought to have a tripositively charged, closed shell with a noble-gas electronic configuration. Therefore, no σ -donor– π -acceptor bonding mode occurs. 3) f-Block elements lack orbital restrictions, so there is no need to maximize orbital overlap as in d-block transition-metal chemistry. 4) Poor overlap of 4f orbitals with the ligand orbitals and the lanthanide contraction contribute to the predominantly ionic character of organolanthanide complexes. According to

the HSAB classification of Pearson,^[4] lanthanide cations are considered to be hard acids, ranked between Sr^{II} and Ti^{IV}. The ionic-bonding contributions cause lanthanide cations to be strongly oxophilic, which can be expressed in terms of the dissociation energy (D_0) of Ln–O bonds (Figure 1).^[+, 5] Table 2 represents the trend in effective ionic radii of these multiply charged cations, which prefer high coordination numbers between 6–12.^[6] As shown in Figure 1, the atomic and ionic radii decrease linearly with increasing atomic number (“lanthanide contraction”). Therefore, metal–ligand interactions are determined by electrostatic factors and thus lanthanide cations preferentially interact with hard ligands. 6) Ln²⁺ complexes are strong reducing agents, for example, Sm²⁺, Eu²⁺, Tm²⁺,^[7] and Yb²⁺ have oxidation potentials of +1.55, +0.35, +2.3, and +1.15 V, respectively.^[8] 7) Lanthanide complexes are active in ligand substitution reactions and attainment of the association–dissociation equilibrium is fast.

The Lewis acidity (Z/r^3 ; *Z* = charge and *r* = ionic radius), is particularly low in complexes derived from the large Ln³⁺ cations.^[9] Hence these systems are considered in organic synthesis to be mild Lewis acidic catalysts. However the Sc³⁺ ion, as the smallest rare-earth-metal cation, is the most Lewis acidic and lies on the borderline between lanthanide–early transition metal–aluminum. The Yb³⁺ ion is the second smallest lanthanide cation (after Lu³⁺) and is hence the most

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[+] The elements specified in Figure 1 include scandium and yttrium, which are not formally defined as lanthanide elements, but as rare earth metals. For the sake of simplicity, in this review these two elements are also abbreviated to Ln.

Table 1. Characteristic features of lanthanide elements.

Element	Configuration of outer electron shell				E^0 (Ln $\rightarrow$ Ln ³⁺ + 3e ⁻) [V]	E^0 (Ln ²⁺ $\rightarrow$ Ln ³⁺ + e ⁻) [V]	E^0 (Ln ³⁺ $\rightarrow$ Ln ⁴⁺ + e ⁻) [V]
	Atom	Ln ²⁺	Ln ³⁺	Ln ⁴⁺			
La	5d ¹ 6s ²	5d ¹	[Xe]	–	+ 2.52		
Ce	4f ² 6s ²	4f ²	4f ¹	[Xe]	+ 2.48		– 1.74
Pr	4f ³ 6s ²	4f ³	4f ²	4f ¹	+ 2.46		ca. – 3.2
Nd	4f ⁴ 6s ²	4f ⁴	4f ³	4f ²	+ 2.43		
Pm	4f ⁵ 6s ²	4f ⁵	4f ⁴	–	+ 2.42		
Sm	4f ⁶ 6s ²	4f ⁶	4f ⁵	–	+ 2.41	+ 1.55	
Eu	4f ⁷ 6s ²	4f ⁷	4f ⁶	–	+ 2.41	+ 0.35	
Gd	4f ⁷ 5d ¹ 6s ²	4f ⁷ 5d ¹	4f ⁷	–	+ 2.40		
Tb	4f ⁹ 6s ²	4f ⁹	4f ⁸	4f ⁷	+ 2.39		
Dy	4f ¹⁰ 6s ²	4f ¹⁰	4f ⁹	4f ⁸	+ 2.35		
Ho	4f ¹¹ 6s ²	4f ¹¹	4f ¹⁰	–	+ 2.32		
Er	4f ¹² 6s ²	4f ¹²	4f ¹¹	–	+ 2.30		
Tm	4f ¹³ 6s ²	4f ¹³	4f ¹²	–	+ 2.28	ca. + 2.3	
Yb	4f ¹⁴ 6s ²	4f ¹⁴	4f ¹³	–	+ 2.27	+ 1.15	
Lu	4f ¹⁴ 5d ¹ 6s ²	–	4f ¹⁴	–	+ 2.26		

Lewis acidic rare earth metal but one (Sc³⁺). The higher Lewis acidity of the Yb³⁺ ion over the Lu³⁺ ion may originate from an incomplete 4f orbital. The Yb³⁺ ion is one electron short of a fully occupied 4f orbital, which increases its electron affinity over the Lu³⁺ ion. A similar argument can be extended to the anomaly of the Lewis acidities of Gd³⁺ and Eu³⁺ ions (half-filled 4f orbital).

The stability of ligands is ordered according to their tendency to hydrolyze, in the case of organolanthanide

complexes, or to compete with the solvent, in the case of inorganic complexes, because fast acid–base ligand exchange is characteristic of organolanthanide chemistry (Figure 2). Organolanthanide complexes containing σ bonds to, for example, alkyl and alkoxides groups, readily hydrolyze with moisture to form the hydroxides.^[2d] Even ligands with lower pK_a values than water, such as OAr, tend to hydrolyze because of the formation of insoluble hydroxides. However, the presence of hard conjugate bases or chelating anions

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Rearrangements”, the Chemical Society of Japan Award (Shinpo-Sho) on “Asymmetric Transmission and Asymmetric Synthesis based on the [2,3] Wittig Rearrangements”, the Society of Synthetic Organic Chemistry Japan Award (Asahi-Kasei Award) on “Asymmetric Synthesis based on Carbonyl-Ene Reactions”, the IBM award on “Highly Efficient Asymmetric Catalysis”, the Ichimura science award on “Development of Asymmetric Catalytic Friedel–Crafts Reactions and their Industrial Application”; he was the Bristol-Myers-Squibb Lecturer (Colorado State University), Lilly Research Laboratories Lecturer (Ohio State University), the Boehringer Ingelheim Award Lecturer (University of Montreal), and Visiting Professor in the Université Paris-Sud and Taiwan.

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K. Mikami



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H. Matsuzawa

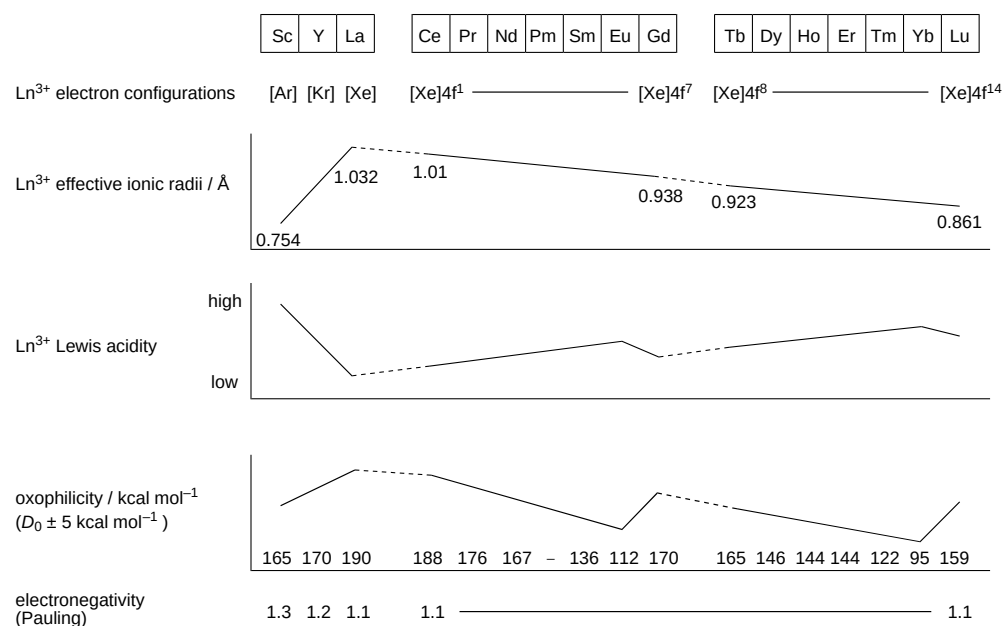


Figure 1. Characteristic features of lanthanide ions and elements. D_0 = dissociation energy of the Ln–O bond.

Table 2. Effective ionic radii (Å) of Ln^{3+} , Ln^{2+} , and Ln^{4+} ions.

Ln^{n+}	Coordination number					
	6	7	8	9	10	12
Sc^{3+}	0.754		0.870			
Y^{3+}	0.900	0.96	1.019	1.075		
La^{3+}	1.032	1.10	1.160	1.216	1.27	1.36
Ce^{3+}	1.01	1.07	1.143	1.196	1.25	1.34
Pr^{3+}	0.99		1.126	1.179		
Nd^{3+}	0.983		1.109	1.163		1.27
Pm^{3+}	0.97		1.093	1.144		
Sm^{3+}	0.958	1.02	1.079	1.132		1.24
Eu^{3+}	0.947	1.01	1.066	1.120		
Gd^{3+}	0.938	1.00	1.053	1.095		
Tb^{3+}	0.923	0.98	1.040	1.095		
Dy^{3+}	0.912	0.97	1.027	1.083		
Ho^{3+}	0.901		1.015	1.072	1.12	
Er^{3+}	0.890	0.945	1.004	1.062		
Tm^{3+}	0.880		0.994	1.052		
Yb^{3+}	0.868	0.925	0.985	1.042		
Lu^{3+}	0.861		0.977	1.032		
Sm^{2+}		1.22	1.27	1.32		
Eu^{2+}	1.17	1.20	1.25	1.30	1.35	
Tm^{2+}	1.03	1.09				
Yb^{2+}	1.02	1.08	1.24			
Ce^{4+}	0.87		0.97		1.07	1.14
Tb^{4+}	0.76		0.88			

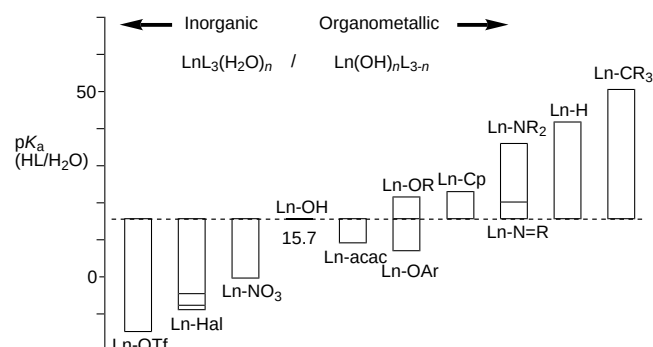
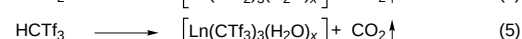
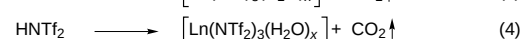
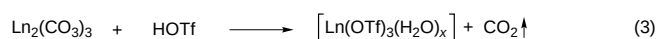
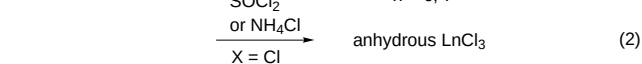
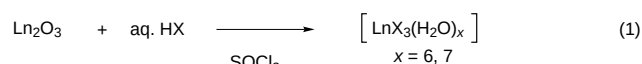


Figure 2. Hydrolysis of organolanthanide and inorganic lanthanide complexes.

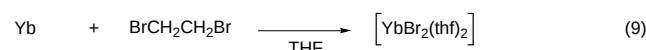
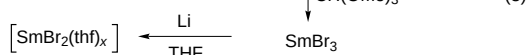
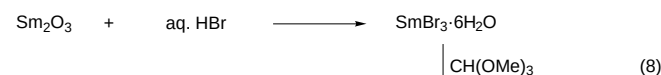
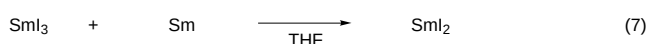
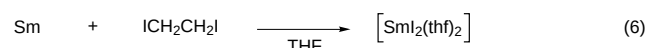
(e.g. acac = acetylacetonate) can afford water-stable complexes. These complexes can be effective Lewis acids in alcoholic, water, and even in amine solvents.

Lanthanide trihalides, LnX_3 , are generally prepared from lanthanide oxide, Ln_2O_3 , as hydrates. The dehydration of $\text{LnCl}_3/(\text{H}_2\text{O})_x$ ($x = 6, 7$) using NH_4Cl or SOCl_2 is the laboratory method of preparing anhydrous lanthanide chlorides [Eq. (1) and (2)].^[10] In the case of $\text{X} = \text{Cl}$, thermal dehydration leads to the formation of undesirable lanthanide oxychlorides. Lanthanide carbonate can be



used as a precursor for LnX_3 with evolution of carbon dioxide [Eq. (3)–(5), Tf = triflyl].^[11]

Lanthanide dihalides, LnX_2 , are the only precursors for Ln^{II} -organometallic compounds [Eq. (6)–(9)]. SmI_2 is widely employed as a THF solution in organic synthesis.^[3a,c-e, 12]



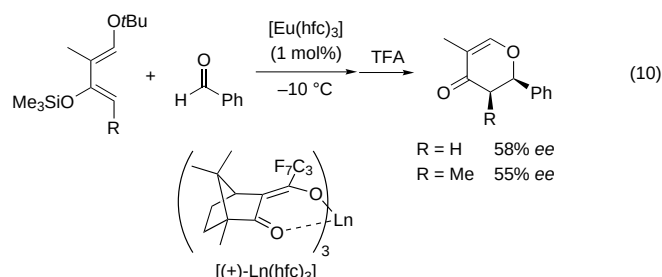
2. Asymmetric Catalysis with Ln^{III} Complexes

2.1. Initial Experiments

Because the metal–ligand interaction is of electrostatic origin, optimal charge balance of the Ln^{III} cations should be achieved by three stable anionic ligands. Identical anions form

either neutral homoleptic complexes (MX_n) or ate complexes $[\text{MX}_n]^{z-}[\text{Y}]^{z+}$. Chelating anions are useful in synthesizing heterometallic complexes.

Bednarski, Maring, and Danishefsky reported the first example of asymmetric catalysis with an Ln^{III} complex, using a homoleptic chiral NMR shift reagent, $[\text{Eu}(\text{hfc})_3]$ (hfc = heptafluoropropylhydroxymethylene) [Eq. (10)] TFA = trifluoro-



acetic acid].^[13] They clarified the mechanism of the asymmetric hetero-Diels–Alder reaction (Figure 3).^[14] Generally, Lewis acid complexes such as $\text{BF}_3 \cdot \text{OEt}_2$ or TiCl_4 provide first the Mukaiyama aldol product and then the cyclized product upon acidic workup (Figure 3a). However, lanthanide-catalyzed hetero-Diels–Alder reactions proceed in a concerted manner (Figure 3b).

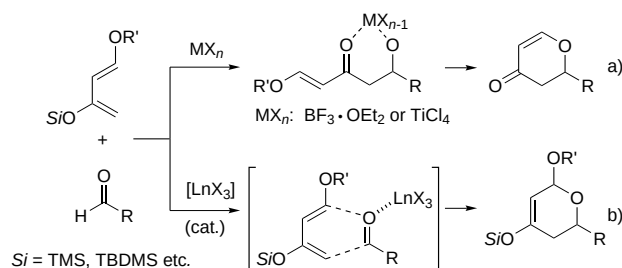


Figure 3. The dichotomous mechanisms of the hetero-Diels–Alder reactions promoted by a) stoichiometric or b) catalytic Lewis acid. TMS = trimethylsilyl, TBDMS = *tert*-butyldimethylsilyl.

The major problem associated with the catalysis of the Mukaiyama aldol reaction of silyl enol ethers by the standard Lewis acid complexes such as $\text{BF}_3 \cdot \text{OEt}_2$ or TiCl_4 is the transmetalation of the starting silyl enol ether to give eventually the β -metalloxycarbonyl chelate intermediate stoichiometrically (Figure 4a). We tested lanthanide complexes as Lewis acid catalysts for the synchronous aldol reaction (Figure 4b). First, we examined a chiral shift reagent^[15] with a C_2 -symmetric polyfluoro ligand, (+)- or (–)-dppm (see Equation (11) for the structure of dppm) for the catalysis of the aldol reaction of a variety of silyl enol ethers derived from esters or ketones, with aldehydes, acetals, and ketones. Unfortunately, the enantioselectivity of the (+)- $[\text{Eu}(\text{dppm})_3]$ -catalyzed aldol reaction is low. However, the Eu catalysts provided remarkable levels of recognition between

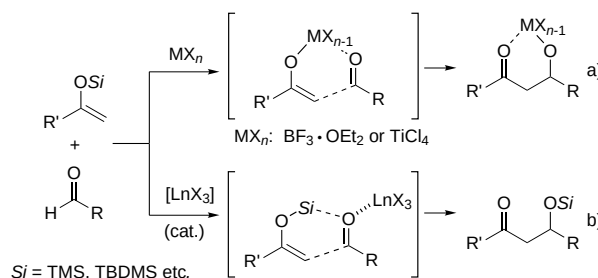
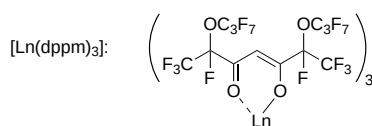
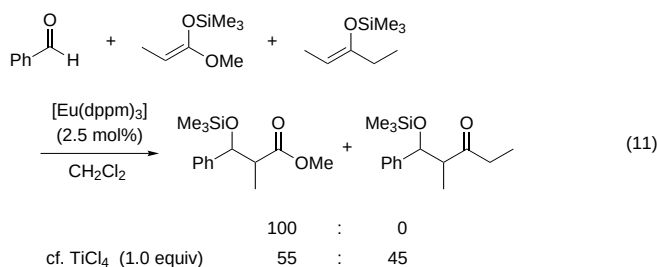


Figure 4. The envisaged mechanisms of aldol reaction catalyzed by a) standard Lewis acids and b) Ln^{III} complexes.



carbonyl electrophiles and silyl enol ether nucleophile partners.

2.2. Aldol Reactions

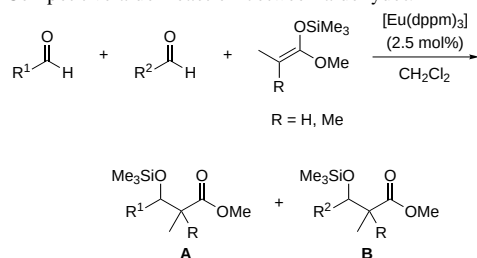
2.1. Molecular Recognition

The $[\text{Eu}(\text{dppm})_3]$ catalysis exhibits remarkable levels of chemoselectivity in terms not only of carbonyl electrophiles but also of their silyl enol ether nucleophile partners [Eq. (11)].^[16]

The $[\text{Eu}(\text{dppm})_3]$ catalyst was effective only for the reactions of aldehydes or α,β -unsaturated ketones with ketene silyl acetals, but totally ineffective for the reaction of acetals with ketene silyl acetal, ketones with ketene silyl acetal, and aldehydes with ketone-derived silyl enol ethers. This unique selectivity in catalysis is exemplified by a competitive aldol reaction of benzaldehyde with a ketene silyl acetal and a silyl enol ether. The Eu^{III} catalyst gave the ketene silyl acetal-derived aldol product exclusively [Eq. (11)]. In sharp contrast, a nearly 1:1 mixture of aldol products was obtained by stoichiometric use of TiCl_4 .

In addition, the Eu^{III} catalysis shows high level of aldehyde discrimination in competitive aldol reactions (Table 3). First, the Eu^{III} catalysts are more sensitive to the steric demand in aldehydes than the stoichiometric use of TiCl_4 (entry 1). Second, the Eu^{III} catalysts can recognize the subtle difference in electronic effects on benzaldehyde derivatives (entry 2–4). Interestingly, *p*-nitrobenzaldehyde ($\sigma_{p-\text{NO}_2} = +0.78$)^[17] is less reactive than benzaldehyde in the Eu^{III} -catalyzed process

Table 3. Competitive aldol reaction between aldehydes.



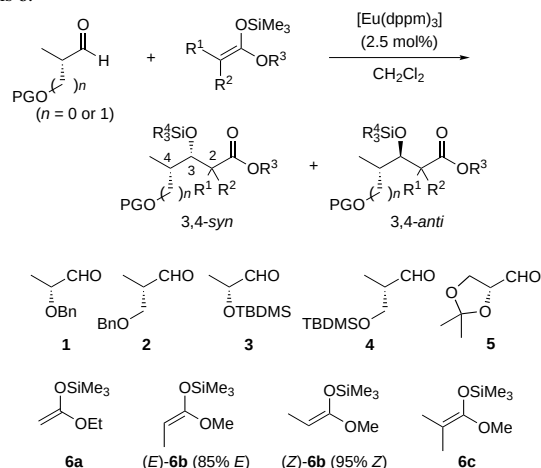
Entry	R ¹ CHO	R ² CHO	A:B
1 ^[a]			> 98:2 (77:23) ^[b]
2 ^[a]			> 95:5
3 ^[a]			87:13
4 ^[a]			95:5 (68:32) ^[b]
5 ^[c]			97:3

[a] R = H in ketene silyl acetal. [b] Stoichiometric amount of TiCl₄. [c] R = Me in ketene silyl acetal.

(entry 2). Similarly, *p*-methoxybenzaldehyde is more reactive than benzaldehyde (entry 3). More significantly, the Eu^{III} catalyst shows remarkable preference for *o*-methoxybenzaldehyde ($\sigma_{\text{O-Me}} = -0.27$ to -0.67)^[17] over benzaldehyde (entry 4), although the former is sterically more hindered. These results suggest that the relative reactivity of aldehydes in the Eu^{III}-catalyzed process is determined almost solely by the coordinating ability of aldehydes to the Eu^{III} complex, not by the electrophilicity of the aldehydes themselves. A similar argument can be extended to explain the high levels of molecular recognition of α -benzyloxy aldehyde and α -silyloxy aldehyde (entry 5); the former is preferentially complexed as a chelate ligand. Indeed, the 3,4-*syn* diastereomer is the major product (see Section 2.2.2).

2.2.2. Diastereoselective Catalysis by Induced Stereochemical Fit

Diastereoselectivity in the Eu^{III}-catalyzed aldol reaction is not high with a simple aldehyde such as benzaldehyde. However, the catalytic reaction of alkoxy aldehydes **1–5** with ketene silyl acetal **6** exhibited excellent stereoselectivity (Table 4).^[18] The Eu^{III} catalyst recognizes the difference not only in the different protecting groups of the aldehydes (PG) but also the different steric demands of **6**, and hence dictates either chelation (3,4-*syn*) or nonchelation (3,4-*anti*) selections^[19] in the catalytic aldol reactions of the α - and β -alkoxy aldehydes **1–4**. In Table 4, the results indicate that not only the degree but also the sense of 3,4-diastereofacial selection (chelation vs. nonchelation) is critically induced by the steric bulk of **6**. The characteristic features are as follows: 1) 3,4-*syn*/*anti* selectivities are primarily dependent on the kind of alkoxy protecting groups. Benzyl-protected aldehydes **1** and **2**

Table 4. Eu^{III}-catalyzed aldol reaction of alkoxyaldehydes with ketene silyl acetals **6**.

Entry	Aldehyde	6	Yield [%]	3,4- <i>syn</i> :3,4- <i>anti</i>
1	1	6a	75	> 99: < 1 (98:2) ^[a]
2		(E)-6b	78	89:11 (> 99:1) ^[a]
3		(Z)-6b	100	96:4
4		6c	80	92:8 (> 99:1) ^[a]
5	2	6a	35	68:32 (68:32) ^[a]
6		6c	30	36:64 (> 99:1) ^[a]
7	3	6a	90	74:26
8		(E)-6b	80	5:95
9		(Z)-6b	90	19:81
10		6c	55	29:71
11	4	6a	65	45:55
12		6c	62	19:81

[a] Stoichiometric amount of TiCl₄.

gave the predominantly 3,4-*syn* product (entries 1–6) through chelation control. In contrast, the sterically hindered silyl protection (**3**, **4**) leads mainly to the 3,4-*anti* product through the nonchelate mode (entries 7–12). 2) The reaction of the α -alkoxy aldehydes **1** and **3** gave a higher distribution of 3,4-*syn* products (entries 1–4 and 7–10) than that of the β -alkoxy aldehydes **2** and **4** (entries 5, 6, 11, and 12). 3) The bulkier ketene silyl acetal **6c** tends to give 3,4-*anti* products, even with the α -benzyloxyaldehyde **1**. In particular, a change-over of the 3,4-selectivity from *syn* to *anti* was observed in the reaction with the aldehydes **2** and **3** (entries 5, 6, and 7–10). Of particular interest is that the degree of 3,4-*syn* selectivity decreases with increasing steric bulkiness of **6** in the order **6a** > **6b** > **6c** (entries 1–4). These results are in direct contrast to the general trend that “the more bulky ketene silyl acetals are therefore the more selective”^[19] as observed by a stoichiometric use of TiCl₄ (entries 1–6).

This unique trend in the stereoselectivity of Eu^{III}-catalyzed aldol reactions is likely to reflect the complexation state of the Eu^{III} ion with the aldehydes, namely chelation versus nonchelation. In fact, LIS (lanthanide-induced shifts) NMR spectroscopic analysis qualitatively indicated that the order of chelate complexation ability to the aldehyde was **1** >> **2** > **3** > **4**.^[20] The stereochemical control of the Eu^{III} catalysis is rationalized by the dichotomous catalytic cycles and the equilibrium between chelate and nonchelate complexes with aldehydes (**1–4**; Figure 5). In view of the Curtin-Hammett

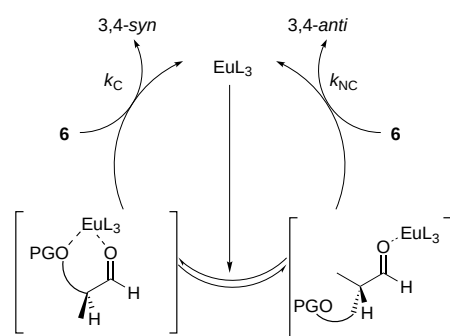
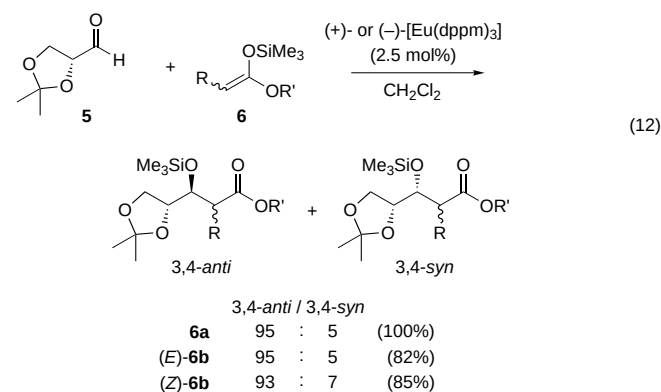


Figure 5. Catalytic cycles for chelation (k_C) versus nonchelation (k_{NC}) reactions. L = ligand.

principle,^[21] the diastereofacial selectivity in the Eu^{III} -catalyzed aldol reaction is sensitive to the size of the ketene silyl acetal; sterically demanding ketene silyl acetals tend to react preferentially via the nonchelate complex rather than through the congested chelate complex.

An interesting and general problem lies in the reaction with the glyceraldehyde acetonide (**5**) which arises from the competition between α and β chelation to the metal complexes involved [Eq. (12)].^[22] A high level of 3,4-*anti*-diaste-



reofacial selectivity was observed in the Eu^{III} -catalyzed reaction, which can be explained by β -chelation control.^[23]

However, our high 3,4-*anti* selectivity should not be interpreted by β chelation, because the β -chelation ability of Eu^{III} catalysts is not high (Table 4). Therefore the high 3,4-*anti* selectivity is rationalized by tridentate chelation caused by the high coordination number (commonly 6–9) of lanthanides (Figure 6).

Figure 6. Tridentate chelation model.

2,3-diastereoselectivity is also observed in the Eu^{III} -catalyzed aldol reaction.^[24] Inspection of Table 5 reveals several significant features of the Eu^{III} catalysis. Aldehyde **3** afforded the 3,4-*anti*-2,3-*syn* product selectively (nonchelation/*syn*) via the well-accepted antiperiplanar transition state (**AP**; entries 1–3 and Figure 7). In contrast, aldehyde **1** predominantly gave the 3,4-*syn*-2,3-*anti* product (α chelation $\rightarrow$ *anti*), but the 2,3-diastereoselectivity depends on the geometry of the ketene silyl

Table 5. Eu^{III} -catalyzed aldol reactions of aldehyde (**1**, **3**, or **5**) and ketene silyl acetal **6**.

Entry	Alde- hyde	R	3,4- <i>syn</i> [%]		3,4- <i>anti</i> [%]		Yield [%]
			2,3- <i>anti</i>	2,3- <i>syn</i>	2,3- <i>anti</i>	2,3- <i>syn</i>	
1	3	Me (95% <i>Z</i>)	5	14	1	80	90
2	3	Me (85% <i>E</i>)	2	3	1	94	80
3	3	OBn (100% <i>Z</i>)	2	5	0	93	58
4	1	Me (95% <i>Z</i>)	73	23	0	4	95
5	1	Me (85% <i>E</i>)	40	49	1	10	78
6	1	Et (95% <i>Z</i>)	92	8	0	0	83
7	1	OBn (100% <i>Z</i>)	98	2	0	0	93
8	1	OMe (100% <i>Z</i>)	97	3	0	0	81
9	1	OSiMe ₃ (85% <i>Z</i>)	98	2	0	0	75
10	5	Me (95% <i>Z</i>)	6	1	14	79	85
11	5	Me (85% <i>E</i>)	3	2	33	62	82
12	5	OBn (100% <i>Z</i>)	33	18	0	49	53

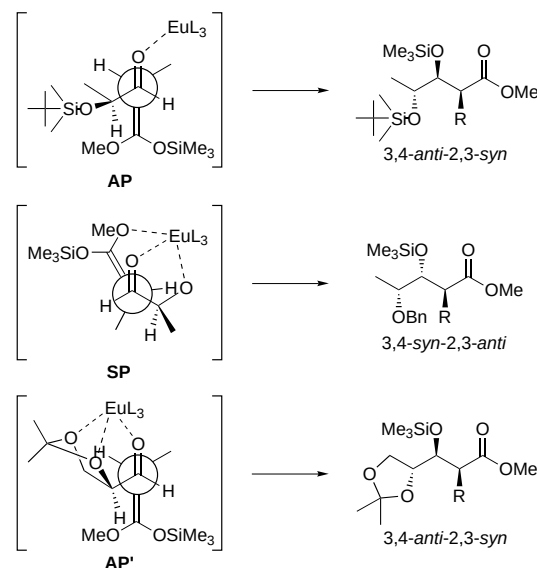


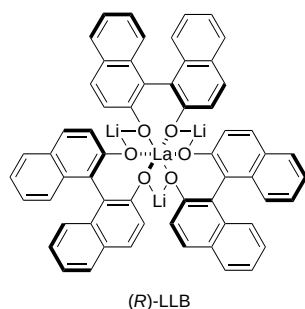
Figure 7. Antiperiplanar (**AP**: nonchelation, **AP'**: chelation) versus synperiplanar (**SP**) transition states in the aldol reaction.

acetal **6** (entries 4–9). Most striking is the high 2,3-*anti* diastereoselectivity observed with (*Z*)-ketene silyl acetals, in direct contrast to the high 2,3-*syn* selectivity widely observed for aldol reactions under chelation control with a stoichiometric amount of Lewis acid, such as TiCl_4 .^[25] The unusual stereoselectivity reflected in the products is best rationalized by assuming the rarely observed synperiplanar transition state (**SP**),^[26] which is favored by the additional coordination of the

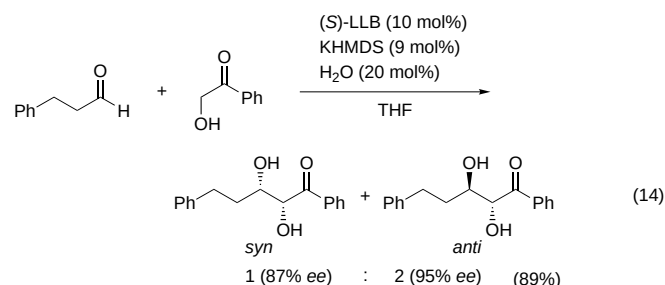
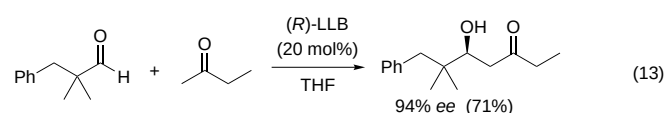
methoxy group in (*Z*)-ketene silyl acetal to the Eu^{III} complex that is chelated by the α -benzyloxyaldehyde **1**. The aldehyde **5**, binding in a tridentate chelation mode to the Eu^{III} catalyst, provided preferentially 3,4-*anti*-2,3-*syn* product (α,β -chelation $\rightarrow$ *syn*) through the antiperiplanar transition state (**AP**). Thus, the stereocontrol by Eu^{III} catalysis is a result of the induced stereochemical fit in the complexation state of aldehyde–Eu^{III}, which dictates the transition state geometry and thus the stereochemistry of the products.

2.2.3. Enantioselective Catalysis

The asymmetric aldol reaction is one of the most powerful carbon–carbon bond-forming reactions. However, an unavoidable drawback in the asymmetric catalysis of this reaction is the necessity to preconvert the ketone moiety into a more reactive species such as a silyl enol ether or ketene silyl acetal.^[27] Shibasaki reported that the chiral heterobimetallic complex,^[28] LaLi₃-tris(binaphthoxide) (LLB), is an efficient



asymmetric catalyst for direct aldol reactions of aldehydes and unmodified ketones. The LLB catalyst functions not only as a base to remove an α -proton of the ketone, but also as an acid in the final step of the reaction, giving the aldol product in high yield and with high enantioselectivity [Eq. (13)].^[29]



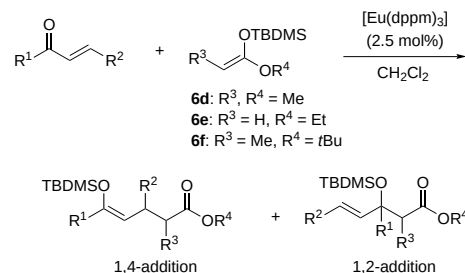
The LLB catalyst also works well for the direct aldol reaction of aldehydes with α -hydroxy ketones to provide 1,2-dihydroxy ketones in high enantiomeric excess [Eq. (14); KHMDS = potassium hexamethyldisilazane].^[30]

2.3. Michael Addition

2.3.1. Molecular Recognition

Eu^{III} catalysts exhibit unique recognition in their reaction with α,β -unsaturated carbonyl compounds, in which the competition between aldol (1,2-addition) and Michael (1,4-addition) reaction arises (Table 6).^[16] The Eu^{III} catalyst is

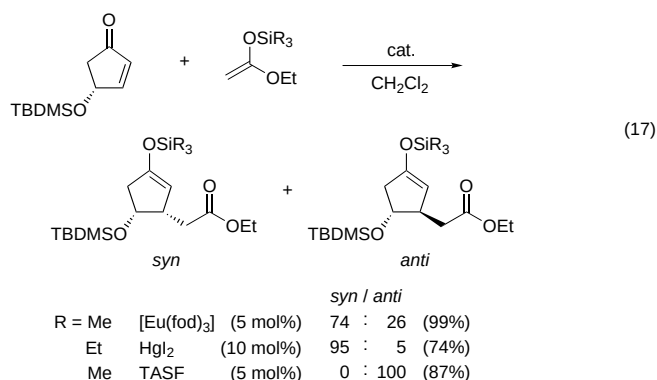
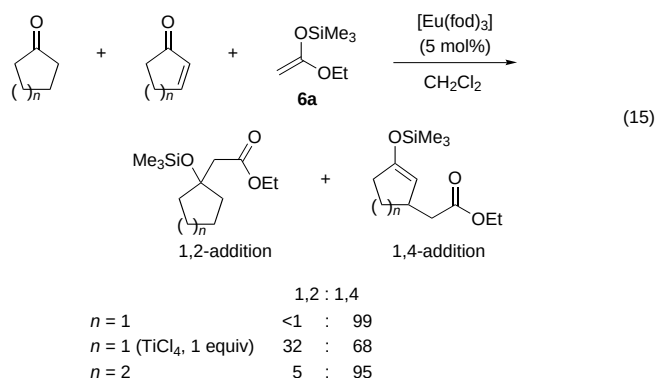
Table 6. Selectivity of 1,4-addition versus 1,2-addition in Eu^{III}-catalyzed reactions.



Entry	Enone	6	Yield [%]	1,4:1,2
1		6d	85	> 95:5
2		6d	65	44:56
3		6e	85	15:85
4		6e	85	100:0
5		6f	100	100:0

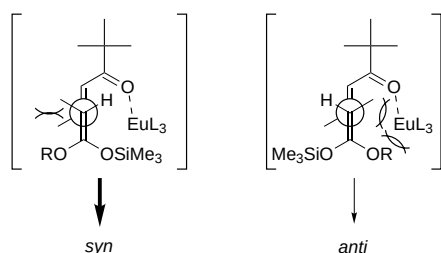
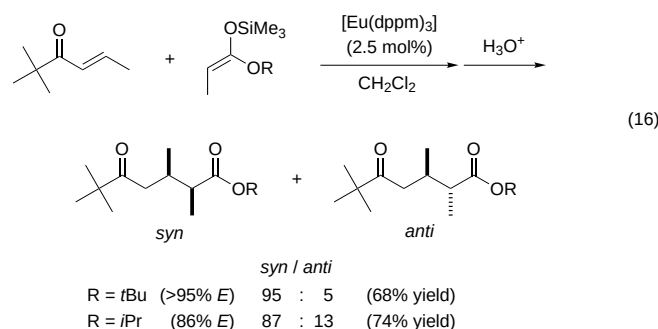
sensitive to the steric parameters not only in the α,β -unsaturated carbonyls but also in the ketene silyl acetals **6**. The β -unsubstituted enal ($R^1 = R^2 = H$) preferentially afforded the 1,4-addition product in a silyl enol ether form (entry 1), whereas the β -substituted enal ($R^2 = Me$) reacted with **6d** to deliver both 1,2- and 1,4-addition products (entry 2). The former product predominated over the 1,4-addition product with the sterically less demanding ketene silyl acetal **6e** (entry 3). In contrast, the Eu^{III}-catalyzed reaction with α,β -unsaturated ketones such as cyclopentenone afforded the 1,4-addition product exclusively, even when a less bulky ketene silyl acetal **6e** was used (entry 4 and 5).

A significant discrimination between saturated and α,β -unsaturated ketones was observed in the Eu^{III}-catalyzed reactions with **6a** [Eq. (15); fod = 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione].^[31] The competition of the cyclic ketone and enone led to the exclusive formation of the 1,4-addition product. This discriminating ability of the Eu^{III} catalysis is remarkable when compared with the poor ability of stoichiometric TiCl₄.



2.3.2. Diastereoselective Catalysis by Induced Stereochemical Fit

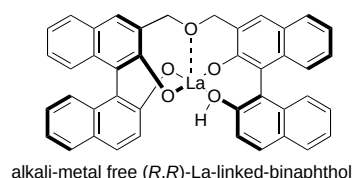
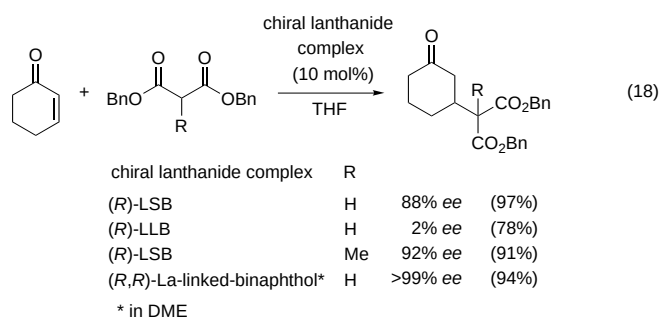
The diastereoselectivity in Eu^{III}-catalyzed Michael additions is generally not high. Both cyclic and acyclic enones gave low to moderate levels of *syn* selectivity, regardless of the geometry of the ketene silyl acetal.^[32] However the extremely high level of *syn* selectivity was observed with the sterically congested *tert*-butyl (*E*)-propenyl ketone when an equally sterically bulky ketene silyl acetal was employed [Eq. (16)].



The principal advantage of Eu^{III}-catalyzed Michael addition is that the product is obtained as a silyl enol ether form, which is synthetically useful for further transformations. Michael addition to 4-silyloxycyclopentenone delivered the silyl enol ether product as a synthetic key intermediate for prostanoids with high *syn* selectivity [Eq. (17)].^[33] This high *syn* selectivity contrasts with the extremely high *anti* selectivity observed in the tris(diethylamino)sulfonium difluoromethylsilicate (TASF)-catalyzed reaction. The stereochemical reversal generally found in Lewis acid catalysis (for example, with HgI₂),^[34] is explained in terms of stereoelectronic effects based on the Cieplak model.^[35]

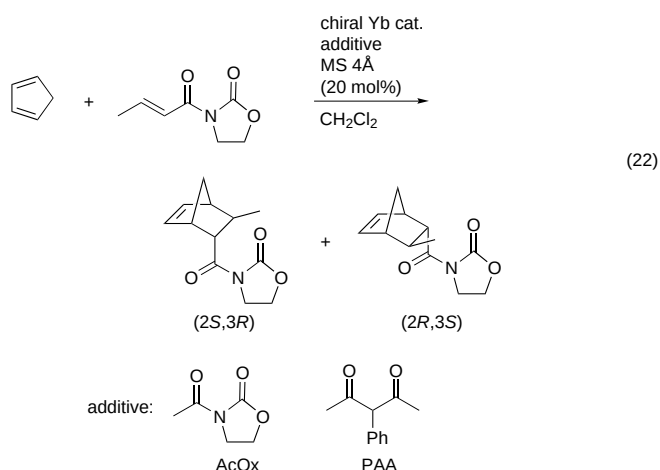
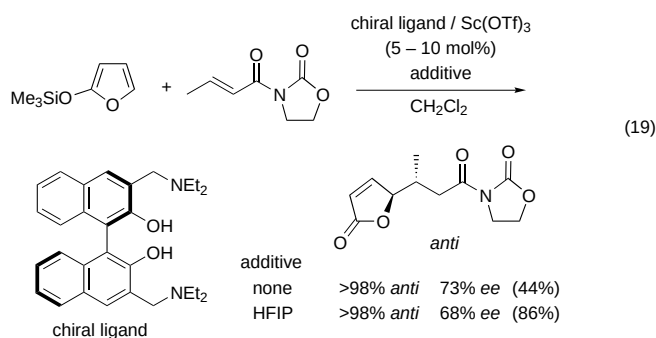
2.3.3. Enantioselective Catalysis

Shibasaki and co-workers reported that LaNa₃tris(bi-naphthoxide) (LSB) is ineffective for the asymmetric nitro-aldol reaction.^[36] However it is an effective catalyst for the enantioselective Michael addition of various enones with malonates, affording the Michael adducts in up to 92 % *ee* and in nearly quantitative yield [Eq. (18)].^[37] The highly enantioselective catalysis of LSB thus observed contrasts directly with the ineffectiveness of LLB (described in Section 2.2.3) in the asymmetric Michael addition.



Recently, a highly efficient and stable asymmetric catalyst, an La-linked-binol complex, was also developed^[38] for the enantioselective Michael addition reaction [Eq. (18)], which gives the Michael adduct in an enantioenriched form. The notable advantage of the La-linked-binol complexes emphasized here is their high stability and, hence, can be stored even under air.

Kitajima and Katsuki reported an enantioselective Michael addition catalyzed by a chiral Sc^{III} complex prepared from Sc(OTf)₃ and binol derivatives bearing a tertiary aminomethyl group [Eq. (19)].^[39] They achieved excellent diastereoselectivity and good enantioselectivity, but the yield was moderate. The addition of hexafluoroisopropanol (HFIP) suppressed the undesired Diels–Alder-type product, and improved the yield of the Michael reaction.

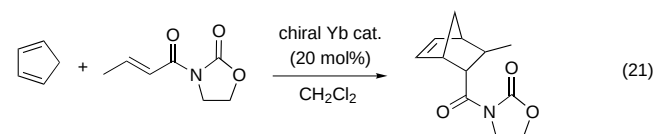
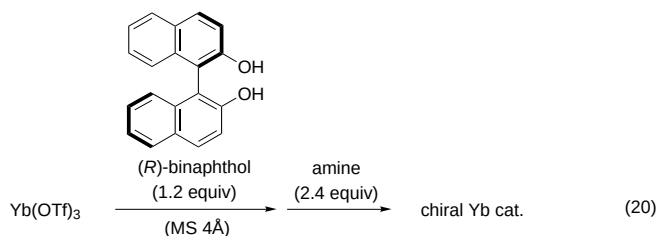


additive	Y [%]	endo / exo	ee [%]
AcOx	77	89 : 11	93 (2S,3R)
PAA	83	93 : 7	81 (2R,3S)

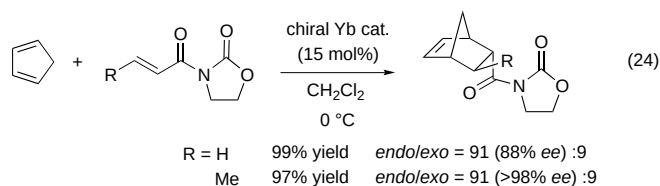
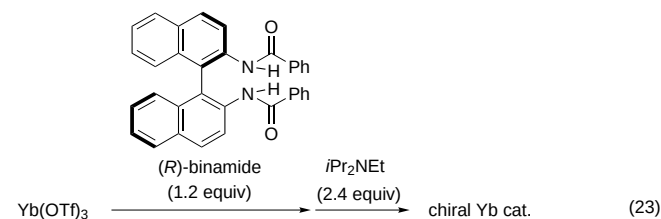
2.4. Diels–Alder Reaction

2.4.1. Diels–Alder Reactions with Chiral Lanthanide Complexes

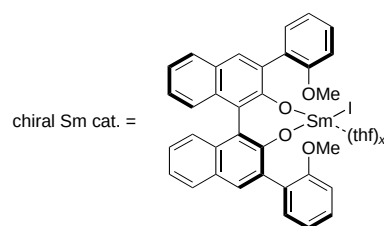
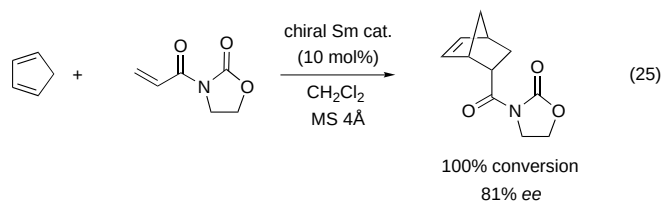
Kobayashi et al. succeeded in the chiral modification of the water-stable Lewis acid complex Ln(OTf)₃^[40] with binaphthol [Eq. (20)].^[41] Significantly, the use of a bulky amine led to an



Amine	MS	T [°C]	Yield [%]	endo / exo	ee [%]
Et ₃ N	-	23	87	76 : 24	33
<i>i</i> Pr ₂ EtN	-	23	82	85 : 15	70
<i>i</i> Pr ₂ EtN	MS 4Å	23	88	87 : 13	83
<i>i</i> Pr ₂ EtN	MS 4Å	23	91	86 : 14	90
<i>i</i> Pr ₂ EtN	MS 4Å	0	77	89 : 11	95



(81 % ee (−28 °C) vs. 28 % ee (−25 °C), respectively) [Eq. (25)]. The 3,3′-bis(2-methoxyphenyl)binaphthol is more sterically hindered than binaphthol and is capable of tri- or tetracoordination to the samarium center.



increase in the enantioselectivity [Eq. (21)], the sense of which depends critically on the kind of additive used [Eq. (22)].^{[42][43]}

Nakagawa and co-workers synthesized 1,1′-(2,2′-bisacylamino)binaphthalene (binamide) and examined the function of this ligand in the asymmetric Diels–Alder reaction using the chiral ytterbium catalyst [Eq. (23) and (24)].^[44] Screening various bulky amines with diisopropylethylamine led to the best result in this reaction. Qian and co-workers also described complexes of Ln(OTf)₃ and binaphthyl derivatives, and their use in asymmetric reactions.^[45]

Collin and co-workers synthesized the enantiopure samarium binaphthoxides by the reaction of the dipotassium salts of binaphthol and 3,3′-bis(2-methoxyphenyl)binaphthol with samarium triiodide.^[46] In the asymmetric Diels–Alder reaction, samarium 3,3′-bis(2-methoxyphenyl)binaphthoxide gave a higher enantioselectivity than the samarium binaphthoxide

2.4.2. Lanthanide Fluorous “Super” Lewis Acid

In the mid-1990s, the concept of fluorous biphasic catalysis (FBC) was introduced for use as an environmentally benign recycling process (Figure 8).^[47] Phosphane or phosphite

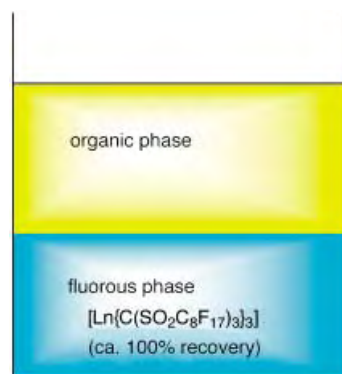
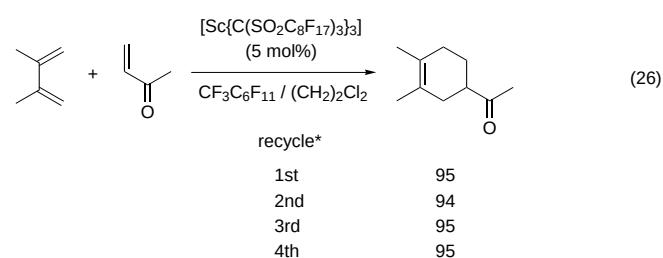


Figure 8. Catalysis in fluorous/organic biphasic system.

ligands with fluorous “ponytails” and hydrocarbon spacers have been developed to immobilize late-transition-metal catalysts for hydroformylation, hydride reduction, hydrogenation, alkene epoxidation, and hydroboration in nonpolar media.^[48] The design and immobilization of strong Lewis acid catalysts in this unorthodox nonpolar media for Lewis acid catalysis^[49] remain a challenge.^[50] We have reported that numerous (nine) fluorous “ponytails” of sufficient length (perfluorooctyl, C₈F₁₇) can be employed for fluorous-phase immobilization of lanthanide catalysts. The key to the success of the catalysts is the powerful electron-withdrawing effect of the perfluoroalkanesulfonylmethide group^[51] without a hydrocarbon spacer.

We have reported the “super” Lewis acidities and the complete recovery of the Ln^{III} tris(perfluorooctanesulfonyl)methide complexes for the Diels–Alder reaction in a fluorous phase [Eq. (26)].^[52] The Diels–Alder reaction was carried out



*The catalyst in the fluorous phase was recycled

at 35 °C, in the presence of a catalytic amount (5 mol %) of Sc^{III} complex. The two heterogeneous phases were separated to give acetylcyclohexene, which was isolated in a good yield. The Sc^{III} methide complex was completely (>99.9%) recovered and reused. Sc^{III} and Yb^{III} tris(perfluorooctanesulfonyl)methide complexes can be immobilized in recyclable fluorous phases and are extremely efficient Lewis acid catalysts for alcohol acylation, Friedel–Crafts acylation, and Mukaiyama aldol reaction, by virtue of the highly electron-withdrawing

effect of tris(perfluorooctanesulfonyl)methide ponytails without a hydrocarbon spacer. In addition, these lanthanide complexes could be reused as solid catalysts in organic solvent without the addition of fluorous solvent (Figure 9).^[51b, 53]

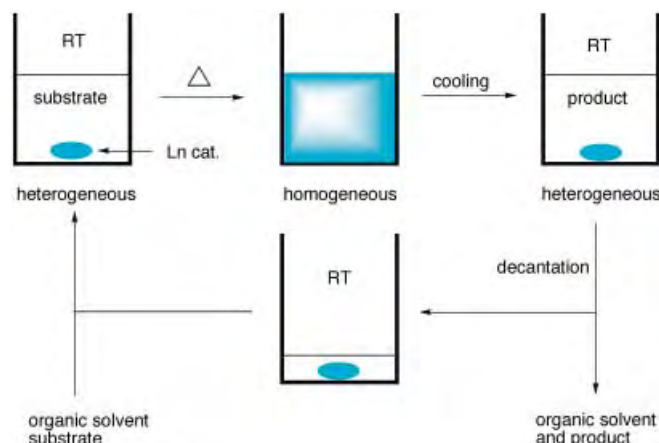
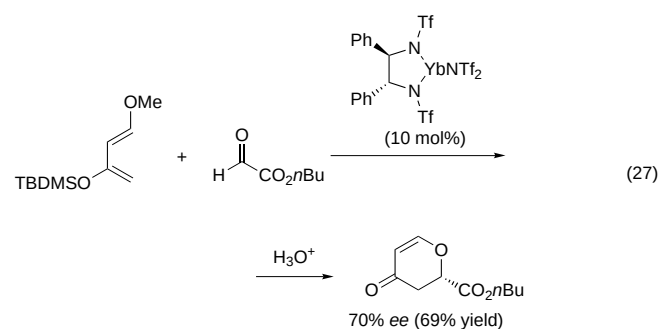


Figure 9. Use and reclamation of lanthanide complexes from organic solvents.

2.5. Hetero-Diels–Alder Reactions^[20, 54]

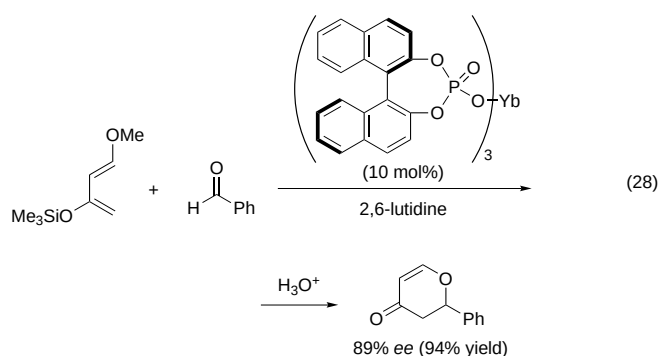
We found that the lanthanide triflate/binaphthol complex which was generated by treatment with KH or NaH only led to a low enantioselectivity. However, the use of lanthanide triflate, bis(triflyl)amide, or chiral bis(triflyl)amide complexes generated with KH or NaH provides a higher level of enantioselectivity [Eq. (27)].^[55] We found that the use of KOH instead of KH provides a similarly high level of



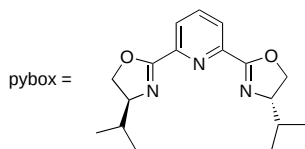
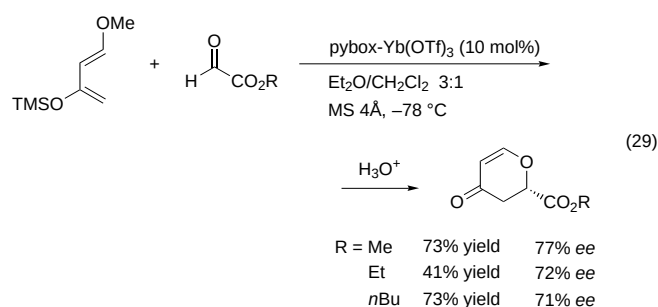
enantioselectivity, which indicates the stability of the lanthanide triflate/bis(triflyl)amide complex in the presence of water. Consequently, the addition of water to the hetero-Diels–Alder reaction conditions led to the highest enantioselectivity.

Inanaga and co-workers reported the use of chiral binaphthol-derived phosphate complexes for the hetero-Diels–Alder reaction with the Danishefsky diene [Eq. (28)].^[56] This complex is insoluble in dichloromethane but becomes soluble upon addition of a tertiary amine to the solution. They also observed a significant, positive nonlinear effect.

Qian and Wang performed asymmetric hetero-Diels–Alder reactions catalyzed by various chiral bis(oxazoline)–



lanthanide complexes.^[57] From these studies, the ytterbium triflate/*i*Pr-pybox complex was the best catalyst in this reaction [Eq. (29); pybox = bis(oxazolanyl)pyridine].^[58] It is

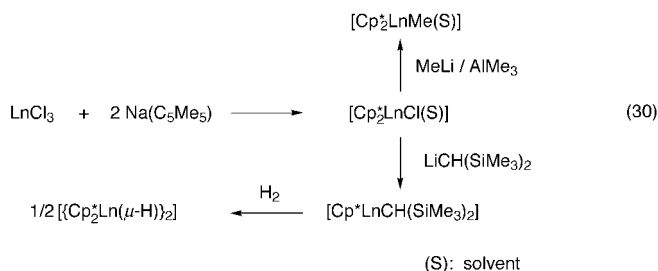


interesting that higher enantioselectivity was obtained using the sterically less-demanding methyl glyoxylate and by slow addition of Danishefsky diene.

2.6. Hydrogenation

2.6.1. Lanthanide Metallocene Catalysts

Much attention has been focused on lanthanide metallocene complexes since the discovery of their high catalytic activity for polymerization of cyclopentadienyllanthanide complexes [Eq. (30)].^[59] Marks has developed the enantioselective hydrogenation of 2-phenyl-1-butene [Eq. (31)].^[59a, 60] Incorporation of a chiral menthyl group in the 3-position of an *ansa*-bis(cyclopentadienyl)ligand leads to two diastereomeric



complexes of samarium (Figure 10). These complexes are active catalysts for the hydrogenation of 2-phenyl-1-butene under mild conditions (25 °C, *p*(H₂) 760 mm Hg, 5 min). Even with a 70:30 diastereomeric mixture of the menthyl-substituted samarium-metallocene complex, good [64% *ee* (*R*)] to excellent [96% *ee* (*S*)] enantioselectivities were obtained at 25 and –80 °C, respectively.

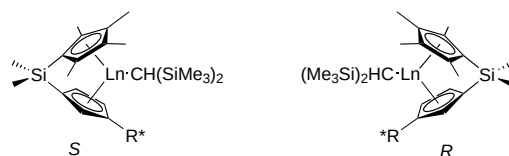
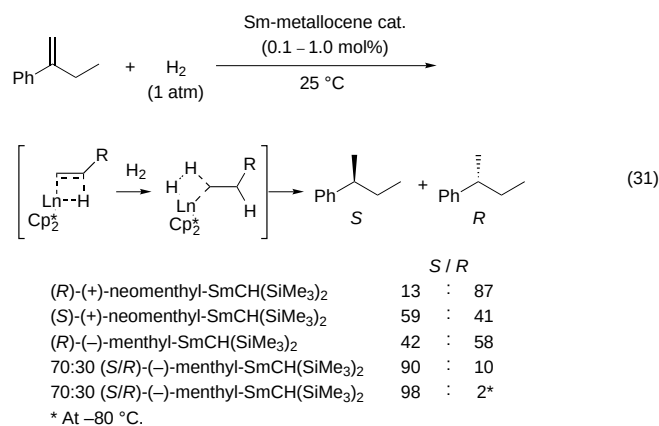


Figure 10. Chiral lanthanide-containing metallocene complexes. Ln = La, Nd, Sm, Y, Lu; R* = (+)-neomenthyl, (–)-menthyl, (–)-phenylmenthyl.

3. Asymmetric Reactions with Ln^{II} Catalysts

3.1 Reagents and Reactions

Kagan reported the use of a THF solution of SmI₂ as a one-electron reducing reagent in organic synthesis.^[3a, 12] Then, Inanaga found that the addition of hexamethyl phosphoramide (HMPA)^[61] causes a remarkable increase in the reducing ability of SmI₂; SmI₂ with 4 equiv of HMPA has the highest reducing ability with an oxidation potential of –2.05 V.^[62] The resultant Sm^{III} species may be used in situ as a Lewis acid catalyst. In turn, the Sm^{III} species can be reduced to an Sm^{II} species to complete the catalytic process and regeneration of not only SmI₂ but also of the chiral ligands coordinated to the Sm^{II/III} center (Figure 11).

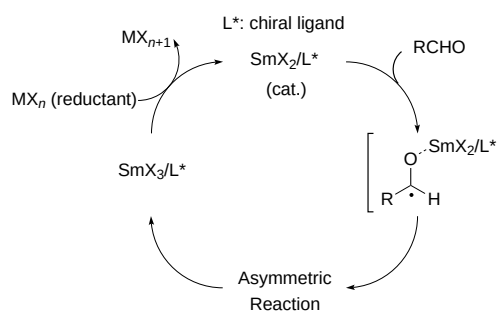
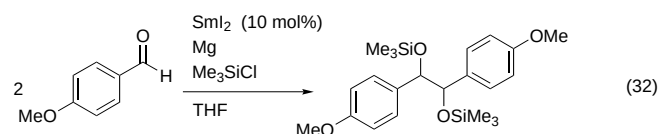


Figure 11. Catalytic cycle of asymmetric Sm^{II/III}-mediated reactions.

3.2. Pinacol Coupling

Pinacol coupling^[63] has long been known using titanium^[64] and zinc reagents.^[65] Lanthanides such as Ce^{II},^[66] Sm^{II},^[67] and Yb^{II}^[68] were also shown to be effective.

Endo and co-workers reported that a catalytic quantity of SmI₂ is good enough for the reductive coupling reaction of aliphatic and aromatic aldehydes and ketones in the presence of Mg/Me₃SiCl [Eq. (32)].^[69] On the basis that reactions with



both catalytic and stoichiometric SmI₂ exhibit the same level of diastereoselectivity, the samarium-catalyzed coupling reaction has been concluded to proceed prior to silylation of the alkoxide (Figure 12). In the presence of only Mg/Me₃SiCl, the

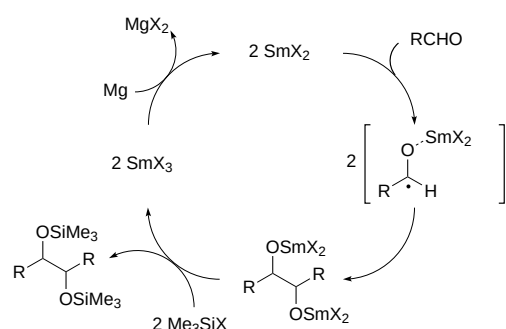
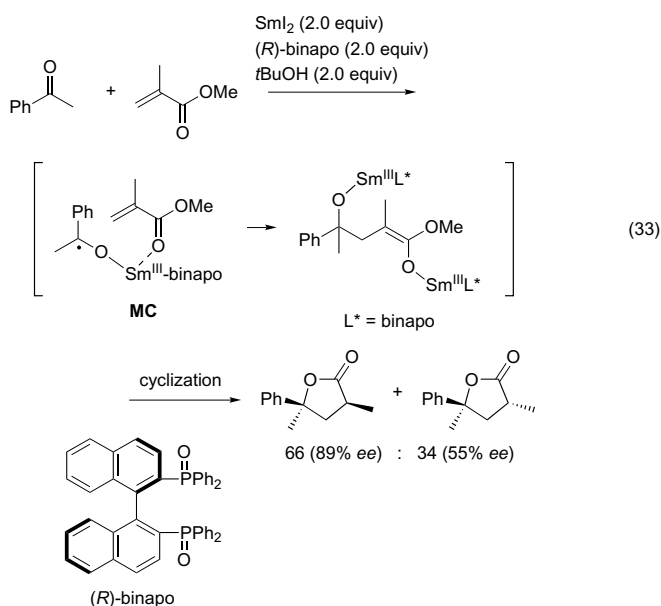


Figure 12. Proposed mechanism for the samarium-catalyzed pinacol coupling reaction.

coupling reaction of benzaldehyde does not occur. In the absence of Me₃SiCl, a complex mixture of products is formed, presumably because of inefficient turnover of the Sm^{II} catalyst. Using an inexpensive alloy of the light lanthanides, acetophenone can be reductively coupled in 70% yield without Me₃SiCl.^[70] However, no reaction takes place in the absence of SmI₂.

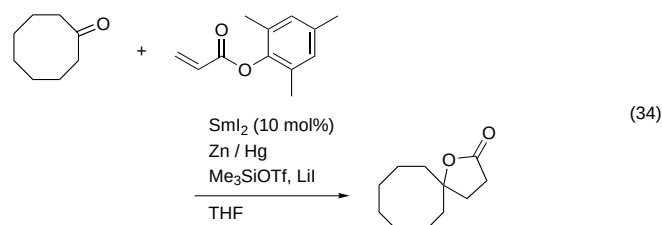
3.3. Radical Addition Reactions

Inanaga et al. reported on Sm^{II}-mediated radical addition reactions to α,β -unsaturated esters.^[71] We have recently reported the first successful Sm^{II}-mediated, asymmetric, radical addition reaction [Eq. (33)].^[72, 73] The ligand binapo is the best chiral ligand to date in this type of asymmetric radical addition reaction. The ketyl samarium intermediate can be trapped by α,β -unsaturated esters through formation of a medium ring chelate species (**MC**)^[73] to form new carbon–carbon bonds. One equivalent of binapo to SmI₂ is necessary to give a high level of enantioselectivity. Unfortunately, upon mixing SmI₂ and binapo in a 1:2 ratio, a precipitate was formed. Asymmetric protonation of the



resultant samarium enolate takes place to control the second stereogenic center of the α -substituted γ -butyrolactone with the assistance of binapo ligands on the samarium enolate.

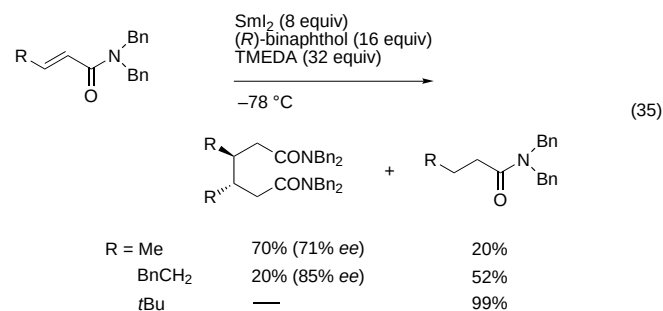
This asymmetric radical addition reaction might be established as a catalytic process by the catalytic use of not only SmI₂ but also chiral ligands coordinated to the samarium center. This expectation is based on the elegant study by Corey on a catalytic process for the radical addition reaction by the use of 10 mol % of SmI₂ with Zn–Hg, Me₃SiOTf, and LiI [Eq. (34)].^[74]



3.4. Radical Homocoupling Reaction of β -Monosubstituted Acrylic Acid Amides

The stereocontrol of radical reactions, especially intermolecular ones, remains one of the most difficult problems in modern organic synthesis. However, unlike free radicals, conjugated ketyl radicals have anionic character. Therefore, it should be possible to differentiate the enantiotopic face of the ketyl radicals kinetically for the subsequent reaction, by coordinating their counterions with the appropriate chiral ligand. According to this idea, Inanaga and co-workers performed the ligand-controlled enantioselective hydrodimerization of acrylamide derivatives, which proceeded through the formation of conjugated ketyl radicals.^[75] The reaction was carried out using SmI₂ (8 equiv), (*R*)-binol (16 equiv), and tmeda (tmeda = *N,N,N',N'*-tetramethylethyl-

enediamine; 32 equiv) in THF at -78°C for 4 h [Eq. (35)]. High enantioselectivities (up to 85 % *ee*) were obtained when primary alkyl-substituted acrylic amides were used as substrates. As the β -substituent becomes bulkier, the yield of the



coupling product decreases (when $R = t\text{Bu}$, the only product was the monoamide). The postulated transition state is a nine-membered chelate structure (Figure 13). In the transition

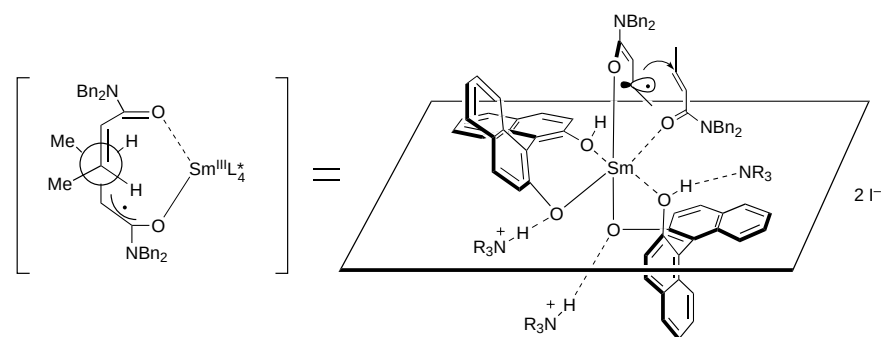


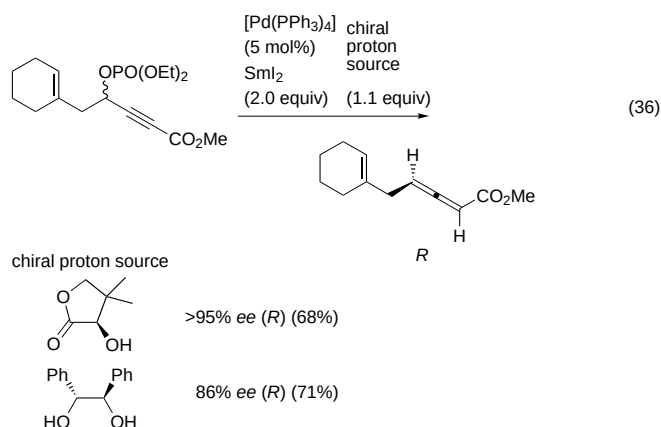
Figure 13. A possible transition state for asymmetric hydrodimerization of crotonamide.

state, the conjugated ketyl radical and the ligated crotonamide are in a *cis*-arrangement in the chiral coordination sphere of the samarium center.

3.5. Dynamic Kinetic Protonation of the Samarium Carbanion

We have reported that the reduction of secondary propargylic phosphates provided allenes with higher regioselectivity than did the propargylic acetates, through SmI_2 -mediated reduction followed by protonation in the presence of a palladium(0) catalyst.^[76] We further reported that SmI_2 -mediated reduction of secondary propargyl phosphates gives allenic esters with high regio- and enantioselectivity through dynamic kinetic protonation, without a chirality-transfer process [Eq. (36)].^[77]

The starting propargylic phosphate can be prepared by asymmetric carbonyl-ene reaction with an alkynyl analogue of glyoxylate catalyzed by a binaphthol–titanium complex, followed by phosphorylation.^[78] The cationic allenylpalladium(II) species are converted into carbanionic organosamarium(III) species by sequential one-electron reductions with two equiv of SmI_2 (Figure 14). This carbanionic Sm^{III} species racemizes readily. This result suggests the possibility of



dynamic kinetic resolution^[79] using chiral proton sources,^[80] even when starting from racemic phosphates; namely a deracemization process of a racemic allenylsamarium(III) species. The organosamarium(III) species, formed by reduction

of phosphates with Sm^{II} , are strongly oxophilic and Lewis acidic. Thus, chiral diols and hydroxycarbonyl compounds can be effective as proton sources, since the chelation of such chiral alcohols with Sm^{III} constructs a favorable asymmetric environment.

The sense of asymmetric protonation to provide (*R*)-allenic ester using (*R*)-hydrobenzoin and (*R*)-pantolactone can be well explained by the transition state model (Figure 15), in which there is severe steric repulsion between alkyl

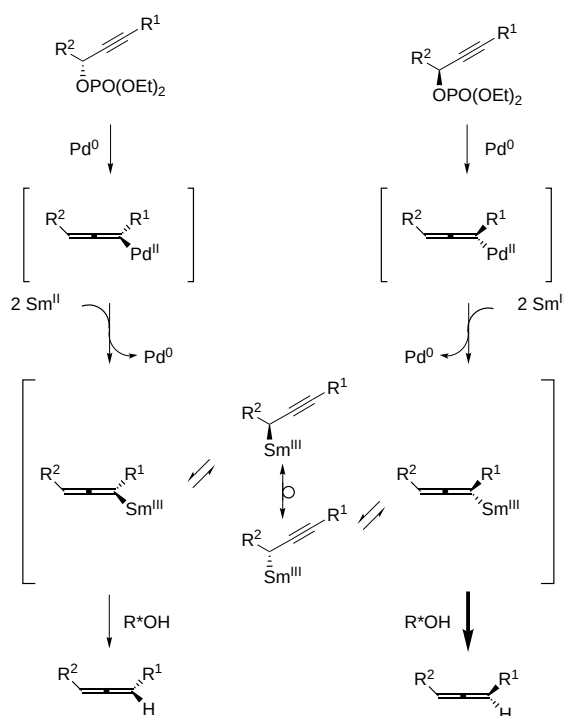


Figure 14. Dynamic kinetic resolution of racemic allenylsamarium(III) species by asymmetric protonation.

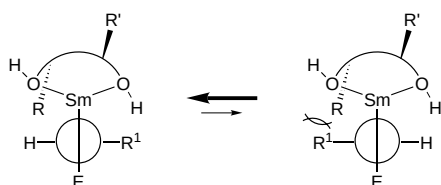


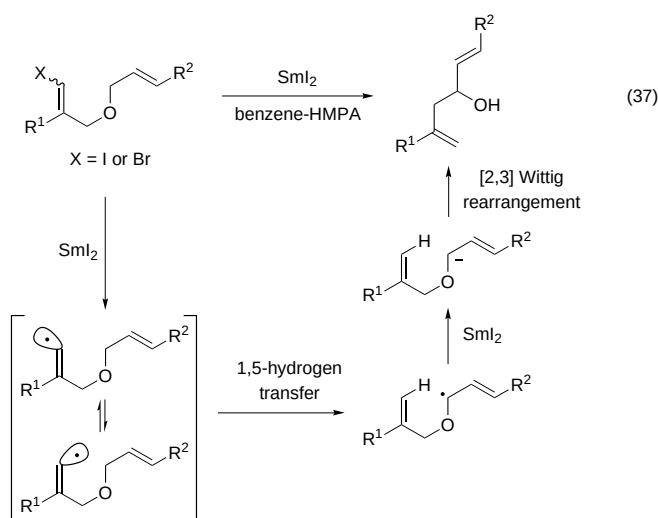
Figure 15. Chiral allene formation by asymmetric protonation.

groups in the right-hand-side (see Figure 15) diastereomer. Thus, protonation proceeds through the favorable diastereomer on the left-hand side, to give highly enantioenriched allenic ester.

3.6. Wittig Carbanion Rearrangement

In the very important field of carbanion chemistry, the [2,3] Wittig rearrangement has a wide application in asymmetric syntheses of natural products such as steroids;^[81] an enantioselective version of the Wittig rearrangement has therefore been a true challenge. The regioselectivity of the [2,3] and [1,2] Wittig rearrangement of bisallylic and allyl propargyl ethers has been reported;^[82] deprotonation at the α - and γ -position of less substituted allylic ethers or of γ -substituted propargylic ether moieties gives a [2,3] Wittig rearrangement product. However, γ -unsubstituted propargylic ether derivatives are metalated at the terminal acetylenic position and, in turn, the allylic carbanion is generated to give the [1,2] Wittig rather than [2,3] Wittig rearrangement products.^[82d]

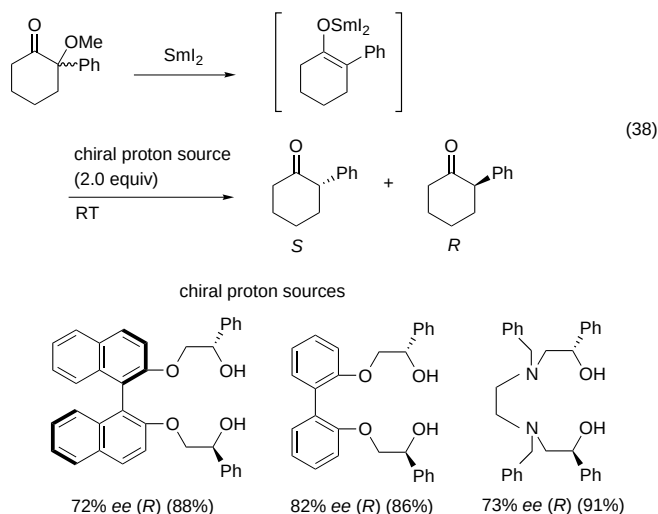
Kunishima and Tani reported highly regiocontrolled [2,3] Wittig rearrangement by the judicious choice of benzene–HMPA as the solvent, in which a radical species can be generated; this is otherwise difficult, particularly in THF solution [Eq. (37)].^[83] This method facilitates the synthesis of



the less favorable regioisomer under the standard conditions.^[82] In a similar manner, enantioselective carbanion rearrangement might be demonstrated by the proper choice of a chiral coordinating ligand to samarium to make this process catalytic and asymmetric.

3.7. Samarium Enolate Reaction

In a similar manner, the enantioselective protonation of enolates is an effective method for preparing chiral carbonyl compounds [Eq. (38)]. Therefore, a catalytic process for the



enantioselective protonation of enolates has become an important target in synthetic chemistry. In 1986, Molander reported that a wide range of α -substituted carbonyl compounds are rapidly reduced under mild conditions by SmI_2 in the presence of a proton source such as methanol and proposed a reaction mechanism in which reductive cleavage of the carbon–heteroatom bond takes place with two equiv of SmI_2 to give the samarium enolate.^[84] A transition-state model of the protonation has already been proposed, in which a chiral proton source coordinates to the Sm^{III} ion as a tetradentate ligand.^[85] This model clearly explains the enantioselectivities. In the transition state (TS_1 , Figure 16), the substituent in the C2 position of the enolates is far

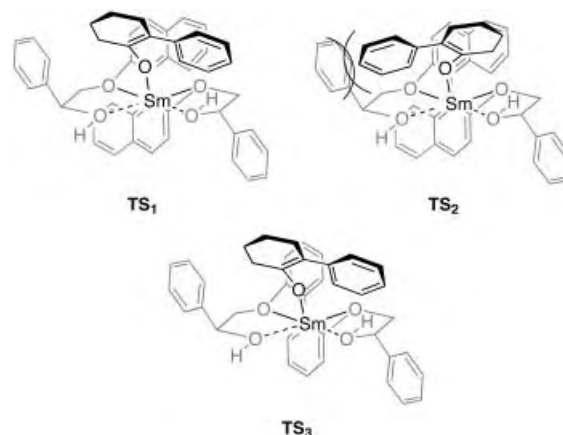


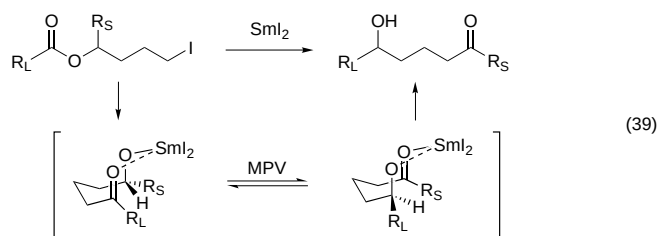
Figure 16. Transition states for asymmetric protonation of samarium enolates.

from the benzene ring and has no repulsive interaction with it. Consequently, protonation at the top side, namely from the *si* face of the enolate, gives the *R* product. The biphenyl auxiliary is easily adjustable to the favorable conformation TS_3 .

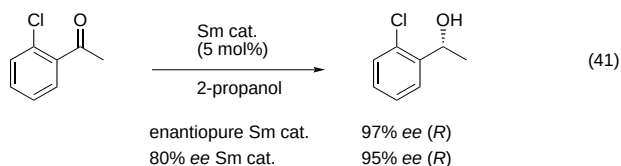
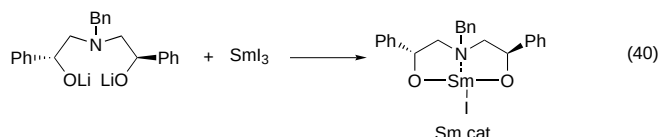
4. Sequential Sm^{II} to Sm^{III} Catalysis

4.1. Meerwein–Ponndorf–Verley (Tiščenko) Reactions

In 1977, Kagan and co-workers suggested that the catalytic activity of Sm^{III} complexes in Meerwein–Ponndorf–Verley (MPV) reactions is a consequence of the (intramolecular) pseudo-Barbier reaction initiated by SmI₂ [Eq. (39)].^[86] Evans et al. reported that Sm^{III} alkoxide complexes exhibit a



higher catalytic activity for MPV reactions than Al complexes [Eq. (40)].^[87] A samarium(III) complex with an enantiopure chiral tridentate ligand gave a high level of enantioselectivity



tivity [Eq. (41)]. The order of the catalytic activity and the level of enantioselectivity are as follows: Sm, Tb > Nd > Y >> Lu >> Sc. As expected from the high coordination number and oligomeric nature of the samarium complexes, a high level of positive nonlinear phenomena (asymmetric amplification) was observed: thus, a Sm complex of 80% ee purity provides the reduced alcohol in 95% ee, an equally high level of enantioselectivity to that obtained with an enantiopure samarium complex.

5. Perspectives

Asymmetric catalysis of organic reactions has been greatly advanced by the creation of lanthanide complexes with chiral ligands, which maximize the characteristic features of the central lanthanide cations. For further development of asymmetric lanthanide catalysis, the recyclable use of lanthanide complexes is important in “green chemistry”.^[88] It is possible to reclaim and reuse triflate, bis(sulfonyl)amide, and tris(sulfonyl)methide salts of lanthanides. However, the lanthanide catalysts recovered from the aqueous phase have the serious disadvantage that water must be removed prior to

reuse. For easy recyclable use, the preparation of polymer-bound lanthanide catalysts^[89] is promising. As an alternative, lanthanide complexes with perfluorinated ligands (“fluorous ponytail”) can also be immobilized, but in a fluorous fluid phase (biphasic fluid) rather than in the solid phase^[52, 90].

High stereoselectivities have been reached by the use of samarium(II) complexes, which exploit the strong oxophilicity of the samarium ion. It is important that the catalytic use of SmI₂ with or without chiral ligands has been established. To minimize the number of resultant samarium(III) species, including chiral species in some cases, a reducing metal (for example, magnesium) is employed. However, the reported methods are limited in the range of applicable reactions or by their excessive use of reducing metals. If these problems were overcome and recyclable use were to be established, nontoxic and nonharmful lanthanide complexes would certainly play a greater role in green (asymmetric) catalysis.

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Relativity, Gold, Closed-Shell Interactions, and $\text{CsAu} \cdot \text{NH}_3$

Pekka Pyykkö*

The chemical properties of gold are strongly influenced by relativistic effects. One example is the large electronegativity of Au, which qualitatively explains the stability of (solid or liquid) cesium auride, Cs^+Au^- , and other systems with Au^- ions. An especially impressive compound is $\text{CsAu} \cdot \text{NH}_3$, the structure and bonding of which are discussed. Future possibilities for finding further aurides are outlined.

Relativity and Gold

Relativistic effects in chemistry are due to the high speeds of electrons when they move near a heavy nucleus. These effects can be described by the Dirac equation, or some approximation to it, and explain many of the differences and some of the similarities between the fifth and sixth row of the periodic table. A well-known example is the case of silver versus gold. These valence-shell relativistic effects increase roughly like Z^2 , where Z is the full nuclear charge, and become comparable in size with various shell structure effects on the 6th row ($Z = 55-86$).

To be more specific, the nonrelativistic ("NR") 5d and 6s orbital energies of Au are similar to the 4d and 5s orbital energies of Ag, whereas the relativistic energies ("R") are not, both in the metal atoms M and in their diatomic hydrides MH.^[1-3] The original data of ref. [1] are shown in Figure 1. The relativistic bond length contraction also behaves roughly as Z^2 and is able to pull in Au–L (L = ligand) single bond lengths to, or below, those of the corresponding Ag–L, and to make the Au–L bond strengths at the same time larger than those of the corresponding Ag–L.^[1, 4]

A further particularity is that, along a row, from Group 1 to Group 18, there is a local gold maximum^[3-5] of relativistic effects at Group 11 (for all coinage metals, Cu–Au), thereby making these elements more "relativistic" than their left-hand or right-hand neighbors. Such a local maximum is seen in all properties of the *ns* shells (for an example, see Figure 2). This anomaly can be qualitatively ascribed to the interaction of

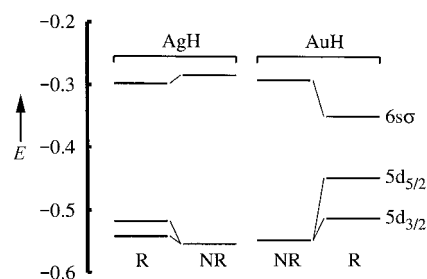


Figure 1. The relativistic (R) and nonrelativistic (NR) orbital energies of AgH and AuH. The data are taken from Desclaux and Pyykkö,^[1] who concluded from them and the bond length data "...that the chemical difference between silver and gold may mainly be a relativistic effect." E in Hartree.

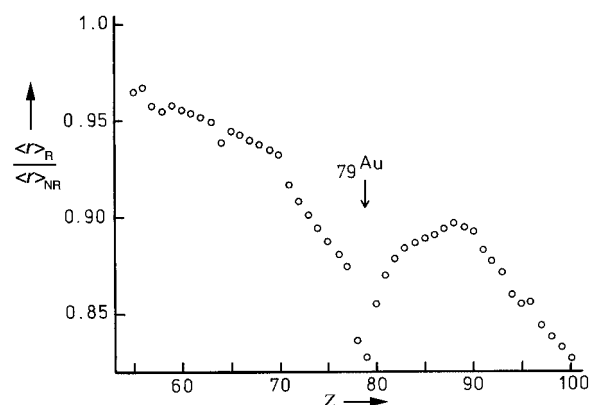


Figure 2. The ratio of relativistic (r_R) and nonrelativistic (r_{NR}) 6s-shell radii in the atomic ground states of the elements 55–100 (reproduced from Pyykkö and Desclaux;^[3] copyright © 1979 American Chemical Society).

relativistic effects and shell structure effects, caused in particular by the overlap between the $(n-1)d$ and ns shells. Figure 2 has not only gone into textbooks^[6] but has become a bit of an icon for the world's gold industries.^[7] In quantum chemistry the simple molecules AuH and Au₂ have become classical test cases for relativistic effects.^[1, 8, 9] The most accurate benchmark results^[10-13] on these two molecules are reproduced in Table 1.

A wide literature exists on relativistic calculations on gold compounds. There are predictions for subsequently observed new species, such as diatomic AuF (predictions in ref. [15, 16], observation in ref. [16]) or the first triple bond to gold in $\text{Au}\equiv\text{C}^+$ (prediction in ref. [17], observation in ref. [18]). The possibility of covalent chemical bonds between gold and

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Table 1. Latest relativistic benchmark results on AuH and Au₂ and the corresponding nonrelativistic reference values. Bond lengths R_e in pm, vibrational frequencies ω_e in cm⁻¹, and dissociation energies D_e in eV. Note the agreement between all-electron (AE) and pseudopotential (PP) methods.

Molecule	R_e	ω_e	D_e	Method	Ref.
AuH	175.0	1565	1.79	NR AE CCSD(T)	[10]
	152.5	2288	2.92	R AE CCSD(T)	[10]
	174.7	1575	2.086	NR PP CCSD(T)	[11]
	152.7	2306	3.124	R PP CCSD(T)	[11]
	151.0	2330	3.31	R PP CCSD(T)	[12]
	152.4	2305	3.36	exp.	[12]
Au ₂	248.8	187	2.19	R AE cp-CCSD(T)	[13]
	249.0	187	2.23	R PP CCSD(T)	[12]
	247.2	191	2.302(8)	exp.	[14]

xenon in species like AuXe⁺ and XeAuXe⁺ was pointed out in ref. [19]. Meanwhile, both species have been observed by mass spectrometry.^[20] Several bulk compounds with covalent Au–Xe bonds, such as (AuXe₄)(Sb₂F₁₁)₂, have recently been synthesized and theoretically studied;^[21–23] for comments on [21], see ref. [24].

The higher gold hydrides AuH₃ [(H₂)AuH] and AuH₅ [(H₂)AuH₃] were observed in matrices.^[25] Numerous studies exist on gold clusters (see for example ref. [26, 27]). The role of relativity in the change of the oxidation state from Au^I to Au^{III} in halide complexes has been explicitly demonstrated.^[28] A wide field are the studies of the aurophilic attraction between Au^I ions in compounds.^[29, 30] This attraction turned out to be a dispersion (van der Waals) effect, strengthened by relativistic effects for gold. Its strength can reach that of a strong hydrogen bond. Typical Au^I–Au^I equilibrium distances, R_e , are about 300 pm. For the latest theoretical study, analyzing the various detailed contributions, see ref. [31].

Against this background, exactly how large are the relativistic effects on various observable properties of the gold atom or of metallic gold? The latest available answers are given in Tables 2 and 3, respectively. For the first ionization potential, IP1, of gold it is seen that the best relativistic calculation deviates from the experimental value, which is very accurate, by only 0.0285 eV, while the corresponding nonrelativistic value lies 2.169 eV below the experimental one. (The NR limits can often be taken by using the

Table 2. Atomic properties of some noble metals.

Property	Cu	Ag	Au	111	Pt
electronic configuration	3d ¹⁰ 4s ¹	4d ¹⁰ 5s ¹	5d ¹⁰ 6s ¹	6d ⁹ 7s ²	5d ⁹ 6s ¹
EA [eV]					
experimental ^[a]	1.23578(4)	1.30447(2)	2.30861(3)	1.56 ^[33]	2.12510(5)
calculated ^[b]		1.350	2.295		
calculated ^[c]		1.140	1.283		
IP1 [eV]					
experimental ^[d]	7.72636(2)	7.576237(25)	9.22554(2)	10.6 ^[e]	
calculated ^[b]		7.512	9.197		
calculated ^[c]		6.948	7.057		
IP2 [eV]	20.29240	21.49	20.203(25) ^[36]		
IP3 [eV]	36.841	34.83			

[a] From ref. [32], when not otherwise stated. [b] Relativistic calculation, ref. [34]. [c] Nonrelativistic calculation, ref. [34]. [d] From ref. [35], when not otherwise stated. [e] Ref. [33], ionization to a 6d⁹7s² state.

Table 3. Properties of solid noble metals.

Property	Ag (R)	Ag (NR)	Ag (exp)	Au (NR)	Au (R)	Au (exp)
a_0 [pm] ^[37]	403	411	409	429	407	408
E_{coh} [eV] ^[37]	3.34	3.01	2.95	3.03	3.96	3.81
B_0 [GPa] ^{[37][a]}	127	106	100.7	108	182	173.2
$\Delta E_{\text{interband}}$ [eV] ^[38]			4	2.38		2.4

[a] The bulk modulus, $B_0 = -V(\text{d}p/\text{d}V) = [V(\text{d}^2U/\text{d}V^2)]V_0$.

same approximations but a very large speed of light.) For the electron affinity, EA, of gold—of special importance here—the best relativistic calculation is 0.014 eV and the non-relativistic one 1.026 eV below the experimental value. Notably, almost half of the electron affinity of gold comes from relativity; the calculated NR value for gold is close to that of silver. The experimental EA of gold (2.30861(3) eV) is not qualitatively different from that of iodine, 3.059038(10) eV.^[32]

For the pure metals it is seen from Table 3 that relativistic effects compress gold to the same lattice parameter, a_0 , as silver. For the cohesive energy, E_{coh} , and the bulk modulus, B_0 , of Ag and Au, the NR values are similar for the two metals while the R values are clearly higher for gold. Thus the same size and stronger bonds for gold, compared to silver, both come from relativity. Finally, the attribution of the yellow color of gold to relativity^[3, 39] rests on the result that the relativistic interband energy, $\Delta E_{\text{interband}}$, between the top of the 5d band and the Fermi level is close to the experimental value, while the NR interband energy would be much larger.^[38] Comparative R/NR calculations of the reflectivity do not seem to exist.

We conclude that relativistic effects are beyond doubt there and influence the properties of gold and its compounds. The main effects at atomic orbital level are the energetic stabilization and radial contraction of the 6s shell and the concomitant destabilization and expansion of the 5d shell.

QED?

How much would these conclusions change, if one goes to still deeper physics, Quantum Electrodynamics (QED), where the main effects are vacuum polarization and self-energy (vacuum fluctuation)? According to the first calculations for the valence electrons of heavy elements,^[40] these new effects would only amount to about –1% of the Dirac-level relativistic effects for gold. Thus the conclusions above remain unchanged.

In other words, earlier relativistic quantum chemistry was about “101 % right” and including it in chemistry textbooks was quite safe. QED would contribute about –0.026 eV to IP1(Au), compared to relativity which contributes +2.14.^[34] Thus the QED terms will be small, but not totally negligible. Indeed, the inclusion of QED may have been “the last train from Physics to Chemistry”, at the level of fundamental interactions. The bottleneck for theoretical accuracy on the IP or EA of Au is now in the electron correlation.

Lanthanide Contraction

Lanthanide contraction, in the sense of partial screening of the subsequent 6s valence shell by the filled 4f electrons, was used in the older inorganic literature to explain the properties of gold and other 6th-row elements. An early point made by Kenneth S. Pitzer,^[41] by including or omitting the 4f shell in atomic calculations, was that both lanthanide contraction and relativity are needed to reproduce the experimental trend. Their effects are roughly comparable and go in the same direction.

Cesium Auride

Cesium auride was discovered in 1943 by Sommer.^[42] A review of the experimentally known alkali metal auride phases was given by Zachwieja.^[43] Hensel^[44] reviewed the physical properties of CsAu(l) and other liquid ionic alloys. One characteristic feature of them is the deep conductivity minimum at 1:1 stoichiometry (Figure 3). Hensel quotes for the first evidence on auride, Au^- , ions a qualitative observation by Heymann and Weber^[46] that sodium alloys with gold

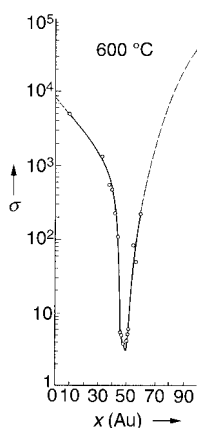


Figure 3. Electric conductivity, σ (in $\text{Ohm}^{-1} \text{cm}^{-1}$), of liquid cesium–gold alloys at 600 °C (reproduced with permission from ref. [45]; copyright © 1975 Elsevier). $x(\text{Au})$: content of Au in atom %.

dissolve to some extent in molten NaBr. The empirically known high stability of the $6s^2$ electron configuration was brought to the argument by Goodman.^[48] Some of these auride species are listed in Table 4. Furthermore, cryptated aurides (Au^- inside a crown ether) are known.^[51] Note that bases like alkali metals are able to disproportionate metallic gold to auride aurates, containing Au^{-1} and Au^{I} ions. An example is $[\text{CsAu}]_4[\text{Cs}_3\text{AuO}_2]$ or $\text{Cs}_7\text{Au}_5\text{O}_2$.^[49]

Band structure calculations exist on CsAu. A R/NR comparison shows that without relativity the system would be a metal, instead of a semiconductor.^[52] Melts of CsAu have also been simulated.^[53] Although the results are dependent on the input parameters, it is interesting to note that Au–Au distances of about 300 pm were found.^[53a] In contrast, Matsunaga et al. calculated a much longer first Au–Au maximum of the radical distribution function.^[53b]

Table 4. Some known aurides.

Auride	Year	Ref.	Comment
RbAu, CsAu	1943	[42]	
M_3AuO ; $\text{M} = \text{K} - \text{Cs}$	1993	[47]	ternary auride oxides
$\text{Rb}_5\text{Au}_3\text{O}_2$, $\text{M}_7\text{Au}_5\text{O}_2$; $\text{M} = \text{Rb}, \text{Cs}$	2000	[49, 50]	auride aurates
$[\text{N}(\text{CH}_3)_4]\text{Au}$	2002	[51]	first nonmetal auride; isostructural with $\text{N}(\text{CH}_3)_4\text{Br}$.

Parenthetically, in liquid ammonia, also the argentide ion, Ag^- , has been created electrochemically,^[54] despite the smaller value of $\text{EA}(\text{Ag})$. This system shows a UV band at 382 nm. More generally, in several cases a compound of two metals exhibits a clearly ionic character (with or without electronic conductivity). Hensel quotes as examples Mg_3Bi_2 , Li_3Bi , and Li_4Pb .^[44]

From CsAu to BaAu₂

Knowing that Rb and Cs afford aurides, Goodman asked in 1958 whether their neighbor Ba would do so.^[48] The compound BaAu_2 mentioned by him had actually been prepared by Biltz and Weibke in 1938.^[55] It was characterized as a semiconductor by Shishkin,^[56] and has an AlB_2 -type crystal structure with Au–Au 277 pm and a yellow color.^[57] It has for some reason attracted much less attention than CsAu.

From Au^- to Pt^{2-} ?

How about one step to the left, from Au^- to a formal Pt^{2-} ? Goodman also mentioned the possible existence of Na_2Pt and BaPt .^[48] The most favorable case would be Cs_2Pt , which remains unknown. So does solid BaPt . An attempt to synthesize the latter in the gas phase also failed.^[58] Recalling that highly charged anions have been quoted^[73] for mercury (e.g. Hg_4^{6-}) despite the low electron affinity of this element, Goodman's proposal for a formal Pt^{2-} or “platinide” ion in a compound would not be absurd.

Closed-Shell Attractions

While dispersion (van der Waals) interactions are well-known, it was only relatively recently that they were identified as the mechanism^[29, 30] behind the “aurophilic” or “metallophilic” attractions studied by Schmidbaur^[59] and others. Analogous effects between Ag^{I} ions were discussed by Jansen.^[60] Such interactions are found in bridged or unbridged pairs, oligomers, chains, and sheets. They can involve, among others, main-group elements (notably Se and Te), d^{10} ions like Au^{I} , s^2 ions like In^{I} and Tl^{I} , and also d^8 ions like Ir^{I} , or almost any combination of those above; for a recent summary, see Gade.^[61] Note that extremely strong $6s^2$ – $6s^2$ attractions were found for the two diatomic systems AuBa^- and AuHg^- by Wesendrup and Schwerdtfeger.^[62] The latter has a calculated

bond length of about 300 pm, similar to the interauride distances discussed below.

In addition to the dispersion contributions $V(R) = -C_6 R^{-6}$, where R is the M–M distance, V the M–M interaction strength, and C_6 the van der Waals coefficient, virtual charge transfer terms were found to play a role near the equilibrium distance, R_e .^[63] They decrease exponentially at large values of R . Relativistic effects increased $V(R_e)$ for M = Au by 27% in one particular calculation on the model $(\text{ClAuPH}_3)_2$.^[64] The aurophilic interaction thus is not fundamentally relativistic. Electron correlation in a wave-function-based calculation (such as MP2 or CCSD(T)) must be used to reproduce it. Density functional theory (DFT) calculations on the monomers can supply the coefficients C_6 at large R values but cannot be used for a supramolecular approach near R_e because dispersion effects are not built into this theory. One point is that various mechanisms can lead to various power laws, for example, the interaction of two stationary electric dipoles leads to $C_3 R^{-3}$ and dispersion effects to $C_6 R^{-6}$. Concerning DFT, treating the two molecules as a “super-molecule” does not even lead to this power law but rather to exponential decay. Also the interaction energy near the van der Waals minimum is unreliable, because the specific form of correlation energy, related to two local dipole moments, is not properly described.

CsAu · NH₃

CsAu · NH₃ (**1**), was obtained by Mudring et al.^[65] by dissolving CsAu in NH₃(l) and subsequently evaporating the ammonia. It shows remarkable features:

- 1) The crystal is deep blue.
- 2) The Au^{−1} ions form zig-zag chains with an Au–Au distance of 302 pm (Figure 4). Such an interaction might be called an “auridophilic attraction”. Although it takes place between d^{10s²} Au^{−1} ions, it surprisingly yields a similar distance as the aurophilic attraction between two d¹⁰ Au^I ions, that could be thought to be smaller. The nature of this effect is not yet clear. Both dispersion effects and net bonding, resulting from partial oxidation from the top of the 6s band, could play a role. The observed Mössbauer isomer shift at gold (CsAu 7.00, RbAu 6.70, **1** 5.96, Au −1.23) does not show a full −1 auride charge and keeps the latter possibility open. A priori, attractive interactions between auride ions in compounds should not be a surprise. Such metallophilic attractions are known be-

tween other d^{10s²} systems. A well-known example is the Tl^I–Tl^I case; here the interaction is rather weak, and indeed the compounds tend to have longer M–M distances.^[66] Another example are the smallest nonmetallic mercury clusters, Hg_{*n*}. Here the typical Hg–Hg distances are of the order of 350 pm for $n = 2–6$.^[67]

- 3) The crystal contains solvent molecules. Water of crystallization is common, but also examples of “ammonia of crystallization” exist, apart from the well-known inner solvation shell ammonia complexes of transition metals: In his review on Zintl phases, Corbett^[68] quotes $\text{Na}(\text{NH}_3)_n^+$ cations in crystals. A coordination chemistry of the alkali metals with tertiary amines also exists. There are ammonia molecules coordinated to a superoxide anion, O₂[−],^[69] and examples of ammonia in alkali metal pnictides are known.^[70] Their Cs–N distances are comparable with that in **1** (323 pm). In **1**, each NH₃ binds to two Cs⁺ ions, on one side through the nitrogen lone pair (see Figure 4a). The slabs of composition CsAu are intercalated by single NH₃ layers (see Figure 4b). For a discussion on the solvent properties of liquid ammonia, see ref. [71].
- 4) Thermogravimetrically it was shown that the ammonia is released at 225(5) K, below the boiling point of ammonia (239 K). Here a measurement of the ammonia vapor pressure as a function of temperature would yield its vaporization enthalpy through the Clausius–Clapeyron relation $\Delta H_{\text{vap}} = R T^2 \text{d}(\ln p)/\text{d}T$.
- 5) Both ¹H and ¹³³Cs NMR and ¹⁹⁹Au Mössbauer data were reported. The Cs chemical shift is about 420 ppm from that of 1M CsNO₃(aq) and hence shows no Knight shift typical of metals. The signal has a high-frequency tail, absent in CsAu. The nature of this tail is still not convincingly understood. The proton spectrum suggests hindered rotation of the ammonia molecules about their threefold axes at lower temperatures; at 180 K the line width changes, indicating more free rotation. Here a measurement of the spin–lattice relaxation times, T_1 , could yield the activation energies for ammonia rotation. Indeed, this measurement has later been done and yielded an apparent activation energy of 88(3) meV (or 8.5(3) kJ mol^{−1}).^[72] This value is about 10% less than in ammonia.
- 6) The DFT calculations reported should be acceptable for the other, dominant, bonding contributions but would have a problem with any dispersion-type interactions.

Ammoniates

In addition to the recent work quoted under point 3 of the list above, readers should be reminded of the thorough investigations of alkali metal, alkaline earth metal, and ammonium halide ammoniates, mostly published about eight decades ago (Table 5). A rule of thumb is that ammoniates are formed by compounds containing cations with a relatively high charge density (e.g., Li, Mg, Ca).^[82] The same holds for salts containing easily polarizable anions (e.g., NaI and RbI). Against this background, if we regard gold as a further halogen, compound **1** is a natural member of the series in Table 5, and may only be one particular case in a much larger

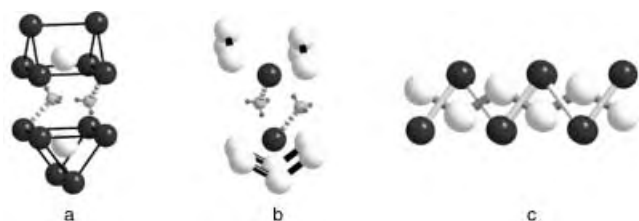


Figure 4. Details of the experimentally determined structure of **1** in the crystal (by courtesy of Dr. Anja-Verena Mudring). a), b) Coordination of the ammonia molecules; c) the gold chains. Large white spheres: Au, large black spheres: Cs, small gray spheres: N.

Table 5. Ammoniates formed by the alkali metal, alkaline earth metal and ammonium halides. The numbers give the number of NH₃ molecules (from Lagowski^[82]).

Cation	Cl [−]	Br [−]	I [−]	Ref.
Li ⁺	6.5, 5, 4, 3, 2, 1	6.5, 5, 4, 3, 2, 1	7, 5.5, 5, 4, 3, 2, 1	[74, 75]
Na ⁺	5	5.75, 5.25	6, 4.5	[74]
K ⁺	—	4	6, 4	[74]
NH ₄ ⁺	3	—	4, 3, 2, 1	[76–78]
Rb ⁺	—	3	6	[74]
Cs ⁺	—	—	—	[74]
Ca ²⁺	8, 4, 2, 1	8, 6, 2, 1	8, 2, 1	[79]
Sr ²⁺	8, 1	8, 2, 1	8, 6, 2, 1	[80]
Ba ²⁺	8	8, 4, 2, 1	10, 9, 8, 6, 4, 2	[81]

group. Note that gold is the only “halogen” that forms an ammoniate with cesium. The calculated relativistic and non-relativistic static electric polarizabilities of a free Au[−] ion are 93 and 256 a.u., respectively.^[83] The largest halide polarizability, that of I[−], is 69 a.u.,^[84] not much below the 93 a.u. for auride (1 a.u. of polarizability (α) $\triangleq$ 1.6488 $\times$ 10^{−41} C² m² J^{−1} in SI units).

A further question: If we can have NH₃ and H₂O solvent molecules in a crystal, how about HF? Indeed, upon crystallization from anhydrous HF compounds like Ca(H-F)(AsF₆) or its Pb and La equivalents were obtained.^[85] The HF molecule in these compounds is connected directly to the metal.

Final Comments

Chemistry is a science of analogies and coincidence. Much of the reasoning above was based on seeing the auride ion as a chemical analog to a halogenide, like iodide. Noting that we deal here with very electropositive reagents, one could borrow Feynman's^[86] adage “*There is plenty of room at the bottom*” (with which he meant small devices or “nanotechnology”) to point out the possibility of further surprises at the low end of the electronegativity scale. The serendipitous discovery and investigation of CsAu·NH₃ (**1**) at Stuttgart, Bonn, Évora (Portugal), and Santiago de Chile^[65] may open a number of doors.^[87]

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Teaching the Right Reasons: Lessons from the Mistaken Origin of the Rotational Barrier in Ethane**

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...when will chemistry textbooks begin to serve as aids, rather than barriers, to this enriched quantum-mechanical perspective...

F. Weinhold (2001)

When I was first properly introduced to chemistry in the 9th grade, electrons (“chemical glue”) were simply described as single dots around atoms. Magically, sharing the dots meant a “chemical bond” and one had only to count up to eight to figure out how many electrons were shared and how many bonds you would have. Easy. We counted ions, balanced redox reactions, and had fun with oxidation numbers for inorganic and simple organic species. Then things became more complicated. We were introduced to Bohr’s model, in which you could only have two electrons in the innermost shell and eight in the next; beyond that, who knows what. That all had to do with some complicated quantum theory that we could not possibly understand in detail, so we were asked just to accept it. We did, until two years later when suddenly we were told that Bohr’s model is really too much of an approximation and that chemical bonding is far more complicated. It should be expressed using the intricate laws of quantum mechanics, namely, in terms of molecular orbitals. All bond types (multiple, metallic, back-bonding, etc.) suddenly became unique and things were *really* complicated mathematically. I remember well the funny-looking dumbbell-shaped, colorful styrofoam models of the various *d* orbitals, and thought that nature could not possibly be that complicated; in any case, two years from then they would tell us otherwise anyway. So I decided not to accept anything that had to do with this awkward quantum theory, only to be quizzed in the next class session. Needless to say, I received the worst grade in my chemical life and was embarrassed in front of the entire class. Shortly thereafter I decided to become a chemist.

The reason that I am telling this story is because there are, as always, two sides to it. Teachers, on the one hand, can confuse and frustrate their students by trying to depict chemistry in the most up-to-date, albeit complicated fashion. On the other hand, motivated students will despise simple models if more appropriate ones continually replace them. Frustration may be the final result. The simplification approach may be acceptable at the high school level because easily understandable explanations, although possibly inadequate, do get the message across. At higher scholastic levels, however, this is no longer acceptable because we owe it to the students to teach them our current knowledge and interpretation of science. The convenience of visually pleasing explanations for intricate chemical phenomena must not outweigh proper physical descriptions. These are available through modern quantum mechanics within the Born–Oppenheimer approximation that allows approximate solutions of the electronic Schrödinger equation in the form of potential energy hypersurfaces. Hence, quantum mechanics provides us with an accurate theoretical description. The subsequent interpretation is a model that may be useful but not absolutely necessary for our understanding.

A timely case in point is the rotational barrier of ethane, an old, yet much debated subject.^[1] Understanding the origin of such a barrier is essential to just about any form of structural chemistry, from the conformational analysis of simple alkanes to protein folding.^[2]

A recent paper by Pophristic and Goodman^[3] on this topic, which emphasized the importance of hyperconjugative interactions^[4] in the preferred staggered conformation of ethane, came as somewhat of a surprise to me, simply because I thought the conclusions had been reached in the work of others published long ago. As an admirer of the elegance and non-intuitive beauty of molecular orbital theory, I have been telling my students exactly what is detailed in the paper, and I had apparently falsely assumed that everybody else did just the same. Skimming through several undergraduate organic textbooks, however, quickly revealed that virtually all of them (with a few notable exceptions^[5–7]) make steric repulsion of the hydrogen atoms (“bumping”) or of the C–H bonds responsible for the barrier in ethane. I learnt that I was quite lucky to have had organic chemistry teachers who chose not to “fall” for, as Goodman and Pophristic put it, the seductively transparent steric repulsion explanation, and instead present-

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ed the subtle quantum superposition-based hyperconjugation model.^[8]

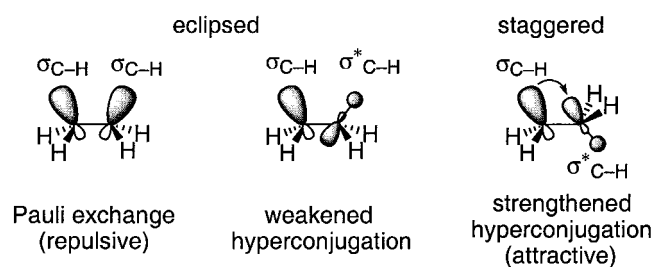
While the notion of a hindered rotation in ethane is often credited to Pitzer and Kemp (1936),^[9] Ebert (1929)^[10] and then Wagner (1931)^[11] may have been the first to propose this. Their physicochemical measurements based on the molar heat capacity of ethane were first left unconfirmed^[12] but were supported soon thereafter by Eucken and Weigert in 1933.^[13] Teller and Weigert established the presence of a hindered rotation by quantum theoretical computations on the temperature dependence of the molar heat capacity of ethane.^[14] Needless to say, even then these propositions were discussed vehemently, and the Kemp and Pitzer paper, which does, however, not cite the earlier work of Ebert or Wagner, seems to settle the dispute between the various groups.^[9] Independently, Wilson (incidentally, not citing the 1936 Kemp and Pitzer publication) emphasized the presence of an appreciable rotational barrier of about 3 kcal mol⁻¹ and showed that this cannot be a consequence of nuclear spin and symmetry effects.

This early work demonstrated that the internal rotational potential energy of ethane has three degenerate minima corresponding to the only stable conformation: the staggered conformer.^[15] These conformers are separated from each other by slightly higher-lying (about 3 kcal mol⁻¹),^[16] degenerate eclipsed conformations. But what is the origin of the rotational barrier? Steric repulsion between bonds arising from the overlap of two filled C–H bond orbitals (and hence violating the Pauli exclusion principle)^[17] in the eclipsed conformation indeed seems an attractive explanation. Pophristic and Goodman showed, however, by using a computational method that allowed them to “switch off” this interaction, that the two curves representing the torsional angle between the two methyl groups—one curve with all interactions present, the other with the exchange repulsion absent—coincide. That is, the staggered conformation is preferred regardless of the presence of exchange repulsion. It is therefore not valid to assume, as most textbooks do, that steric considerations play the leading role in deciding the minimum conformation of ethane, and possibly many other structures. This finding is also transferable to other simple systems such as the internal rotational barriers of methanol^[18] and methylamine that are both much lower (1–2 kcal mol⁻¹) than for ethane, despite shorter central heavy-atom–carbon bond lengths (see below).^[19] Steric interactions seem to dominate, however, for *n*-butane and higher alkanes that suffer from exchange repulsion between the two methyl group C–H bonds within van der Waals contact.

Clearly, there must be a second, less obvious, quantum-mechanical interaction responsible for the observed conformational preference: namely, hyperconjugation.^[20] This interaction arises from partial electron transfer from filled $\sigma_{\text{C-H}}$ bonding and unfilled $\sigma_{\text{C-H}}^*$ orbitals. Despite the fact that a lower-lying occupied orbital interacts with a higher-lying empty orbital, quantum mechanics tells us that this interaction is stabilizing in nature.^[21] If the hyperconjugative interactions between the methyl groups are turned off in Pophristic and Goodman’s model calculations, the preference for the staggered conformation of ethane is lost. Hence, the preferred

conformation does not relieve steric congestion, but achieves optimal “internal delocalization” (resonance) stabilization (Scheme 1).

It is noteworthy that Mulliken concluded as early as 1939 that “...hyperconjugation in ethane [is present but] should not



Scheme 1. Steric and quantum-mechanical models for explaining the preference for the staggered form of ethane.

appreciably hinder free rotation” and, somewhat inconsistently, “...that the observed hindering potentials are entirely consistent with the existence of appreciable energy effects due to hyperconjugation, which might manifest themselves in other ways than in conjunction with free rotation.”^[20]

Hyperconjugation is largely responsible for inducing the elongation of the carbon–carbon bond that accompanies the internal rotation.^[22] That is, the torsional coordinate includes expansion of the C–C bond;^[23, 24] if this elongation is not taken into consideration, the $\sigma_{\text{C-H}} \rightarrow \sigma_{\text{C-H}}^*$ rationalization may therefore not be valid. This finding is also supported by the large decrease in the barrier for disilane (ca. 1 kcal mol⁻¹)^[25] that is a result of the attenuation of the pairwise repulsions, which are more important in the more polarized Si–H bonds of disilane than in ethane and the diminished hyperconjugation between the Si–H bonds.^[26]

The hyperconjugative model also explains related conformational preferences such as the anomeric effect (that is, the hydroxyl group in glucose at the anomeric carbon atom next to the oxygen atom in the ring is often in the sterically crowded axial position. This axial orientation results from the electronic preference of an OCOC unit for the synclinal rather than antiperiplanar orientation).^[27, 28] The anomeric interaction is very often incorrectly described as a dipole–dipole repulsive interaction^[29] (“rabbit ears” on oxygen atoms in sugars, for example), rather than an attractive interaction. A simple comparison of the heats of formation of, for example, 1,3- versus 1,4-dioxane, emphasizes the inherently stabilizing nature of this effect: 1,3-dioxane is 5.5 kcal mol⁻¹ more stable.^[30]

There are many examples of this kind where we attempt to take the easy way out, or worse, actually believe what we have heard over and over again, even if it is incorrect. Take Lewis structures, for example, which only describe geometries but not electronic structures:^[31] ammonium cations do not have a positive partial charge on the nitrogen atom, despite the formal electron count. The charge resides on the electro-positive elements, that is, the hydrogen atoms in NH_4^+ .^[32] Bases abstract protons from ammonium cations and do not attack the nitrogen atom! The same is true for many oxygen-containing cations (hydronium, oxonium, acyl cation, proto-

nated enols, etc.) that virtually never contain a positively charged oxygen atom.^[33]

Although the key paper under consideration is a convincing validation of the hypothesis that hyperconjugation controls the ethane barrier, this idea is by no means new. As already noted above, Mulliken appears to have been the first to propose this possibility in 1939,^[20] and there was a continuous flow of publications that utilized increasingly sophisticated studies of this attractive idea, especially those of Lowe,^[34–36] England and Gordon,^[37] as well as Brunck, Weinhold, and Reed.^[2, 19, 38] The Pophrastic and Goodman paper re-emphasizes, by analyzing in detail a straightforward yet intricate problem, that chemistry often is not as easy as we hope it to be and as we would like to teach it. In this context, Weinhold cunningly states: “when will chemistry textbooks begin to serve as aids, rather than barriers, to this enriched quantum-mechanical perspective [...]?”^[39]

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Carbohydrate Arrays as Tools for Glycomics

Kerry R. Love and Peter H. Seeberger*

Carbohydrates are the key components of glycolipid and glycoprotein cell-surface molecules responsible for recognition, adhesion, and signaling between cells.^[1] These processes are essential for normal tissue growth and repair, bacterial and viral invasion of host organisms,^[2] as well as tumor-cell motility and progression.^[3] A better understanding of protein–carbohydrate interactions would greatly aid in the elucidation of intercellular signaling pathways, possibly leading to improved diagnostic and therapeutic tools.

DNA and protein microarrays arrays, prepared by attachment of the biopolymers to a surface in a spatially discrete pattern, have enabled a low-cost, high-throughput methodology for screening interactions involving these molecules. Oligonucleotide arrays were constructed in situ on glass slides by photolithographic methods^[4] or by using ink-jet technology.^[5] The polymerase chain reaction (PCR) allowed for quick amplification of libraries of complementary DNA (cDNA), to provide insight into cellular processes involved in the regulation of gene expression.^[6] Protein arrays on glass slides, microwells,^[7] and three-dimensionally modified gel-pad chips^[8] have been used for high-throughput screening of protein activity and determination of protein–protein, protein–DNA, and protein–ligand interactions.^[9]

The development of carbohydrate biosensors and arrays has recently received increased attention. Carbohydrates are by nature chemically more complicated substrates and several key challenges must be addressed to create carbohydrate arrays: 1) sugars must be displayed at the reducing end for successful protein recognition; 2) the many hydroxyl groups may be difficult to differentiate and linker systems have to take advantage of high-affinity interactions for surface attachment of the carbohydrate; and 3) access to carbohydrates of defined structure is difficult as both isolation and synthesis are very challenging.

Two linker systems have been devised for the attachment of carbohydrates to a surface. The first technique exploits the natural affinity of biotin for streptavidin,^[10] while the second method relies on the formation of alkane thiolate monolayers on a gold surface.^[11]

Biotin–Streptavidin-Based Linkers

Initial efforts to understand lectin–carbohydrate binding utilized the biotin–streptavidin interaction for the display of oligosaccharides (Figure 1). The anomeric asparagine residues of twelve glycans were biotinylated and immobilized onto a 96-well titer plate coated with streptavidin to characterize the binding properties of six common lectins.^[12]

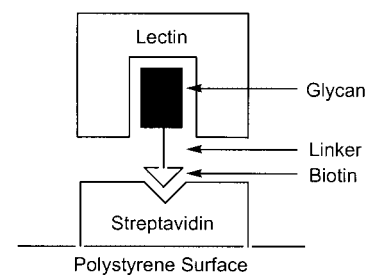
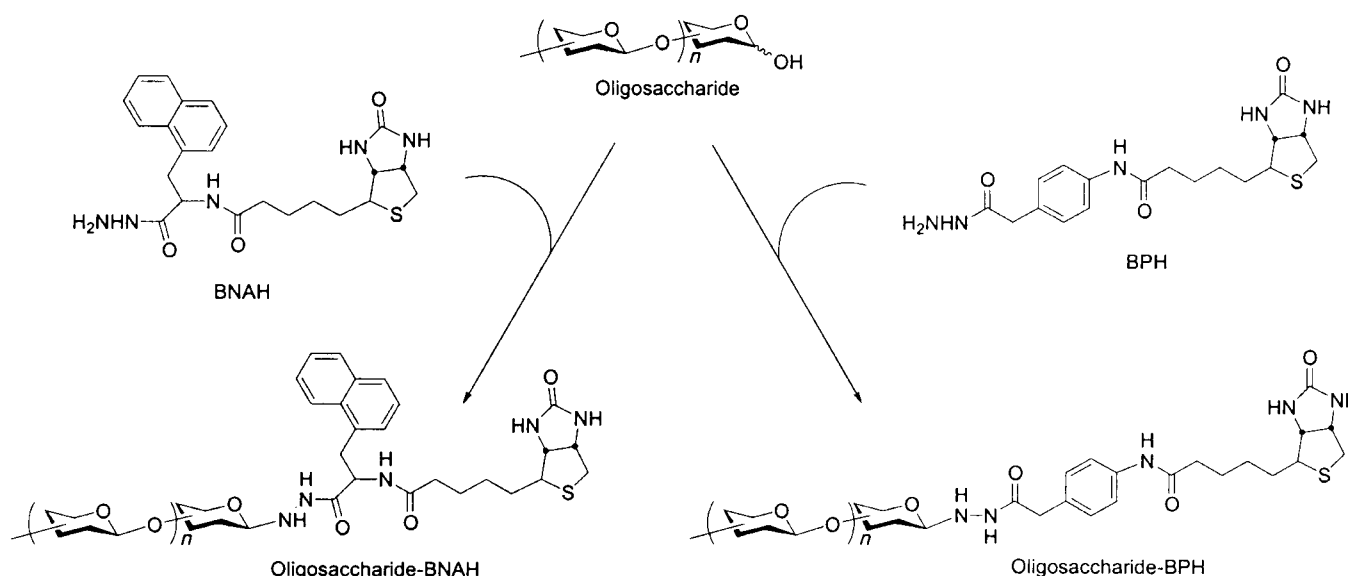


Figure 1. Surface display of carbohydrates for lectin-binding assays by interaction of biotin with streptavidin.

Characterization of lectin binding was simplified by inclusion of a 4-(biotinamido)phenylacetylhydrazine (BPH) chromophore, in the linker portion of the carbohydrate (Scheme 1)^[13] and was monitored by surface plasmon resonance (SPR) spectroscopy.^[14] This methodology was expanded to include a biotinyl-L-3-(2-naphthyl)-alaninehydrazide (BNAH) linker containing a chromophore with both UV-absorbing and fluorescent properties (Scheme 1).^[15] The binding of monoclonal antibodies and selectins to surface-immobilized sialyl-Lewis^a (SLe^a) and sulfo-Le^a-related oligosaccharides was monitored.^[16] Unexpectedly low binding signals between sulfo variants and L- and P-selectins highlighted the importance of the use of the correct ligand on the streptavidin matrix. The length of the spacer between the biotinyl tag and the oligosaccharide is a critical factor in the binding signal, as it limits both nonspecific ligand–ligand and ligand–surface interactions.

Most recently, biotinylated oligosaccharides have been used to probe poorly understood protein–carbohydrate interactions. A library of immobilized galactosyl ceramide (GalCer) analogues were individually probed for interaction with the HIV cell-surface glycoprotein gp 120.^[17] A heparin sulfate glycosaminoglycan was similarly immobilized and interacted with a 3-O-sulfotransferase isoform-1 (3-OST-1)

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Scheme 1. Incorporation of chromophores into a linker for display of carbohydrates on a streptavidin-coated surface. The biotin-terminated linker is attached to the reducing end of an oligosaccharide through hydrazide formation under mild conditions.

in an effort to improve antithrombin III binding.^[18] These studies illustrate the potential of the biotin–streptavidin interaction to immobilize sugars for the screening of protein–carbohydrate interactions.

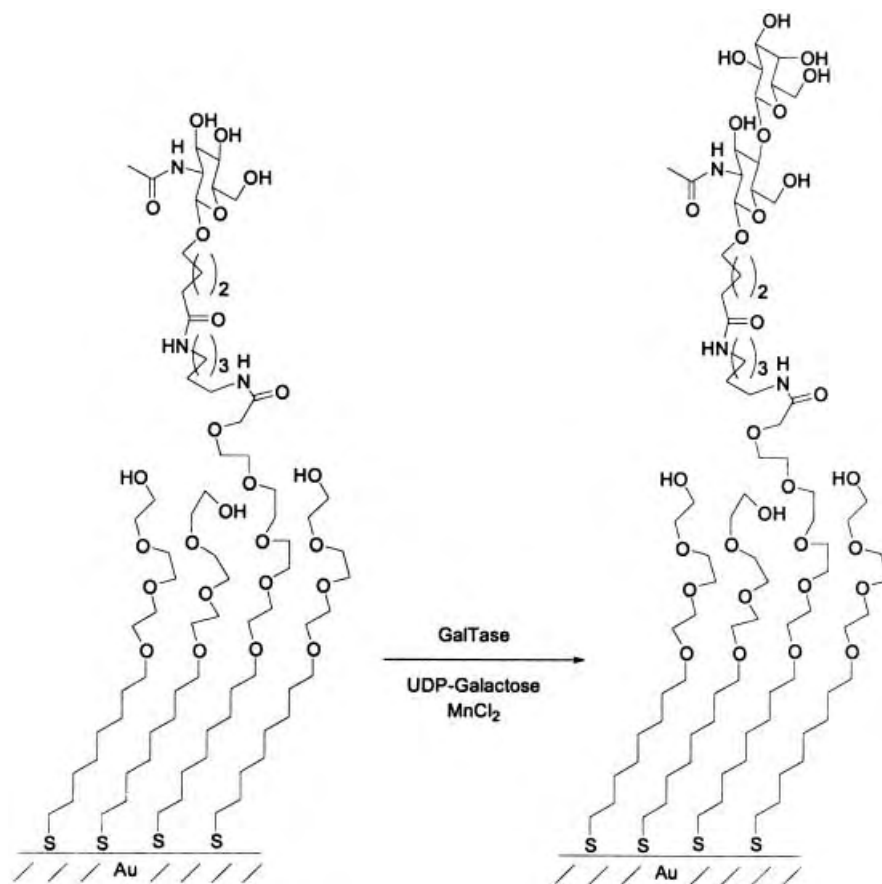
Carbohydrate Self-Assembled Monolayers (SAMs)

Self-assembled monolayers of alkane-thiols on a gold-coated substrate allow for the display of densely packed structures on a surface.^[11] The reactivity and properties of a monolayer depend entirely on the exposed functional groups, which may be elaborated to create defined surfaces. Hydroxylated surfaces present a readily derivatized moiety for the attachment of biomolecules, such as a thiol-terminated hexasaccharide.^[19]

Subsequently, several SAMs were formed using thioglucose monosaccharides.^[20] Characterization by reflection absorption infrared spectroscopy (RAIRS)^[21] indicated that the orientation of the carbohydrates in each SAM was dependent on the anomeric thiol moiety. Thus, the nonreducing end of mannose was appropriately displayed to allow the lectins access to each monosaccharide unit. Interactions between this SAM and two lectins, concanavalin A (Con A) and *tetragonolobus purpureas*, were detected by using SPR spectroscopy. Con A exhibited clear selectivity for the mannose-containing SAM, as observed by SPR spectroscopy.^[20]

Enzymatic modification of a carbohydrate-based SAM was demonstrated by

Houseman and Mrksich.^[22] A mixed SAM presenting both *N*-acetylglucosamine (GlcNAc) and tri(ethylene glycol) groups was subjected to bovine β -1,4-galactosyltransferase (GalTase; Scheme 2). The transfer of galactose was quantified by inclusion of [¹⁴C]uridine diphosphogalactose ([¹⁴C]UDP-



Scheme 2. A self-assembled carbohydrate monolayer. *N*-acetylglucosamine groups presented on the surface may be glycosylated when incubated with galactose and GalTase. Recognition of this glycosylation may be observed by lectin binding to the newly formed disaccharide.

Gal) and showed that enzyme activity directly corresponds to the density of the monolayer.^[22]

Carbohydrate-based SAMs were also used to correlate protein specificity and ligand density. Exposure of three SAMs displaying one of three disaccharides, a natural ligand, a synthetic ligand, and a control ligand, to *Bauhinia purpurea* lectin showed a change in the binding selectivity from the natural ligand to a synthetic ligand as the surface density increased.^[23] These observations suggest that one protein may elicit more than one response by binding to several carbohydrate ligands. Thus, changes in the composition and density of cell-surface carbohydrates may substantially influence downstream regulatory pathways.

Carbohydrates and SAMs: The Development of a Carbohydrate Array

The ability to detect the presence of carbohydrates displayed on SAMs by a biological means made this technique a good candidate for the simultaneous display and detection of carbohydrate analytes. A cyclopentadiene-terminated linker, which enabled the attachment of biomolecules through a rapid and irreversible Diels–Alder reaction to a SAM displaying reactive quinone groups,^[24, 25] immobilized ligands in a discrete location (Scheme 3).^[26] Following initial proof-of-principle on a peptide chip,^[27] a carbohydrate array was created by spotting solutions containing carbohydrate–cyclopentadiene conjugates onto specific regions of a monolayer displaying reactive benzoquinone groups.^[28]

This multivalent carbohydrate array consisted of ten different monosaccharides and was probed by the addition of a series of five fluorescently labeled lectins.^[28] Each lectin was observed to interact specifically with its known carbohydrate ligands, thus the array demonstrated utility in the selective identification of protein substrates. Arrays could also be enzymatically modified, as demonstrated by incubation with GalTase, followed by a lectin-binding assay.^[22]

Houseman and Mrksich also used their surface chemistry to create a carbohydrate chip for the study of protein inhibition.

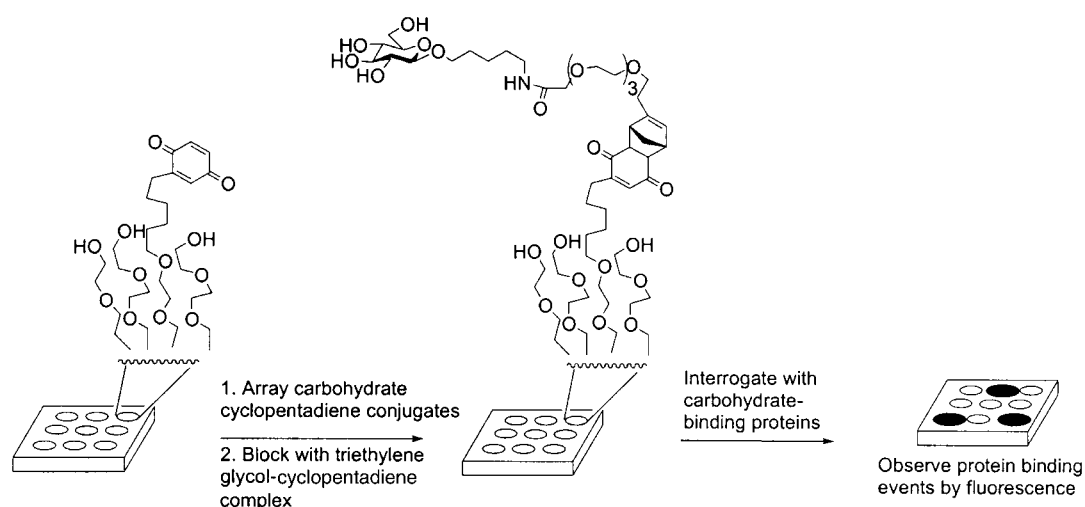
A series of solutions containing Con A and various concentrations of α -methyl mannose (0–4 mM) were arrayed onto monolayers presenting either α -mannose, β -glucose, or α -N-acetylglucosamine.^[28] After an incubation period, the amount of lectin binding for each concentration of soluble ligand was determined by fluorescence spectroscopy, thus the relative binding affinities of each carbohydrate for Con A were verified.

Another carbohydrate array for the detection of antibodies to a series of dextrans was recently reported.^[29] Dextrans of varying glycosidic linkage composition and molecular weight were arrayed onto nitrocellulose-coated glass slides. The carbohydrate microarray was applied to detect human serum antibodies to microbial pathogens that typically express dextrans, including several strains of *Pneumococcus*, group B *Meningococcus*, and *Haemophilus influenzae*.

Comparison of Carbohydrate Microarrays and Outlook

Both biotin–streptavidin and SAM-based methods for biomolecule conjugation have been successfully employed for the presentation of carbohydrates on a surface. In each case, incubation of the surface with various lectins has confirmed known carbohydrate-binding specificities. While SAMs have recently shown potential in the synthesis of a carbohydrate array, biotin–streptavidin-based carbohydrate presentation has been limited to the display of a unique substrate on each individual surface. “Arrays” have been generated, but require the physical separation of different biomolecules, typically using a 96-well enzyme-linked immunosorbent assay (ELISA) plate. SAMs seem particularly suited to the construction of biochips owing to the ease of their construction and increased inertness to protein adsorption.^[30] Furthermore, SAMs have demonstrated utility in conjunction with cell cultures;^[31, 32] future generations of carbohydrate chips may be used in whole-cell assays.

The simultaneous detection of carbohydrate analytes by the binding of lectin in the context of a monosaccharide-based array is a powerful development in the emerging field of



Scheme 3. Generation of a carbohydrate array using self-assembled monolayers. A series of cyclopentadiene-functionalized monosaccharides were immobilized on a SAM displaying reactive quinone groups. An irreversible Diels–Alder reaction between the cyclopentadiene and quinone groups leads to localization of each monosaccharide.

glycomics. However, use of array technology to understand the intricate role of carbohydrates in cell-signaling will require the immobilization of longer, more complex oligosaccharides. The development of automated methods for the synthesis of oligosaccharides^[33, 34] in combination with the development of microcontact printing for the deposition of ligands on the surface of a SAM^[35, 36] will make possible the rapid generation of chips containing entire classes of carbohydrates. Interrogation of these surfaces by systematic exposure to fluorescently labeled proteins, including bacterial and viral toxins, will ultimately lead to a better understanding of the role of carbohydrates in numerous signaling processes.

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Direct Electrochemical Aziridination of Alkenes under Metal-Free Conditions

Gerhard Hilt*

The generally accepted advantage of electrochemical conversions is the mass-free electron transfer between the electrode and the substrate, thereby eliminating the need for the waste disposal of a used redox reagent.^[1] Since many chemical redox reagents are produced by electrochemical pathways, it would be an advantage to use the electrochemical power directly for the conversion of the starting materials in redox reactions. From this viewpoint, and because of increasing environmental problems, electrochemical methods will

become more and more attractive in the future. Many classes of substrates could be successfully converted directly at the electrode under electrochemical conditions and the intermediates generated by electron transfer could be employed in synthetically useful follow-up reactions. Among these electrochemical conversions, applications on an industrial scale^[2] and for the production of fine chemicals and laboratory-scale chemicals exist.^[3]

The synthetic value of small, strained, and therefore highly reactive, ring systems is well established, and among these epoxides and aziridines are of great interest.^[4] Indeed, the asymmetric synthesis of epoxides from allylic alcohols^[5] was honored by the award of the Nobel prize to Sharpless in 2001.^[20] Hydroperoxides are used as oxidants as an easily handled source of oxygen, even on a large scale.^[5, 6]

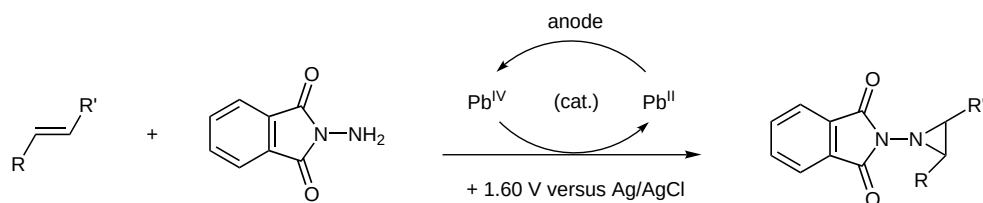
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Similar amination reagents are not described for the analogous aziridination process, so that other methods for the activation of the nitrogen atom in aziridination reagents must be used.^[7] Thus, chemical methods for the activation of nitrogen are applied, such as reactions with stabilized, oxidized nitrogen-containing compounds (for example, hypervalent compounds such as $\text{RI}=\text{NR}'$),^[8] as well as photochemical-initiated metal-catalyzed aziridinations starting from azides.^[8a] Furthermore, acceptor-stabilized hydrazine derivatives can be oxidized in situ by lead(IV) reagents,^[9] as well as *N*-acetoxyhydrazine derivatives, which are preformed from the hydrazine derivative upon oxidation with lead(IV) reagents.^[10] The disadvantage of these methods is the stoichiometric use and the accompanying problems of the disposal of the spent reagents.

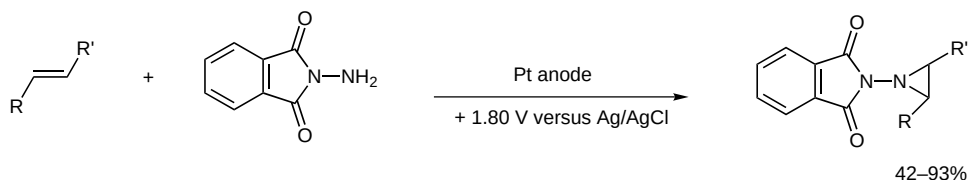
A sustainable electrochemical method for the aziridination of alkenes with catalytic amounts of lead compounds, and electrochemical regeneration of the spent Pb^{IV} species, would be a reasonable improvement, thus avoiding the stoichiometric use of toxic heavy metal oxidizing agents. Of even greater interest would be an aziridination method that would reduce the amount of toxic reagents to a minimum or avoid any of these reagents at all. Siu and Yudin recently published an electrochemical method for a lead-mediated indirect electrochemical oxidation as well as for a direct electrochemical heavy-metal-free aziridination of alkenes using *N*-aminophthalimide as a nitrogen source (see Scheme 1).^[11] In the latter method the *N*-aminophthalimide is directly oxidized at the anode to generate a reactive species which reacts with a variety of alkenes to form the corresponding aziridines.

The restriction that even catalytic amounts of lead represent an ecological hazard could be overcome by using appropriate electrochemical conditions. Electroanalytical measurements revealed that the redox potentials for the $\text{Pb}^{\text{II}}/\text{Pb}^{\text{IV}}$ couple ($E = +1.60$ V versus Ag/AgCl , platinum working electrode) were in the same region as the oxidation potential of the hydrazine derivative ($E = +1.35$ V and $+1.68$ V versus Ag/AgCl ; two irreversible one-electron oxidations). On the other hand, the oxidation of the mainly acceptor-substituted alkenes take place at higher potentials, so that the direct electrochemical oxidation of the hydrazine derivative under potentiostatic conditions was possible, which renders the use of lead as a redox-mediator obsolete (Scheme 2).

The electrochemical reactions were conducted under potential-controlled conditions in a divided electrochemical cell with a silver wire as a quasi-reference elec-



Scheme 1. Indirect lead-mediated electrochemical aziridination of alkenes.

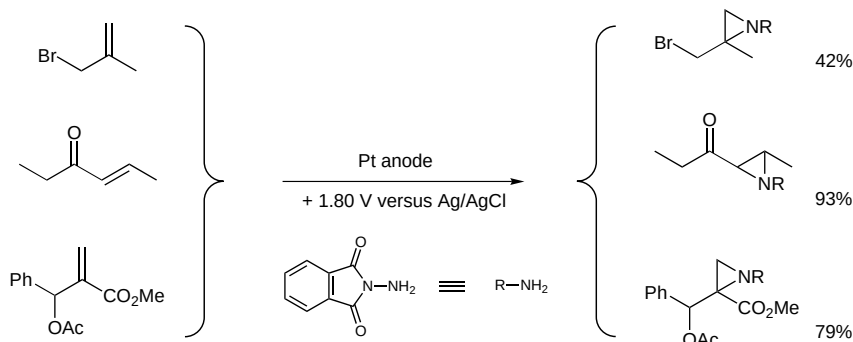


Scheme 2. Direct electrochemical aziridination of alkenes.

trode,^[12] which minimizes the disadvantages that sometimes accompany the use of a conventional reference electrode. Further operative simplifications, such as an undivided cell (conversions in a quasi-divided cell can be envisioned)^[13] or electrolysis under galvanostatic conditions might be possible, so that researchers not equipped for specialist electrochemistry could use this simple and clean methodology for the synthesis of aziridines in the future. The synthetic utility of the reaction could be enhanced further if the cathodic deprotection (to generate the free aziridine) could also be realized under electrochemical conditions.^[14]

However, the synthetic value of the electrochemical aziridination was demonstrated when unfunctionalized, acceptor-substituted and highly functionalized alkenes were aziridinated in good to excellent yields. Some selected examples of the direct electrochemical aziridination are shown in Scheme 3. The methodology described above for the functionalization of alkenes under electrochemical conditions represents an interesting reaction with potential for further developments.

An asymmetric version of the reaction cannot be realized by direct electrochemical reaction of the hydrazine derivative at the electrode. However, the use of chiral transition-metal catalysts (such as chiral titanium complexes) can be envisioned, so that an electrochemically initiated and transition-metal-catalyzed asymmetric variant could be realized. Further developments towards an electrochemical removal of the



Scheme 3. Preparative direct electrochemical aziridination of functionalized alkenes.

phthalimide group as well as the use of primary amines as a nitrogen source would also be of great interest.

Among the most recent interesting developments, which include a) paired electrolysis on industrial scale,^[15] b) electrochemical regeneration of azadicarboxylic esters,^[16] c) electro-enzymatic reaction in flow-through reactors,^[17] d) electro-catalytic coupling reactions,^[18] and e) selective electrochemical fluorinations,^[19] the electrochemical aziridination can be seen as a further highlight in electroorganic synthesis.

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Microwave-Assisted Reactions in Organic Synthesis—Are There Any Nonthermal Microwave Effects?

Response to the Highlight by N. Kuhnert

Christopher R. Strauss*

In his recent Highlight,^[1] mentioned in the title, Kuhnert presented “two representative examples of microwave chemistry” that he claimed, “illustrate the confusion caused by an uncritical consideration of published results and lead to an overestimate of the capabilities of the method”. In subsequent sections, he outlined the benefits of modern microwave reactors and discussed recent results by Kappe and Stadler^[2, 3] who had employed such systems to allow one, in Kuhnert’s words, to “cautiously” conclude “that all speculation of special and nonthermal effects in microwave heating has no basis”. Kuhnert summarized that through the recent “thorough work of Kappe’s group, the comparison of thermal- and microwave-heating methods is possible for the first time”.

Although others also appear to have cause for grievance about the Highlight, the purpose of this Correspondence is to address misrepresentations and omissions with regard to our work and also to contextualize the two publications of Stadler and Kappe, mentioned above, as contributions to a body of literature rather than as the definitive work that Kuhnert had portrayed.

In order to “illustrate the confusion” about the existence or otherwise of “special and nonthermal effects in microwave heating”, Kuhnert cited the intramolecular Claisen–Schmidt condensation of hexane-2,5-dione with 0.05 % aqueous NaOH at 200 °C to afford 3-methylcyclopent-2-enone, that we had reported.^[4] He commented that “as no direct comparison with a thermal procedure under comparable conditions was undertaken, some room remains for speculation about nonthermal effects”. To the best of our knowledge, for this particular reaction, no confusion had been expressed previously and no speculation by others had occurred. Indeed, what grounds were there for confusion or speculation? In contrast with Kuhnert’s assertion, we had reported not only the reaction conducted by microwave heating in a batch

reactor (MBR) of our own design,^[5] but also with a commercial prototype continuous microwave reactor (CMR) embodied by our patent^[6, 7] and with conventionally heated autoclaves both on the 500-mL scale and the 3-L scale! Contrary to our being criticized by Kuhnert for failure to undertake comparative studies, single reports of the use of such a diverse array of equipment for carrying out one specific reaction are rare. We concluded^[4] that the result with the autoclave “was similar to that obtained with the MBR and agreed with earlier findings that the kinetics of microwave-heated and conventionally heated reactions do not differ significantly if the temperature is known and the solution is thermally homogeneous”. The earlier findings to which we had referred were presented in our 1993 paper entitled *A Comparison of Reaction Kinetics Observed under Microwave Irradiation and Conventional Heating*.^[8] (The publication year quoted is not a misprint.) In that work, we had measured for the first time the kinetics of microwave-heated and conventionally heated reactions. The paper contained theoretical discussion and repudiated findings of other groups who had claimed a nonthermal microwave effect. Unfortunately, Kuhnert’s Highlight did not refer to that work or to an even earlier paper that had led us to the same conclusion.^[9] Nor did it refer to a 1996 paper entitled *Reactions of Allyl Phenyl Ether in High-Temperature Water with Conventional and Microwave Heating*^[10] in which we had concluded on p. 7359, “These findings indicate that if the microwave conditions can be adequately mimicked (a proviso that may not always hold) conventional heating will produce a comparable outcome”.

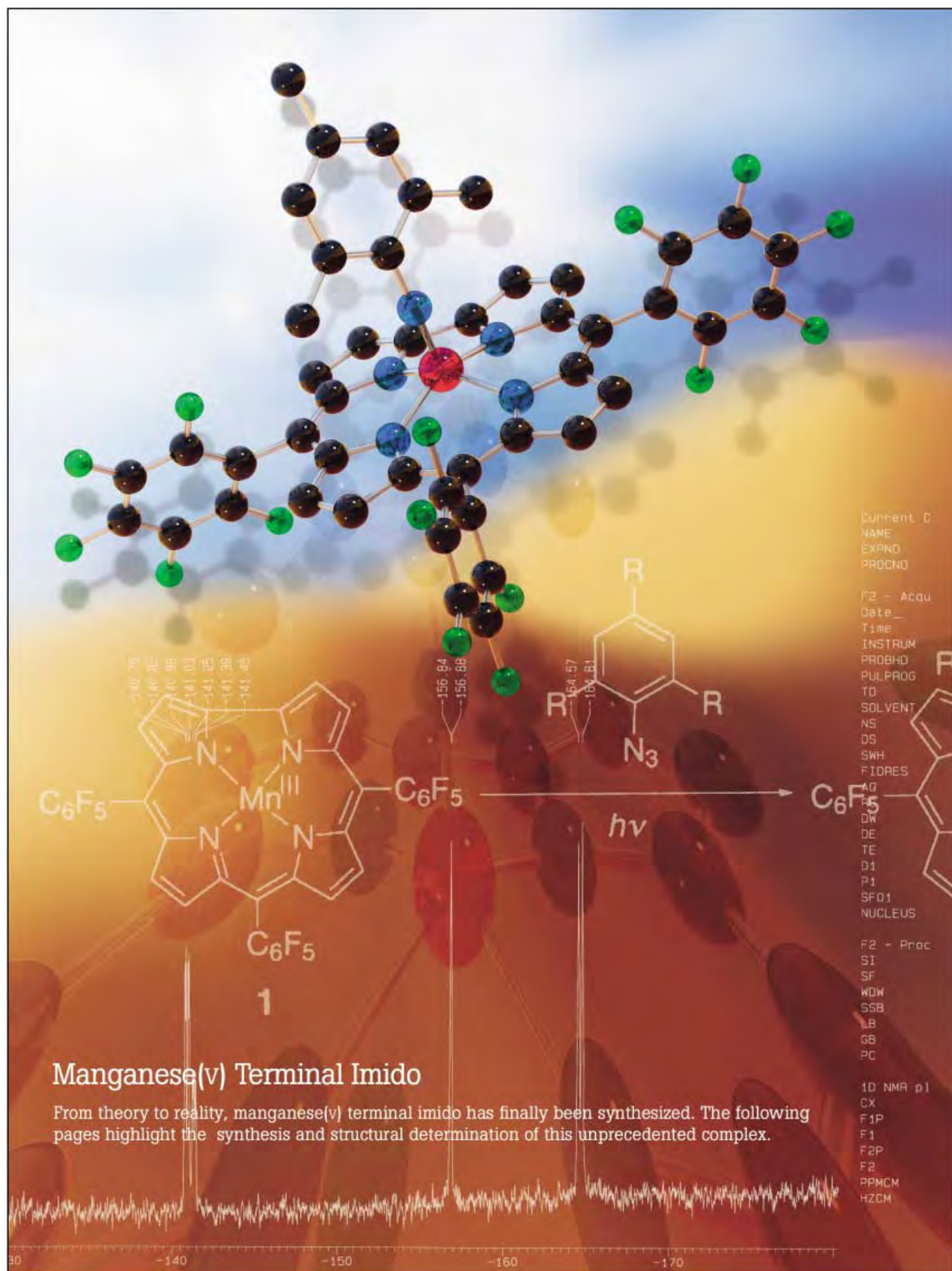
Although our invited review^[11] was cited (as reference [8] in the Highlight^[1]), Kuhnert did not appear to take into account the section entitled *Rate Studies and Investigations into “Microwave Effects”* in which we summarized and critically evaluated the literature up to 1995 on those aspects.

Many studies into the effects of microwave heating on reaction outcomes (including the reports of Kappe and Stadler, mentioned above) have concerned conversions or yields obtained by microwave and conventional heating under apparently comparable conditions within a given time. Measurement of the kinetics of reactions, though, requires more rigorous experimental regimes and far more

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time and effort. An Arrhenius plot for a single reaction conducted by a specific heating method, for example, may be obtained only after 50 experiments or so. For a carefully conducted comparative study of microwave and conventional heating, data from about 100 experiments would be needed. To measure kinetics in a microwave environment in the early 1990s, major technical difficulties first had to be overcome. Dedicated reactors were required. Our paper entitled *A New Microwave Reactor for Organic Synthesis and Kinetics Studies*^[13] provided a basis not only for our kinetics studies but also for the present commercially available pressurized microwave batch reaction systems that Kuhnert advocated in his Highlight. To underscore this point, even Kappe and Stadler's work was conducted with a reactor of our design (see reference [6] in the portrayed paper by Kappe and Stadler^[3])!

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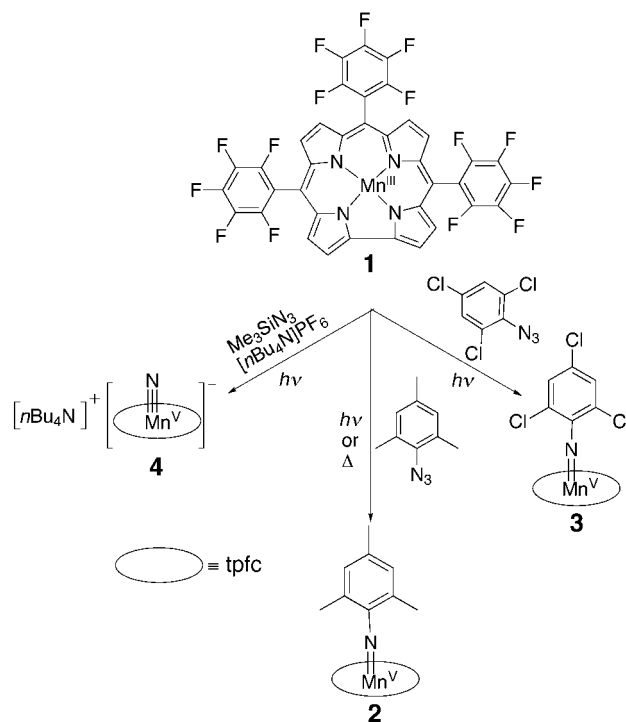
The Elusive Terminal Imido of Manganese(v)**

Rebecca A. Eikey, Saeed I. Khan, and
Mahdi M. Abu-Omar*

The discovery that a (nitrido)manganese(v) porphyrin^[1] can be activated for the aziridination of cyclooctene with trifluoroacetic anhydride (tfaa) has stimulated the development of several catalytic^[2–4] and stoichiometric methods^[5] for metal-mediated nitrene [NR] group transfer. The catalytic tosylation of alkanes by PhI=NTs in the presence of manganese(III) porphyrins has also been reported.^[6] A major goal of research on the use of catalytic manganese(III) and stoichiometric high-valent manganese(v) species is the identification of reaction intermediates. (Imido)manganese(v) compounds have been proposed as the active species responsible for the delivery of the nitrene group to double bonds,^[1,7] similar to what has been postulated for the related metal-mediated oxygen-atom-transfer reaction.^[8] Thus, it is not surprising that while many structures of (nitrido)manganese(v) complexes are known,^[9] neither structures nor definitive spectroscopic characterizations of (imido)manganese(v) complexes are available.^[7,10] Herein, we describe the preparation, molecular structure, and preliminary reactivity studies of novel (imido)manganese(v) corroles. To our knowledge, this report constitutes the first structure of a terminal imido complex of manganese(v).^[7,11]

Corroles, one-carbon atom short analogues of porphyrins, have been shown to stabilize high oxidation states of various transition metals.^[12] The ambiguity of assigning oxidation states that is characteristic of octaalkylcorroles^[13] has been eradicated by the introduction of the electron-poor 5,10,15-tris(pentafluorophenyl)corrole (H₃(tpfc), tpfc = the trianion) by Gross and co-workers.^[14] Recently, Gross and Gray and their co-workers extended the chemistry of manganese corroles beyond the trivalent state by preparing (halo)manganese(IV),^[12c] (oxo)manganese(v),^[12b] and (nitrido)manganese(v)^[12c] corroles. The manganese(IV) corroles were structurally characterized, but the manganese(v) corroles were identified spectroscopically.

Following the literature precedent of using NaN₃ and irradiation in the preparation of high-valent nitrido complexes,^[9c] we have prepared (imido)manganese(v) corroles from the one-pot reaction of organic azides^[15–17] with (tpfc)manganese(III) complex **1** under photolysis (Scheme 1). The reaction of **1** with 2,4,6-trimethylphenyl azide yields the corresponding



Scheme 1. Synthesis of **2**, **3**, and **4** from [Mn^{III}(tpfc)].

manganese(v) imido complex **2** under photolytic as well as under thermal conditions. However, the reaction of **1** with 2,4,6-trichlorophenyl azide affords the desired product **3** only under photolysis. Interestingly, when trimethylsilyl azide (tmsa) was employed as the nitrene [NR] source, the (nitrido)manganese(v) corrole **4**, was isolated upon the addition of a salt, [nBu₄N][PF₆]. The nitrido complex has been prepared previously by the action of NaN₃ followed by photolysis.^[12c] Complexes **2** and **3** are easily purified by chromatography to afford red microcrystalline solids in excellent and consistent overall yields of 80–70%.

The (imido)manganese complex **2** is sensitive to water and air (the latter is most likely to be as a result of the moisture in air since compound **2** persists for days under ambient atmosphere in dry southern California weather). In solution and in the solid state, **2** is stable for months under dry inert atmosphere. On the other hand, solutions of **3** revert to green Mn^{III} species in a couple of days even under inert atmosphere. A complex mixture of organic products is formed alongside the identifiable azo compound.

The ¹H and ¹⁹F NMR spectra of both complexes **2** and **3** exhibit sharp resonance signals in the normal range for chemical shifts, consistent with diamagnetic low-spin d² manganese (Figure 1) centers. The phenyl proton resonances of the imido ligands are shifted upfield (δ = 5.67 and 6.31 ppm for **2** and **3**, respectively) as a result of the ring current of the corrole macrocycle. Noteworthy is that the green intermediate [(TMP)Mn(=NCOCF₃)(OCOCF₃)] (TMP = (5,10,15,20-tetramethylporphyrinato)dianion) proposed by Groves and Takahashi to be responsible for [NR] transfer is paramagnetic.^[1,18] This high-spin configuration of the Mn^V center could be a result of the weaker π-donation ability of the acylimido ligand or to the porphyrin ligand. Recent DFT calculations on

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

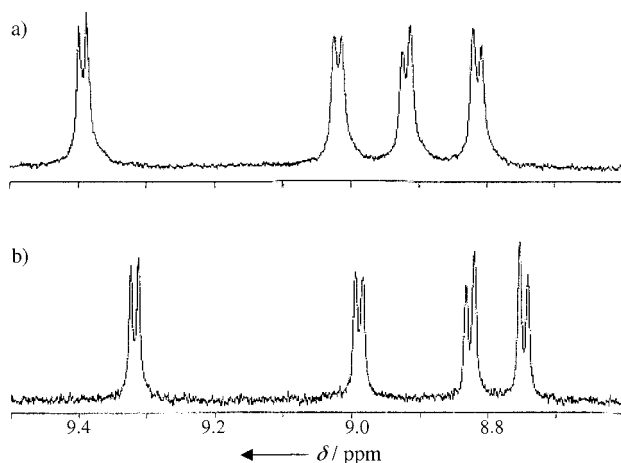


Figure 1. ^1H NMR spectra showing the β -pyrrole region of complexes a) **2** and b) **3** in CD_3CN .

(oxo)manganese(v) corrole and porphyrin complexes showed that diamagnetism is expected for corrole and paramagnetism for porphyrin complexes.^[19] However, a diamagnetic (oxo)- Mn^{V} (hydroxo) porphyrin intermediate has been recently characterized by ^1H NMR spectroscopy.^[10] The identification of **2** and **3** as the imido complexes was confirmed by mass spectrometry. The electronic spectra of these complexes exhibit a single Soret band (410 nm) and a Q band at 528 nm. Figure 2 contrasts the UV/Vis spectrum of **2** with that of **1** and **4**. The most relevant changes are the loss of the split Soret band and the band at 470 nm upon formation of manganese(v).

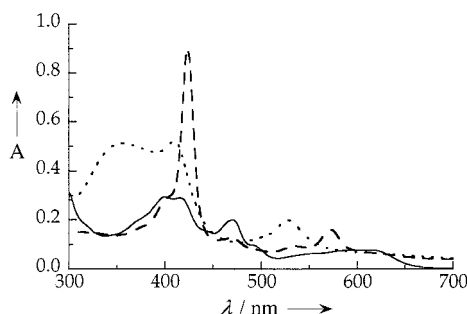


Figure 2. Electronic spectra of a) $[\text{Mn}^{\text{III}}(\text{tpfc})]$ (**1**; $1.5 \times 10^{-5} \text{ M}$; —), b) $[\text{Mn}^{\text{V}}(\text{tpfc})(N\text{-mesityl})]$ (**2**; $1.6 \times 10^{-5} \text{ M}$;), and c) $[\text{Mn}^{\text{V}}(\text{tpfc})(\text{N})]^-$ (**4**; $1.0 \times 10^{-5} \text{ M}$; ---) in acetonitrile.

The molecular structure of **2** was confirmed by single-crystal X-ray analysis (Figure 3).^[20] The highlight features of the structure are 1) a five-coordinate manganese(v) center that is located $0.513 \text{ \AA}$ out of the plane defined by pyrrole nitrogen atoms, 2) a $\text{Mn}\equiv\text{NR}$ bond length of $1.613(4) \text{ \AA}$, and 3) a $\text{Mn-N-C}_{\text{Ar}}$ bond angle of $170.4(4)^\circ$. The $\text{Mn}\equiv\text{NR}$ distance is slightly longer than what is observed for (nitrido)manganese(v) complexes (the average $\text{Mn}\equiv\text{N}$ bond for porphyrin and salen complexes is $1.52 \text{ \AA}$)^[9] and for (oxo)manganese(v) complexes ($\text{Mn}=\text{O}$ bond of $\sim 1.56 \text{ \AA}$).^[21] The Mn-NR bond in our compound, however, is significantly shorter than the Mn-O bond observed for a terminal oxo complex of low-valent manganese(III) ($1.80 \text{ \AA}$) species,^[22] and shorter than the imido

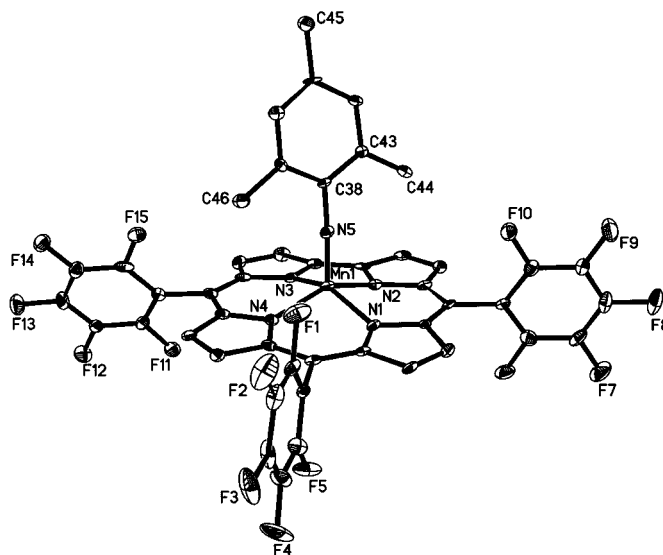
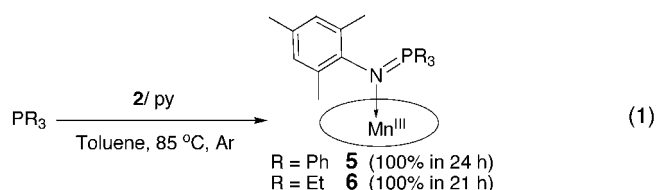


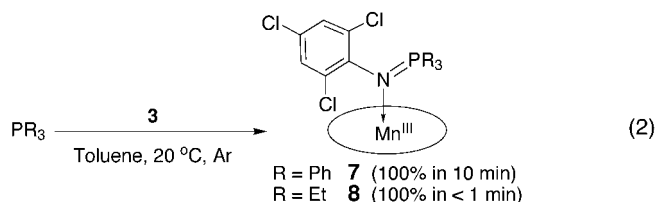
Figure 3. ORTEP diagram (H atoms are omitted for clarity) of **2** (ellipsoids at 50% probability level). Selected bond lengths [$\text{\AA}$] and angles [$^\circ$]: Mn1-N5 $1.613(4)$, $\text{Mn1-N}_{\text{pyrrole}}$ $1.891(4)$ – $1.947(4)$, N5-C38 $1.374(6)$; C38-N5-Mn1 $170.4(4)$, $\text{N5-Mn1-N}_{\text{pyrrole}}$ $103.30(19)$ – $106.37(19)$, and N5-C38-C43 $118.9(5)$.

bonds in $[\text{Mn}^{\text{VII}}(\text{NtBu})_3\text{Cl}]$ (the average Mn-NR bond is $1.66 \text{ \AA}$).^[23] Hence, the Mn-NR bond length and the $\text{Mn-N-C}_{\text{Ar}}$ bond angle in **2** are well within the range for a $\text{Mn}\equiv\text{NR}$ triple bond formulation. The average Mn-N bond lengths for the pyrrole nitrogen atoms in **2** ($1.916 \text{ \AA}$) is the same as those in $[\text{Mn}^{\text{III}}(\text{tpfc})(\text{OPPh}_3)]$ ($1.916 \text{ \AA}$).^[24] This situation is in contrast to the lengthening of the $\text{Mn-N}_{\text{pyrrole}}$ distances observed in $[\text{Mn}^{\text{IV}}(\text{tpfc})\text{Br}]$ ($1.925 \text{ \AA}$) and $[\text{Mn}^{\text{IV}}(\text{tpfc})\text{Cl}]$ ($1.932 \text{ \AA}$)^[12c] and to the lengthening of the $\text{Cr-N}_{\text{pyrrole}}$ distances found in $[(\text{tpfc})\text{Cr}^{\text{V}}(\text{O})]$ (1.927 – $1.943 \text{ \AA}$).^[25] The cause of this lengthening in the $\text{Mn-N}_{\text{pyrrole}}$ and $\text{Cr-N}_{\text{pyrrole}}$ bonds was attributed to the “pronounced doming of the corrole framework” in the manganese(IV) and chromium(V) structures. In our structure, the pyrrole nitrogen atoms are essentially in the same plane as the 19-membered carbon macrocycle. In both **2** and $[(\text{tpfc})\text{Cr}^{\text{V}}(\text{O})]$, the metals are displaced out of the plane defined by the pyrrole nitrogen atoms. However, the displacement is larger in $[(\text{tpfc})\text{Cr}^{\text{V}}(\text{O})]$ ($0.6 \text{ \AA}$) resulting in a strong interaction of the bonding orbitals of the pyrrole nitrogen atoms with the π orbitals of the CrO moiety, which results in lengthening of the $\text{Cr}\equiv\text{O}$ bond ($1.57 \text{ \AA}$) and doming of the ligand.^[25]

Preliminary investigations of the reactivity of (imido)manganese(v) corroles suggested that olefins are not reactive enough to accept an $[\text{NR}]$ group from **2** or **3**. This finding is not surprising, given that Mn^{III} salen complexes, which are excellent epoxidation catalysts,^[26] did not fair well in aziridination reactions.^[2b,c] Interestingly, the analogous compound $[(\text{tpfc})\text{Mn}^{\text{V}}(\text{O})]$ was shown to be unreactive towards oxygen-atom transfer to alkenes, which suggests that a higher oxidation state of manganese is responsible for catalysis.^[12b] However, in the presence of pyridine (py), the terminal mesitylimido group of **2** transfers to organic phosphanes yielding the iminophosphane adduct of manganese(III) corrole [Eq. (1)]. The UV/Vis spectrum of **5** (λ_{max} in nm = 401



and 421 (split Soret), 493, 607 (Q band)) is similar to that of [(tpfc)Mn^{III}(OPPh₃)].^[12b] (The spectra of **5** and **6** are displayed in the Supporting Information.) Even though the reactions of **2** with phosphanes are sluggish, complex **3** with the electron-withdrawing trichlorophenyl substituent is much more reactive and is more sensitive to the nucleophilicity of the R₃P group [Eq. (2)]. This finding is in agreement with electrophilic [NR] group transfer from the manganese(V) center. While [NR] transfer from activated (nitrido)manganese(V) salen complexes^[5] and from complex **2** require pyridine as an additive, reactions of complex **3** [Eq. (2)] do not require pyridine, demonstrating the importance of the R substituent on the imido ligand.



Both of our complexes **2** and **3** are less reactive than their proposed porphyrin and salen counterparts if the latter complexes are indeed the species responsible for nitrene [NR] transfer, which remains to be shown. This difference in reactivity could be a result of the ability of the corrole ligand to stabilize high oxidation state manganese(V) centers, or to the difference in the electron-withdrawing ability of the R substituent on the imido ligand. The latter is an appealing explanation given that complex **3** is more reactive than **2**.

In conclusion, we have described a facile one-step synthesis of novel (imido)manganese(V) complexes containing the electron-poor corrole tpfc as the ancillary ligand. The molecular structure of [(tpfc)Mn^V(N-mesityl)] is consistent with a low-spin d² configuration and a Mn–NR triple bond. Preliminary reactivity studies proved that these new and structurally well-defined (imido)manganese(V) complexes are suitable for [NR]-group transfer only to electron-rich substrates, such as organic phosphanes. The results reported herein set the stage for making and exploring other Mn^V and new Mn^{VI} imido species, for designing an efficient catalyst for [NR]-group transfer from organic azides,^[27] and for developing the parallel alkylidene/carbene [CR₂] organometallic chemistry.

Experimental Section

Toluene was dried by distillation over CaH₂. Acetonitrile was dried by distillation over CaH₂, deoxygenated, and stored under argon prior to use. For recrystallization purposes, pentane was purified by sulfuric acid before distillation over CaH₂. Photolysis experiments were carried out with a Hanovia Model 73A36 550-W medium pressure mercury lamp at 25 °C.

2: Method A. A solution of mesityl azide (36 mg, 230 μmol) and **1** (18 mg, 21 μmol) in toluene (10 mL) was refluxed under argon for 30 min or until the disappearance of [Mn^{III}(tpfc)] as monitored by TLC (12:1 mixture of pentane:diethyl ether). Evaporation of the solvent under reduced pressure followed by column chromatography (silica gel, 60 Å, 12:1 mixture of pentane:diethyl ether) resulted in isolation of **2**. Yield: 16 mg (75 %). MS (negative ion FAB): *m/z* (%) 982 (100) [M[−]], 848 (33) [M–Nmes[−]]; UV/Vis (CH₃CN): λ [nm] (log ε) = 354 (4.53), 410 (4.53), 528 (4.14); ¹H NMR (400 MHz, CD₃CN, 25 °C): δ = 9.39 (d, *J* = 4.5 Hz, 2H), 9.03 (d, *J* = 4.1 Hz, 2H), 8.93 (d, *J* = 4.7 Hz, 2H), 8.82 (d, *J* = 4.9 Hz, 2H), 5.67 (s, 2H), 1.53 ppm (s, 3H), −0.61 (s, 6H); ¹⁹F NMR (400 MHz, CD₃CN, 25 °C): δ = −140.82 (d, *J* = 20.0 Hz, 2F), −141.00 (d, *J* = 20.0 Hz, 2F), −141.27 (d, *J* = 24.0 Hz, 1F), −141.41 (d, *J* = 24.0 Hz, 1F), −156.79 to −156.93 (m, *J* = 16.0 Hz, 3F), −164.55 (m, *J* = 16.0 Hz, 3F), −164.79 ppm (m, *J* = 20.0 Hz, 3F).

Method B. A solution of mesityl azide (64 mg, 397 μmol) and **1** (28 mg, 33 μmol) in acetonitrile (5 mL) was photolyzed under argon for 4–5 days. Evaporation of the solvent under reduced pressure and purification of the residue as in Method A resulted in isolation of **2**. Yield: 12 mg (37 %).

3: A solution of 2,4,6-trichlorophenyl azide (36 mg, 162 μmol) and **1** (10 mg, 12 μmol) in acetonitrile (2.5 mL) was photolyzed under argon for 4–5 days. Evaporation of the solvent under reduced pressure and purification of the residue as in Method A resulted in isolation of **3**. Yield: 11 mg (81 %). MS (negative ion FAB): *m/z* (%) 1043 (9) [M[−]], 864 (100) [MN–Ar[−]], 848 (11) [M–NAr[−]]; UV/Vis (Toluene): λ [nm] (log ε) = 396 (4.22), 488 (3.63), 540 (3.75); ¹H NMR (400 MHz, CD₃CN, 25 °C): δ = 9.31 (d, *J* = 4.5 Hz, 2H), 8.99 (d, *J* = 4.3 Hz, 2H), 8.83 (d, *J* = 4.9 Hz, 2H), 8.77 (d, *J* = 4.9 Hz, 2H), 6.31 ppm (s, 2H); ¹⁹F NMR (400 MHz, CD₃CN, 25 °C): δ = −140.31 (d, *J* = 20.0 Hz, 2F), −140.94 (t, *J* = 20.0 Hz, 3F), −141.47 (d, *J* = 24.0 Hz, 1F), −156.65 (m, *J* = 24.0 Hz, 3F), −164.31 to −164.61 ppm (m, *J* = 8.0 Hz, 6F).

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Light-Harvesting Dendrimers: Efficient Intra- and Intermolecular Energy-Transfer Processes in a Species Containing 65 Chromophoric Groups of Four Different Types**

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Dedicated to J. Fraser Stoddart
on the occasion of his 60th birthday

An antenna for light harvesting is an organized system in which several chromophoric molecular species absorb the incident light and channel the excitation energy to a common acceptor component.^[1] Light-harvesting antennas are essential devices for natural photosynthetic processes.^[2] In the last decade, dendrimers^[3] have been extensively used to construct artificial antenna systems as suitable chromophoric groups may be incorporated into their regular branched structures.^[4,5] Another interesting aspect of dendrimer chemistry is the presence of internal cavities where ions or neutral molecules can be hosted.^[6,7] Energy-transfer processes between the

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chromophoric units present in the dendrimer branches and hosted species have also been investigated.^[7a,c,f]

Continuing our studies in this field,^[8] we have designed and synthesized a dendrimer that 1) contains 64 chromophoric units of three different types, and 2) is able to host a dye molecule. We have found that in such a host–guest system the encapsulated dye molecule collects electronic energy from all of the 64 chromophoric units of the dendrimer with high efficiency.

Dendrimer **1** (Scheme 1) consists of a polyamine core surrounded by 8 dansyl-, 24 dimethoxybenzene-, and 32 naphthalene-type units (dansyl is the commonly used name for the 5-dimethylamino-1-naphthalenesulfonyl chromophoric group). It can be viewed as the combination of the poly(propylene amine) (POPAM) dendrimer **2** with eight attached dendrons **3** (Scheme 1).

The absorption and emission spectra of dendrimer **2**, dendron **3**, and eosin **4** are shown in Figure 1. Dendron **3** contains three dimethoxybenzene- and four naphthalene-type

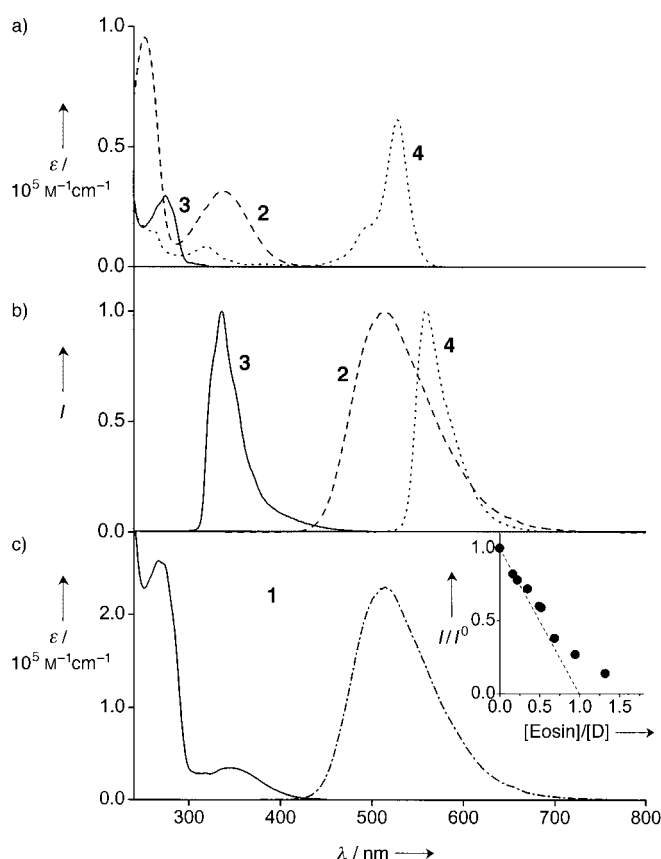
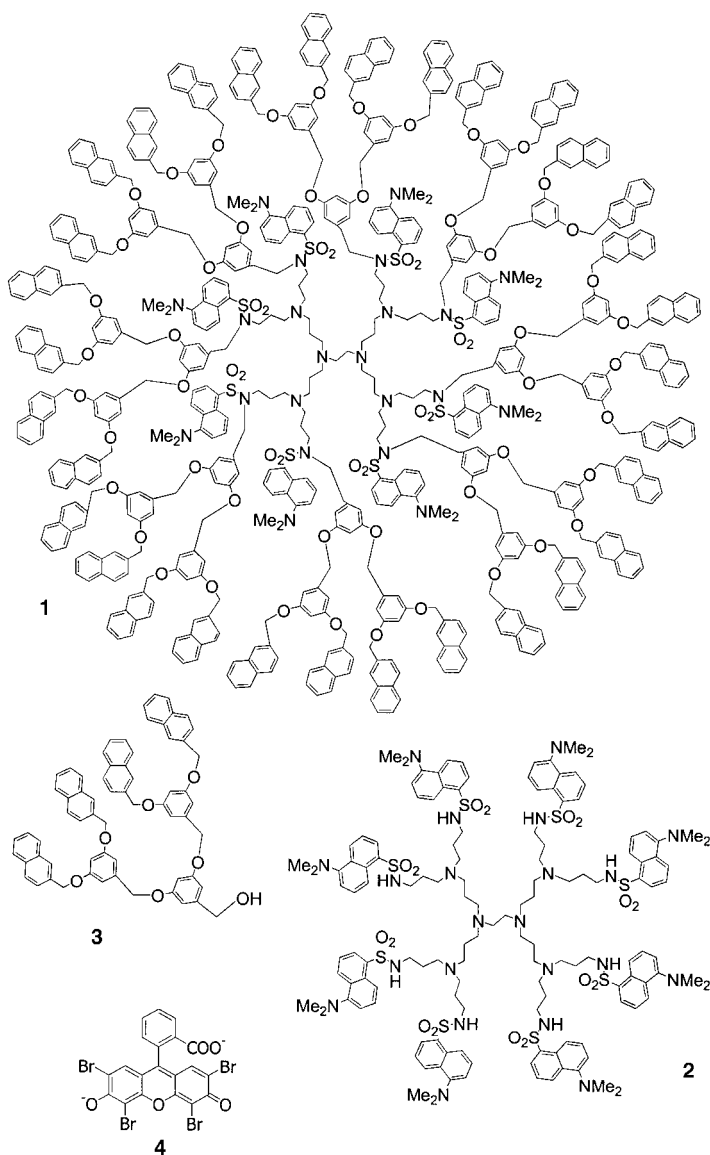


Figure 1. Absorption (a) and emission (b) spectra of dendron **3** (—, λ_{ex} = 287 nm), dendrimer **2** (---, λ_{ex} = 343 nm), and eosin **4** (•••, λ_{ex} = 500 nm). Absorption (—) and emission spectra (•••, arbitrary unit, λ_{ex} = 370 nm) of dendrimer **1** (c). Inset: decrease of dansyl fluorescence intensity on increasing [eosin]:[**1**] ratio. Experimental conditions: in dichloromethane at 298 K in all cases.

chromophoric units, whose absorption and fluorescence bands strongly overlap. The fluorescence band maximum (λ_{max}), quantum yield (Φ), and lifetime (τ) of dendron **3** are 336 nm, 0.019, and 4.6 ns, respectively. Dendrimer **2** exhibits the absorption bands of its dansyl chromophoric units (λ_{max} = 255 nm, ϵ = 96 300 M^{−1} cm^{−1}; λ_{max} = 340 nm, ϵ = 29 500 M^{−1} cm^{−1}). The broad fluorescence band shows a maximum at 514 nm with Φ = 0.27 and τ = 16 ns. Since eosin is not soluble in CH₂Cl₂, solubilization was achieved by addition of [18]crown-6.^[7f,8c] Under such conditions, a solution of eosin in CH₂Cl₂ shows a strong absorption band in the visible region (λ_{max} = 529 nm, ϵ = 61 000 M^{−1} cm^{−1}), and a fluorescence band with λ_{max} = 555 nm, Φ = 0.65, and τ = 3.8 ns. It is noticeable (Figures 1 a and b) that the fluorescence band of dendron **3** strongly overlaps the absorption band of dendrimer **2**, and that the fluorescence band of dendrimer **2** strongly overlaps the absorption band of eosin **4**.

The absorption spectrum of dendrimer **1** (Figure 1 c) is that which may be expected from the sum of the absorption spectra of its components, namely dendrimer **2** and eight dendrons **3**. The emission spectrum of **1** shows a strong dansyl-type fluorescence band, whereas the intensity of the fluorescence band of the units of dendron **3** is almost completely quenched ($\geq 95\%$). Since the fluorescence lifetime of dendron **3** is 4.6 ns, the rate constant for the quenching process



Scheme 1.

has to be at least $4 \times 10^9 \text{ s}^{-1}$. The quenching is accompanied by the sensitization of the dansyl fluorescence, which presumably occurs by singlet–singlet Förster-type energy transfer^[9] from the dimethoxybenzene- and naphthalene-type units to the dansyl units. This transfer is favored by 1) the large spectral overlap between donor emission and acceptor absorption, 2) the high molar absorption coefficient of the acceptor, and 3) the high fluorescence quantum yield of the donor.^[10] From the experimental viewpoint, however, the energy-transfer efficiency is difficult to measure because of band overlap. The estimated value of $80 \pm 25 \%$ does not allow us to rule out the presence of a minor quenching path based on electron transfer.

Previous investigations^[7f,8c] have shown that solutions of POPAM dendrimers such as **2** in CH_2Cl_2 are able to extract eosin, presumably in its monoprotonated form, from aqueous solutions. In such host–guest systems, the fluorescence of the dansyl units of the dendritic host was found to be quenched very efficiently by the presence of the guest. Therefore, we thought it was worthwhile investigating whether dendrimer **1**, whose “core” consists of the POPAM dendrimer **2**, was able to host eosin.

When a solution of dendrimer **1** in CH_2Cl_2 ($8.2 \times 10^{-6} \text{ M}$) was shaken with aqueous solutions containing eosin, the organic phase became colored, which indicated that eosin had been extracted. We have also confirmed^[7f,8c] that, in the absence of dendrimer, extraction of eosin by CH_2Cl_2 was practically negligible. The concentration of eosin extracted by the dendrimer, measured from the increase of the eosin absorption in the CH_2Cl_2 phase, was found to increase with increasing eosin concentration in the aqueous phase. Extraction of eosin is accompanied by the quenching of the dansyl fluorescence, which confirms that eosin interacts with the dendrimer.^[11] Eosin is likely to be located in the amine core of the dendrimer since: 1) as we have seen above, eosin is also extracted by dendrimer **2**, which does not contain naphthalene and dimethoxybenzene units, 2) the Fréchet dendron **3** does not extract eosin, thus indicating that the aromatic peripheral groups do not strongly interact with eosin, and 3) one of the major driving forces for the host–guest interaction is an acid (acidic eosin)–base (internal amine units) relationship, as already suggested by Baars and Meijer.^[6] for similar xanthene dyes.

The slope of the fluorescence quenching plot (Figure 1c, inset) at low eosin concentration ($[\text{eosin}]:[\mathbf{1}]$ less than 0.3) is approximately -1 , which indicates complete quenching of the fluorescence of any dansyl units of the dendritic host, even when each host can only encapsulate one eosin molecule.^[12] Assuming that the intensity of the unquenched fluorescence of a dansyl unit of a dendrimer hosting an eosin molecule is no greater than 5% of the original intensity (in an “empty” dendrimer), and considering that the intrinsic lifetime of the dansyl fluorescence is 16 ns, the rate constant for the quenching process must be higher than $1.2 \times 10^9 \text{ s}^{-1}$. A high quenching constant is indeed expected in view of the strong overlap between the emission spectrum of the dansyl units and the absorption spectrum of the eosin molecules (Figure 1a, b). A value of about $1 \times 10^{11} \text{ s}^{-1}$ can be estimated from the equation of the dipole–dipole (Förster) mechanism taken

at an average r value of 1 nm. Comparison between fluorescence intensities obtained upon excitation at 370 nm (dansyl absorption) and 520 nm (eosin absorption) showed that the quenching of the dansyl fluorescence by eosin does occur with high efficiency (at least 0.8). In summary, the excitation spectrum of the host–guest system closely matches the absorption spectrum, which demonstrates that eosin is able to collect light energy from the three different chromophoric groups of the host dendrimer **1**.

Examination of the fluorescence properties of the eosin molecules encapsulated into the dendrimers has revealed other interesting features of this fluorescent-host–fluorescent-guest system. When eosin is hosted in a solution of the dendrimer in dichloromethane, the fluorescence quantum yield is 0.29 and two exponential decays are observed, even at very low eosin concentration where there is a maximum of one eosin molecule per dendrimer. This observation suggests that eosin molecules can occupy two distinct sites (or two families of substantially different sites) in the interior of the dendrimer, a phenomenon that has been previously observed for poly(propylene amine) dendrimers.^[7f,8c] At least two different sites for the inclusion of a spin probe within an alternatively functionalized POPAM dendrimer have previously been noted by Jansen and Meijer.^[13]

In conclusion, we have shown that an eosin molecule encapsulated into dendrimer **1** (Figure 2) collects electronic energy from all 64 chromophoric units of the dendrimer, which consist of three different chromophoric types. Both intramolecular (that is, within the dendrimer) and intermolecular (dendrimer-host→eosin-guest) energy-transfer processes occur very efficiently by a Förster-type mechanism, because of the strong overlap between the emission and absorption spectra of the relevant donor/acceptor units.

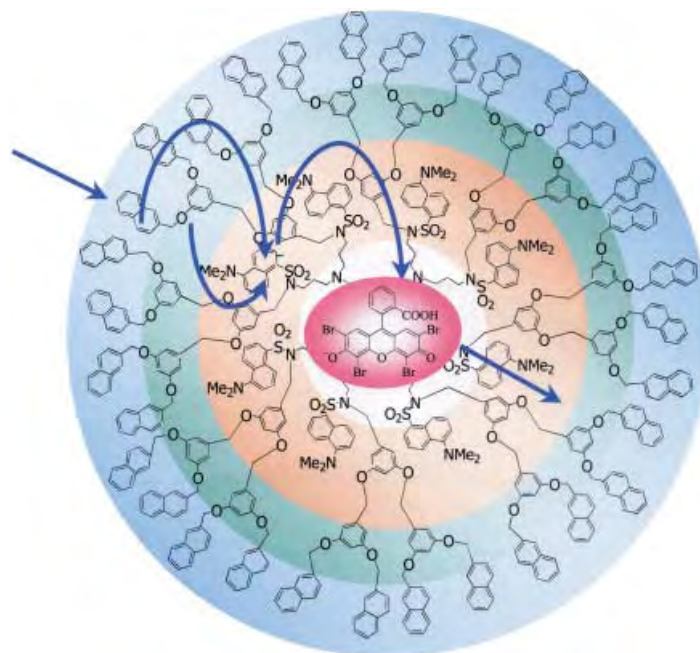


Figure 2. Schematic representation of the intramolecular (that is, within the dendrimer) and intermolecular (dendrimer-host→eosin-guest) energy-transfer processes. The exact eosin location is unknown.

Experimental Section

All syntheses were routinely carried out under an argon atmosphere. Starting materials (POPAM dendrimer G2, 3,5-dihydroxybenzyl alcohol, 2-bromomethylnaphthalene, dansyl chloride) were purchased from Aldrich. 3,5-Bis(3',5'-bis(2''-oxymethylnaphthyl)benzyloxy)benzyl bromide (obtained from precursor **3**) and **2** were synthesized according to literature procedures.^[14,15]

1: Cesium carbonate (200 mg) was added to a solution of **2** (50.0 mg, 0.019 mmol) in DMF (10 mL) under argon. 3,5-bis(3',5'-bis(2''-oxymethylnaphthyl)benzyloxy)benzyl bromide (193.0 mg, 0.19 mmol) in DMF (10 mL) was added to this solution, and the mixture was stirred for seven days, then filtered and the solvent evaporated. The residue was dissolved in CH₂Cl₂, washed with water, saturated NaHCO₃ solution, and again with water, then dried over Na₂SO₄ and evaporated. Purification by column chromatography on SiO₂ (63–100 µm) with chloroform/methanol (20:1) as eluent yielded a light-yellow solid in 48 % yield, m.p. 103–108 °C, *R*_f = 0.08 (chloroform/methanol 20:1). ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 1.59 (brs, 24H, CH₂), 2.13 (brs, 32H, NCH₂), 2.47 (brs, 52H, N(CH₃)₂ and N(CH₂)₂N), 3.35 (s, 16H, SO₂NCH₂), 4.30 (s, 16H, SO₂NCH₂Ar), 4.44 (s, 32H, ArOCH₂Ar), 4.97 (s, 64H, ArOCH₂Naph), 6.23 (m, 16H, CH_{Ar}), 6.35 (m, 8H, CH_{Ar}), 6.54–6.74 (brm, 56H, 48 CH_{Ar} and 8 CH_{Dans}), 7.22–7.51 (brm, 104H, 96 CH_{Naph} and 8 CH_{Dans}), 7.59–7.87 (bm, 136H, 128 CH_{Naph} and 8 CH_{Dans}), 8.14 (m, 8H, CH_{Dans}), 8.29 ppm (m, 16H, CH_{Dans}); ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): δ = 25.1, 44.9, 45.1, 50.1, 50.5, 51.2, 101.6 (2C), 106.6 (2C), 114.9, 119.3, 123.1, 125.3, 125.9, 126.1, 126.2, 127.6, 127.9, 128.2, 129.3, 129.6, 129.9, 130.1, 130.2, 132.9, 133.1, 134.2, 135.0, 138.6, 139.1, 151.6, 159.8, 159.9 ppm; C₆₅₄H₅₈₀N₂₂O₆₄S₈; *M*_w = 10028.24.

In all experiments, the aqueous phase was buffered at pH 7.0 using a phosphate buffer. Spectroscopic equipment and techniques have been described elsewhere.^[8b] The experiments were carried out in air-equilibrated solutions. Fluorescence quantum yields were standardized^[16] using naphthalene (*Φ* = 0.23 in deaerated cyclohexane)^[17a] for dendron **3**, quinine sulfate (*Φ* = 0.55 in 1N H₂SO_{4(aq)} solution)^[17b] for dendrimers **1** and **2**, and fluorescein (*Φ* = 0.90 in NaOH; 0.01M)^[17c] for eosin **4**.

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- [11] Dynamic quenching can be ruled out because of the short lifetime of dansyl fluorescence and the very low concentration (less than 10^{-5} M) of extracted eosin.
- [12] The curvature of the plot (Figure 1c, inset) at high eosin concentrations can be related to the fact that each dendrimer can host more than one eosin molecule, so that even at relatively high [eosin]:[**1**] ratios, there are still some “empty” dendrimers, which is in agreement with the unquenched fluorescence lifetime.
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Synthesis of Amphiphilic Conjugated Diblock Oligomers as Molecular Diodes**

Man-Kit Ng and Luping Yu*

Nearly three decades ago Aviram and Ratner proposed that individual molecules of the type donor–spacer–acceptor (D–s–A) placed between two electrodes would act as molecular rectifiers under a suitable bias voltage.^[1] Previous attempts to provide experimental proof of molecular rectifiers were complicated by difficulty in establishing reproducible electrical contacts between the metal and single molecules, the junction rectifying effect at the metal–molecule interface due

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to the Schottky barrier and/or salt formation, and the work function difference (however small) between anode and cathode in most configurations of metal/molecules/metal heterostructures. Still, there is uncertainty about the number of active molecules investigated in these microscopic systems.^[2–6] More recently, as the drive towards miniaturizing electronic components intensifies, the development and realization of molecular-scale electronic devices based on assemblies of atoms and/or molecules has become an ultimate goal.^[7] Various basic device components such as molecular wires, rectifying diodes, field-effect transistors, and single-electron transistors have been demonstrated in a host of materials, ranging from semiconductor and metal nanowires, carbon nanotubes, fullerenes, and small organic molecules to biomolecules.^[2–13] However, there is no report on p-n junction molecules that are akin to those in semiconductors but with much more structural versatility. These functional molecular components are crucial to the development of molecular electronics.

Just like semiconductor materials, the inspiration for p-n junction molecules can be found in semiconducting organic materials, conjugated polymers, and oligomers. These materials have been exploited as key electronic components in the development of a number of technologically important applications such as light-emitting diodes, plastic transistors, photovoltaic solar cells, sensory devices, and diode lasers.^[14] These materials have tremendous structural versatility: p-type and n-type polymers with semiconducting properties have been synthesized. We introduce a new and useful concept in designing p-n junction molecules, a relatively simple diblock molecule incorporating two different conjugated blocks with opposite electronic demands. We show that this conjugated diblock molecule indeed exhibits a diodelike rectifying effect.

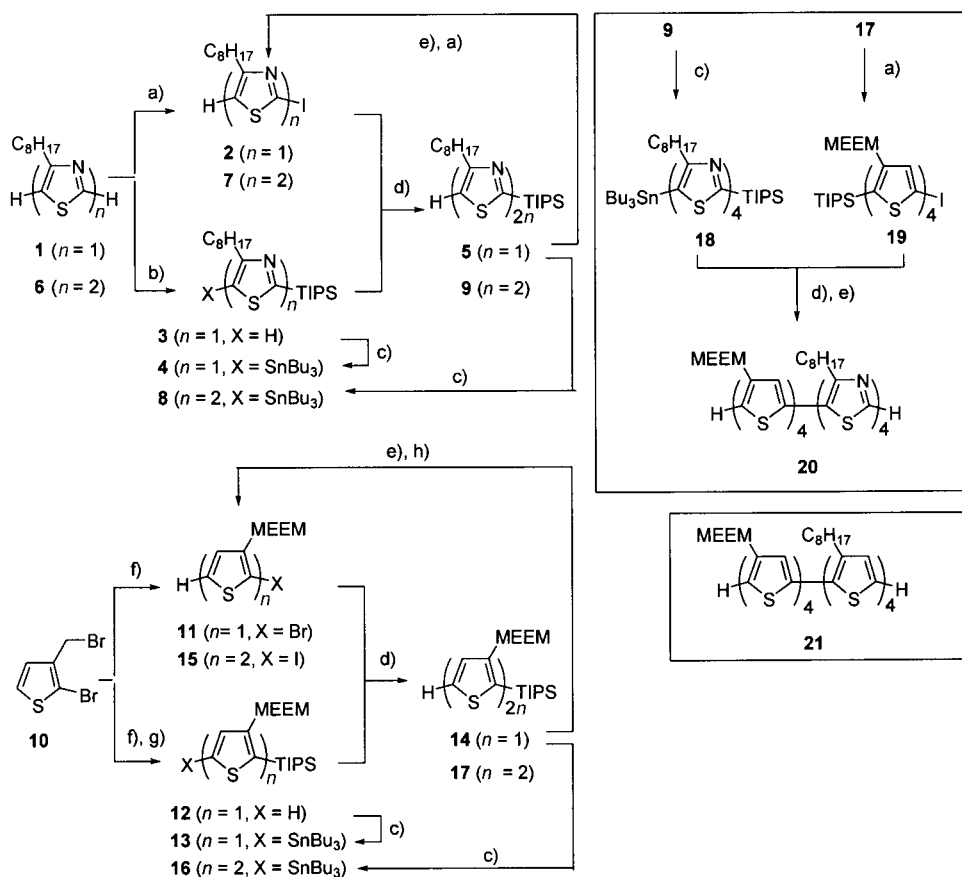
Polythiophenes (PT) and oligothiophenes (OT) are well-known p-type semiconducting materials, whereas polythiazoles are known to be electron-deficient compounds.^[15] Our first target molecule was a regioregular, head-to-tail coupled diblock co-oligomer comprising an electron-rich oligo(3-alkylthiophene) as the donor block and an electron-poor oligo(4-alkylthiazole) as the acceptor block. Two different alkyl side groups with contrasting hydrophilicity/hydrophobicity were selectively incorporated in the two blocks. The surfactant-like amphiphilic conjugated diblock oligomer can be

manipulated by the Langmuir–Blodgett (LB) technique at the air–water interface.

The synthetic approach to the diblock co-oligomer is shown in Scheme 1. The diblock co-oligomer **20** was synthesized by a Stille coupling between **18** and **19**, which were both obtained almost quantitatively from the corresponding precursors **9** and **17**, respectively. It is noteworthy that electrophilic iodination of **17** proceeded with complete chemo- and regioselectivity at the unsubstituted α position. After the Stille reaction was completed, in situ desilylation by addition of excess TBAF afforded the amphiphilic head-to-tail coupled oligothiophene-oligothiazole diblock system **20**.

For the purpose of comparison with the p-n junction molecules, a reference compound, amphiphilic octathiophene **21** with the same alkyl side chains, was also synthesized (Scheme 1). This reference compound is almost an exact replica of the diblock molecule except for the replacement of the nitrogen atoms on the electronegative thiazole ring by methine groups.

The amphiphilic conjugated diblock molecule was oriented at the air–water interface by the Langmuir–Blodgett technique, with the donor part adjacent to the water subphase and the acceptor block away from it. A typical pressure–area (P – A) isotherm of the diblock molecules is shown in



Scheme 1. Synthetic approach to diblock co-oligomer **20** and reference compound **21**. Reagents and conditions: a) LDA, THF, -78°C , then I_2 ; b) LDA, THF, -78°C , then TIPSOTf; c) $n\text{BuLi}$, TMEDA, THF, -78°C , then Bu_3SnCl ; d) 2.5 mol % $[\text{Pd}_2(\text{dba})_3]$, 20 mol % PPh_3 , 50 mol % Cu_2O , DMF, 115°C ; e) TBAF, THF, RT. f) NaH, diethyleneglycol monomethyl ether, THF, 0°C ; g) $n\text{BuLi}$, Et_2O , -78°C , then TIPSOTf; h) NIS, $\text{CHCl}_3/\text{HOAc}$. LDA = lithium diisopropylamide, TIPSOTf = triisopropylsilyl trifluoromethanesulfonate, TMEDA = tetramethylethylenediamine, dba = dibenzylidene acetone, TBAF = tetrabutylammonium fluoride, NIS = *N*-iodosuccinimide; MEEM = methoxyethoxyethoxymethyl.

Figure 1 a. As the molecular monolayer is compressed, the surface pressure increases slowly in the region between 230 and $130 \text{ \AA}^2 \text{ mol}^{-1}$, followed by a kink at $P \sim 14 \text{ mN m}^{-1}$ ($A \sim 130 \text{ \AA}^2 \text{ mol}^{-1}$), which is tentatively assigned as a phase

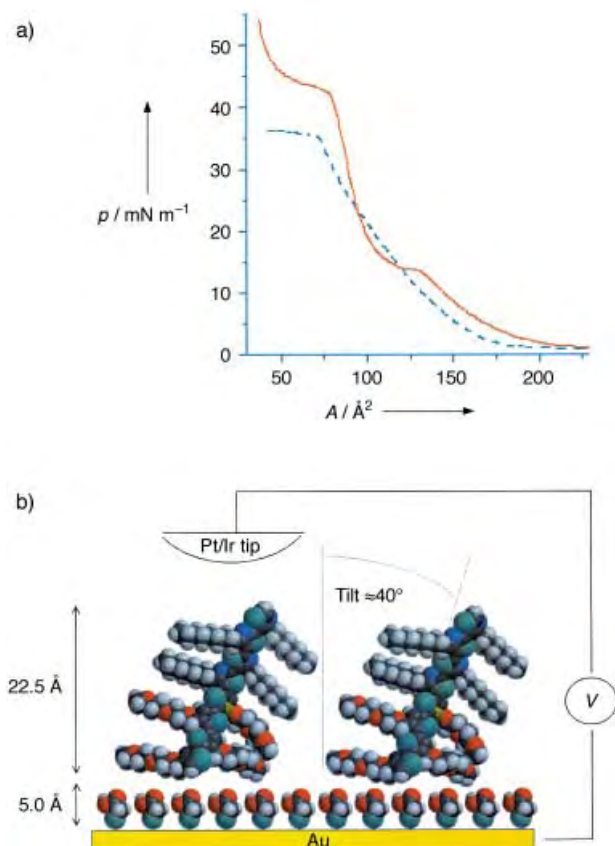


Figure 1. a) Surface pressure–area isotherms of conjugated diblock oligomer **20** (red solid line) and the reference model oligomer **21** (blue dashed line). Monolayers of **20** and **21** were transferred to a hydrophilic gold substrate at 35 mN m^{-1} and 28 mN m^{-1} , respectively, 5 mN m^{-1} below collapse pressure. b) Plausible orientation of a LB monolayer of diblock molecules on a hydrophilic gold surface modified with a thioglycolic acid monolayer.

transition from the initially flat-lying conformation of the monolayer to an increasingly more perpendicular orientation. This is followed by a monotonic increase in surface pressure with a characteristically steeper slope (solid-state region). Close packing of the molecules continues until collapse of the monolayer was observed at approximately $80 \text{ \AA}^2 \text{ mol}^{-1}$. Extrapolation of the linear portion of the solid-state region of the isotherm to zero surface pressure gives an estimate of the area ideally occupied by an isolated molecule ($112 \text{ \AA}^2$) at infinite dilution. This value is in fairly good agreement with that determined ($115 \text{ \AA}^2$) from the space-filling model of the AM1-optimized geometry in the gas phase (Figure 1 b). The Langmuir monolayer was subsequently transferred onto glass, silicon wafer, or hydrophilic gold substrates with a transfer ratio of 1.0 ± 0.05 . The LB monolayer was fully characterized by optical ellipsometry and UV/Vis spectroscopy. After careful drying of the sample, the electrical properties of the monolayer were investigated by using scanning tunneling

microscope (STM) and scanning tunneling spectroscopy (STS).

After a stable STM scan was obtained, the feedback loop for the STM control was briefly interrupted. The Pt/Ir STM tip (grounded to zero potential) was then held at a constant position above the film; the tip–sample separation was determined by the impedance used, which typically ranged from 60 to $300 \text{ G}\Omega$ in our experiments. High impedance was used throughout the STM experiment to avoid large fluctuations in tip movement and prevent mechanical damage to the sample surface. The voltage was then ramped from positive to negative bias while the current tunneling through both the air gap and the molecule was recorded. These current–voltage (I – V) measurements were performed at various setpoint tunnel currents in order to minimize artifacts resulting from strong tip–sample interactions. As can be seen from Figure 2 a, pronounced asymmetric I – V behavior was consistently observed at various setpoint tunneling currents, indicative of intrinsic molecular p–n junction character in the diblock molecule. In the STM convention, the direction of easy electron flow corresponds to electron tunneling from the STM

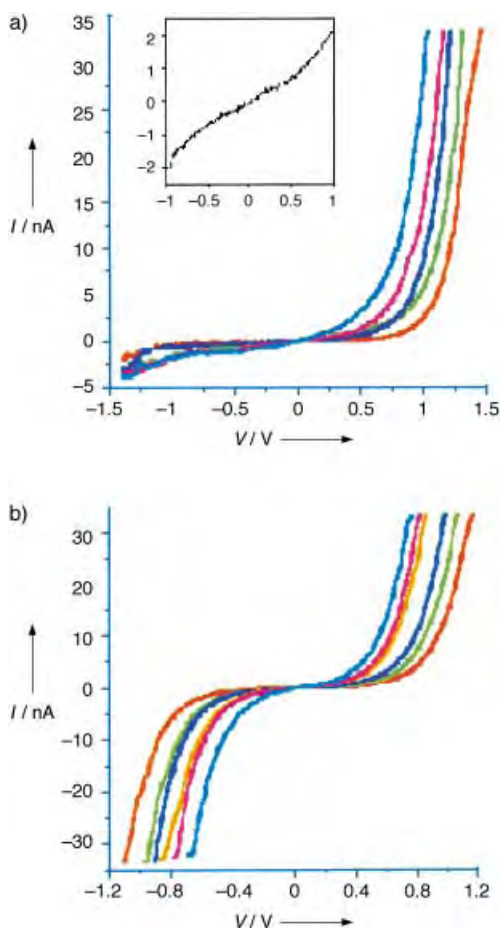


Figure 2. a) Current–voltage plots for a LB monolayer of diblock oligomer **20** measured with the tunneling current setpoint at different values ($I_{\text{set}} = 2$ (red), 4 (green), 6 (blue), 8 (purple), 10 pA (light blue)) and a bias voltage of $+600 \text{ mV}$. The inset shows the I – V characteristics of a gold surface modified with a thioglycolic acid monolayer. b) I – V curves for a LB monolayer of the reference oligomer **21** measured with the tunneling current setpoints at different values ($I_{\text{set}} = 1$ (red), 2 (green), 4 (blue), 6 (orange), 8 (purple), 10 pA (light blue)) and a bias voltage of $+600 \text{ mV}$.

tip to the acceptor part (oligothiazole) of the sample. The average turn-on voltage in the positive sample bias region is about 0.65–0.75 eV, whereas only small current signals were recorded in the reverse bias. The rectification ratio remains small in the low-bias regimes but increases gradually to about 18 at a bipolar bias of 1.0 V. The slight differences in turn-on voltages at various current setpoints result mainly from the difference in tunneling gap resistances between the tip and molecules, as was previously observed.^[16] The differential conductance (dI/dV) was obtained from the data in Figure 2 a, which is roughly proportional to the local density of states (LDOS) of the sample. It is a good measure of the rectifying behavior of the diblock molecules. Large asymmetry is observed in the corresponding conductance versus voltage spectra with threshold voltages at a bipolar bias of about 0.7 V (Figure 3 a). It is clear that the direction of easy electron flow is from the tip to the thiazole block and then to the thiophene block. This is consistent with the fact that the thiophene block is electron donating and the thiazole block is electron accepting. In the excited state the thiazole block would bear negative charge, the thiophene block positive charge, and the electrons would flow from the thiazole to the thiophene block.

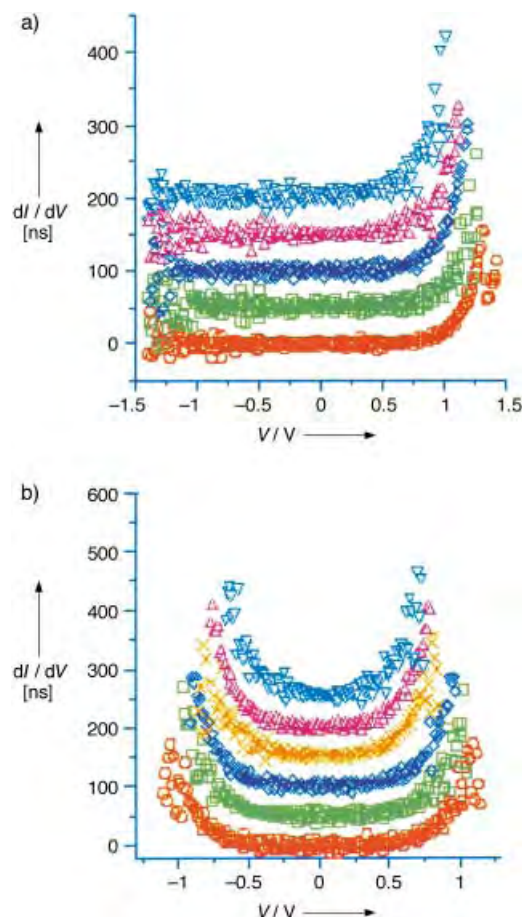


Figure 3. a) Differential conductance (dI/dV) of a LB monolayer of diblock oligomer **20** obtained from the data shown in Figure 2 a ($I_{\text{set}} = 2$ (red), 4 (green), 6 (blue), 8 (purple), 10 pA (light blue)). Each curve has been offset in the vertical direction for clarity. b) Differential conductance (dI/dV) of a LB monolayer of reference oligomer **21** obtained from the data shown in Figure 2 b ($I_{\text{set}} = 1$ (red), 2 (green), 4 (blue), 6 (orange), 8 (purple), 10 pA (light blue)). Each curve has been offset in the vertical direction for clarity.

Many rectifying diodes based on molecular systems have been reported previously, but few are truly of molecular origin.^[2–6] In order to exclude contributions to the observed I – V asymmetry from other effects such as molecule interfacial effect between the LB monolayer and the underlying thioglycolic acid monolayer, the difference in the work functions of the electrodes (Au substrate and Pt/Ir tip), or other poorly controlled experimental parameters, control LB films of the reference molecule were prepared and subjected to STS studies under the same experimental conditions as described above. The spectroscopic measurements revealed only symmetric I – V behavior at various setpoint currents (Figure 2 b). The corresponding tunneling differential conductance clearly shows the molecular wire behavior, again with threshold turn-on voltages depending upon the preset tunneling gap resistance (Figure 3 b). The electron-transfer mechanism (tunneling or through-bond transfer) for the rectifying effect observed in our diblock system is not completely clear at this stage; further theoretical treatment to clarify this point is in progress.

In summary, an amphiphilic conjugated diblock oligomer exhibiting a molecular p–n junction has been synthesized and its rectification effect demonstrated. The synthetic approach developed is rather general for coupling heterocycles and should lead to the synthesis of other p–n junction molecules. The clear distinction between the I – V behaviors for the diblock and the reference molecules in the present study constitutes concrete evidence for the molecular origin of the observed rectifying effect.^[17] The rectifying conjugated molecule described in this report provides an easy entry to molecular-scale electronic components for the design of logic circuits. Many variations in structure and electronic properties of this diblock system can be envisaged, and optimizations of these features are the subject of ongoing efforts.

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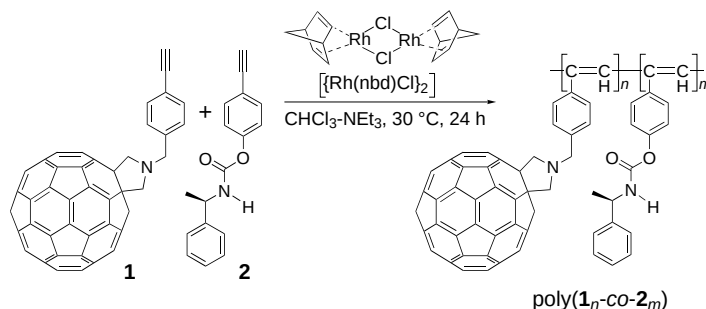
A Helical Array of Pendant Fullerenes on an Optically Active Polyphenylacetylene**

Tatsuya Nishimura, Kohei Takatani, Shin-ichiro Sakurai, Katsuhiro Maeda, and Eiji Yashima*

The synthesis of [60]fullerene-containing polymers with a well-defined structure has aroused considerable interest in recent years because of their possible applications in the wide fields of materials^[1] and biological sciences.^[2] However, previous studies of C₆₀-based polymers have mainly focused on their structures and properties, either in the bulk state or as thin films. We have previously reported that stereoregular polyphenylacetylenes bearing optically active side groups form a predominantly one-handed helical structure and exhibit a characteristic induced circular dichroism (CD) in the main chain region, both in solution as well as in the solid state.^[3] We have also investigated the effect that the bulkiness of the phenyl-group substituents of the achiral comonomers had on the formation of the helical conformations derived from copolymers with optically active bulky phenylacetylenes in solution. We found that the optical activity (CD intensity and specific rotation) of the copolymers increased with increased bulkiness of the achiral comonomers.^[3b] This unique cooperative property of helical polyphenylacetylenes stimulated us to synthesize an optically active, C₆₀-based helical polyphenylacetylene where the pendant achiral C₆₀ moieties would possibly be arranged in a helical array, with a one-handed screw-sense, thus showing optical activity in the fullerene region. Tour and co-workers recently reported an elegant method to construct a helical array of C₆₀ molecules through electrostatic interactions of a water-soluble, cationic C₆₀ derivative, with the phosphate groups along the DNA backbone acting as a template. However, the chiroptical property of the complex has not yet been reported.^[4]

Optically active, *cis-transoidal* polyphenylacetylenes with pendant C₆₀ groups were prepared by the copolymerization of an achiral C₆₀-bound phenylacetylene (**1**) and an optically active phenylacetylene with an (*R*)-[(1-phenylethyl)carba-

moyl]oxy substituent (**2**) on the phenyl group,^[3b] using a rhodium catalyst [{Rh(nbd)Cl}₂] (nbd = norbornadiene, Scheme 1). The fullerene monomer was prepared by the reaction of C₆₀ with *N*-(4-ethynylbenzyl)glycine by using the



Scheme 1. Synthesis of poly(**1-co-2**_m).

Prato reaction.^[1a,5] The copolymerization results are summarized in Table 1. The fullerene homopolymer was insoluble in common organic solvents, but the copolymers were partially soluble in THF and chloroform, depending on the content of

Table 1. Copolymerization results of achiral **1** and optically active **2** with [{Rh(nbd)Cl}₂] in chloroform in the presence of triethylamine at 30 °C for 24 h.^[a]

Entry	1 [mol %]	2 [mol %]	1 + 2 [M]	Yield [%] ^[b]	Polymer		
					Yield [%]	MeOH-insoluble part 1 [mol %] ^[c]	<i>M</i> _n × 10 ^{−4} ^[d]
1	100	0	0.016	60.4	–	100	–
2	10	90	0.043	–	52.0	12.3	8.4
3	20	80	0.033	15.2	72.0	22.1	1.8
4	30	70	0.026	60.5	20.8	26.9	2.4

[a] [**1** + **2**]/[triethylamine] = 1; [**1** + **2**]/[Rh] = 50. [b] Chloroform insoluble part. [c] Estimated by ¹H NMR spectroscopy. [d] Determined by SEC (polystyrene standards).

the C₆₀ units. Figure 1 shows the CD and absorption spectra of poly(**1**_{0.1-co-2}_{0.9}) in THF. The copolymer exhibited an intense induced CD (ICD) in the π-conjugated main-chain region (280–500 nm), the magnitude of which monotonically increased with decreasing temperature. A similar temperature-dependent relationship for the Cotton effect observed in the main-chain region of optically active polyphenylacetylenes was also observed for the homopolymer, poly-**2**.^[6] These observations suggested that the induced helical conformation of the copolymer was dynamic in nature as a result of cooperative interactions among the pendant groups, and the helical screw-sense preference (right- and left-handed helices) of the copolymer increased with a decrease in temperature.

Poly(**1**_{0.1-co-2}_{0.9}) displayed almost no detectable absorption and CD at wavelengths over 600 nm in dilute solution (Figure 1) because of the low concentration of the C₆₀ units. However, at higher concentrations, a remarkable CD induction was observed above 600 nm at temperatures lower than −40 °C, which is characteristic of the fullerene chromophore for the copolymer (inset in Figure 1); the ICD intensity further increased at −80 °C. The sudden onset and rapid increase in the optical activity of the achiral C₆₀ cores in the copolymer are indicative of a helical array of the C₆₀ units with

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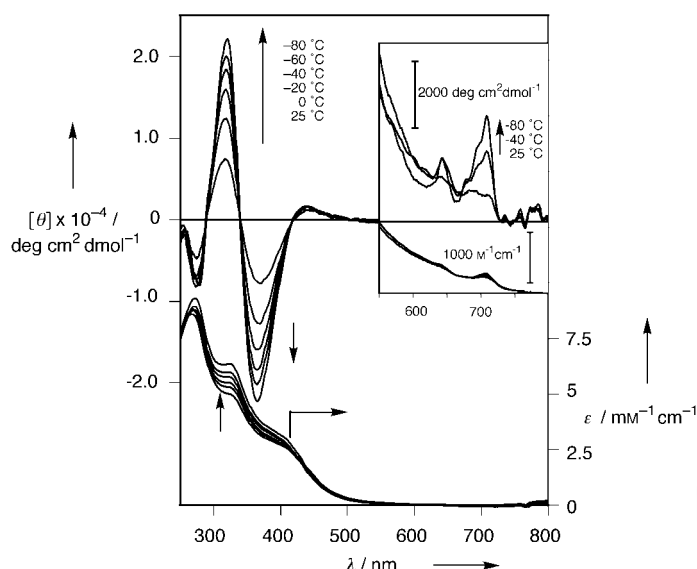


Figure 1. CD and absorption spectra of poly($1_{0.1}$ -co- $2_{0.9}$) in THF solution (0.11 mg mL^{-1}) at various temperatures. The inset shows the corresponding CD and absorption spectra in the fullerene region in THF at a higher concentration (4.6 mg mL^{-1}). The molar concentrations were calculated based on the monomer units and C_{60} units (inset).

a one-handed screw-sense through the polyphenylacetylene (Figure 2) because the C_{60} units themselves are achiral.^[7] The other copolymers (poly($1_{0.2}$ -co- $2_{0.8}$) and poly($1_{0.3}$ -co- $2_{0.7}$)) also exhibited similar ICDs in the same wavelength region (600–800 nm). This is, to the best of our knowledge, the first induction of chirality upon achiral fullerenes, derived from

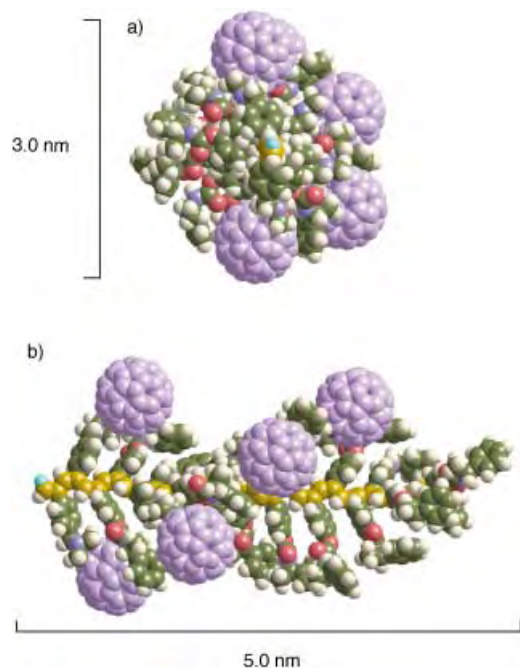


Figure 2. A possible helical structure of poly($1_{0.2}$ -co- $2_{0.8}$) (20-mer). Space-filling models are shown in the top (a) and side views (b). The fullerene units are assumed to arrange in a left-handed helical array along the right-handed polyacetylene main chain. The helix-sense is tentative, but the copolymer should have a helical conformation (either a right- or left-handed helix), as it exhibits an ICD in both the main-chain and the fullerene chromophoric regions.

their helical arrangement in polymers. The estimated CD intensities for the fullerene chromophore region of the copolymers were based on the content of C_{60} incorporated into the copolymer chains.^[8] These values were as large as those for chiral monosubstituted fullerenes^[9] and C_1 -symmetric chiral bis-substituted fullerenes,^[10] but were smaller by one or two orders of magnitude than their C_2 -symmetric counterparts.^[11]

Atomic force microscopy (AFM) provided an insight into the structure and morphology of the helically arranged C_{60} -based copolymers. Figure 3 shows typical AFM images of the high-molecular-weight fraction of poly($1_{0.1}$ -co- $2_{0.9}$) deposited

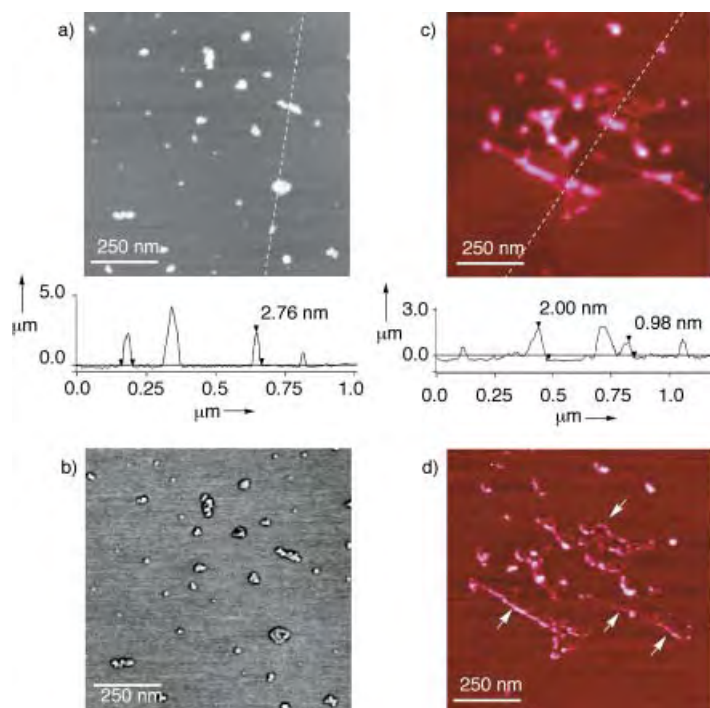


Figure 3. Tapping-mode AFM height (a, c) and phase (b, d) images of poly($1_{0.1}$ -co- $2_{0.9}$) cast from a dilute solution in THF on mica (a, b) and HOPG (c, d). The higher-molecular-weight part of the copolymer obtained by SEC fractionation was used. The height profiles measured along the white lines in the images are also shown. The arrows in (d) indicate the typically observed left-handed helices.

on a freshly cleaved mica surface and on highly oriented pyrolytic graphite (HOPG). The high-molecular-weight fraction of poly($1_{0.1}$ -co- $2_{0.9}$) was obtained by size exclusion chromatography (SEC) fractionation using THF as the eluent. The AFM images on mica cast from the fractionated dilute THF solution reveal isolated particles (average height: $2.6 \pm 1.3 \text{ nm}$), which are formed because the pendant C_{60} groups of the copolymer aggregate on mica to form an assembly (cluster) through repulsive interactions between the hydrophobic C_{60} units and hydrophilic mica substrates.^[12] On the other hand, rather extended and individual copolymer chains (average height: $2.1 \pm 0.8 \text{ nm}$) can be seen together with isolated particles on HOPG prepared by the same procedure. These results indicate that the attractive force between the pendant C_{60} groups and the substrate plays a critical role in the morphology of the C_{60} -based polymers.^[13]

The phase images of the copolymer on HOPG feature a particularly interesting left-handed helical shape (marked by arrows in Figure 3d).^[14] Although we could not distinguish the C₆₀ and chiral pendant groups of the copolymer by using AFM, these helical-shaped images may be closely correlated to the macromolecular helical chirality of the polyphenylacetylenes. Scanning tunneling microscopy (STM) may be useful to obtain higher resolution images on HOPG and the results will give us direct information concerning the helicity of the copolymers.^[15] The work is now in progress.

In summary, we have prepared and characterized the first example of an optically active helical polymer bearing pendant achiral C₆₀ groups which arrange in a helical array with a predominant screw-sense along the polymer backbone. Although such a helical array of the C₆₀ units, which exhibits optical activity in the fullerene chromophore region, is presently possible at low temperatures, we believe that the rational design and synthesis of helical polyacetylenes using more bulky chiral pendant groups will afford more stable C₆₀-based helical polymers. This methodology is also useful for constructing a novel helical polymer with the desired pendant in a one-handed helical array.

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Changeable Pore Sizes Allowing Effective and Specific Recognition by a Molybdenum-Oxide Based “Nanosponge”: En Route to Sphere-Surface and Nanoporous-Cluster Chemistry**

Achim Müller,* Erich Krickemeyer, Hartmut Bögge, Marc Schmidtman, Soumyajit Roy, and Alois Berkle

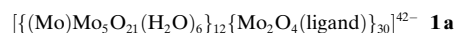
Dedicated to Professor Jean-Marie Lehn

A current challenge in nanotechnology is to mimic material constructions and molecular-recognition-type responsive sensing of biological systems. This challenge becomes especially attractive when nanometer-sized objects can be constructed with tailor-made building blocks, this is possible with our unique giant sphere or ring-shaped molybdenum oxide based objects which are made up of {(Mo)Mo₅} building blocks and show a huge variety of functionalities, and hence reactivities, comparable to the much smaller fullerenes.^[1]

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Herein we refer to the unusual spherical molybdenum oxide based nanoobject **1a** (see ref. [1a]) which has responsive reactivity—like that of a nanosponge. This type of nanoobject may open up new techniques in supramolecular nanotechnology for efficient and specific recognition by a large number of pores/receptor sites, similar to the classical macrocyclic ligands.^[2] The maximum pore diameter of a related $\{\text{Mo}_n\text{O}_m\}$ ring is currently around 0.8 nm. However, the pores sizes are variable since fixed basic pentagonal $\{(\text{Mo})\text{Mo}_5\}$ type units (pent) of the cluster object $\{(\text{pent})_{12}(\text{link})_{30}\}$ can be connected with different linkers (link).



Whereas monotopic receptors can only accept one guest, polytopic receptors can bind several (different) substrates/guests simultaneously. This latter type of interaction depends, corresponding to cooperative effects, not only on the type and number of binding sites but also on the overall object symmetry. For the host system **1a** investigations of cooperative, allosteric, and regulatory effects are all, in principle, possible. Additionally in the reported compound, there are quite a large number of different sets of equivalent atoms of the cluster shell which mark out two Platonic and four Archimedean solids, two of which, the rhombitruncated icosidodecahedron and the rhombicosidodecahedron, are the most complex of these solids and are observed now for the first time in chemistry (see Table 1). The results presented herein can be considered as a starting point for *sphere-surface* and *nanoporous-cluster* chemistry with the possibility of use for extended structures and also for interdisciplinary aspects, such as, modeling spherical virus surfaces,^[3a] for problems of discrete mathematics regarding spherical-object tilings,^[4,5] as well as for catalytic and biomimetic processes because of the presence of large pores providing access to the nano-sized cavities. Spherical-object tilings were important for understanding virus structures in connection with Buckminster Fuller's geodesic-dome constructions^[3] and even fascinated the artist M. C. Escher.^[4c] Additionally, a new type of endohedral clusterization of the associated H_2O molecules is observed upon encapsulation of guest molecules which close the pores, a situation formally comparable to a cell response on extracellular molecules interacting with a cell-surface receptor.

Spherical nanoobjects of the type $\{(\text{pent})_{12}(\text{link})_{30}\}$, with icosahedral symmetry, can be constructed from 12 $\{(\text{Mo})\text{Mo}_5\}$ type pentagonal units and 30 (different) linkers,^[1] allowing not only overall object sizing but also a sizing of the (because of symmetry reasons) large number of (twenty) tailor-made pores. The construction principle corresponds to that

Table 1. Chemistry creates icosahedral tilings of a sphere: Archimedean and Platonic solids formed by different sets of equivalent atoms of the shell of **2a**.^[a]

Atom sets	Platonic/Archimedean solid
12 Mo(O ₇)	icosahedron (Platonic)
20 C	dodecahedron (Platonic)
30 (P/S)	icosidodecahedron
30 {Mo ₂ }	truncated icosahedron
60 N	rhombicosidodecahedron
12 × 5 Mo(O ₆)	rhombicosidodecahedron
120 H	rhombitruncated icosidodecahedron

[a] In the text we always refer to idealized polyhedra; see also Figure 5 for H_2O clusters.

of icosahedral/spherical viruses.^[3] If the linker is built up, for example, by a binuclear $\{\text{Mo}_2\}$ type unit, that is, two edge-shared $\{\text{MoO}_6\}$ octahedra, the pores on the surface of the spherical system correspond to $\{\text{Mo}_9\text{O}_9\}$ rings with diameters between around 0.6–0.8 nm which are formed by three $\{\text{Mo}_2\}$ and three $\{\text{Mo}_1\}$ type units^[1] (see Figure 1 a,b). In the case of

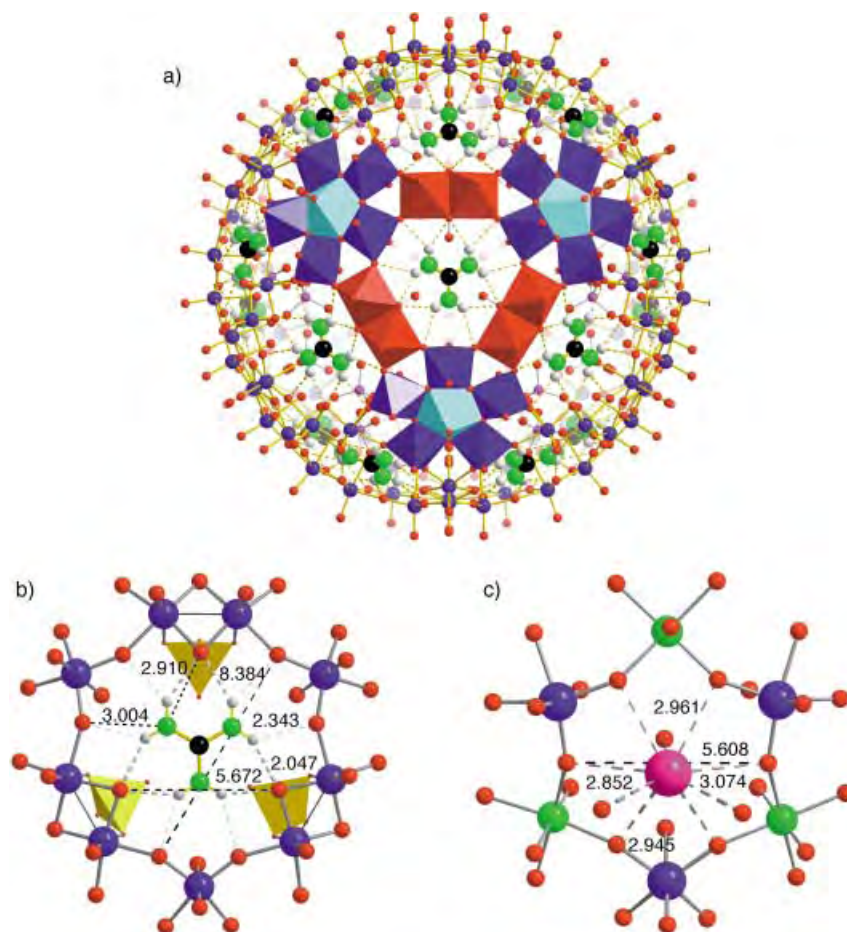


Figure 1. a) Structural details of the spherical cluster anion **2a** in ball and stick representation (diameter approximately 3 nm and cavity diameter around 2 nm), in which three pentagonal $\{(\text{Mo})\text{Mo}_5\}$ units (light and dark blue) and three $\{\text{Mo}_2\}$ linkers (red) are highlighted in polyhedral representation and form an $\{\text{Mo}_9\text{O}_9\}$ ring/pore with an encapsulated $(\text{NH}_2)_3\text{C}^+$ ion (C black, N green). b) The interatomic distances for the $\{\text{Mo}_9\text{O}_9\}$ rings in **2a** reflecting the interaction between the receptors and substrates, these are comparable with those known from related single host–guest systems with classical macrocycles^[2d,g,17] (Mo blue, O red, C black, H gray, N green, the PO_2H_2^- and SO_4^{2-} ligands are shown as yellow tetrahedra). c) The interatomic distances of the unpublished cluster with $\{\text{M}_6\text{O}_6\}$ rings and integrated K^+ ions mentioned in ref. [6c]; K^+ large pink sphere, Mo/V linker atoms green, Mo blue, O red.

mononuclear linkers M^{n+} ($M = \text{Fe}^{3+}$,^[6a] MoO^{3+} ,^[6b] or $\{\text{VO}^{2+}/\text{MoO}^{3+}\}$ ^[6c]) the correspondingly smaller $\{\text{Mo}_6\text{O}_6\}$ rings are formed and are just large enough to “capture” K^+ ions^[6c] (Figure 1c). Remarkably, each of the 20 pores/rings has, in principle, receptor properties comparable to those of the classical crown ethers of supramolecular chemistry.^[2] It could now be shown that the icosahedral clusters **1a**, known with different ligands^[6d] which stabilize the $\{\text{Mo}_2\text{O}_4\}^{2+}$ linker groups, have, for example, the appropriate pore size to “encapsulate” rather large complementary substrates present in the solution, for example, guanidinium cations (Figure 2).

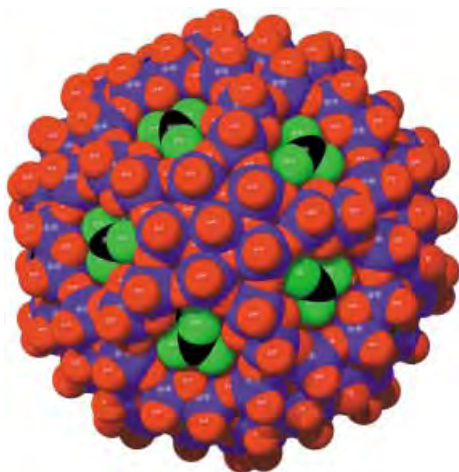
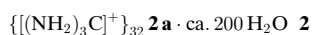
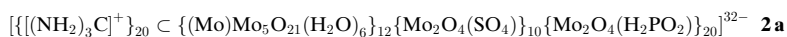


Figure 2. Structure of **2a** (space filling representation) illustrating the “lock and key” type complementarity between the host and its $[(\text{NH}_2)_3\text{C}]^+$ guests (color code as in Figure 1b).

Correspondingly, by reaction of **1a** (with ligand = H_2PO_2^-) with guanidinium sulfate species **2a** is formed and isolated as the crystalline guanidinium salt **2** (space group $R\bar{3}m$) in nearly quantitative yield. As the unit cell of **2** can be approximately reduced to a cubic type we find besides rhombus-shaped crystals also truncated cubes and octahedra. Compound **2** was characterized by elemental analysis, thermogravimetry (to determine the amount of water of crystallization), spectroscopy (IR, Raman), single-crystal X-ray diffraction analysis^[7] and bond valence sum (BVS)^[8] calculations (to determine the positions of the H_2O ligands and to differentiate between the Mo^{VI} and Mo^{V} centers) as well as with ^{13}C solid-state NMR spectroscopy.



In **2** the guanidinium cations $[(\text{NH}_2)_3\text{C}]^+$, with regard to their shape and symmetry, fit exactly into the pores, that is, the $\{\text{Mo}_9\text{O}_9\}$ rings (similar to the K^+ ions into the smaller $\{\text{M}_6\text{O}_6\}$ rings; see Figure 1c and ref. [6c]), and the C_3 axes of the icosahedral point group (I_h) pass through their centers. The interaction between the macrocyclic ring, that is, the bridging oxygen atoms of the binuclear $\{\text{Mo}_2\}$ units, and the three H_2N groups of the 20 guanidinium cations is through hydrogen

bonding and corresponds to that observed in a monotopic receptor (see Figure 1b).^[17]

A fragment of **2a**, based on the 12 pentagonal $\{(\text{Mo})\text{Mo}_5\}$ units with altogether 60 $\{\text{MoO}_6\}$ octahedra, is an inorganic analogue of the most simple so-called $T=1$ virus type containing only 12 pentamers (= 60 proteins).^[3] In both cases the 60 units are packed around the fivefold axes. Noteworthy is the next larger so-called $T=3$ icosahedral virus type—for instance the tomato bushy stunt virus (TBSV)—in which, besides the 12 pentamers, additionally 20 hexamers, that is, 120 proteins are placed around the local sixfold axes of an icosadeltahedron (Figure 3).^[3a] a situation comparable to the positioning of the $20 \times 6 = 120$ H atoms of the guanidinium cations of **2a** on an icosadeltahedron (Figure 3). Reactions of the ball-type cluster with its 20 receptors can be regarded as models for the manipulation of spherical icosahedral viruses.^[9a]

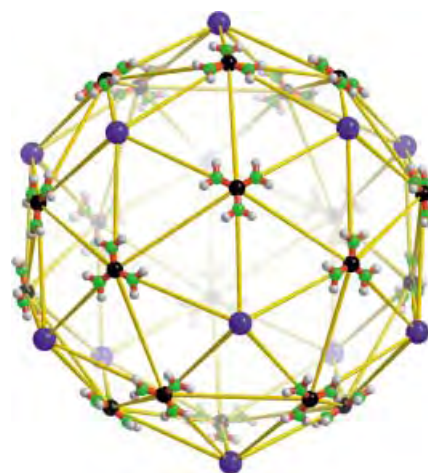


Figure 3. The atoms of the guanidinium cations placed on the icosadeltahedron shown which is obtained by subdividing the surface of the icosahedron (formed by the 12 $\{\text{Mo}(\text{O}_7)\}$ centers of **2a**) into 60 equilateral triangles (see ref. [3]). The fivefold axes of the icosahedron coincide with those of the icosadeltahedron and correspondingly, the threefold axes of the icosahedron with the “new” local sixfold axes. The icosadeltahedron has local sixfold symmetry elements (relating its subunits/faces) which are not elements of the icosahedral symmetry group.^[3] Interestingly, the 120 H atoms pack around the sixfold axes like proteins of the TBSV $T=3$ spherical virus type.^[3] The 12×5 MoO_6 octahedra of the pentagonal $\{(\text{Mo})\text{Mo}_5\}$ groups of **2a** are correspondingly packed around the fivefold axes (color code as in Figure 1b).

Chemistry can perform icosahedral tilings of the sphere: Compound **2a** is a remarkable Keplerate^[1a] (for a mathematical interpretation see ref. [9b,c]) with an as-yet-unparalleled large number of sets of equivalent atoms forming different types of Platonic and Archimedean solids (Figure 4 and Table 1). A particularly nice sequence of truncation is observed by proceeding from the dodecahedron marked out by the 20 carbon atoms of the guanidinium cation through the distorted rhombicosidodecahedron formed by the related 60 N atoms to the distorted rhombitruncated icosidodecahedron marked out by the 120 H atoms, while it should be noted that the truncation of the rhombitruncated icosidodecahedron leads to the rhombicosidodecahedron (Figure 4). The 120-

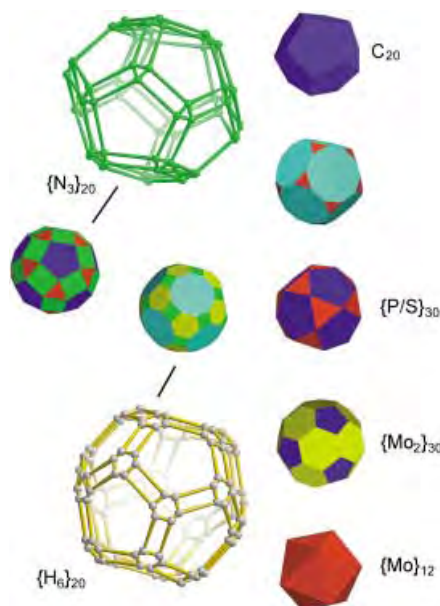


Figure 4. The stepwise truncation of the two Platonic solids, the dodecahedron and icosahedron, gives a series of Archimedean solids, that is, the truncated dodecahedron and the four others given in Table 1. Four of the five shown idealized Archimedean and the two Platonic solids are marked out by equivalent sets of atoms of **2a** (see Table 1). Additionally, the real distorted Archimedean solids $\{N_3\}_{20}$ and $\{H_6\}_{20}$ of **2a** are shown.

vertex solid represents the most complex Archimedean solid comprising 12 decagons, 20 hexagons, and 30 tetragons. To our knowledge the two polyhedra with 60 and 120 vertices have not been observed in chemistry until now. Additionally, the 30 P/S atoms form an icosidodecahedron, the 12 Mo(O₇) atoms an icosahedron, the 12 × 5 Mo atoms of the {(Mo)Mo₅} units a rhombicosidodecahedron, and the 20 {Mo₂} linkers a distorted truncated icosahedron.

Important aspects in this chemistry are the possibility of closing the giant-ball type structure with the 20 pores which are large enough to allow the passage of small species into the central cavity, and the possibility of a complete removal of substrates from solution, a phenomenon comparable to the effective recognition by a nanosponge. Guanidine plays a central role in many processes of the chemical and pharmaceutical industry^[10] and there is an extensive coordination, supramolecular, as well as solid-state chemistry of the cation; it functions as a sterically flexible ligand,^[11] anion receptor,^[12a] and is used in crystal engineering to lead to host frameworks.^[12b] Closing the pores drastically decreases the negative charge of the cluster, stabilizes it, and influences the structure of the remarkable (H₂O)_n cluster,^[13] a nanodroplet of water, incarcerated in the open clusters.^[1a] This effect is formally comparable with a process (signal transduction) by which a cell converts an extracellular signal into a response.^[18] Without the integrated cations the water structure seems to be influenced by the interaction with the crystal water through the pores. This is not the case in **2a** and we observe only highly symmetrical (H₂O)_n polyhedra—hierarchic endohedral clusterization—in the form of dodecahedra and rhombicosidodecahedra (Figure 5). An interesting aspect would also be the self-organization of solvent molecules encapsulated in a

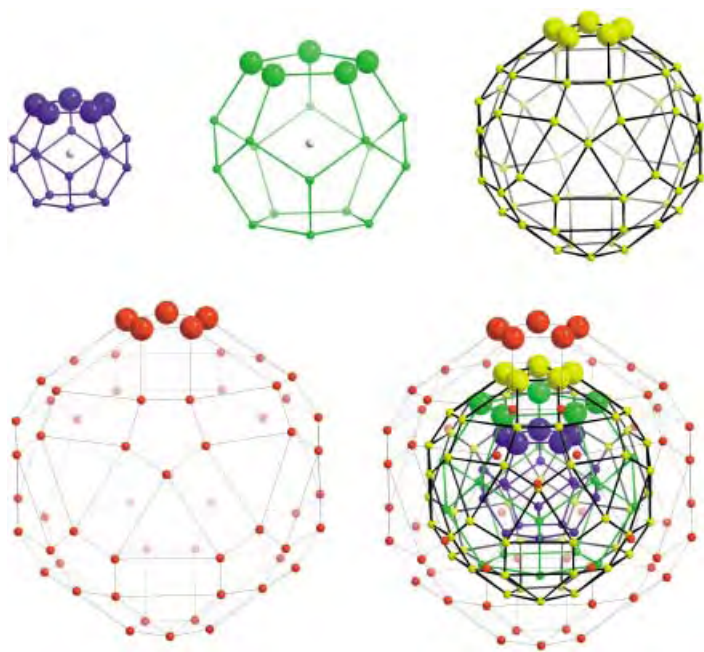


Figure 5. Endohedral hierarchic clusterization of water molecules in the cavity of **2a** resulting in $\{H_2O\}_{20}$ dodecahedra (blue and green) and $\{H_2O\}_{60}$ rhombicosidodecahedra (yellow). The second $\{H_2O\}_{60}$ rhombicosidodecahedron (red) is marked out by the 60 H₂O ligands coordinated to the 12 × 5 Mo atoms of the pentagonal {(Mo)Mo₅} units. The set of pentagons marked out by the larger spheres highlights that all the pentagons are parallel with the same orientation of the C₅ axes; all the polyhedra have a common center which is indicated by a white sphere, see note added in proof.

closed sphere (the interaction of the water molecules within the polyhedra and between these, will be studied later).

Spherical shell type objects, where the subunits exist in identical environments, are interesting in several aspects: They are easily isolable and often the preferred target of self-assembly processes based on simple units because of their high stability (the surface area is minimum while the strain energy is evenly distributed over the surface). Consequently, these spherical-shell-type objects can be used as adjustable molecular containers, which can be constructed with different building blocks, as in the present situation, while allowing chemical reactions at quite different functional groups which are abundant at the surface. Note: It is impossible to construct a spherical system from one building block only (see, for example ref. [4b]).

Supramolecular chemistry started with selective binding of alkali-metal cations by natural and synthetic macrocyclic ligands, followed later by strong and selective binding of anionic as well as neutral complementary substrates.^[2] We could now cross the frontier to a rather large multitude of receptor sites positioned on a stable nanoobject. While it became evident—mainly as a result of the initiative and work of J.-M. Lehn^[2]—that a *receptor–substrate supramolecule* is characterized by its geometric (structure/conformation), thermodynamic (stability, entropy, and enthalpy of formation), and kinetic (role of formation and dissociation) features, new categories of receptor–substrate type appear in the present polytopic *super–supramolecule* and offer the chance to study a variety of relevant cooperative effects.

To summarize, the present results highlight that the spherical cluster type under investigation, having a large number of receptor sites, can exist with different linkers, for instance with mononuclear and dinuclear metal centers, and correspondingly with different pore sizes with the consequence that it can act as an effective and specific nanosponge for complementary substrates. The related reactivity should in principle be different from that of monotopic receptors and can be influenced by changing the electronic properties of the host shell.^[14] This is a situation comparable to substrates placed on “classical” surfaces, for example, related industrially important metal-oxide surfaces,^[15] where the reactivity of the substrates can also be influenced by changing surface properties.^[16] The route to “revolutionary” new materials is long but it exists.

Note added in proof (August 26, 2002): The 100 encapsulated water molecules form altogether a novel icosahedral cluster with tetrahedrally coordinated oxygen atoms.

Experimental Section

2: A mixture of (NH₄)₄₂1a·300H₂O (ligand = H₂PO₃[−])^[6d] (2.5 g, 0.09 mmol) and [(NH₂)₂CNH]₂SO₄ (1.9 g, 8.8 mmol) in H₂O (200 mL) was heated to 90 °C for a short time. The dark-brown solution was kept in an open beaker at room temperature for 1 week (crystallization starts after 1 day). The dark-brown crystals (rhombus type, truncated cubes, and octahedra) which precipitated were collected by filtration over a glass frit, washed with 2-propanol (95 %) and dried in air. Yield: 2.3 g (92 % based on 1a). Characteristic IR bands (KBr, pellet, 1800–500 cm^{−1}): $\tilde{\nu}$ = 1655 (s, δ (H₂O)/(H₂N)₃C⁺), 1180 (w(SO₄)), 1124 (w-m), 1075 (vw), 1038 (w) (H₂PO₂), 976 (m), 945 (sh) (ν (Mo=O)), 851 (m), 793 (s), 725 (s), 631 (w-m), 567 (m) cm^{−1}; characteristic Raman bands (solid; λ_e = 1064 nm): $\tilde{\nu}$ = 948 (w, ν (Mo=O)), 871 (s), $\approx$ 845 (sh), 361 (m), $\approx$ 315 (w), 296 (w-m) cm^{−1}. Elemental analysis for C₅₂H₇₉₆Mo₁₃₂N₁₅₆O₆₇₄P₂₀S₁₀ (%; calculated with 150H₂O because the crystals of **2** lose part of the crystal water when removed the mother liquor): C 2.23, H 2.87, N 7.80, P 2.21, S 1.15, found: C 2.5, H 2.9, N 7.1, P 1.9, S 0.9.

The compound type can also be obtained with only one type of ligand coordinated to {Mo₂} linkers, for instance by treating **1a** with guanidinium chloride. But as the crystal quality of the related products was too poor for the results to be reported here.

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- [7] a) Crystal data for **2**: C₅₂H₇₉₆Mo₁₃₂N₁₅₆O₆₇₄P₂₀S₁₀, M_r = 28901.33 g mol^{−1}, rhombohedral, space group *R3m*, a = 62.865(2), c = 76.470(4) Å, V = 261 720(17) Å³, Z = 12, ρ_{calc} = 2.200 g cm^{−3}, μ = 2.005 mm^{−1}, $F(000)$ = 169 152, crystal size = 0.30 × 0.20 × 0.20 mm³. Crystals of **2** were removed from the mother liquor and immediately cooled to 188(2) K on a Bruker AXS SMART diffractometer (three circle goniometer with 1 K CCD detector, Mo_{K α} radiation, graphite monochromator; hemisphere data collection in ω at 0.3° scan width in three runs with 606, 435 and 230 frames (ϕ = 0, 88 and 180°) at a detector distance of 5 cm). A total of 454 502 reflections (0.65 < θ < 25.03°) were collected of which 52 923 reflections were unique (R_{int} = 0.0911). An empirical absorption correction using equivalent reflections was performed with the program SADABS. The structure was solved with the program SHELXS-97 and refined using SHELXL-93 to R = 0.0820 for 35 303 reflections with $I > 2\sigma(I)$, R = 0.1384 for all reflections; max./min. residual electron density 3.336 and −2.227 e Å^{−3} (SHELXS/L, SADABS from G. M. Sheldrick, University of Göttingen, **1993/1997/2001**; structure graphics with DIAMOND 2.1 from K. Brandenburg, Crystal Impact GbR, **2001**). Further details on the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666); e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-412658; b) Not all of the lattice guanidinium cations could be located because of the disorder problem which as usual affects the location of lattice ingredients in the large cavities between the giant objects. That the intramolecular (H₂)N–N(H₂) distances (2.3 Å) are not very different from intermolecular (H₂)N–O(H₂) distances (2.5–2.9 Å) is the additional explanation for why many guanidinium cations could not be found in the crystal structure, as this situation allows the cations to be integrated into the crystal-water lattice in many different ways. But the number of cations is evident from numerous analyses (also after recrystallization of **2**). The presence of only protonated guanidinium units could be demonstrated by ¹³C solid-state NMR spectroscopy.
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An Inclusion Complex with [Gd(dmf)₈]³⁺ Ions Encapsulated in Pockets of an Anionic Array of [Cu₆(CN)₉]³⁻ Units; A Cyanide-Bridged Cu–Gd Layer Structure**

Shengming Liu, Edward A. Meyers, and Sheldon G. Shore*

Lanthanide–transition-metal complexes are attracting increasing attention because of their novel structures and the realization of applications in materials science^[1,2] and catalysis.^[3] It is of interest to not only continue preparing materials for which applications are known, but also to expand structural and chemical knowledge through the preparation and evaluation of new types of lanthanide–transition-metal complexes. With this goal in mind, we have extended our lanthanide–transition-metal studies from Group 10 transition metals^[4] to Group 11 Cu^I complexes. Herein, we report the synthesis and structural characterization of an extended three-dimensional ionic inclusion complex, [Gd(dmf)₈Cu₆(CN)₉·2 DMF]_∞,^[5] which contains sequestered lanthanide cations, and an extended layered complex, [Gd₂(dmf)₈Cu₄(CN)₁₀]_∞.^[6] These complexes constitute new structural classes of lanthanide–transition metal systems.

Although ionic inclusion complexes are known,^[7] examples of an encapsulated ion within a charged cage are rare. The new inclusion complex is prepared by a three-component metathesis reaction [Equation (1)]. The anionic three-dimen-

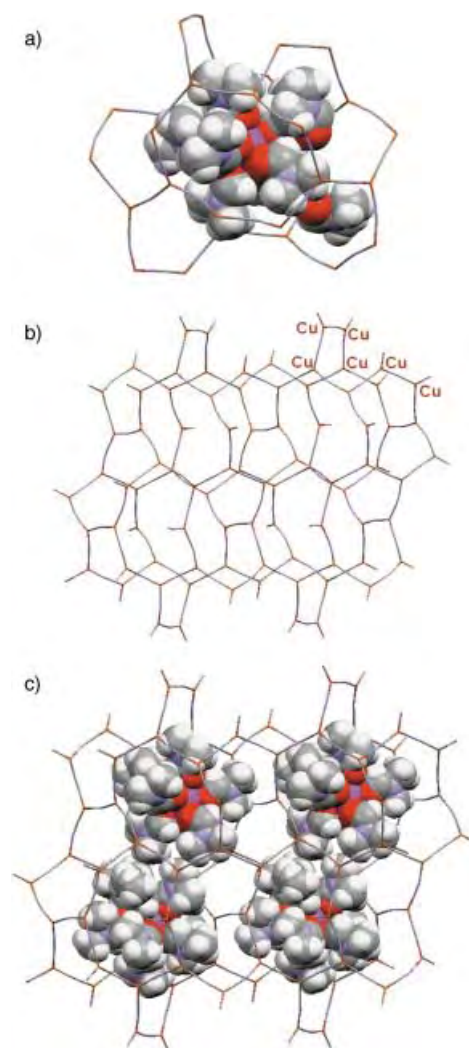


Figure 1. The structure of [Gd(dmf)₈Cu₆(CN)₉]_∞. a) One pocket with an encapsulated [Gd(dmf)₈]³⁺ ion and two DMF molecules. b) The partial structure of the anionic network with four vacant pockets; connections between Cu atoms represent cyanide bridges. c) Four pockets with trapped [Gd(dmf)₈]³⁺ ionic guests.

sional host lattice, [Cu₆(CN)₉]³⁻, sequesters a cationic guest, [Gd(dmf)₈]³⁺, and two free DMF solvent molecules in each “pocket” (Figure 1). In a slightly modified procedure [Equation (2)], the two-dimensional, infinite, puckered-layer complex [Gd₂(dmf)₈Cu₄(CN)₁₀]_∞ (Figure 2) is formed in which the two Gd^{III} and three Cu^I atoms are bridged by cyanide ligands to form pentagonal rings. Either complex can be prepared in near-quantitative yield.

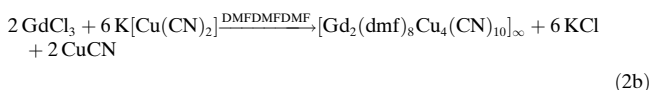
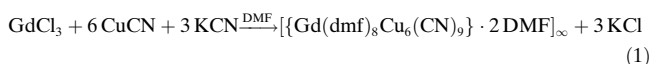


Figure 1 b shows the anionic network [Cu₆(CN)₉]³⁻, while Figure 1 a illustrates a pocket that contains a trapped [Gd(dmf)₈]³⁺ ion and two free DMF molecules. All of the

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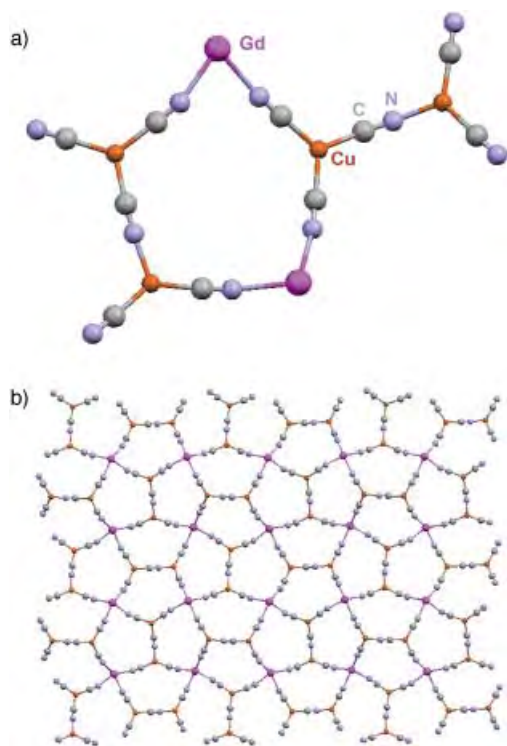


Figure 2. Molecular structure of $[\text{Gd}_2(\text{dmf})_8\text{Cu}_4(\text{CN})_{10}]_\infty$. a) The repeating unit of $[\text{Gd}_2(\text{dmf})_8\text{Cu}_4(\text{CN})_{10}]_2$; DMF molecules are omitted for clarity. b) A single layer of the two-dimensional complex; DMF molecules are omitted for clarity.

Cu atoms are coordinated to three cyanide groups. The three-dimensional anionic framework of pockets is formed through Cu-CN-Cu bridges. This is in contrast to previously reported three-dimensional arrays, which consist of four-coordinate copper centers.^[7a] Each pocket has 30 copper atoms connected to 36 cyanide linkages and is irregular in shape; the approximate dimensions of the enclosure are $16 \times 11 \times 24 \text{ \AA}$. Each pocket is associated with 14 neighboring pockets. The coordination geometry of the Gd center in $[\text{Gd}(\text{dmf})_8]^{3+}$ is square-antiprismatic. The approximate diameter of the cation (greater than $12.0 \text{ \AA}$) is wider than the width of the largest window (less than $10.2 \text{ \AA}$) of the pocket, thus trapping the cation in the pocket along with two DMF molecules. This structure differs from interpenetrating networks.^[7c-f]

Figure 2a reveals the repeating unit ($[\text{Gd}(\text{dmf})_4\text{Cu}_2(\text{CN})_5]_2$) of the extended, layer-structured complex $[\text{Gd}_2(\text{dmf})_8\text{Cu}_4(\text{CN})_{10}]_\infty$. In this unit, two Cu^{I} atoms are linked through a cyanide bridge with each Cu^{I} atom joined to two Gd^{III} atoms through cyanide bridges. This generates the five-membered-ring building block. Each Gd^{III} atom is bonded to four DMF molecules and four bridging cyanide ligands, which leads to a square-antiprismatic coordination geometry. In our previous structural studies of lanthanide-transition-metal cyanide complexes,^[4] we have not encountered arrays composed of pentagons. Figure 2b shows a single puckerd layer of the two-dimensional complex with DMF molecules omitted for clarity. Adjacent layers are eclipsed and the interlayer distance is about $6.9 \text{ \AA}$.

The two compounds reported here are prepared under different conditions. For the following reasons, we account for

the variation in the products based on the difference in procedures. The inclusion complex is formed from an initial reaction mixture that contains CuCN, KCN, and GdCl_3 . It is believed that the low solubility of CuCN in DMF results in a low concentration of $\text{K}[\text{Cu}(\text{CN})_2]$ at any given time. This favors the probability for preferentially forming $[\text{Gd}(\text{dmf})_8]^{3+}$ over Cu-CN-Gd bridges. Such a situation would allow for the slow assembly of the copper-cyanide anionic pocket around the solvated gadolinium cation. It should be noted that the formation of the crystalline inclusion complex requires several weeks. On the other hand, the layer complex is produced when CuCN and KCN are first allowed to form $\text{K}[\text{Cu}(\text{CN})_2]$ [Reaction (2a)] and then the GdCl_3 is added to the reaction mixture [Reaction (2b)]. $\text{K}[\text{Cu}(\text{CN})_2]$ has significant solubility in DMF and contains CN-Cu-CN-Cu-CN^[8] linkages that can couple to Gd atoms to generate the CN-Gd-CN-Cu-CN-Cu-CN-Gd building units that are the basic units of the layer structure. The layer structure crystallizes from a solution in DMF after about one day. It will be worthwhile to determine if these procedures can be generalized for lanthanide(III)-copper(I) systems of the types described here.

Experimental Section

All manipulations were carried out on a standard high-vacuum line or in a dry-box under an atmosphere of dry, pure nitrogen. The purification of dimethylformamide (Baker) and the activation of molecular sieves (4 Å, Linde) are described in a previous publication.^[4d] FTIR spectra were recorded on a Mattson Polaris Fourier-transform spectrometer at 2 cm^{-1} resolution. All samples were prepared in the dry-box. Elemental analyses of materials were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Single-crystal X-ray diffraction data for $[\text{Gd}(\text{dmf})_8\text{Cu}_4(\text{CN})_{10}]_2 \cdot 2\text{DMF}$ and $[\text{Gd}_2(\text{dmf})_8\text{Cu}_4(\text{CN})_{10}]_\infty$ were collected on an Enraf-Nonius KapapCCD diffraction system, which employs graphite-monochromated MoK_α radiation ($\lambda = 0.71073 \text{ \AA}$). Data integration was carried out for Lorentz and polarization effects using the Denzo-SMN package (Nonius BV, 1999).^[9] Absorption corrections were applied using the SORTAV program^[10] provided by MaXus software.^[11] The structure was solved by direct methods and refined using the SHELXL-97 (difference electron-density calculation, full-matrix least-squares refinements) structure solution package.^[12] Data merging was performed using the data preparation program supplied by SHELXL-97. After all nonhydrogen atoms were located and refined anisotropically, hydrogen atoms on DMF molecules were calculated assuming standard CH geometries. Two DMF solvent molecules crystallize with one molecule of $[\text{Gd}(\text{dmf})_8\text{Cu}_4(\text{CN})_{10}]_\infty$ in the formation of the inclusion complex, $[\text{Gd}(\text{dmf})_8\text{Cu}_4(\text{CN})_{10}]_2 \cdot 2\text{DMF}$. CCDC-184355 and -184356 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

$[\text{Gd}(\text{dmf})_8\text{Cu}_4(\text{CN})_{10}]_2 \cdot 2\text{DMF}$: GdCl_3 (178 mg, 0.674 mmol), CuCN (362 mg, 4.04 mmol), and KCN (132 mg, 2.02 mmol) were stirred in DMF (ca. 25 mL) at room temperature over 14 days. The resulting solution was filtered, leaving a white precipitate (KCl) and a colorless filtrate. Colorless crystals suitable for X-ray analysis precipitated from the solution after three weeks in near-quantitative yield. IR (KBr): $\tilde{\nu} = 2115(\text{s}) \text{ cm}^{-1}$ (CN). Samples for elemental analysis were obtained by washing the crystals with dry hexane in a dry-box and then drying under vacuum for 30 min. 4.5 DMF molecules per empirical unit were lost after washing and drying, as determined by the elemental analysis. Elemental analysis (%) calcd for $\text{C}_{25.5}\text{H}_{38.5}\text{N}_{14.5}\text{O}_{5.5}\text{Cu}_6\text{Gd}$: C 26.07, H 3.30, N 17.29; found: C 26.27, H 3.77, N 17.12.

$\text{K}[\text{Cu}(\text{CN})_2]$: A flask was charged with KCN (0.73 g, 11.2 mmol), CuCN (1.00 g, 11.2 mmol), and DMF (30 mL) in a dry-box. After stirring for one

week the solvent was removed under vacuum. A white crystalline powder (in near-quantitative yield) was obtained.

$[\text{Gd}_2(\text{dmf})_8\text{Cu}_4(\text{CN})_{10}]_{\infty}$: GdCl_3 (120 mg, 0.455 mmol) and $\text{K}[\text{Cu}(\text{CN})_2]$ (210 mg, 1.36 mmol) were stirred in DMF (ca. 25 mL) at room temperature over 7 days. The resulting solution was filtered, leaving a white precipitate (KCl) and a colorless filtrate. The solution was concentrated under vacuum, from which colorless crystals (in near-quantitative yield) were obtained the following day. IR (KBr): $\tilde{\nu} = 2112(\text{s}) \text{ cm}^{-1}$ (CN).

Samples for elemental analysis were obtained by washing the crystals with hexane in a dry-box and then drying under vacuum for 30 min (there was no loss of solvent). Elemental analysis (%) calcd for $\text{C}_{17}\text{H}_{28}\text{N}_9\text{O}_4\text{Cu}_2\text{Gd}$: C 28.89, H 3.99, N 17.84; found: C 28.86, H 4.08, N 17.69.

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An Antibody that Reconstitutes the “Base-On” Form of B₁₂ Coenzymes**

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The cobalt-coordinating 5,6-dimethylbenzimidazole (DMB) nucleotide is a structural feature of coenzyme B₁₂ and of methylcobalamin^[1,2] that controls the reactivity of these organometallic cofactors.^[3,4] The DMB nucleotide and the functionalized corrin ring are both important for tight and selective binding to B₁₂ apoenzymes. Several coenzyme B₁₂ dependent enzymes were recently shown to bind the B₁₂ cofactor in an unanticipated “base-off/His-on” form,^[5–7] in which the DMB nucleotide is displaced from the cobalt center by a histidine residue from the protein. In contrast, diol dehydratase binds coenzyme B₁₂ “base-on”, as described in a crystal structure at the end of the 1990s.^[8] Here we report on a monoclonal antibody raised against coenzyme B₁₂, which binds the “base-on” form of natural coenzyme B₁₂ analogues that prefer to be “base-off” in solution. This B₁₂ antibody thus causes an unprecedented “reverse” coordinative “base-off” to “base-on” reconstitution, which also results in a significant change in the reactivity of the bound B₁₂ coenzyme.

Over the last 15 years, antibodies have proved useful as catalysts for a set of remarkable chemical reactions and as receptors for probing ligand-binding mechanisms.^[9–14] Versatile cofactors such as coenzyme B₁₂ have considerable potential to extend the chemistry of these systems. To investigate the ability of antibodies to recognize and modulate the chemical reactivity of corrinoid coenzymes, we have raised monoclonal antibodies against coenzyme B₁₂ (**1**). Although other antibodies that recognize B₁₂ derivatives are known,^[15] their binding properties were never scrutinized spectroscopically.

For immunization, coenzyme B₁₂ (**1**) was coupled to the carrier protein thyroglobulin (TG) with a succinic acid

linker^[16] (48 haptens/TG). An immune response was elicited against the TG–hapten conjugate, and a panel of monoclonal antibodies with good antigen recognition was prepared and purified by conventional means.^[17] After initially screening 20 antigen binders by competition ELISA (enzyme-linked immunosorbent assay),^[18] antibody 2C2 was selected for detailed characterization because it recognized both the DMB nucleotide and the corrin ring.

Antibody 2C2 binds **1** with an estimated dissociation constant (K_d) of $9.8 \pm 2.6 \mu\text{M}$. As summarized in Table 1, vitamin B₁₂ (**2**; Scheme 1) and several B₁₂ derivatives compete

Table 1. Apparent ligand dissociation constants with antibody 2C2.^[a]

Ligand	K_d [μM]
coenzyme B ₁₂ (1)	10
vitamin B ₁₂ (2)	65
dicyanocobinamide (3)	740
pseudocoenzyme B ₁₂ (4)	68
adenosyl factor A (5)	29

[a] Determined by competition ELISA.^[18] Coenzyme B₁₂ conjugated to bovine serum albumin was immobilized to a microtiter plate and bound antibody was detected using glucose oxidase conjugated goat antimouse IgG antibody in the presence and absence of various ligands. Absorbance at 405 nm was determined after developing the plates with 2,2'-azino-di(3-ethylbenzothiazoline-6-sulfonate) (ABTS).

effectively with the antigen. Dicyanocobinamide (**3**), an analogue of **1** and **2** lacking the nucleotide function, is the weakest corrinoid ligand tested, and neither benzimidazole nor 2-amino-isopropylribazole phosphate^[19] alone compete with the antigen. These results suggest that the complete cobalt-coordinating nucleotide loop is required for formation of the B₁₂–antibody complex. To test this hypothesis, pseudocoenzyme B₁₂ (**4**)^[20,21] and Co β -5'-deoxyadenosyl factor A (**5**)^[21,22] were also investigated as competitive inhibitors. These natural coenzyme B₁₂ analogues differ from **1** by the replacement of the DMB base by adenine and 2-methyladenine, respectively (Scheme 1). In aqueous solution, **4** and **5** exist mainly in the base-off form, as deduced from UV/Vis, CD, and ¹H NMR spectroscopy.^[20,21] As expected, these base-off adenosylcobamides bind 3 to 7 times weaker than **1**. Clearly, the constitution of the nucleotide base and its intramolecular interaction with the cobalt center play important roles in the recognition of corrinoids by antibody 2C2.

The recognition properties of 2C2 were further examined spectroscopically. Vitamin B₁₂ derivatives show diagnostic absorbances at wavelengths longer than 300 nm,^[21,22] which are easily monitored in the presence of the colorless antibody. Addition of 2C2 to coenzyme B₁₂ (**1**) caused a small shift in the visible part of the UV/Vis spectrum (from 524 to 536 nm) with an 8% decrease of the extinction coefficient. Similar changes have been observed for other B₁₂–protein complexes^[23] and indicate that binding of **1** to the antibody does not significantly alter the coordination pattern of the Co^{III}–corrin. In contrast, dramatic changes were detected upon binding of **4** and **5** to the antibody. In these cases, addition of 2C2 caused a marked decrease in the absorbance at 463 nm and an increase at 529 nm (Figure 1a). The spectra of **4** and **5** bound to 2C2 match that of (base-on) coenzyme B₁₂ (**1**)

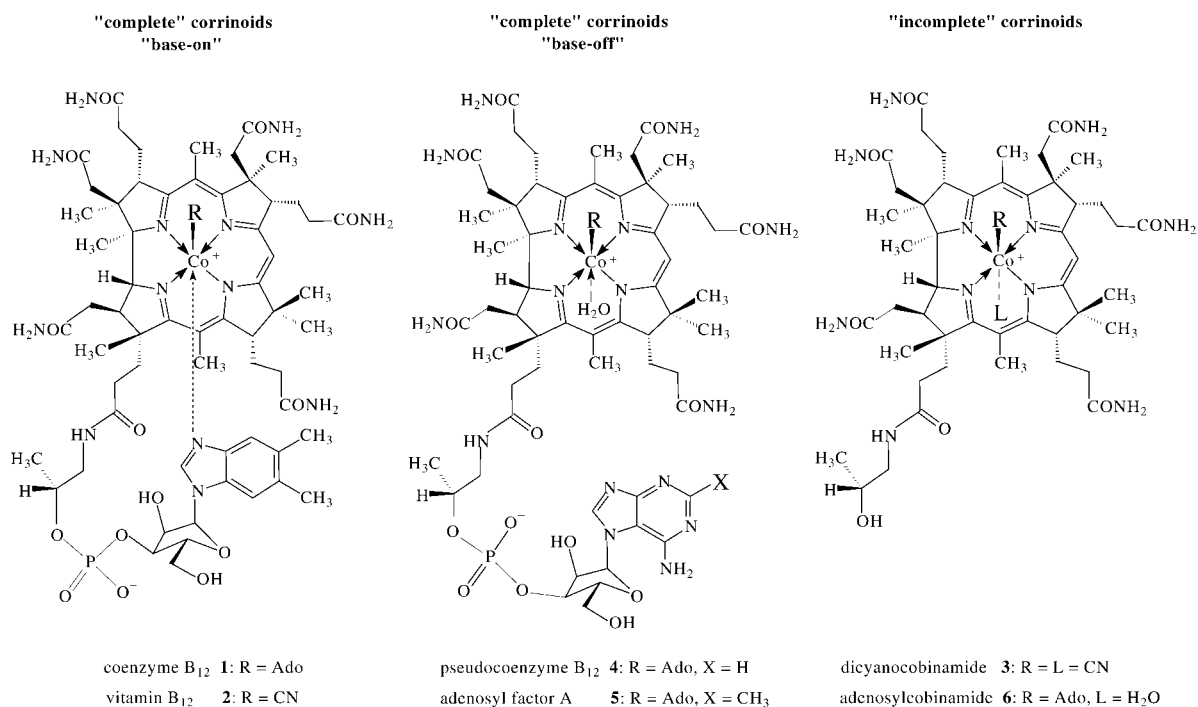
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Scheme 1. Structural formulae of vitamin B₁₂ derivatives. Left: "Complete corrinoids" in their base-on form with a DMB base and varying ligand R. Center: The dominant base-off form of the complete corrinoids with an adeninyl base. Right: Cobinamides as "incomplete corrinoids" (Ado = 5'-deoxy-5'-adenosyl).

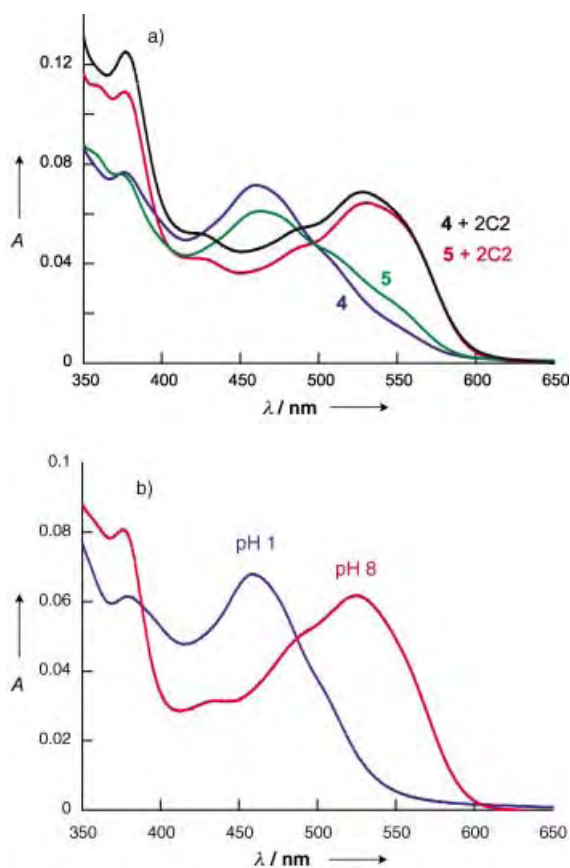


Figure 1. a) UV/Vis spectra of pseudocoenzyme B₁₂ (**4**) and of 5'-deoxyadenosyl factor A (**5**) in aqueous buffer (10 mM phosphate, 160 mM NaCl, pH 7.4; blue and green curves, respectively) and in the presence of approximately 20 μM antibody 2C2 (black and red curves, respectively). b) UV/Vis spectra of aqueous solutions of coenzyme B₁₂ (**1**) at pH 8 (base-on form of **1**; red curve) and at pH 1 (base-protonated base-off form of **1**; blue curve).

remarkably well (Figure 1 b). In contrast, the presence of 2C2 had no effect on the spectrum of 5'-deoxyadenosylcobinamide (**6**), nor did bovine serum albumin alter the spectra of **4** and **5**.

Binding of coenzyme B₁₂ analogues **4** and **5** to 2C2 is thus accompanied by coordination of an N-ligand to cobalt. However, the UV/Vis spectra cannot differentiate clearly between coordination of an internal nucleotide base or an external histidine molecule. Indeed, the insensitivity of these methods to the identity of the axial N-ligand in adenosylcobinamides impeded the discovery of the now well-known base-off/His-on form of protein-bound **1** in enzymes such as methylmalonyl CoA mutase^[6] and glutamate mutase.^[7,24]

On the assumption that 2C2 recognizes the more stable "base-on" form of coenzyme B₁₂ (**1**), it seemed possible that the antibody might force the adenine group of pseudocoenzyme B₁₂ (**4**) and 2-methyladenine in adenosyl factor A (**5**) to coordinate to the cobalt center. The base-on form of these coenzyme B₁₂ analogues, **4b** and **5b**, has not been previously observed, but is known for the corresponding cyano-Co^{III}-corrins pseudovitamin B₁₂ and factor A.^[25] Utilization of binding energy to counterbalance an equilibrium that favors the base-off form of **4** and **5** in solution would help explain their lower affinities for 2C2, compared to **1**.

Transfer NOE experiments with **5** and 2C2 were performed to establish how the corrinoid binds at the antibody active site. Cross-relaxation measurements on protein–ligand complexes deliver information concerning spin-transfer between two protons of a bound ligand and the free state by fast chemical exchange.^[26,27] The NOESY spectrum of **5** in the presence of 2C2 shows an overall increase in NOE intensities and specific increases in the cross-peaks between the heteroaromatic proton H(8N) of the 2-methyladenine base and the corrin e and f side chains of **5** (Figure 2). The latter protons are not

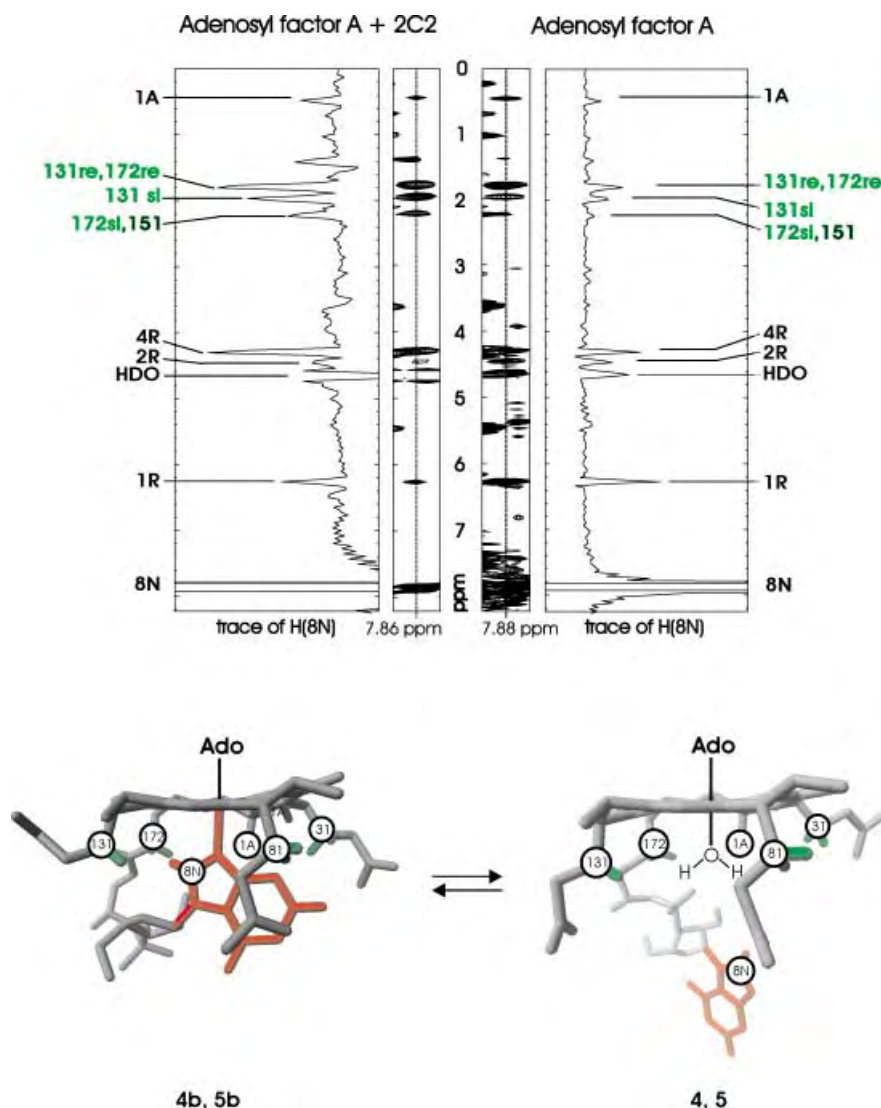


Figure 2. Top: NOE correlations of the signal arising from the H(8N) (at $\delta = 7.86$ and 7.88 ppm) from 500 MHz ^1H NMR spectra of 5'-deoxyadenosyl factor A (**5**) in the presence (left, NOESY spectrum) and in the absence (right, ROESY spectrum) of antibody 2C2. The spectra were recorded in 50 mM potassium phosphate buffer, 100 mM NaCl at pH 7.5 and 26 °C; [**5**] = 1.5 mM and [2C2] = 50 μM . The NOESY spectrum of **5** without 2C2 shows only very weak signals because of the similar magnitude of the correlation times of the B_{12} derivative and the critical correlation time at 500 MHz. The H(8N) of the cobalt-coordinated DMB base in **1** is < 3.5 Å (through space) from the protons at 1A, 131 (H_{re} and H_{si}), 172 (H_{si}), of the corrin ring, and at 4R, of the ribose segment. (Note: the signal at $\delta = 1.5$ ppm is an artefact). Bottom: The base-off/base-on constitutional switch of complete cobalamins by (de-)coordination of their nucleotide base at the corrin-bound cobalt center.

proximal to one another in the base-off form of **5** in free solution, but are apparently juxtaposed in antibody-bound **5**, as expected if the corrinoid adopts a base-on mode (Figure 2).

All of the experimental data thus support the conclusion that the B_{12} antibody 2C2 preferentially binds adenosylcorrinoids in a base-on form, as programmed by the hapten. Binding pseudocoenzyme B_{12} (**4**) and its homologue **5** in this way requires formation of a cobalt–nitrogen bond and (presumably^[3,4]) replacement of a cobalt-bound water molecule. The base-off to base-on restructuring observed here is opposite to that required for binding of coenzyme B_{12} in a base-off/His-on form in the carbon skeleton mutases.^[6,7,24]

The antibody-induced base-off/base-on switch changes the chemical reactivity of the corrinoids. The rate of the conversion of adenosylcobamides (such as **1**, **4**, and **5**) into dicyanocobamides, for example, depends upon the coordination of the nucleotide base.^[22] In the presence of a 2.5-fold excess of antibody, the reaction with cyanide was inhibited by over 90% relative to the reaction in the absence of protein (conditions: 15 μM 2C2, 6 μM B_{12} , 4 mM KCN in phosphate buffer, pH 7.5; $T = 25$ °C; spectrophotometric monitoring at 368 nm: relative rates: $k_{4+2\text{C2}}/k_{4-2\text{C2}} = 0.096$; $k_{5+2\text{C2}}/k_{5-2\text{C2}} = 0.040$). The base-off/base-on switch of these B_{12} derivatives reduces the tendency of the metal centers to react with the cyanide nucleophile. This observation is in line with the known “trans effect” of the nucleotide coordination on the organometallic reactivity of “complete” corrin.^[3,4,22]

The crystal structure of an aptamer^[28] for vitamin B_{12} revealed that the RNA moiety binds (only) the corrin ring of the cobalamin.^[29] Herein, coenzyme B_{12} (**1**) was used to induce the formation of an antibody that selectively recognizes the base-on form of **1** and of other B_{12} coenzymes. The nucleotide loop, which is a unique structural motif of the base-on forms of complete cobamides, steers the reactivity of the cobalt corrin^[3,4] and also serves as a still poorly understood recognition element for selective interactions with B_{12} -binding proteins.^[8] Antibody 2C2 recognizes the intact DMB nucleotide loop and reconstitutes the base-on form of coenzyme B_{12} analogues, whose solution structures are mainly base-off. Antibody 2C2 may represent a functional model for natural B_{12} -binding proteins, such as (human) intrinsic factor and transcobalamin.^[23]

These important B_{12} receptors preferentially bind cobamides with a DMB nucleotide^[23,30] and are selective for structurally related B_{12} derivatives that also prefer a base-on conformation in solution.

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Solid-Phase Synthesis and Biological Evaluation of a Peptidinnamin E Library**

Michael Thutewohl, Lars Kissau, Boriana Popkirova, Ionna-Maria Karaguni, Thorsten Nowak, Michael Bate, Jürgen Kuhlmann, Oliver Müller, and Herbert Waldmann*

Mutations in the genes coding for Ras proteins are found in approximately 30% of all human tumors.^[1,2] The proper function of Ras is critically dependent on posttranslational lipidation. Oncogenic Ras only serves as a molecular switch for the transduction of growth signals if the Ras is S-farnesylated at the C-terminus and if located at the plasma membrane. Thus, inhibitors of the enzyme protein farnesyltransferase (PFT) are of particular interest as new antitumor therapeutic agents.^[1,2] However, some of the most important and fundamental aspects of this application of the signal transduction therapy^[3] remain unclear. The crucial substrate of PFT, the farnesylation of which is suppressed by these compounds, is still unknown.^[2] In this context, inhibitors which induce apoptosis (that is, programmed cell death), and which are bisubstrate inhibitors of the PFT, are of particular interest.^[2,4]

To investigate these biological questions in a focussed but flexible manner, a class of potential PFT inhibitors are required, the structure of which can be varied rapidly and efficiently by combinatorial solid-phase synthesis. This approach should furnish inhibitors which are competitive to the protein substrate, to the farnesylpyrophosphate (FPP), or even to both substrates, as well as substances which induce apoptosis in Ras-transformed cells but not in the untransformed wild-type cells. Peptidinnamin E^[5] (**1**; Scheme 1) is a naturally occurring bisubstrate inhibitor of PFT (IC₅₀ = 42 μM). Based on the total synthesis of this modularly built natural product,^[6] we have developed a solid-phase synthesis

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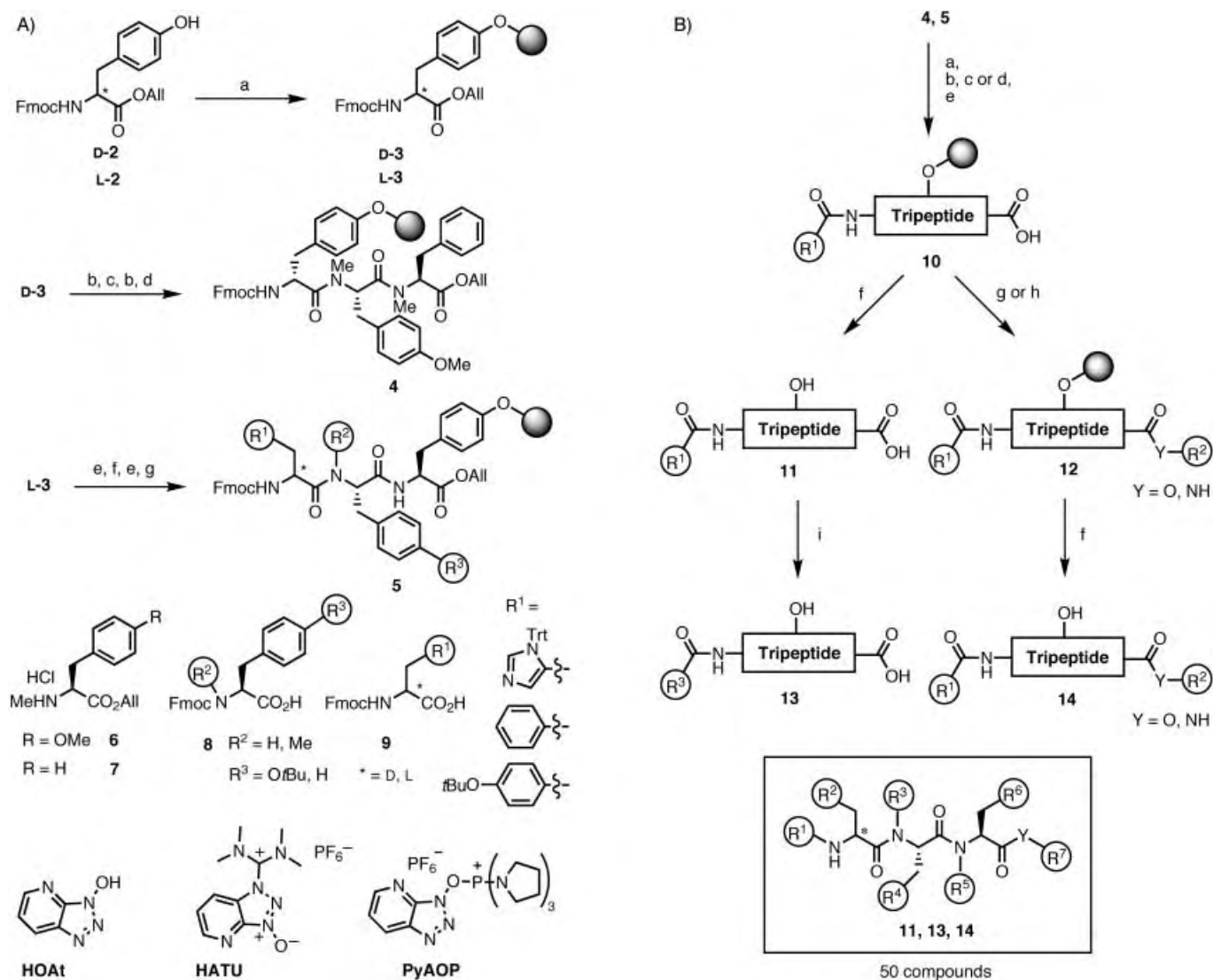
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$IC_{50} = 42 \mu M$

of a library of peptidocinnamin E analogues, as shown in Schemes 2a and 2b.

different positions of the natural product. The orthogonally protected tyrosines **D-2** und **L-2** were attached to Wang resin by using a Mitsunobu reaction^[7] (loading levels 0.5–0.53 mmol g^{−1}, yields between 54–59 %; the loading was determined by the Fmoc method^[8]). To build up the tripeptide unit **4** by C-terminal chain elongation, starting from **D-3**, the allyl ester groups were cleaved by Pd⁰ catalysis, using phenylsilane or *N*-methylaniline as allyl scavengers. The *N*-methylated amino acid building blocks **6** and **7** were attached by application of the highly active reagents HATU and PyAOP (Scheme 2a).^[9]

The alternative N-terminal elongation starting from building block **L-3** by sequential basic Fmoc removal and coupling of the fragments **8** and **9** furnished the tripeptide **5** (Scheme 2a). After removing the Fmoc group from the tripeptides **4** and **5**, various cinnamic acid and hydrocinnamic acid derivatives R¹COOH, as well as benzylchloroformates



Scheme 2. A) a) DEAD, PPh_3 , THF, 0°C , 1 h, RT, 12 h, loading: $0.50\text{--}0.53\text{ mmol g}^{-1}$, 54–59 %; b) $\text{Pd}(\text{PPh}_3)_4$, PhSiH_3 or NMA, 24 h; c) **6**, HATU, HOAt, $i\text{PrNEt}_2$, NMP; $2 \times 24\text{ h}$; d) **7**, PyAOP, HOAt, $i\text{PrNEt}_2$, NMP; $2 \times 24\text{ h}$; e) piperidine/DMF 1:4, $2 \times 5\text{ min}$; f) **8**, HATU, $i\text{PrNEt}_2$, NMP, 2.5 h; g) **9**, HATU, DIPEA, NMP or DIC, HOAt, DMF, 14 h. B) a) Piperidine/DMF 1:4, $2 \times 5\text{ min}$; b) $\text{R}^1\text{CO}_2\text{H}$, HATU, HOAt, $i\text{PrNEt}_2$, NMP, 12 h ($\text{R}^1 = \text{ArCH}_2\text{CH}_2\text{--}$); c) $\text{R}^1\text{CO}_2\text{H}$, PyAOP, DMAP, $i\text{PrNEt}_2$, $\text{CH}_2\text{Cl}_2/\text{DMF}$ 1:2, 12 h ($\text{R}^1 = \text{ArCH}=\text{CH--}$); d) R^1COCl , HOAt, DMAP, $i\text{PrNEt}_2$, $\text{CH}_2\text{Cl}_2/\text{DMF}$ 2:1, 7 h; e) $\text{Pd}(\text{PPh}_3)_4$, morpholine, THF, 4 h; f) TFA/ H_2O 95:5, 5 h; g) R^2NH_2 , PyAOP, $i\text{PrNEt}_2$, NMP, $2 \times 8\text{ h}$ ($\text{Y} = \text{nox}$); h) Cs_2CO_3 , KI, RX, DMF, 24 h, RT ($\text{X} = \text{Br}$) or 24–48 h, 50°C ($\text{X} = \text{Cl}$); i) 10 % Pd/C , H_2 , dioxane or MeOH, 8 h.

R^1COCl , were attached. For the attachment of the cinnamic acids, only a combination of PyAOP and DMAP gave satisfactory results (Scheme 2b). Deprotection of the carboxylic acid group by Pd⁰-catalyzed allyl transfer to morpholine and acidic cleavage of the N-acylated tripeptides **10** from the polymeric support furnished the compounds **11**. Hydrogenation of the double bonds resulted in further analogues **13** with saturated residues R^3 . Starting from the polymer-bound compounds **10**, esters and amides **12** were synthesized by efficient alkylation of the carboxylic acid functionality and PyAOP-mediated amine-coupling, respectively. Acidic release from the resin furnished the compounds **14**. Following this strategy, we synthesized a library of 50 pepticinnamin E analogues by variation of up to eight structural parameters, in overall yields of between 3–63 %, corresponding to an average yield of between 65–91 % per step (in general, 80 % yield). In most cases purities were higher than 90 %.^[10]

The members of the synthesized library were subsequently evaluated in two assays for their potential inhibitory activity towards PFT. We applied a fluorescence-based assay using rat PFT and a dansyl-labelled Ras peptide^[11] which is adapted to the 96 well-plate format.^[12] Moreover, in a second assay, tritium-labelled farnesylpyrophosphate, K-Ras protein as substrate, and human placental PFT were applied.^[13] The library contained two groups of inhibitors (altogether 28 compounds) with remarkable activity. The inhibitors with the highest activities are shown in Scheme 3. The central tripeptide fragment of the natural product is conserved in the inhibitors of type I; the substituent R^1 was varied. In contrast, inhibitors of type II contain structurally varied tripeptides; in particular, they contain a histidine residue. Furthermore, the

structure of the lipophilic substituent R^1 is varied. In both types, the C-terminal diketopiperazine is missing. While compounds **11/1–11/5** inhibit rat PFT in the low, mainly single-digit micromolar range, **13/1** is only weakly active against this enzyme (Table 1). However, the human PFT is inhibited efficiently by **13/1**, as well as by **11/1**, **11/2**, **11/4**, and **11/5**.

Table 1. Inhibition of PFT by selected compounds.

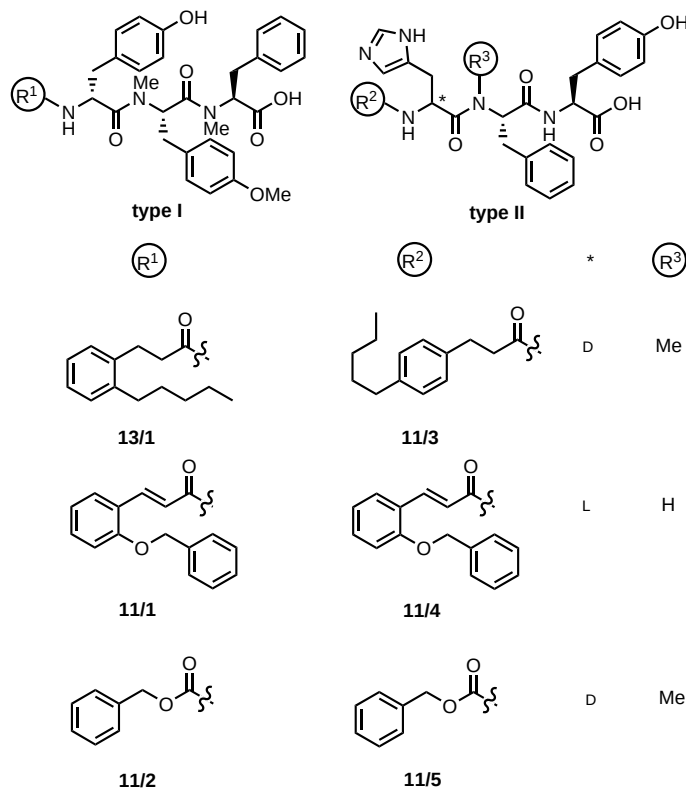
Entry	Compound	PFT (IC ₅₀) [μM] ^[a]	PFT (IC ₅₀) [μM] ^[b]	PFT ^[a] w.r.t. CAAX ^[c]	PFT ^[a] w.r.t. FPP ^[d]
1	13/1	> 50	6.4	n.m.	n.m.
2	11/1	9.3	57 % ^e	n. comp.	comp.
3	11/2	5.3	6.7	n. comp.	comp.
4	11/3	10.5	n.m.	comp.	n. comp.
5	11/4	6.4	19.2	comp.	comp.
6	11/5	8.0	6.4	comp.	n. comp.

[a] Fluorescence test against rat PFT.^[12] [b] Radioactive test against human PFT.^[13] [c] Variation of the dansyl peptide concentration in the presence of the inhibitor with constant FPP concentration. [d] Variation of the FPP concentration in presence of the inhibitor with constant dansyl peptide concentration. [e] 57 % inhibition at 30 μM concentration of inhibitor. comp. = competitive; n. comp. = not competitive; n.m. = not investigated; w.r.t. = with respect to.

Compounds **11/1–11/5** were investigated with regard to their mechanism of inhibition (Table 1, see also the Supporting Information). As a result, **11/1** and **11/2** show competitive inhibition with respect to FPP, while **11/3** and **11/5** compete only with the peptide substrate. Moreover, as hoped, we were able to identify compound **11/4** as a bisubstrate inhibitor. These results of the enzymatic assays demonstrate that different types of inhibitors can be developed efficiently and flexibly on the basis of the natural product pepticinnamin E. The diverse modes of inhibition were examined by molecular modelling experiments.^[14] Figure 1a illustrates the calculated binding mode for the bisubstrate inhibitor **11/4**. It is obvious that both binding pockets are occupied (the substituted cinnamic acid substituent points backwards into the FPP binding pocket) and that the histidine residue is coordinated to the zinc atom in the active center of PFT. Figure 1b shows that the FPP-competitive inhibitor **11/2** blocks the appropriate binding pocket, but not the binding site of the peptide. Figure 1c shows that the peptide-competitive inhibitor **11/3** blocks the peptide binding site, but not the FPP binding site.

Finally we examined, with the help of an assay developed by us,^[15] whether or not the pepticinnamin E library contains compounds which induce apoptosis in Ras-transformed cells but not in the corresponding wild-type cells. In this assay, MDCK-f3 tumor cells from dog kidney were used, which were transfected with oncogenic H-Ras.^[16] A cell-division-inhibiting, morphology-changing, or apoptosis-inducing effect of a substance on MDCK-f3 cells indicates an influence on the Ras signal-transduction cascade.

To our delight, inhibitor **13/1** induced apoptosis in the tumor cell line (Figure 2). After 6 h at 100 μM inhibitor concentration, the final stage of apoptosis was observed, after 6 h at 50 μM concentration, an early stage of apoptosis had occurred. In a comparison experiment under identical con-



Scheme 3. Selected members of the pepticinnamin E library.

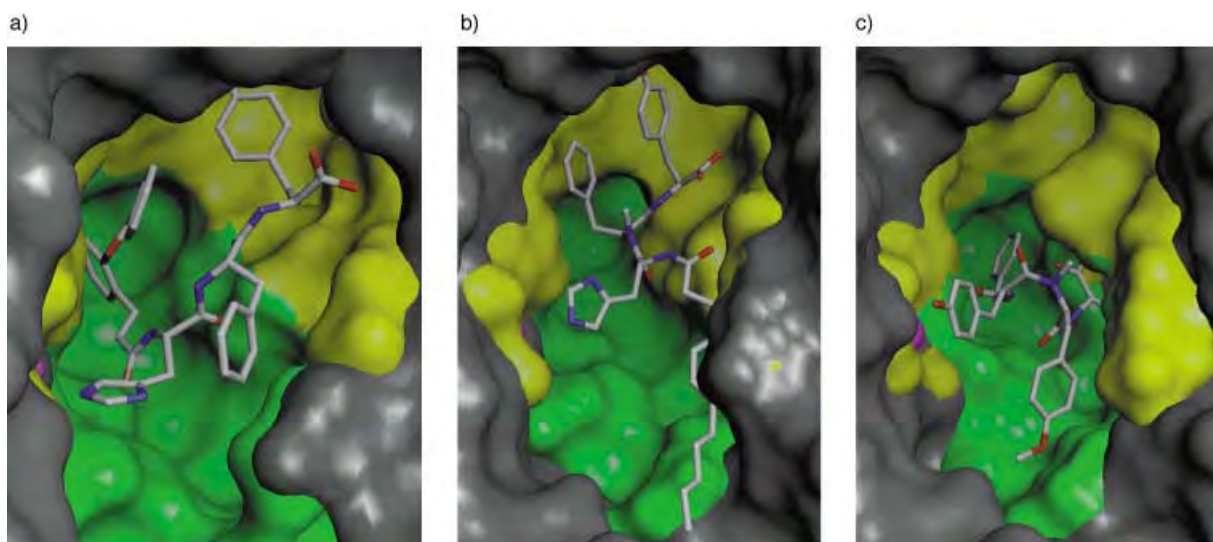


Figure 1. Results of the molecular modeling experiments. The binding site of FPP is shown in green, the binding site of the peptide substrate in yellow. The Zn^{2+} ion in the active center is shown in purple. a) Compound **11/4** in the active site of PFT; b) compound **11/3** in the active site of PFT; c) compound **11/2** in the active site of PFT.

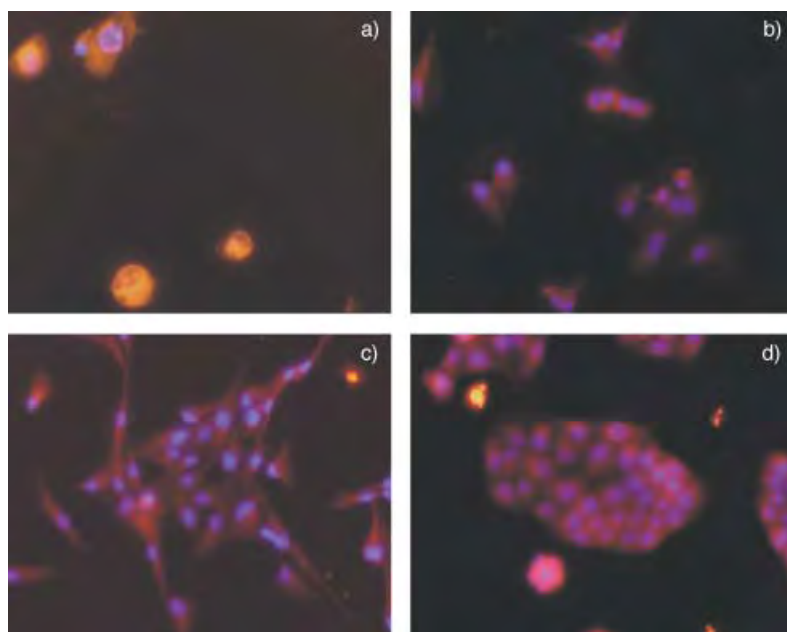


Figure 2. Effect of inhibitor **13/1** on MDCK-f3 cells: a) 100 μM , 6 h (apoptosis); b) 50 μM MDCK-f3 (apoptosis early stage); c) negative control, MDCK-f3 without inhibitor (no apoptosis); d) effect of **13/1** (100 μM , 6 h) on wild-type MDCK cells (no apoptosis).

ditions the wild-type MDCK cells showed no apoptotic effect.^[17] Thus compound **13/1** is not generally cytotoxic and its action is directly involved in influencing the Ras signal pathway.

In summary, we have developed a flexible and efficient solid-phase synthesis of a peptidocinnamin E library furnishing different types of PFT inhibitors and apoptosis-inducing compounds. These effects could be rationalized well by molecular modelling studies. This class of compounds should open up new opportunities in the chemical biology of Ras proteins.^[18]

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human PFT in the buffer medium (8.6 mM MgCl₂, 17.1 μM ZnCl₂, 1.32 mg mL⁻¹ DTT, 86 mM Tris/HCl pH 8.0) were pipetted 10 μL of a [³H]FPP-solution (3.3 mM, 15–30 Ci mmol⁻¹, New England Nuclear) and incubated for 30 min at 37°C. Then the reaction was stopped by addition of 100 μL of a solution of concentrated HCl in ethanol (15%), the precipitated Ras-protein was filtered through filter pads (type B) in a Tomtec-Harvester and the transferred radioactivity was measured by using a Wallac 1024 Betaplate scintillation counter.

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- [17] At 100 μM and higher inhibitor concentrations up to 1 mM no visible effect was observed for MDCK cells.
- [18] Abbreviations: DEAD = Diethylazodicarboxylate, HATU = 1-(bis-(dimethylamino)methylene)-1H-1,2,3-triazolo-[4,5b]pyridinium hexafluorophosphate 3-oxide, PyAOP = 7-aza-1-hydroxybenzotriazol-1-yl-*N*-oxy-tris(pyrrolidino)phosphonium hexafluorophosphate, NMP = 1-methyl-2-pyrrolidone, DIC = *N,N'*-diisopropylcarbodiimide, HOAt = 7-aza-1-hydroxybenzotriazole, DTT = 1,4-dithio-DL-erythritol, DTE = 1,4-dithioerythritol, DIPEA = diisopropylethylamine, NMA = *N*-methylaniline, Fmoc = 9-fluorenylmethoxycarbonyl, DMAP = 4-dimethylaminopyridine, TFA = trifluoroacetic acid.

A Molecular Beacon for Quantitative Monitoring of the DNA Polymerase Reaction in Real-Time**

Daniel Summerer and Andreas Marx*

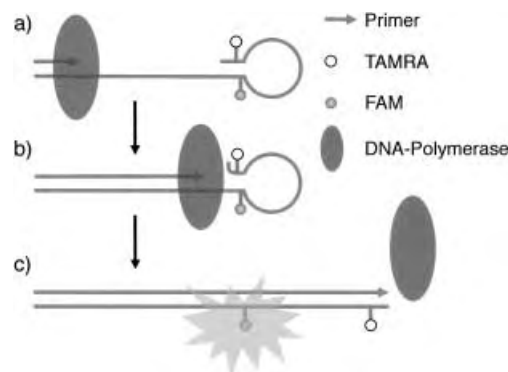
The design of new assay formats that allow fast parallel screening of enzyme function plays a pivotal role in the discovery of new products and reagents ranging from industrial processes to diagnostics.^[1] Furthermore, drug discovery and protein engineering are increasingly performed by combinatorial approaches, in which progress is tightly linked to the development of suitable screening systems capable of measuring desired enzyme properties in a high-throughput parallel fashion.^[1]

DNA polymerases are involved in all DNA syntheses occurring in nature. This decisive role in biological key processes has made these enzymes to attractive drug targets.^[2] Furthermore, DNA polymerases are the workhorses in

numerous important molecular-biological core technologies such as the ubiquitous polymerase chain reaction (PCR), cDNA cloning, genome sequencing, and detection of nucleotide variations within genes.^[3,4] Nevertheless, emerging drug resistances and the need to tailor DNA polymerases for new technologies, for example, faithful genome-wide nucleotide variation detection, fuel the search for further developments.^[4,5] Several approaches to screen DNA polymerases have been reported, all of which have considerable drawbacks,^[6] these include the use of laborious gel-based methods and/or rely on the employment of radioactive isotopes for product detection.^[6a,b] Several fluorescent-based assays are described, which are nevertheless restricted to specific DNA polymerases (such as thermostable enzymes used in PCR)^[7] or endpoint measurements requiring several cost-intensive auxiliary reagents and proteins for signal generation.^[6c–f]

Herein we report a new assay format that translates the proceeding DNA synthesis into a fluorescent signal in real-time. The method uses commercially available reagents and allows quantitative monitoring of enzymatic DNA synthesis in a multiwell plate-reader format even in crude lysates of DNA-polymerase overexpressing cells. Thus, this assay supercedes known methods to screen these important enzymes.

We designed a DNA reporter molecule in such a way that the template strand forms a stable hairpin structure (Scheme 1 a). The stem is equipped with a dye (carboxyfluorescein, FAM) the fluorescence of which is quenched through



Scheme 1. Assay design for real-time observation of the DNA polymerase reaction. a) The template probe labeled with fluorophor (carboxyfluorescein, FAM) and acceptor (*N,N'*-tetramethyl-rhodamine, TAMRA) has a hairpin extension in closed conformation before start of reaction. b) While extension proceeds, the DNA polymerase opens the stem and prevents reannealing by DNA duplex formation. c) The increase in the distance between the two labels is reported by restoration of FAM emission.

resonance energy transfer (RET) by a quencher (*N,N'*-tetramethylrhodamine, TAMRA) brought in close proximity by the hairpin formation.^[8,9] Both, fluorophor and quencher are attached to the C5-position of 2'-deoxyuridines, which can be bypassed by DNA polymerases.^[10] An extended 3'-end of our template hairpin construct allows binding of a primer strand to its complementary site (Scheme 1b). A DNA polymerase triggers opening of the hairpin stem as primer extension proceeds, which results in spatial separation of fluorescent and quencher dyes accompanied by restoration of FAM-emission (Scheme 1).

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

First, we tested the Klenow fragment of *E. coli* DNA polymerase I (*exo*⁻-mutant, KF⁻), an enzyme extensively used as a model for DNA polymerase mechanisms and function.^[11] We carried out primer-extension reactions in 96-well-plate format using a fluorescence kinetic reader with automated liquid dispenser. In principle, standard reactions were initiated by addition of MgCl₂ to a mixture of DNA polymerase and hairpin-template primer complex in the appropriate reaction buffer comprising all four deoxynucleoside triphosphates (dNTP). The reaction was monitored by measurement of FAM-fluorescence intensity at different time intervals. Figure 1a illustrates nicely the applicability of the concept and exhibits that fluorescence increases with prolonging incubation time. Noteworthy, is that in the absence of dNTPs, magnesium ions, or enzyme, no fluorescence increase was observed, strongly indicating that the time-dependent signal generation is a result of DNA polymerase function.

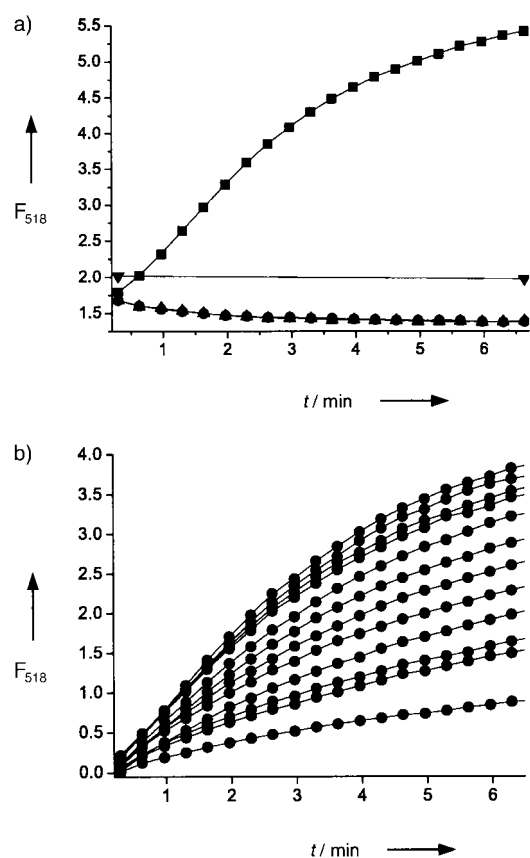


Figure 1. Fluorescent real-time monitoring of DNA synthesis promoted by KF⁻ using the hairpin-template probe. a) Dependence of essential KF⁻ reaction parameters. (■): Reaction conducted at 37°C employing 200 nM hairpin-template primer complex, KF⁻, 62.5 μM of each dNTP and 10 mM MgCl₂ in standard reaction buffer.^[13] FAM fluorescence intensities were measured at 518 nm. Blind measurements were made under the same reaction conditions but without dNTP (●), without KF⁻ (▲), or without MgCl₂ (▼). Presented graphs correspond to raw data without correction for photobleaching or other machine-dependent effects. b) Time courses of reactions employing different dNTP concentrations. Reactions contained KF⁻ and dNTP concentrations ranging from 1.25 μM (lowest curve) to 37.5 μM (highest curve). Data are results of multiple experiments. For clarity, the error bars are not shown. A measurement of an equivalent reaction mix without KF⁻ was conducted in parallel and subtracted from the data from the experiments including KF⁻.^[13]

The kinetics of enzymatic DNA synthesis exhibit Michaelis-Menten dependence of substrate concentration thus, apparent Michaelis-constant (K_M) values can be derived from experiments conducted with a given amount of enzyme and varied substrate concentrations.^[12] We therefore investigated the KF⁻-catalyzed reaction using various dNTP concentrations. The fluorescence-time curves thus obtained show an initial linear signal increase and that with increasing substrate concentrations the reaction rate reaches a maximum (Figure 1b). Remarkably, we obtained a K_M value (3.6 ± 0.2 μM) that compares well with that measured independently using a conventional radiometric assay (3.9 ± 1.1 μM).^[13]

We explored whether the assay is suitable for detecting the interactions of DNA polymerases with inhibitors, for this we employed HIV-1 reverse transcriptase (HIV-1-RT) as a model system. In current HIV drug therapy two classes of RT-inhibitors are in use, differing in their mode of action.^[5] Non-nucleoside RT inhibitors (NNRTIs) are believed to allosterically inhibit RT function, while nucleoside RT inhibitors (NRTIs) are first transformed to 5'-O-triphosphates by cellular processes and then incorporated into the nascent DNA strand by the RT to cause chain termination. To validate whether our assay format rapidly identifies inhibitors of HIV-1-RT acting by both mechanisms, we studied nevirapine and 3'-azido-2',3'-dideoxythymidine triphosphate (AZTTP) which are well characterized NNRTIs and NRTIs, respectively.

Our assay permits real-time monitoring of HIV-1-RT inhibition independent from the mechanism of action (Figure 2). Inhibition profiles from which IC_{50} -values could be obtained were recorded in a single run comprising parallel conducted measurements. Furthermore, the resulting IC_{50} -values of nevirapine (0.13 ± 0.03 μM) and AZTTP (2.10 ± 0.22 μM) correspond well with reported data indicating the suitability of the assay for faithful inhibitor characterization.^[14]

The presented setup should be ideally suited for parallel screening of libraries of DNA polymerase variants in high throughput. In first studies along this line we tested the

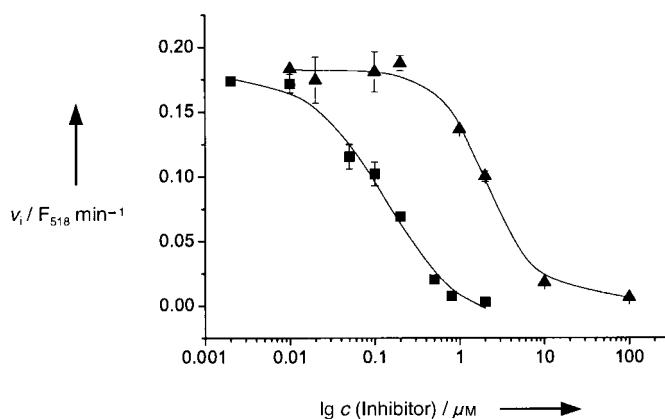


Figure 2. HIV-1-RT inhibition profiles. Reactions were conducted using HIV-1-RT, 200 nM hairpin-template primer complex, and 50 μM of each dNTP in the presence of inhibitors at different concentrations. (▲) AZTTP, (■) nevirapine. An equivalent blind reaction mix in the absence of RT was conducted in parallel and subtracted from the data from the experiments including RT.^[13] Initial apparent reaction rates (v_i) were obtained from data by determination of the slopes of the initial linear portion of individual reaction graphs. Data are results of multiple experiments.^[13]

feasibility of the molecular probe to sense enzymatic activity in crude lysates of DNA polymerase overexpressing cells. Such a capability would greatly simplify and speed up the parallel screening of mutant libraries without the need for tedious and cost-intensive purification steps. Nevertheless, this is a challenging task, since the presence of a vast number of DNA-binding and -modifying proteins in bacterial-cell lysates sets high demands on the robustness of assay formats relying on a DNA reporter molecule. To demonstrate this possible application, we employed the molecular probe in fluorescent-primer extension reactions with the lysates of KF⁻-overexpressing *E. coli* cells.^[13] Strikingly, significant fluorescence increase was observed exclusively when lysates of expression-induced cells harboring KF⁻-coding vectors were employed (Figure 3a).

Lysates obtained from induced cells harboring vectors without KF⁻-coding sequences failed to trigger fluorescence increase in the investigated timeframe. To confirm that signal generation indeed results from DNA synthesis catalyzed by expressed KF⁻, we repeated these experiments employing ³²P-labeled primers with subsequent analysis by denaturing polyacrylamide gel electrophoresis (Figure 3b). The results show that primer extension is only observed when lysates from induced cells carrying KF⁻-coding vectors are employed, strongly indicating that the observed signal generation indeed arises from the desired DNA polymerase function.

In summary, we report here on a new assay format based on a single-molecular probe, which allows quantitative real-time

monitoring of DNA synthesis catalyzed by DNA polymerases. The setup enables the rapid identification and quantitative characterization of small molecules interfering with DNA-polymerase function. Furthermore, we experimentally demonstrated that the presented reporter system is able to monitor DNA polymerase function in real-time directly from lysates of DNA polymerase overexpressing cells. To our knowledge these demands are not met by any of the known methods. Taking these superior properties together, we strongly believe that the presented assay format will find wide applications.

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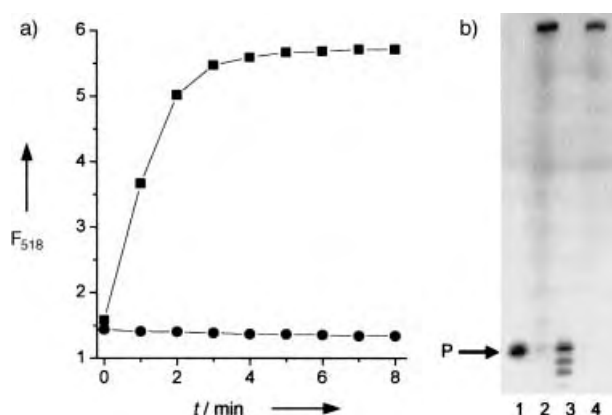
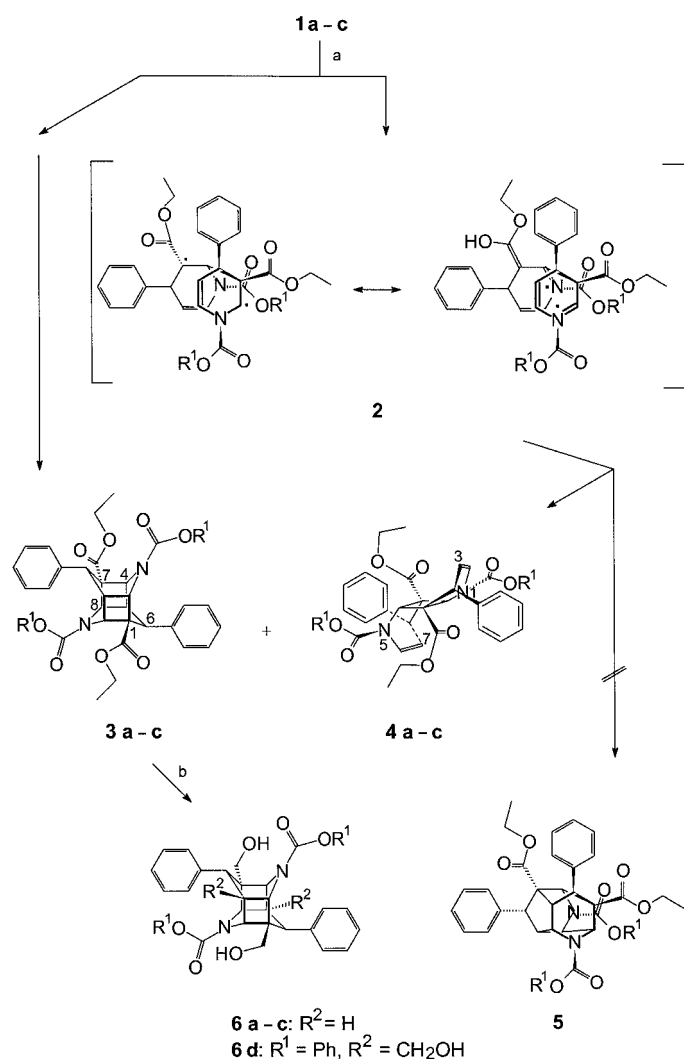


Figure 3. Primer extension reactions promoted by crude lysates of KF⁻-overexpressing *E. coli* cultures using the hairpin-template probe. a) Fluorescence measurement: reactions were conducted at 37°C employing 200 nm hairpin-template primer complex, 200 μM of each dNTP, 10 mM MgCl₂, and lysate of expression-induced *E. coli* cultures in standard reaction buffer.^[13] (■) Reactions employing lysate of *E. coli* cells harboring the KF⁻-coding vector pQKlenowExo⁻ 4 h after induction of expression. (●) Reactions employing lysate of *E. coli* cells harboring the noncoding vector pQE30Xa 4 h after induction of expression. Data are results of multiple experiments. Presented graphs correspond to raw data without correction for photobleaching or other machine-dependent effects. b) Polyacrylamide gel electrophoretic analysis of primer-extension reactions using ³²P-labeled primer template probe. The reaction time was 10 min in all cases. Lane 1: ³²P-labeled primer template probe and dNTPs in KF⁻-reaction buffer (P=primer). Lane 2: Reaction employing commercially purchased KF⁻. Lane 3: Reaction employing lysate of *E. coli* cells harboring noncoding pQE30Xa 4 h after induction of expression. Lane 4: Reactions employing lysate of *E. coli* cells containing KF⁻-coding vector pQKlenowExo⁻ 4 h after induction of expression.^[13]

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Scheme 2. Synthesis of the target structures **6a–c** starting from the monomeric 4-aryl-1,4-dihydropyridines. a) $h\nu$, $\lambda > 270$ nm, 4 weeks, 27 °C, THF, **3a** (44 %), **4a** (33 %), **3b** (46 %), **4b** (32 %), **3c** (41 %), **4c** (38 %); b) LiAlH₄ (1 equiv), 2 h, –8 °C, THF, **6a** (78 %), **6b** (75 %), **6c** (65 %).

kishomocubane **5** was formed.^[7] We are currently investigating the causes of the unexpected outcome of this reaction. In the case of the *anti* dimers we propose a stabilizing conjugated effect of the *N*-oxycarbonyl group on a hypothetical intermediate biradical **2**, which then undergoes bond rotation to form the *anti* dimer. Subsequent selective reduction of the ester groups at the substituted cyclobutane ring of the dimers is accomplished with lithium aluminum hydride at low temperature and provides the target compounds **6a–c**.

The *in vitro* assay to determine the inhibition of the activity of the molecular pump made use of fluorescence measurements of untreated cells and cells that had been treated with P-GP modulators. The ratio of the uptake of a P-GP transporter substrate that shows specific binding and fluorescence, for example, rhodamine 123, by tumor cells and cells that have become resistant through MDR gene transfer was calculated as the ratio of P-GP inhibitory activity *R* (Table 1).^[8] This direct comparison of the fluorescence data ensures that the observed activities observed for the specific P-GP inhibitors is based on the MDR modulators.

Table 1. Effects of the hydroxymethyl-3,9-diazatetraasteranes **6a–d** on the MDR of tumor cells (mouse T-lymphoma).^[a]

Compound	Activity ratio <i>R</i> ^[b,c]	
	3 μ M	30 μ M
6a	1.11	18.62
6b	28.10	30.87 ^[d]
6c	6.81	7.42 ^[d]
6d	0.97	5.40

[a] VRP control with 11 μ M: 7.27. According to ref. [8] 11 μ M is the relevant maximum concentration for MDR modulation. The compounds are active (A) when the ratio is *R* > 1.1, and very active (AA) for *R* values above 10.^[8] [b] $R = \frac{(\text{MDR, treated/MDR, untreated control})}{(\text{parent cell line, treated/parent cell line, untreated control})}$. [c] Average value from two determinations. [d] Saturation concentration for P-GP inhibition.

In the case of the hydroxymethyl cage compounds **6a–c**, the *N*-methoxycarbonyl-substituted compound **6a** showed an activity similar to that of VRP; a linear relationship between the concentration and the inhibitory activity was determined. Structural characteristics required for sufficient activity of MDR modulators include the presence of two lipophilic moieties and a basic nitrogen atom, which was replaced for the first time by Ecker et al. by an ester group that functioned as a hydrogen bonding acceptor.^[9,10] In our compounds the nitrogen atom, a hydrophilic structural element, is replaced by the hydroxymethyl group. The theory that sufficient lipophilicity is requirement for good MDR modulators was supported by the fact that compounds **6b** and **6c**, which contain more lipophilic groups at the *N*-substituents, showed increased activity at low concentrations.^[11] It is interesting that an increase in the total number of potential hydrogen bond donor and acceptor functionalities from four (two hydroxymethyl and two carbamide ester groups) in **6b** to six (four hydroxymethyl and two carbamide ester groups) in **6d**^[12] is accompanied by complete loss of activity at the same low concentration (3 μ M).

Until now the presence of a large number of moieties that can participate in hydrogen bonding, for interaction with the amide groups that are in the proposed bonding site, was considered to be important for an optimal bonding affinity to the P-GP.^[11,13,14] Initial studies on a series of 3,9-dialkyl-3,9-diazatetraasteranes^[15] provide inhibitory activity ratios of 30.19 at 3 μ M and 24.83 at 30 μ M for a 3,9-dibenzyl derivative with four hydroxymethyl groups. This corresponds to the activity of compound **6b**, which contains two hydroxymethyl and two carbamide ester groups and therefore also presents a total of four hydrogen bonding sites. A 3,9-dimethyl-3,9-diazatetraasterane with four hydroxymethyl groups provides *R* values of 0.88 (3 μ M) and 4.7 (30 μ M) and thus does not display any noteworthy P-GP inhibitory activity until a concentration of 30 μ M. This underlines the importance of a bulky lipophilic *N*-substituent for inhibitory activity, as shown by the comparison of the 3,9-dimethoxycarbonyl derivative **6a** with the 3,9-diphenoxycarbonyl derivative **6b**. A decrease in the number of hydroxymethyl groups from four to two leads to a decrease in the inhibitory activity ratio *R* to 16.42 (3 μ M) and 10.69 for the 3,9-dibenzyl derivative (30 μ M) and to 0.67 (3 μ M) and 2.7 (30 μ M) for the 3,9-dimethyl derivative. In the case of four hydroxymethyl groups, similar results are obtained as for the combination of two hydroxymethyl and

two carbamide ester groups. In contrast, the presence of four hydroxymethyl and two carbamide ester groups, and therefore a total of six hydrogen bond donor and acceptor functionalities, is considered to be less favorable. Our results suggest a limit on the number of hydrogen bond donor and acceptor groups, at least for this first series of symmetric modulators, and therefore provide an important contribution to the discussion on the role of hydrogen bonding with respect to activity. A comparison of the concentrations required for sufficient inhibitory activity ($< 3 \mu\text{M}$) and the CC_{50} values for the cytotoxicity of **6b** and **6c** (> 93 and $125 \mu\text{M}$, respectively), obtained from MTT assays^[16] for the determination of lactate dehydrogenase (LDH) activity in metabolically active normal cells (MT-4), makes clear that the novel MDR modulators evoke convincing inhibitory activities at concentrations below those causing cytotoxic effects.

In conclusion, hydroxymethyl-substituted 3,9-diazatetraateranes represent an independent class of novel MDR modulators that show activity at concentrations below cytotoxic levels. A highly interesting characteristic of these compounds is the rigidly symmetric form, which, owing to the extraordinary effect on the target structure, could be a reflection of the composition of the molecular pump or the potential bonding region, whose structure is as yet unknown. The goal of further work is to examine this "symmetry hypothesis" through the synthesis and investigation of unsymmetrical compounds. In order to estimate the clinical potential experiments are planned on additional resistant cell lines, whose MDR is based on the expression of molecular pumps other than the P-GP.

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Fluorescence Spectroscopic Quantification of the Release of Cyclic Nucleotides from Photocleavable [Bis(carboxymethoxy)coumarin-4-yl]methyl Esters inside Cells**

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Caged compounds are an elegant means to produce rapid jumps in the concentration of chemical messenger molecules inside cells.^[1] Caged compounds are photolabile inactive derivatives of biologically active molecules. The biologically active substance is rapidly released by a photochemical reaction. Caged compounds allow the elucidation of complex intracellular processes and their resolution in time and space.

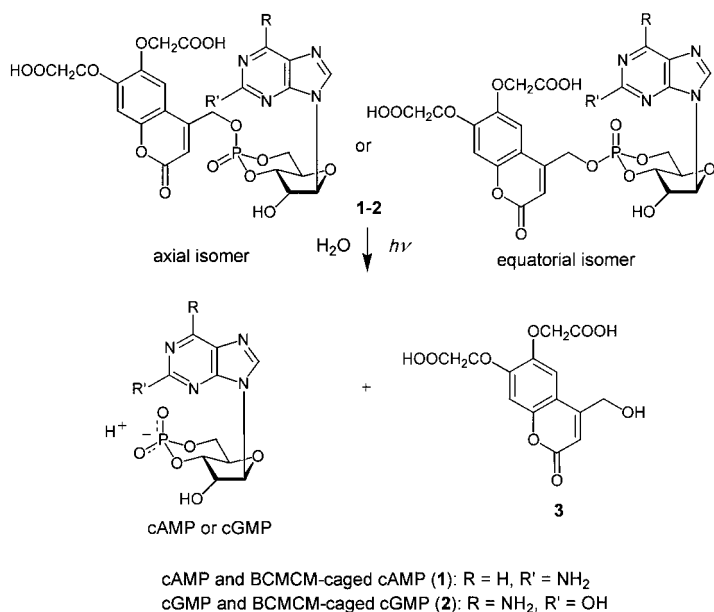
For many applications it would be useful to determine quantitatively the degree of photolysis of the caged compound inside cells. In a few cases this has been possible by a rather complicated calibration of the cellular reaction. Here we show that the determination of the amount of released cyclic nucleotides is feasible by fluorescence measurements, using the axial and equatorial diastereomers of [6,7-bis(carboxymethoxy)coumarin-4-yl]methyl (BCMCM) esters of cyclic adenosine-3',5'-monophosphate (cAMP) **1** and cyclic guanosine-3',5'-monophosphate (cGMP) **2**,^[2] which are excellent phototriggers for cyclic nucleotides.

Upon irradiation with UV light in aqueous buffer solution and inside cells, **1** and **2** rapidly produce (within 2–5 ns) cAMP

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and cGMP, respectively [3] and 6,7-bis(carboxymethoxy)-4-(hydroxymethyl)coumarin (**3**, BCMCM-OH) (Scheme 1). The photolysis proceeds free of competing side reactions with quantum yields of 0.08–0.14.[2] Per molecule of **3**, one molecule of either cAMP or cGMP is produced.



Scheme 1. Photolysis of **1** and **2**.

The fluorescence quantum yields of **1** and **2** are small, whereas the alcohol **3** is strongly fluorescent (Table 1, see also Figure 1a). Therefore, upon photolysis of the caged compounds, the fluorescence is strongly enhanced (in aqueous

Table 1. Fluorescence maxima $\lambda_t^{\max}$, fluorescence quantum yields φ_f and fluorescence life times τ_f of the BCMCM-caged cAMPs and cGMPs **1–2**, as well as of **3** in HEPES–KOH buffer, pH 7.2; $\lambda_{\text{exc}} = 333$ nm.

Compound	$\lambda_t^{\max}$ [nm]	$\varphi_f^{[a]}$	τ_f [ns]
1 (axial)	440	0.015	n.d.
1 (equatorial)	439	0.016	< 0.2
2 (axial)	436	0.012	n.d.
2 (equatorial)	441	0.014	< 0.2
3	431	0.62	3.18

[a] Error limit ± 0.002 (**1,2**) and ± 0.01 (**3**); n.d. = not determined.

buffer 40- to 50-fold increase) (Figure 1b). In HEPES buffer (HEPES = 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethansulfonic acid), the relationship between the degree of photolysis and the increase in fluorescence is linear for all BCMCM-caged cyclic nucleotides. This correlation is shown for the equatorial isomers of **1** and **2** in Figure 2. Therefore, it is feasible to determine the concentration of released **3** and thereby also the concentration of cAMP and cGMP under these conditions.

The fluorescence of **1**, **2**, and **3** in cells is similar to that of the respective substances in aqueous solutions, that is, **3**, which has been introduced into HEK293 cells by using a micropipette, is strongly fluorescent (Figure 3), in contrast to 7-

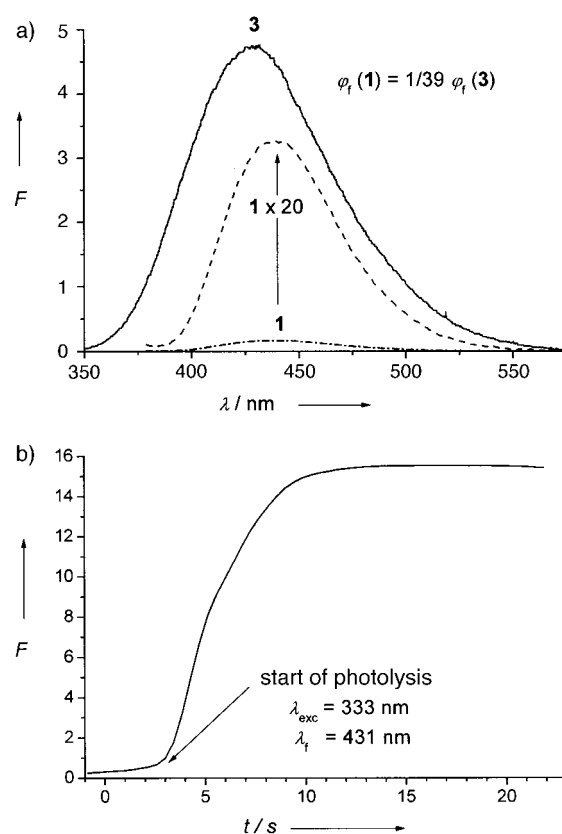


Figure 1. a) Fluorescence spectra of 50 μM solutions of the equatorial isomer of **1** and of **3**. F = relative fluorescence intensity; b) increase in fluorescence of a 50 μM solution of the equatorial isomer of **1** as a function of the irradiation time; solutions in HEPES–KOH buffer, pH 7.2.

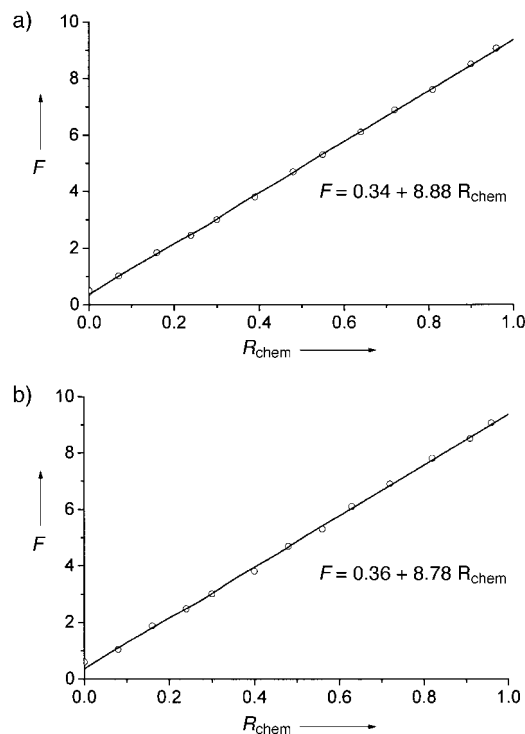


Figure 2. Correlation between the enhancement of the relative fluorescence and the extent of photolysis (R_{chem}) of 50 μM solutions of the equatorial isomers of **1** (a) and **2** (b) in HEPES–KOH buffer, pH 7.2.

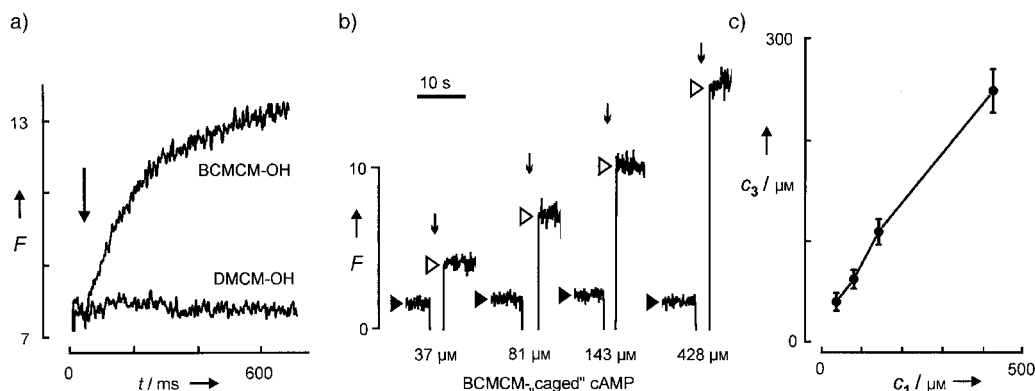


Figure 3. Determination of the photolytically liberated concentration of **3** in HEK293 cells: a) visualization of cell loading with 100 μM BCMCM-OH (**3**) or DCMCM-OH through the patch pipette by monitoring the fluorescence intensity (excitation: 340 nm, emission >420 nm, scaling in counts ms^{-1}). Fluorescence intensity increases with the concentration of **3**; b) determination of the concentration of **3** following photolysis of **1** in four HEK293 cells which were loaded with the indicated concentration of **1** as well as with 35 μM **3** as standard for the calibration of intracellular fluorescence. The fluorescence intensity used for calibration (F_c , filled arrowhead) was measured after subtraction of background light. Following illumination (arrows, $t = 2$ s, $\lambda = 365$ nm), the fluorescence intensity increases to the value F_1 (open arrowheads). The calculated concentration of liberated **3** [$c = (F_1 - F_c)/F_c 35 \mu\text{M}$] was 49 μM , 96 μM , 148 μM , and 271 μM , respectively; c) concentration of photolytically liberated intracellular **3** plotted against the concentration of **1** in the pipette solution (illumination: $t = 2$ s, $\lambda = 365$ nm). Mean values $\pm$ SD obtained from five cells per concentration value. c_1 = concentration of **1**, c_3 = concentration of liberated **3**.

methoxy-[4] and 6,7-dimethoxy-4-(hydroxymethyl)coumarin (DMCM-OH),[5] whose fluorescence is totally quenched inside HEK293 cells.[6] This result indicates that the hydrophilic carboxymethoxy groups in **3** inhibit the quenching of fluorescence by cellular constituents. Therefore, flash photolysis of BCMCM-caged cyclic nucleotides results in a concentration-dependent increase of fluorescence inside cells, as shown in Figure 3b for compound **1**. The concentrations of **3** and thereby that of cAMP, determined by the light-induced

fluorescence enhancement, increase almost linearly with the concentration of photolyzed **1** (Figure 3c).

Figure 4a shows the light-induced increase in intracellular fluorescence and the cAMP-induced current in cells loaded with **1** and expressing the cAMP-gated ion channel of olfactory neurons (CNGA2). Each flash of light incrementally increases both the fluorescence and the current. The concentration of released **3**, which corresponds to the concentration of released cAMP, can be determined from the fractional change in fluorescence (Figure 3). The obtained concentration of released cAMP agrees very well with that independently determined from the incremental increase of open CNGA2 channels[7] (Figure 4b). Similar results were obtained for the release of cGMP from **2** and the release of 8-substituted cyclic nucleotides from the respective BCMCM-caged derivatives. These experiments demonstrate that it is feasible to follow the release of cyclic nucleotides from BCMCM-caged cyclic nucleotides quantitatively by fluorescence measurements. We expect that these measurements can be extended to other BCMCM-caged derivatives, provided their fluorescence is distinctly different from that of the photolysis products.

This technique allows, for the first time, the quantitative dose-response relations of cellular reactions triggered by cyclic nucleotides to be established. Recently it was reported[8] that adenylyl cyclases, which synthesize cAMP, and cAMP-gated channels, appear to colocalize to a subcompartment of a cell line and that diffusional exchange between this compartment and the cytosol is restricted. We did not observe a difference in the concentrations of cytosolic cAMP reported by the fluorescence signal and the "local" cAMP concentration in the vicinity of the CNGA2 channel. The methods described here will allow the hypothesis of cellular subcompartments, in which the diffusion of intracellular messengers is restricted in more quantitative terms, to be tested.

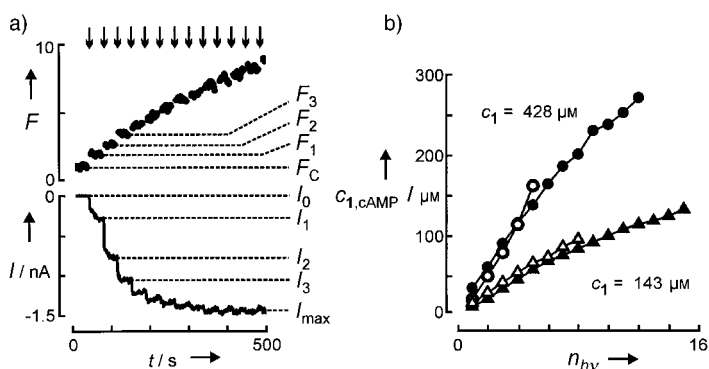


Figure 4. Quantification of the concentrations of **3** and cAMP following photolysis of **1**: a) a HEK293 cell transfected with DNA encoding CNGA 2 channels was loaded with 428 μM **1** as well as with 35 μM **3** for internal calibration. The fluorescence recording (upper trace) shows liberation of **3** during a series of UV flashes ($t = 20$ ms, $\lambda = 365$ nm). The simultaneous current recording (lower trace) shows activation of the CNGA2 channels by photoreleased cAMP. Both fluorescence intensity and current amplitude can be used to calculate photolysis; b) calculation of photolytic liberation of **3** from the increase of fluorescence intensity (see Figure 3), and calculation of cAMP liberation from the relative current $I_{\text{rel}} = I/I_{\text{max}}$ using the Hill equation.[9] The results for quantification of photolysis obtained from fluorescence measurements ($\blacktriangle$) and from analysis of current recordings ($\triangle$) are in good agreement. While the current calibration is limited by the maximal channel activation at roughly 150 μM cAMP, the fluorescence-based calibration can be extended to higher concentrations. I = current; n = number of flashes; $c_{1,\text{cAMP}}$ = concentration of photoreleased cAMP.

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$$c_{\text{cAMP}} = K_{1/2} \cdot \sqrt[n]{\frac{I_{\text{rel}}}{1 - I_{\text{rel}}}}$$

the cAMP concentration that gives half-maximal channel activation (45 μM),^[9] and n is the Hill coefficient (1.8). W. Bönigk, J. Bradley, F. Sesti, F. Müller, I. Boekhoff, G. V. Ronnett, U. B. Kaupp, S. Frings, *J. Neurosci.* **1999**, 19, 5332–5347.

Protonated Benzene: IR Spectrum and Structure of C_6H_7^+ **

Nicola Solcà and Otto Dopfer*

The protonation of aromatic molecules is a central process to organic chemistry. For example, protonated aromatic molecules (AH^+) occur as intermediates in electrophilic aromatic substitution reactions, probably the most characteristic reaction mechanism for aromatic molecules.^[1] Spectroscopic studies in solution reveal that fundamental properties of these ion–molecule reactions depend strongly on the environment.^[1,2] To separate solvation effects from intrinsic molecular properties, gas-phase studies are required.^[3] However, to date, nearly all data about gas-phase protonation processes have come from mass spectrometric methods,^[3] which provide only indirect and often inconclusive structural information. Spectroscopic data for direct and unambiguous structural characterization have not been reported for any

isolated AH^+ ion, mainly because of the difficulties encountered in producing a large abundance of these species. Gas-phase spectra of AH^+ are desirable, not only to investigate fundamental reaction mechanisms, but also to identify these ions in terrestrial and extraterrestrial hydrocarbon plasmas, such as combustion flames^[4] and interstellar media.^[5]

Protonated benzene, C_6H_7^+ , is the simplest protonated aromatic hydrocarbon and for more than half a century has served as a benchmark for investigating the mechanism of electrophilic aromatic substitutions. Most quantum chemical studies consider three binding sites for the proton to the benzene molecule (Figure 1).^[6] The benzenium ion (**1**), often

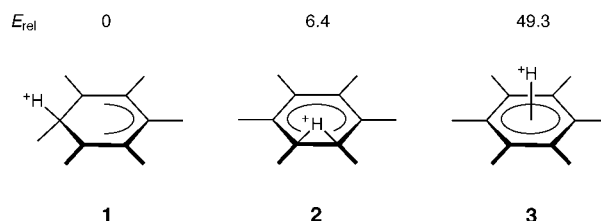


Figure 1. Calculated structures and relative energies (E_{rel} in kcal mol^{-1}) of stationary points on the potential energy surface of C_6H_7^+ .^[14] **1**: σ complex (benzenium ion, Wheland intermediate, global minimum, C_{2v} symmetry); **2**: bridged structure (benzonium ion, first-order transition state, C_s symmetry); **3**: π complex (second-order transition state, C_{6v} symmetry).

called the σ complex or Wheland intermediate, is the global minimum on the calculated C_6H_7^+ potential. The bridged structure **2** is predicted to be the lowest transition state for proton migration between equivalent σ complexes, with an activation barrier of $E_a \approx 6\text{--}11 \text{ kcal mol}^{-1}$. The face-protonated π complex **3** is identified as a second-order transition state which lies $\approx 50 \text{ kcal mol}^{-1}$ above **1**. Apart from **1–3**, several other less stable C_6H_7^+ isomers exist.^[7] These isomers are not considered further, as they do not have a six-membered ring and are thus not created in the present experimental procedure.^[3a,7,8]

Spectroscopic evidence for a σ complex of C_6H_7^+ in the condensed phase comes from NMR,^[9] IR,^[9b,d,10] and UV spectroscopy,^[10] and X-ray crystallography^[9e] of either salts or superacid solutions. The low-temperature NMR spectra are consistent with a static σ complex **1**, whereas spectra recorded at higher temperatures indicate the equivalence of all protons, which is caused by rapid intramolecular exchange.^[9a] The derived activation barrier for proton migration, $E_a = 10 \pm 1 \text{ kcal mol}^{-1}$,^[9a] is consistent with the theoretical values,^[6] assuming that **2** is the lowest transition state for the intramolecular 1,2-proton transfer. The conclusions drawn from gas-phase studies to ascertain the C_6H_7^+ structure without interference from strong solvation effects are controversial. The UV spectrum of isolated C_6H_7^+ ^[11] indeed deviates significantly from the solution spectrum^[10] and contains no conclusive structural information. Structure determination by mass spectrometry^[3,7] suffers from indirect and disputable interpretations.^[3a] Although most studies infer that **1** is the most stable C_6H_7^+ structure,^[3a–d] a recent analysis^[3e] leads to the conclusion that **3** is probably lower in energy by $\approx 3\text{--}4 \text{ kcal mol}^{-1}$.

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The only previous spectroscopic determination of a gas-phase AH^+ structure was recently reported for protonated phenol from IR-photodissociation spectra of its noncovalent complexes with Ar ligands.^[8] The high sensitivity and selectivity of this approach overcome the problems arising from low ion concentrations.^[12] The same technique is applied here to derive the vibrational spectrum and the most stable structure of protonated benzene from the spectra of weakly bound dimers with inert ligands (L). The weak interaction with L causes only a negligible perturbation of C_6H_7^+ and the IR spectra of $\text{C}_6\text{H}_7^+\cdot\text{L}$ dimers closely resemble that of the isolated ion.

Figure 2 compares the IR spectra of $\text{C}_6\text{H}_7^+\cdot\text{Ar}$ (a) and $\text{C}_6\text{H}_7^+\cdot\text{N}_2$ (b) in the vicinity of the C-H stretch vibrations. The positions, widths, and assignments of the transitions observed are collected in Table 1. The two IR spectra are almost identical, which confirms the expectation that the Ar and N_2

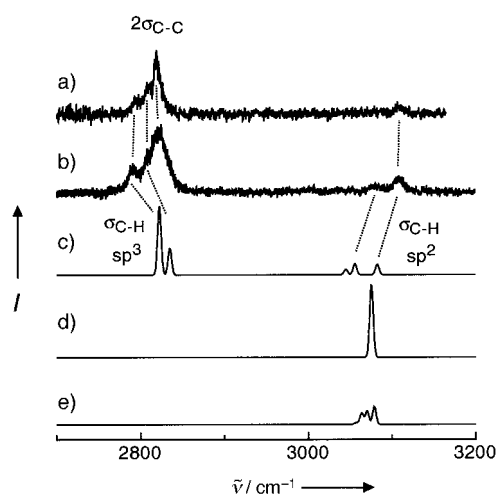


Figure 2. Experimental IR-photodissociation spectra of a) $\text{C}_6\text{H}_7^+\cdot\text{Ar}$ and b) $\text{C}_6\text{H}_7^+\cdot\text{N}_2$ in the range of the C-H stretching vibrations recorded in the C_6H_7^+ fragment channel. These spectra are compared to calculated spectra of three isomeric C_6H_7^+ structures using a convolution width of 5 cm^{-1} .^[14] c) σ complex **1**; d) π complex **3**; e) bridged structure **2**. Corresponding transitions are connected by dotted lines. Aromatic C-H stretching frequencies ($\sigma_{\text{C-H}}$, sp^2) occur between 3000 and 3200 cm^{-1} , whereas bands arising from aliphatic C-H stretches ($\sigma_{\text{C-H}}$, sp^3) appear near 2800 cm^{-1} . The C-C stretch overtone ($2\sigma_{\text{C-C}}$, sp^2) is not included in the simulated spectra.

Table 1. Positions, widths (full-width half maximum in parentheses), and assignments of the transitions [cm^{-1}] observed in the IR spectra of $\text{C}_6\text{H}_{7-n}\text{D}_n^+\cdot\text{Ar}/\text{N}_2$ dimers.

Dimer	Position	Assignment
$\text{C}_6\text{H}_7^+\cdot\text{Ar}$	2795 (6)	sym $\sigma_{\text{C-H}}$ (sp^3)
	2810 (8)	asym $\sigma_{\text{C-H}}$ (sp^3)
	2819 (8)	$2\sigma_{\text{C-C}}$ (sp^2)
	3110 (10)	$\sigma_{\text{C-H}}$ (sp^2)
$\text{C}_6\text{H}_7^+\cdot\text{N}_2$	2792 (9)	sym $\sigma_{\text{C-H}}$ (sp^3)
	2809 (6)	asym $\sigma_{\text{C-H}}$ (sp^3)
	2821 (15)	$2\sigma_{\text{C-C}}$ (sp^2)
	3081 (14)	$\sigma_{\text{C-H}}$ (sp^2)
	3109 (12)	$\sigma_{\text{C-H}}$ (sp^2)
$\text{C}_6\text{H}_6\text{D}^+\cdot\text{N}_2$	2804 (10)	$\sigma_{\text{C-H}}$ (sp^3)
	2821 (16)	$2\sigma_{\text{C-C}}$ (sp^2)
$\text{C}_6\text{D}_6\text{H}^+\cdot\text{Ar}$	2797 (13)	$\sigma_{\text{C-H}}$ (sp^3)

have essentially no influence on the IR spectrum of C_6H_7^+ in this frequency range.^[13] Figure 2c–e shows the IR spectra calculated for the three C_6H_7^+ structures in Figure 1:^[14] the σ complex (c), the π complex (d), and the bridged structure (e). Comparison with the theoretical IR spectra shows that the experimental spectra are clearly dominated by the σ complex **1**, because only this structure gives rise to absorptions near 2800 cm^{-1} . The two bands in the theoretical spectrum of **1** at 2823 and 2835 cm^{-1} arise from the symmetric and antisymmetric C-H stretches of the aliphatic CH_2 group (sp^3 hybridization of the C atom) and are thus an unambiguous spectroscopic fingerprint of **1**. The spectra from the experiments display three transitions in this range at ≈ 2795 , ≈ 2810 , and $\approx 2820\text{ cm}^{-1}$. On the basis of their relative intensities, the first two bands are assigned to the aliphatic C-H stretching modes. Deuteration experiments discussed below show that the third and most intense band observed arises from a C-C stretch overtone ($2\sigma_{\text{C-C}}$) not included in the simulations. Two additional bands at ≈ 3080 and $\approx 3110\text{ cm}^{-1}$ fall in the range of the aromatic C-H stretching modes (sp^2 hybridization of the C atoms). A good agreement of relative band positions and intensities is again only observed with the spectrum calculated for **1**. Thus, the vibrational analysis demonstrates that complexes of **1** clearly dominate the measured IR spectra, whereas dimers involving **2** or **3** provide no (or at most only a minor) contribution. As the employed ion source produces predominantly the most stable AH^+ isomer, the σ complex of C_6H_7^+ (**1**) is concluded to be the lowest energy structure of protonated benzene, in agreement with the calculations.^[6]

The IR spectra of (partly) deuterated $\text{C}_6\text{H}_{7-n}\text{D}_n^+$ ions complexed with Ar or N_2 confirm the assignments of the three bands near 2800 cm^{-1} (Figure 3, Table 1). Transitions assigned to aliphatic C-H stretch modes of the methylene group of the isotopologue $[\text{C}_5\text{H}_5\text{CH}_2]^+$ are marked by filled circles, whereas the $2\sigma_{\text{C-C}}$ overtone of the ring is indicated by an open circle.

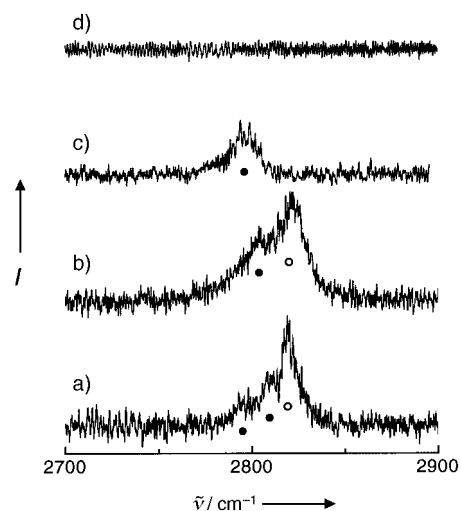


Figure 3. IR-photodissociation spectra of a) $\text{C}_6\text{H}_7^+\cdot\text{Ar}$, b) $\text{C}_6\text{H}_6\text{D}^+\cdot\text{N}_2$, c) $\text{C}_6\text{D}_6\text{H}^+\cdot\text{Ar}$, and d) $\text{C}_6\text{D}_7^+\cdot\text{Ar}$ in the range of the aliphatic C-H stretching vibrations. The intense $2\sigma_{\text{C-C}}$ overtone of the ring (open circle) is not present in the spectra c and d. The number of transitions assigned to aliphatic C-H stretches (filled circles) is the same as the number of H atoms in the methylene group.

In contrast to $\text{C}_6\text{H}_7^+\cdot\text{Ar}$ (Figure 3a), only two bands are observed for $\text{C}_6\text{H}_6\text{D}^+\cdot\text{N}_2$ (Figure 3b), which indicates that the D atom is preferentially incorporated into the methylene group, as $[\text{C}_5\text{H}_5\text{CHD}]^+$. This cation has only one aliphatic C–H stretching mode with a frequency (2804 cm^{-1}) between the two corresponding bands of $\text{C}_6\text{H}_7^+\cdot\text{Ar}$ and $\text{C}_6\text{H}_7^+\cdot\text{N}_2$. The intense overtone at 2821 cm^{-1} does not shift upon single deuteration of the methylene group. The $\text{C}_6\text{D}_6\text{H}^+\cdot\text{Ar}$ spectrum (Figure 3c) features a single band at 2797 cm^{-1} which is assigned to the aliphatic C–H stretch of $[\text{C}_5\text{D}_5\text{CDH}]^+$. Thus, ring deuteration shifts the overtone out of the spectral range investigated. The deuteration experiments give rise to the following main conclusions. According to Equation (1c) in the Experimental Section, single deuteration of C_6H_6 using D_3^+ leads to the production of $[\text{C}_5\text{H}_5\text{CHD}]^+$, and similarly single protonation of C_6D_6 using H_3^+ produces only $[\text{C}_5\text{D}_5\text{CDH}]^+$. Scrambling of the transferred D/H is largely suppressed because of efficient collisional cooling down to $T < 100\text{ K}$ in the ion source.^[15] NMR spectra of the solution have shown that the intramolecular 1,2-proton shift in **1** is indeed suppressed at $T < 130\text{ K}$.^[9a] The assignment of $2\sigma_{\text{C-C}}$ derived from the deuteration experiments is supported by our ab initio calculations and the IR spectra of the salts of the C_6H_7^+ isotopologues in the $1400\text{--}1600\text{ cm}^{-1}$ range.^[9d,10] In line with the given assignments, no C_6D_7^+ transition is observed in Figure 3d.

The main strategy of the present work relies on the fact that the Ar and N_2 ligands have essentially no influence on C_6H_7^+ because of the weak interactions. Calculations confirm that this assumption is indeed valid.^[14] For example, the most favorable binding site for Ar to **1** is intermolecular π bonding to the ring, with a dissociation energy of only $D_e = 1.2\text{ kcal mol}^{-1}$. Hydrogen bonds of Ar to aliphatic or aromatic protons are even less stable ($D_e < 0.8\text{ kcal mol}^{-1}$). Although the interaction of **1** with N_2 is somewhat stronger ($D_e = 2.7\text{ kcal mol}^{-1}$ for the π bond), the spectra of $\text{C}_6\text{H}_7^+\cdot\text{Ar}$ and $\text{C}_6\text{H}_7^+\cdot\text{N}_2$ are very similar. The predicted frequency shifts for the C–H stretching vibrations of **1** upon complexation with Ar or N_2 ^[14] are significantly smaller than the widths of the observed transitions (Table 1). Hence, the perturbation of **1** by Ar or N_2 is rather minor and certainly much smaller than the solvation effects in previous condensed-phase spectra. For example, the IR spectra of $\text{C}_6\text{H}_7^+\cdot\text{Ar}$ and $\text{C}_6\text{H}_7^+\cdot\text{N}_2$ are very different from those recorded in a salt matrix^[9d] with respect to both band positions and intensities, which emphasizes the severe effects of solvation in the salt spectra.

In conclusion, the σ complex of C_6H_7^+ (**1**) has unambiguously been identified as the most stable structure of protonated benzene by means of IR spectroscopy, which thus solves the long-standing controversial discussion about the ground-state geometry of this fundamental ion. Interestingly, the proton differs from larger “spherical” closed-shell ions (e.g., alkali metal and ammonium ions), which prefer the formation of a π complex (cation– π interaction) rather than a σ complex.^[16] The presented C_6H_7^+ spectrum opens the possibility for its identification in fundamental organic reaction mechanisms (e.g., aromatic substitution and proton transfer) and various hydrocarbon plasmas. The potential of the experimental approach will be used to characterize the drastic

effects of stepwise solvation on the properties of ion–molecule reactions, by characterizing $\text{AH}^+\cdot\text{L}_n$ cluster ions as a function of cluster size (controlled solvation).

Experimental Section

IR spectra of $\text{C}_6\text{H}_7^+\cdot\text{L}$ are obtained in a tandem mass spectrometer coupled with an ion source and an octopole ion trap.^[8,15] The cluster-ion source combines a pulsed molecular-beam expansion with electron-impact ionization. The expanded gas mixture is produced by bubbling either Ar/ H_2 /He or N_2 / H_2 /He buffer gas at room temperature and $\approx 10\text{ bar}$ stagnation pressure through a reservoir filled with liquid C_6H_6 . For deuteration experiments, C_6D_6 and/or D_2 are used.^[17] A major reaction sequence for the generation of $\text{C}_6\text{H}_7^+\cdot\text{L}$ proceeds by electron-impact ionization of H_2 [Eq. (1a)], rapid exothermic proton-transfer reactions [Eqs. (1b) and (1c)], and subsequent three-body association in the high pressure region of the supersonic expansion [Eq. (1d)]:



$\text{C}_6\text{H}_7^+\cdot\text{L}$ dimers are selected by an initial quadrupole mass spectrometer and interact in the adjacent octopole with a tunable IR laser pulse generated by an optical parametric oscillator laser system. Resonant vibrational excitation induces the cleavage of the intermolecular bond according to Equation (2):



The produced C_6H_7^+ fragment ions are selected by a second quadrupole mass spectrometer and monitored as a function of the laser frequency to obtain the IR action spectrum of $\text{C}_6\text{H}_7^+\cdot\text{L}$.

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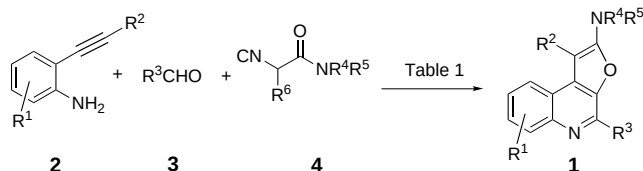
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Synthesis of Furoquinolines by a Multicomponent Domino Process**

Aude Fayol and Jieping Zhu*

Polysubstituted furan has been found as a key structural unit in many bioactive natural products and pharmaceuticals.^[1] It is also a reactive species that, upon appropriate activation, can be engaged in complex chemical transformations.^[2] The development of efficient furan syntheses has thus attracted chemists for decades and continues to be an active and rewarding research area.^[3,4] Besides polysubstituted furans, various annulated derivatives such as benzo-, thieno-, isoxazolo-, furo-, pyridino-, pyridazino-, and indolo-furan have been synthesized and their properties investigated.^[5] Cyclization of acyclic precursors and derivatization of an appropriately functionalized furan ring are two main strategies used for the elaboration of polysubstituted furans. New technologies such as solid-phase synthesis^[6] and multicomponent reactions^[7] have recently been developed for the preparation of this heterocycle.

Furoquinoline alkaloids, typical constituents of the *Rutaceae* and *Solanaceae* plant species, are the most widely distributed of quinoline alkaloids.^[8] Antimicrobial, antitumor, and antiemetic activities have been attributed to both natural and synthetic analogues of these molecules.^[9] While several synthetic routes to individual furoquinolines have been developed, most of them were linear and involved harsh reaction conditions.^[10,11] In connection with our ongoing project aimed at using oxazoles as a starting point to reach diverse druglike heterocycles,^[12] we report herein a conceptually novel multicomponent domino synthesis of furo[2,3-c]quinoline **1** (Scheme 1) from readily available substrates.^[13,14]



Scheme 1. A three-component synthesis of furo[2,3-c]quinoline.

Using methyl 3-(2-aminophenyl)prop-2-ynoate (**2a**), heptanal (**3a**), and isocyanacetamide (**4a**) as substrates, a survey of reaction conditions is summarized in Table 1. The reaction proceeded in refluxing toluene to provide the desired furoquinoline **1a** ($R^1 = H$, $R^2 = CO_2CH_3$, $R^3 = (CH_2)_5CH_3$, $NR^4R^5 = \text{morpholinyl}$), albeit in low yield. Both lithium bromide^[15] and camphorsulfonic acid were detrimental to

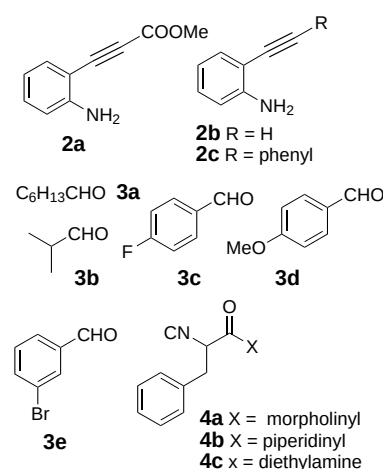
Table 1. Three-component synthesis of furoquinoline in toluene, a survey of conditions.^[a]

Entry	Additive	<i>t</i> [h]	Yield [%]
1	none	12	26
2	LiBr ^[b]	12	15
3	CSA ^[c]	12	22
4	NH ₄ Cl ^[b]	12	75

[a] Concentration of substrate: 0.1M in toluene, reaction time: 15 h, reaction temperature: RT, followed by heating under reflux. [b] 1.0 equiv. [c] 0.15 equiv. CSA = Camphorsulfonic acid.

the desired transformation, while ammonium chloride^[16] promoted the reaction sequence efficiently, providing **1a** in 75 % yield.

The scope of this novel multicomponent reaction was examined using three *ortho*-alkynyl anilines,^[17] five aldehydes, and three isocyanacetamides as substrates (Scheme 2). Some



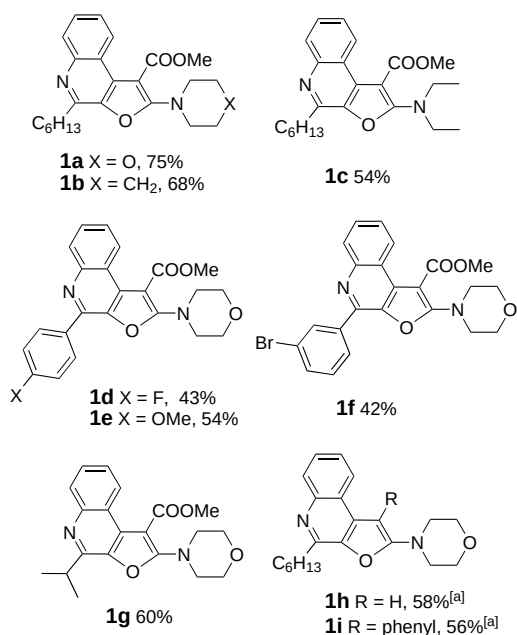
Scheme 2. Starting materials for the multicomponent reaction.

representative furoquinolines synthesized are shown in Scheme 3. The potential and general applicability of this novel three-component domino process is readily seen from these selected examples. Aniline derivatives bearing both electronically poor and electronically neutral acetylene units participated in the reaction. For the aldehyde substrate, aliphatic aldehydes, including sterically hindered isobutyraldehyde, and aromatic aldehydes bearing electron-donating or -withdrawing groups were suitable. Various substituted amino groups were easily incorporated by varying the isocyanacetamide substrate. The presence of aryl bromide and ester functional groups in furoquinolines should, in principle, allow us to functionalize further the molecules by following standard procedures.

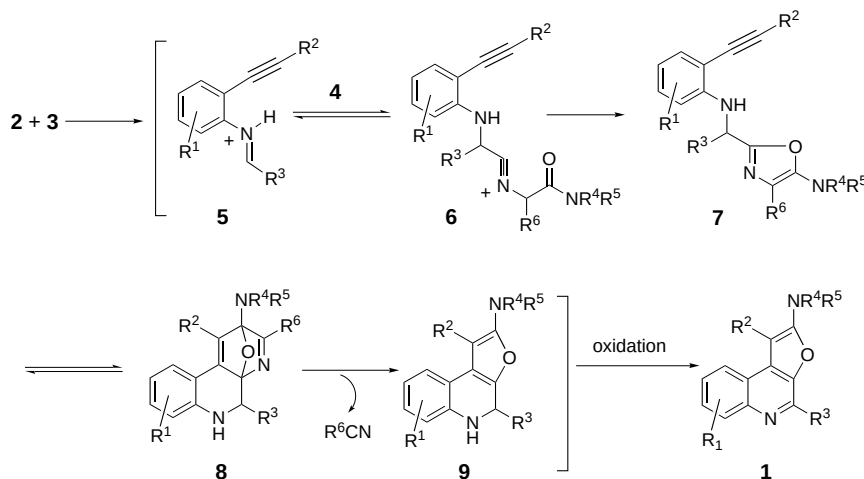
Various reaction pathways are possible by mixing these polyfunctionalized starting materials; the thus-observed clean reaction is remarkable. Although no detailed mechanistic study has been carried out, a reaction sequence leading to furoquinolines **1** is shown in Scheme 4. Thus, a three-component reaction between an aniline **2**, an aldehyde **3**, and an isocyanide **4** was expected to give an oxazole **7**.^[12] Cycloaddition of an oxazole as an aza-diene with the properly predisposed triple bond would produce an oxa-bridged

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Scheme 3. Furo[2,3-c]quinolines synthesized. Conditions: NH₄Cl, 0.1M solution in toluene, room temperature then reflux, 15 h. [a] *O*-Xylene was used as the solvent (room temperature then under reflux) for the synthesis of **1h** and **1i**.

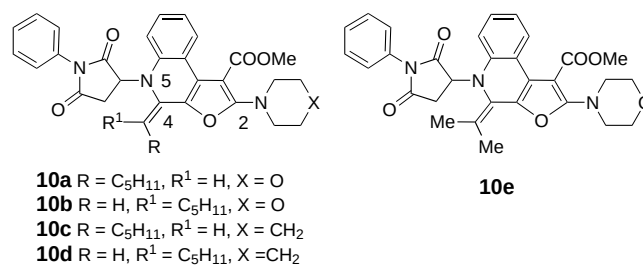


Scheme 4. Three-component synthesis of furo[2,3-c]quinoline; a possible reaction sequence.

heterocycle **8**.^[18] The latter, after extrusion of the nitrile unit by a retro-Diels–Alder reaction, would provide the furan **9**, oxidation of which by atmospheric oxygen furnished the furoquinolines **1**. At least six distinct reactions, including condensation of an aldehyde and an amine, nucleophilic addition of an isonitrile to an imine, the ring-chain tautomerization of the nitrilium intermediate, intramolecular Diels–Alder cycloaddition of oxazole, retro-Diels–Alder, and oxidation, occurred in this one-pot process. All these steps took place in an ordered manner to provide the final compound with concomitant creation of five chemical bonds. Two irreversible steps (the formation of oxazole and the retro-Diels–Alder reaction) cause the observed reaction sequence to be a unique and productive process.^[19] To provide evidence

for this reaction sequence, we were able to isolate and fully characterize the oxazole **7a** (R¹ = H, R² = CO₂CH₃, R³ = C₆H₁₃, NR⁴R⁵ = morpholinyl, R⁶ = Bn) by quenching the reaction mixture after four hours under the standard reaction conditions. Furthermore, when the anilines **2b** and **2c** were used as substrates, only the corresponding oxazoles **7** were produced even after prolonged heating in toluene. In these cases, heating a xylene solution under reflux was required to initiate and complete the cycloaddition process.

With an efficient synthesis of furo[2,3-c]quinoline in hand, its reactivity was briefly examined. Reaction of **1a** with *N*-phenylmaleimide gave **10a** and **10b** (Scheme 5) in 73 % yield.



Scheme 5. Alder–ene products of the reaction between furo[2,3-c]quinolines and *N*-phenylmaleimide.

Apparently, the formal Alder–ene reaction dominates over the Diels–Alder cycloaddition of furan in this polycyclic ring system, probably because of the cross-conjugation of the π systems. The presence of the 2-*N,N*-dialkylamino group may render the N-5 atom of the quinoline ring more nucleophilic, by analogy with the reactivity of 4-*N,N*-dimethylaminopyridine (DMAP). The Alder–ene adducts **10c** and **10d** were prepared in a similar manner from **1b**. Even with the furoquinoline **1g**, which bears a sterically demanding isopropyl substituent at the C-4 atom, the same type of reactivity was observed, leading to adduct **10e** in 35 % yield.

We reasoned that the conditions of this Alder–ene reaction might be compatible

with the three-component synthesis of furoquinolines, hence a four-component synthesis of **10** was sought. Heating a solution of **2a**, **3a**, and **4a**, followed by addition of *N*-phenylmaleimide, provided **10a** and **10b** in 45 % overall yield.

In conclusion, we have developed a novel, multicomponent, domino process for the synthesis of functionalized furo[2,3-c]quinoline from simple and readily accessible substrates. The significant feature of this procedure is the exploitation of the dual reactivity of both a *ortho*-alkynyl aniline (nucleophile then dienophile)^[20] and an isocyanoacetamide (amphinucleophile). The operational simplicity and good chemical yield makes these novel heterocycle syntheses highly attractive in diversity-oriented parallel synthesis.^[21]

Experimental Section

A solution of the aniline **2a** (50.0 mg, 0.28 mmol), heptanal (**3a**; 46 μ L, 0.34 mmol), and ammonium chloride (15.0 mg, 0.28 mmol) in toluene (3 mL) was stirred at room temperature for 1 h. The isocyanoacetamide **4a** (83.0 mg, 0.34 mmol) was added and the reaction mixture was heated under reflux for 15 h. After being cooled to room temperature, the reaction mixture was diluted with water and extracted with dichloromethane. The combined organic extracts were washed with brine, dried, and the solvent removed under reduced pressure. Purification of the crude mixture by flash chromatography (SiO₂, EtOAc/heptane = 1/10 to 2/3, gradient) provided the furo[2,3-c]quinoline **1a** (83.2 mg, 75 %) as an oil. IR: $\tilde{\nu}$ = 2956, 2929, 2860, 1698, 1593, 1551, 1450, 1114, 1091 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ = 0.89 (t, *J* = 7.4 Hz, 3 H), 1.35–1.45 (m, 6 H), 1.88 (q, *J* = 7.4 Hz, 2 H), 3.13 (t, *J* = 7.4 Hz, 2 H), 3.70 (m, 4 H), 3.92 (m, 4 H), 3.98 (s, 3 H), 7.51 (td, *J* = 8.1, 1.3 Hz, 1 H), 7.63 (td, *J* = 8.1, 1.3 Hz, 1 H), 8.10 (dd, *J* = 8.1, 1.3 Hz, 1 H), 8.92 ppm (dd, *J* = 8.1, 1.3 Hz, 1 H); ¹³C NMR (CDCl₃, 62.5 MHz): δ = 14.3, 22.6, 28.6, 29.3, 31.7, 33.4, 49.4 (2 C), 51.5, 66.6 (2 C), 91.0, 122.3, 125.0, 126.0, 127.5, 129.4, 141.2, 145.7, 147.4, 163.6, 164.4, 167.7 ppm; MS (EI) *m/z* 396 [*M*], 397 [*M*+1], MS (ESI, positive mode) *m/z* 397 [*M*+1], 435 [*M*+K].

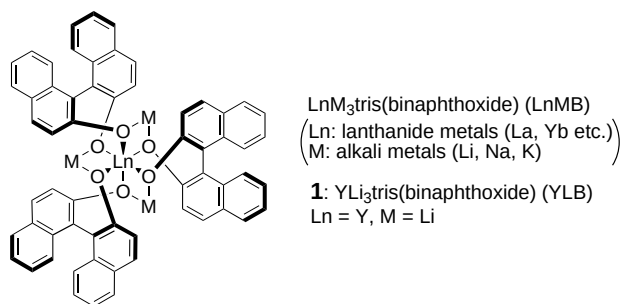
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An Asymmetric Cyanation Reaction and Sequential Asymmetric Cyanation–Nitroaldol Reaction Using a [YLi₃{tris(binaphthoxide)}] Single Catalyst Component: Catalyst Tuning with Achiral Additives**

Jun Tian, Noriyuki Yamagiwa, Shigeki Matsunaga, and Masakatsu Shibasaki*

Chiral catalysts are generally designed and optimized to promote one specific asymmetric reaction.^[1] The increasing demand for efficient and environmentally benign synthetic processes, however, requires the development of chiral catalysts that promote sequential, mechanistically different, asymmetric reactions. In regard to achiral organometallic reagents, our group and others recently reported multiple actions of a single-metal catalyst component.^[2,3] Asymmetric sequential reactions, in which mechanistically different asymmetric reactions were involved, were achieved only by using two sets of chiral catalyst species.^[4] In general, the chiral environment suitable for two distinct asymmetric reactions is different, which makes the development of asymmetric sequential reactions with a single catalyst component highly challenging. We report herein the first example of an asymmetric sequential reaction with a multifunctional [YLi₃{tris(binaphthoxide)}] (YLB; **1**, Scheme 1)^[5] single catalyst component, in which tuning of the chiral catalyst by achiral additives had a key role in constructing a proper chiral environment for each asymmetric reaction;^[6,7] the cyanation and nitroaldol reactions. The strategy is summarized in Figure 1.



Scheme 1. Structure of heterobimetallic [LnM₃{tris(binaphthoxide)}] and **1** (Ln = Y, M = Li).

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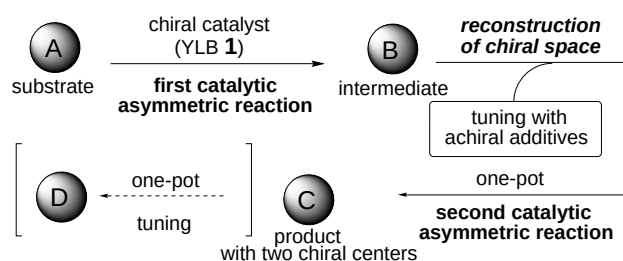


Figure 1. Chiral catalyst tuning strategy with achiral additives for tandem asymmetric catalysis.

We previously developed families of lanthanide heterobimetallic asymmetric catalysts, [LnM₃{tris(binaphthoxide)}] (LnMB, Scheme 1),^[5] which promote various asymmetric reactions, such as the nitroaldol reaction.^[5a] To develop a novel sequential asymmetric reaction, we first planned to survey new types of asymmetric reactions using LnMB catalysts. On the basis of previous cyanation reactions utilizing Ln–CN active species as a cyanide source,^[8] we investigated an asymmetric cyanation reaction of aldehyde with heterobimetallic LnMB catalysts.

The initial screening of both CN sources and metal sources revealed that commercially available ethyl cyanoformate (**3**)^[9] and (*S*)-**1** prepared from [Y(HMDS)₃] (HMDS = hexadimethylsilazide), (*S*)-binol, and BuLi,^[5b] were promising candidates for catalysis of asymmetric reactions.^[10] With **1** (10 mol %), H₂O (10 mol %), and **3**, cyanation of the aldehyde **2a** proceeded at –60 °C to afford **4a** in 84 % yield and 58 % *ee* (Table 1, entry 1). Interestingly, without addition of H₂O, no reaction proceeded (entry 2). To fine-tune the chiral environment, various achiral additives were surveyed and Ar₃P(O) **5** was determined to be the most suitable in terms of enantioselectivity. Addition of both H₂O and Ph₃P(O) (**5a**; 10 mol %) significantly improved both the reaction rate and enantioselectivity (entry 4). The best selectivity was obtained by adding 30 mol % of H₂O (entry 6). The use of the Ar₃P(O) (**5**) was optimized; [2,6-(CH₃O)₂C₆H₃]₃P(O) (**5b**) had the best reactivity and selectivity (entry 7). Moreover, by adding 10 mol % of BuLi, the reaction proceeded smoothly at –78 °C to afford **4a** in 94 % *ee* (entry 8). The optimized

Table 1. Catalyst tuning for first reaction: asymmetric cyanation reaction with **1**.

Entry	H ₂ O [mol %]	Additives		BuLi [mol %]	<i>t</i> [h]	<i>T</i> [°C]	Yield [%]	<i>ee</i> [%]
		Ar ₃ P(O) [mol %] ^[b]						
1	10	–	0	0	9	–60	84	58
2	0	–	0	0	7.5	–60	0	–
3	0	5a	10	0	8.5	–60	93	64
4	10	5a	10	0	2.5	–60	88	83
5	20	5a	10	0	2.5	–60	74	88
6	30	5a	10	0	2.5	–60	54	89
7	30	5b	10	0	1.5	–60	97	92
8	30	5b	10	10	2	–78	96	94

[a] Reaction conditions: **3** (1.2 equiv), **1** (10 mol %); [b] **5a**: Ar = phenyl, **5b**: Ar = 2,6-dimethoxyphenyl.

reaction conditions for cyanation, **1** (10 mol %), H₂O (30 mol %), BuLi (10 mol %), Ar₃P(O) **5b** (10 mol %), and **3** (1.2 equiv), were applicable to various aldehydes (Table 2). In all cases, good yields and *ee* values were achieved using aromatic aldehydes (entries 1–2), α,β -unsaturated aldehydes (entries 3–4), α -unsaturated (entries 5–6), α -monosubstituted (entries 7–10), and α,α -disubstituted aliphatic aldehydes (entry 11). To our knowledge, the present system has one of the broadest substrate generalities yet reported.^[11] In addition, a preliminary survey revealed that the reaction proceeded smoothly with lower catalyst loading (entry 8 and entry 9), maintaining good reactivity and selectivity. On the basis of previous cyanation reactions that used Ln–CN active species,^[8] we speculate that a similar nucleophilic Y–CN active species is involved in the present system. Detailed mechanistic investigations are in progress.

After developing this novel asymmetric cyanation reaction, we then applied YLB to sequential asymmetric reactions by

Table 2. A novel catalytic asymmetric cyanation reaction with optimized additives.

$\text{RCHO} + \text{NC-CO}_2\text{Et} \xrightarrow[\text{THF}]{\text{(S)-YLB 1 additives}} \text{R-CH(OH)-CN-CO}_2\text{Et}$						
Entry	Aldehyde (R)	Product	Cat. [x mol %]	<i>t</i> [h]	Yield [%]	<i>ee</i> [%]
1	2a Ph	4a	10	2	96	94
2	2b 1-naphthyl	4b	10	2	97	90
3	2c (<i>E</i>)-CH ₃ (CH ₂) ₂ CH=CH	4c	10	3	100	92
4	2d (<i>E</i>)-PhCH=CH	4d	10	3	100	91
5	2e CH ₃ (CH ₂) ₄	4e	10	3	93	94
6	2f CH ₃ CH ₂	4f	10	2	79 ^[b]	92
7	2g (CH ₃) ₂ CH	4g	10	2	88 ^[b]	98
8	2g (CH ₃) ₂ CH	4g	5	2	82 ^[b]	96
9 ^[c]	2g (CH ₃) ₂ CH	4g	1	9	96	90
10	2h <i>c</i> -C ₆ H ₁₁	4h	10	2	97	96
11	2i (CH ₃) ₃ C	4i	10	3	93	87

[a] Reaction conditions: **3** (1.2 equiv), (S)-**1** (*x* mol %), H₂O (3x mol %), BuLi (*x* mol %), **5b** (*x* mol %), THF, –78 °C, Ar = 2,6-dimethoxyphenyl. [b] The yield of product isolated was lower because the product was volatile. [c] The reaction was performed on a 6.0 mmol scale. 1.8 mol % of BuLi was used.

combining the cyanation reaction with the previously reported asymmetric nitroaldol reaction,^[5a] in which Li-binaphthoxide functioned as a Brønsted base to deprotonate CH₃NO₂. As expected, the optimized chiral environment constructed by YLB, and Ar₃P(O) **5b** was not suitable for the nitroaldol reaction at all. As shown in Table 3, YLB and H₂O promoted

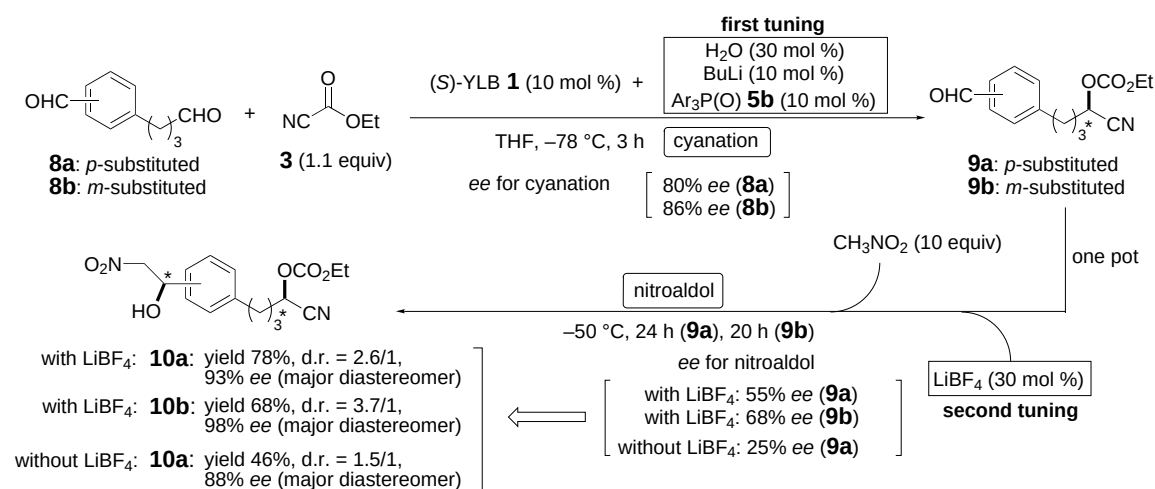
Table 3. Catalyst tuning for second reaction: asymmetric nitroaldol reaction with **1**.

$\text{RCHO} + \text{CH}_3\text{NO}_2 \xrightarrow[\text{THF}]{\text{(S)-YLB 1 additives}} \text{R-CH(OH)-CH(NO}_2\text{)-R}$						
Entry	Aldehyde (R)	Product	Ar ₃ P(O) 5b [mol %]	LiBF ₄ [mol %]	<i>t</i> [h]	Yield [%]
1	2a Ph	7a	0	0	20	82
2	2a Ph	7a	10	0	20	68
3	2a Ph	7a	10	30	20	84
4	2j 4-CH ₃ -C ₆ H ₄	7j	10	0	26	51
5	2j 4-CH ₃ -C ₆ H ₄	7j	10	30	26	84

[a] Reaction conditions: **6** (10 equiv), (S)-**1** (10 mol %), H₂O (30 mol %), THF, –40 °C.

the nitroaldol reaction of **2a** to afford **7** in 62% *ee* (entry 1).^[12,13] However, the *ee* value dropped dramatically to 11% on the addition of **5b** (entry 2). This phenomenon is not surprising in asymmetric catalysis, which makes tandem asymmetric catalysis with a single catalyst component highly challenging. We thought that further elaborate tuning of the YLB with the aid of additional achiral additives might enable us to reconstruct a chiral environment of YLB **1** suitable for a second asymmetric nitroaldol reaction. Indeed, addition of the Li cation to the catalyst systems was effective for the reconstruction. With LiBF₄ (30 mol %), a similar *ee* value (59%) was obtained even in the presence of **5b** (entry 3). Currently, we speculate that Li cations interact with **5b**, which leads to the dissociation of **5b** from **1** and the reconstruction of the chiral space.

Finally, by tuning the YLB catalyst with achiral additives (H₂O, **5b**, BuLi, and LiBF₄), a novel sequential asymmetric cyanation–nitroaldol reaction was performed (Scheme 2).



Scheme 2. Sequential catalytic asymmetric cyanation–nitroaldol reaction with and without adequate catalyst tuning.

Chemoselective cyanation reaction of the aliphatic aldehyde group in the dialdehyde **8** was performed at -78°C using **1**, H_2O , BuLi , **5b**, and **3**. LiBF_4 was then added to the reaction mixture, followed by the addition of CH_3NO_2 (10 equiv). The mixture was stirred at -50°C for 24 h (**9a**) and 20 h (**9b**) to afford the desired product **10**. The *ee* values of the major diastereomers were 93 % (**10a**: yield 78 %, d.r. = 2.6/1) and 98 % (**10b**: yield 68 %, d.r. = 3.7/1), respectively. Without a second tuning with LiBF_4 , the yield (46 %:**10a**), d.r. (1.5/1:**10a**), and *ee* value (88 %:**10a**) decreased, which supports the effectiveness of the catalyst tuning strategy to achieve tandem asymmetric catalysis with a single chiral catalyst component. Calculated *ee* values for the second nitroaldol reaction itself were 55 % *ee* (**9a** with LiBF_4), 68 % *ee* (**9b** with LiBF_4), and 25 % *ee* (**9a** without LiBF_4), respectively (Scheme 2).

In summary, we have developed a new, highly enantioselective cyanation reaction and successfully demonstrated the first tandem asymmetric catalysis with a single YLB catalyst component. Tuning the chiral environment in YLB with achiral additives such as $\text{Ar}_3\text{P}(\text{O})$ (**5**) and LiBF_4 had a key role in the present sequential asymmetric cyanation–nitroaldol reactions. The strategy can be regarded as a chiral “allosteric enzyme” model and would, in principle, lead to tandem asymmetric catalysis to promote more than two mechanistically distinct asymmetric reactions in one pot with a single catalyst component (Scheme 1), creating the possibility for a more efficient and environmentally benign synthesis of optically active, complex molecules. Efforts to improve the second nitroaldol reaction and mechanistic investigations to clarify the exact roles of achiral additives are currently in progress.

Experimental Section

To tris(2,6-dimethoxyphenyl)phosphane oxide (**5b**) (27.6 mg, 0.06 mmol) in a test tube was added an (*S*)-YLB/ H_2O solution (2.0 mL, 30 mM in THF, 0.06 mmol). The solution was stirred at room temperature. After completely dissolving **5b**, $n\text{BuLi}$ (0.06 mmol) was added to the mixture. This catalyst solution was cooled down to -78°C , dialdehyde **8a** (0.6 mmol) and ethyl cyanoformate (**3**) (0.66 mmol) were added and stirred at -78°C . After stirring for 3 h, LiBF_4 (90 μL , 2.0 M in THF, 0.18 mmol) was added and the mixture was stirred at -50°C for 30 min. Then, CH_3NO_2 (325 μL , 6.0 mmol) was added and the mixture was stirred at -50°C . After stirring for 24 h, 1 M aq. HCl was added to the solution and the organic components extracted with diethyl ether. The organic layer was washed with brine and dried over Na_2SO_4 . After evaporating the solvent, the residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate = 6/1) to give **10a** (156.6 mg, 0.47 mmol, yield 78 %, d.r. = 2.6/1, 93 % *ee* for major diastereomer) as a colorless oil.

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A Trigonal-Bipyramidal Ferric Aqua Complex with a Sterically Hindered Salen Ligand as a Model for the Active Site of Protocatechuate 3,4-Dioxygenase**

Hiroshi Fujii* and Yasuhiro Funahashi

Protocatechurate 3,4-dioxygenase (3,4-PCD) has been found in soil bacteria and is known to play a role in degrading aromatic molecules in nature.^[1,2] The enzyme is classified as an intradiol dioxygenase and cleaves catechol analogues bound to the iron(III) site into aliphatic products with incorporation of both atoms of molecular oxygen. It has been proposed that the enzyme does not activate an iron-bound oxygen molecule, but rather induces an iron-bound catecholate to react with O_2 .^[2] Therefore, knowledge of the structure and electronic state of the iron site is essential to under-

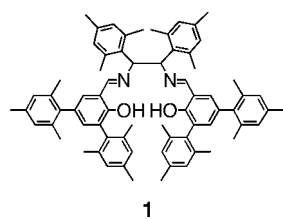
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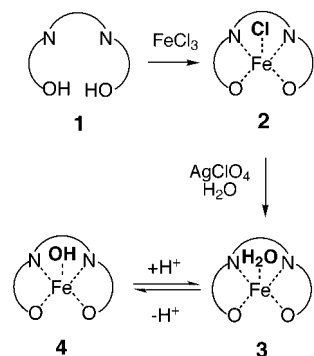
[**] We thank Dr. M. Tomura for helpful comments on the structure solution; Dr. K. Inoue, Dr. H. Kumagai, and Dr. M. A. Tanaka for assistance with the X-ray machine; and Dr. T. Ogura and Mr. K. Oda for their help in obtaining the Raman data. This work was supported by Grants in Aid from the Ministry of Education, Science, Sport, and Culture, Japan.

standing the unique reaction of 3,4-PCD.^[2,3] A previous crystal structure analysis of 3,4-PCD from *Pseudomonas putida* revealed a distorted trigonal-bipyramidal ferric iron center with four endogenous protein ligands (Tyr408, Tyr447, His460, and His462) and a solvent-derived water molecule (see Figure 2).^[4] To understand the structure–function relationship of 3,4-PCD, attempts have been made over several decades to prepare inorganic model complexes of 3,4-PCD. However, no iron(III) complex that reproduces the active site of 3,4-PCD has been characterized. We report here the first example of a distorted trigonal-bipyramidal ferric aqua complex with a sterically hindered salen ligand that not only duplicates the active site but also mimics the spectral characteristics of 3,4-PCD.

The sterically hindered salen ligand bis-(3,5-dimesitylsalicylidene)-1,2-dimesitylethylenediamine (**1**) was prepared in 77 % yield by the reaction



of 3,5-dimesityl-2-hydroxybenzaldehyde and 1,2-dimesitylethylenediamine in hot methanol. The ferric chloride complex **2** was obtained by treatment of **1** with anhydrous FeCl₃ in hot ethanol (Scheme 1). Figure 1a shows the X-ray crystal structure of **2**.^[5] The bond distances and angles of **2** are nearly identical to those of the ferric chloride complex of salen.^[6] The iron(III) site of **2** is square-pyramidal, which is common for five-coordinate salen–iron complexes.^[6,7] The



Scheme 1. Schematic representation of the synthesis of **2–4**.

absorption and ¹H NMR spectra of **2** are also similar to those of the ferric chloride complex of salen. This indicates that the mesityl groups introduced into the salen ligand do not represent a steric hindrance in the formation of the iron complex. In contrast to the normal square-pyramidal structure of **2**, the ferric aqua complex **3**, which is obtained from **2** upon treatment with AgClO₄·H₂O (Scheme 1), exhibits a drastic structural change. Figure 1b shows the X-ray crystal structure of **3**.^[5] The +3 oxidation state of iron in **3** is proven by the presence of the perchlorate anion. While the bond angles for O(1)–Fe–N(2) and O(2)–Fe–N(1) in **2** are 154.1° and 143.3° ($\tau = 0.18$), those in **3** are 166.6° and 137.7° ($\tau = 0.48$), respectively.^[8] The τ value of **3** is close to that of 3,4-PCD ($\tau = 0.44$).^[4,8] The ferric

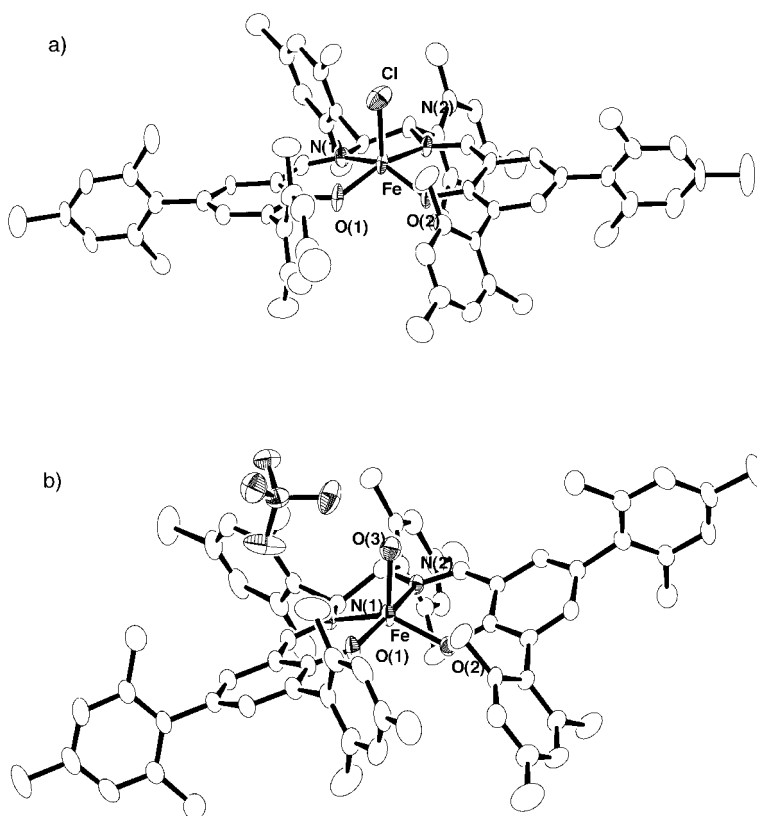


Figure 1. Thermal-ellipsoid plots (50% probability) of a) **2** and b) **3**. Hydrogen atoms and solvents of crystallization have been omitted for clarity. Selected bond distances [Å] and angles [°]: **2**: Fe–Cl 2.234(3), Fe–O(1) 1.881(6), Fe–O(2) 1.878(5), Fe–N(1) 2.102(6), Fe–N(2) 2.087(6); O(1)–Fe–N(2) 154.1(3), O(2)–Fe–N(1) 143.3(3). **3**: Fe–O(1) 1.863(3), Fe–O(2) 1.876(3), Fe–O(3) 2.009(3), Fe–N(1) 2.084(3), Fe–N(2) 2.060(3); O(1)–Fe–N(2) 166.6(1), O(2)–Fe–N(1) 137.7(1).

iron site of **3** exhibits a distorted trigonal-bipyramidal structure with the phenolate O(2), imino N(1), and water oxygen O(3) atoms serving as equatorial ligands and the phenolate O(1) and imino N(2) atoms serving as axial ligands (see Figure 2).

Complex **3** is the first example of a structurally defined ferric complex with the same coordination mode as the active site of 3,4-PCD (Figure 2). Interestingly, the structural change is induced by the replacement of the external chloride ligand in **2** with water. As reported for 3,4-PCD, the axial Fe–O(1)

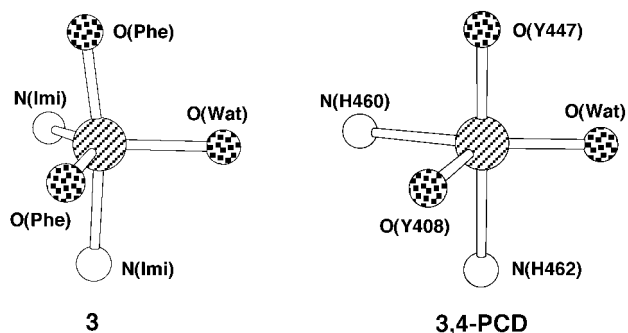


Figure 2. Comparison of the coordination sphere of **3** to that of the structurally characterized 3,4-PCD (data from PDB accession code 2PCD). Imi = imino, Phe = phenolate, Wat = water.

bond is longer than the equatorial Fe–O(2) bond, but the difference of 0.013 Å is smaller than that seen for 3,4-PCD (0.09 Å). The Fe–N bond distances of **3** are shorter than those of 3,4-PCD.^[4] The O(1)–Fe–N(2) angle of 166.6° in **3** is nearly identical to that in 3,4-PCD (167°).^[4] The Fe–O(3) bond distance in **3** is 2.016 Å and thus longer than the value of 1.90 Å found in 3,4-PCD; the iron-bound water in 3,4-PCD is thought to coordinate as a hydroxide group under physiological conditions.^[9]

The spectroscopic characteristics of **3** in solution are also similar to those of 3,4-PCD. The absorption spectrum of **3** shows absorption peaks at λ_{max} (ϵ ; $\text{mm}^{-1}\text{cm}^{-1}$) = 313 nm (15.3), 433 nm (4.5), and 535 nm (4.6) in THF/H₂O (7/3) (Figure 3). The two bands in the visible region are LMCT bands from two distinct phenolate ligands. As found for 3,4-

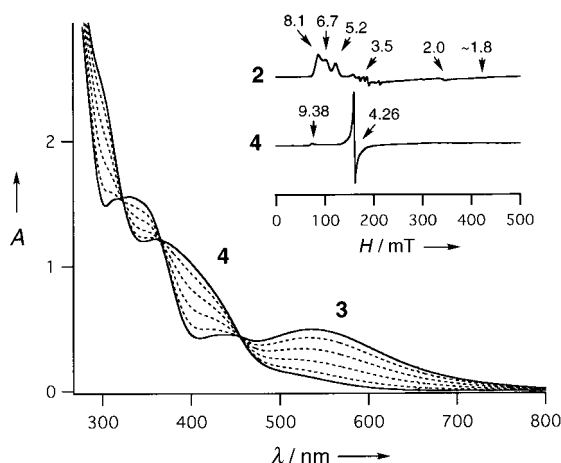


Figure 3. Changes in the absorption spectrum as a result of the pH-dependent reversible alternation between the aqua complex **3** and the hydroxide complex **4** in THF/H₂O (7/3). 0.1 M HClO₄ and NaOH were used to change the pH value, $I = 0.1$, NaClO₄ was the supporting electrolyte. Measurements were made at pH 3.9, 6.5, 7.1, 7.5, 8.0, and 10.3. Inset: EPR spectra of the chloride complex **2** in CH₂Cl₂ at 4 K and the hydroxide complex **4** in THF/H₂O (7/3) at 2 K.

PCD,^[2,3,10] this is supported by the excitation profiles of resonance Raman bands for **3**, which show two $\tilde{\nu}_{\text{CO}}$ bands from two distinct phenolate ligands at 1304 and 1338 cm^{-1} .

The absorption spectrum of **3** shows a reversible acid–base transition with formation of the hydroxide complex **4** (see Scheme 1), with isosbestic points depending on the proton concentration (Figure 3). The absorption spectrum of **4** is very similar to that of 3,4-PCD, except for a blue shift of the absorption peak (**4**: 370 nm, 3,4-PCD: ca. 460 nm).^[11] From the change in the absorption spectrum, the $\text{p}K_{\text{a}}$ value of the iron-bound water molecule is estimated to be about 7.0 in THF/water (7/3), suggesting that the Lewis acidity of the iron center in **3** and **4** is close to that seen for 3,4-PCD.^[12]

Because of the steric hindrance of the mesityl groups in the salen ligand, the monomeric hydroxide complex **4** is obtained without formation of the μ -oxo dimer.^[13] The monomeric structures of **3** and **4** are further confirmed by ¹H NMR and EPR spectroscopy. The ¹H NMR spectra of **3** and **4** in CD₂Cl₂ show large downfield shifts of the signals for the 4- and 6-protons in the salicylidene group.^[14] While the EPR spectrum

of **2** exhibits signals at $g = 8.1, 3.5$, and ca. 1.8,^[15] those of **3** and **4** show signals at $g = 9.19, 4.26$ and $g = 9.38, 4.26$, respectively (inset of Figure 3). These EPR spectra indicate that, even in solution, **3** ($E/D \approx 0.21$) and **4** ($E/D \approx 0.25$) have much more rhombic iron centers than **2** ($E/D \approx 0.10$). The zero-field splitting parameters, that is, the D values, of **3** and **4** were determined to be about 2.1 cm^{-1} and 1.1 cm^{-1} , respectively. The g values and zero-field splitting parameters of **4** are also nearly identical to those of 3,4-PCD ($g = 9.35$ and 4.3, $E/D = \approx 0.28$, $D = 1.6 \text{ cm}^{-1}$).^[16] All of the spectral characteristics of **3** and **4**, which are similar to those of 3,4-PCD but different from those of **2**, suggest that the trigonal-bipyramidal structure is retained in solution.

In conclusion, by using a sterically hindered salen ligand, we have obtained a distorted trigonal-bipyramidal ferric aqua complex that duplicates the structural and spectral characteristics of 3,4-PCD. The present results imply that the iron-bound water ligand is essential to the trigonal-bipyramidal structure in 3,4-PCD; the effect of this water ligand is being investigated in our group.

Experimental Section

2: Ligand **1** (2.446 g, 2.5 mmol) in hot ethanol (75 mL) was added to anhydrous FeCl₃ (0.406 g, 2.5 mmol) in ethanol (25 mL). After being heated at 80 °C for 5 min, the resulting dark red solution was allowed to stand at room temperature to give a dark brown precipitate. The precipitate was isolated by filtration and dried. A crystal suitable for X-ray structure analysis was obtained by recrystallization from acetonitrile. Yield: 1.474 g (53 %); elemental analysis calcd for [C₇₀H₇₄N₂O₂ClFe](C₂H₅OH): C 77.72, H 7.25, N 2.52; found: C 77.56, H 7.14, N 2.53.

3: Complex **2** (55.6 mg, 0.050 mmol) was dissolved in THF, and 1 equiv of AgClO₄·H₂O (12.3 mg, 0.055 mmol) was added. After the precipitated AgCl was removed by filtration, the solvent was removed by evaporation. The residue was dissolved in CH₂Cl₂ and the solution was filtered. Slow diffusion of hexane to the filtrate gave a deep purple crystalline product. Yield: 35.3 mg (62 %); elemental analysis calcd for [C₇₀H₇₆N₂O₇ClFe](CH₂Cl₂)₂(H₂O)_{0.4}: C 65.23, H 6.14, N 2.11; found: C 65.54, H 6.33, N 2.20.

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respectively. CCDC-179137 (**2**) and CCDC-179138 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit @ccdc.cam.ac.uk).

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Micro/Nanoengineering of the Self-Organized Three-Dimensional Fibrous Structure of Functional Materials

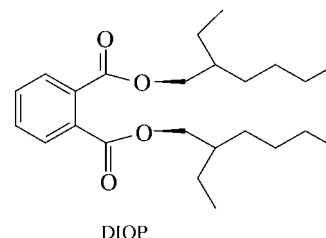
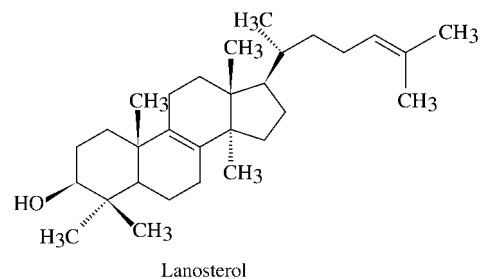
Xiang Y. Liu* and Prashant D. Sawant

Supramolecular functional materials^[1] with 3D fibrous network structures formed by interconnecting nanosized fibrils have important applications in, for example, drug delivery, coatings, lithography, catalyst supporters, scaffolds for tissue engineering, the engineering of nanostructural and self-supporting porous materials, and novel separation for macromolecules.^[1–5] Macroscopic properties, in particular, the rheological properties of supramolecular functional materials are determined by the microstructure of fibrous networks. The fibrous networks with permanent interconnections will effectively entrap and immobilize liquid in the meshes and promote the formation of self-supporting rigid gels, which possess the elastic properties of ideal solids and the viscosity

properties of a Newtonian liquid.^[2,4,6] In contrast, systems consisting of nonpermanent or transient interconnecting (such as entangled) fibrils or needles reveal only viscous weak gels at low concentrations.^[2]

Significant efforts have been devoted to the identification of novel systems with a desirable microscopic structural organization that can enable formation of such functional materials.^[2,4,5] One such route includes the screening of a large number of potential gelator/solvent systems capable of forming 3D self-organized interconnecting fibrous networks.^[2,4–7] However, through the lack of suitable materials, screening is very difficult. Thus for a given system, it would be extremely desirable to construct or engineer interconnecting 3D fiber networks at the micro- or nanolevel with such organization that materials with the expected functionalities can be created. We aim to illustrate a completely new approach to engineering such materials by constructing permanent 3D interconnecting nanofibrous networks from a system consisting of separate fibers.

The materials to be examined were obtained by dissolving lanosta-8,24-dien-3 β -ol:24,25-dihydrolanosterol (L/DHL), 56:44 molar ratio, Sigma) in diisooctylphthalate (DIOP, 99% purity, Aldrich) at approximately 125 °C, and then cooling the sample to approximately room temperature.



Scanning electronic microscopy (SEM) coupled with a CO_2 super-critical fluid-extraction technique (Thar Design) was applied to examine the micro- and nanostructure of the fibrous networks. The latter technique is used to remove the liquid captured in the networks without disturbing their overall structure.^[8]

An opaque and viscous paste was obtained on cooling the aforementioned system (10 wt% L/DHL) to room temperature (Figure 1a, inset). The system consists of only non-branched fibers or needles, which are in temporary contact with each other (Figure 1a).

Our strategy is to create networks with permanent interlinking from such a system. An additive, ethylene/vinyl acetate copolymer (EVACP, $(\text{C}_4\text{H}_6\text{O}_2\cdot\text{C}_2\text{H}_4)_n$, $M_w = \text{ca. } 100\,000$, 40% in vinyl acetate), is introduced to achieve the microstructured architecture. Surprisingly, under identical

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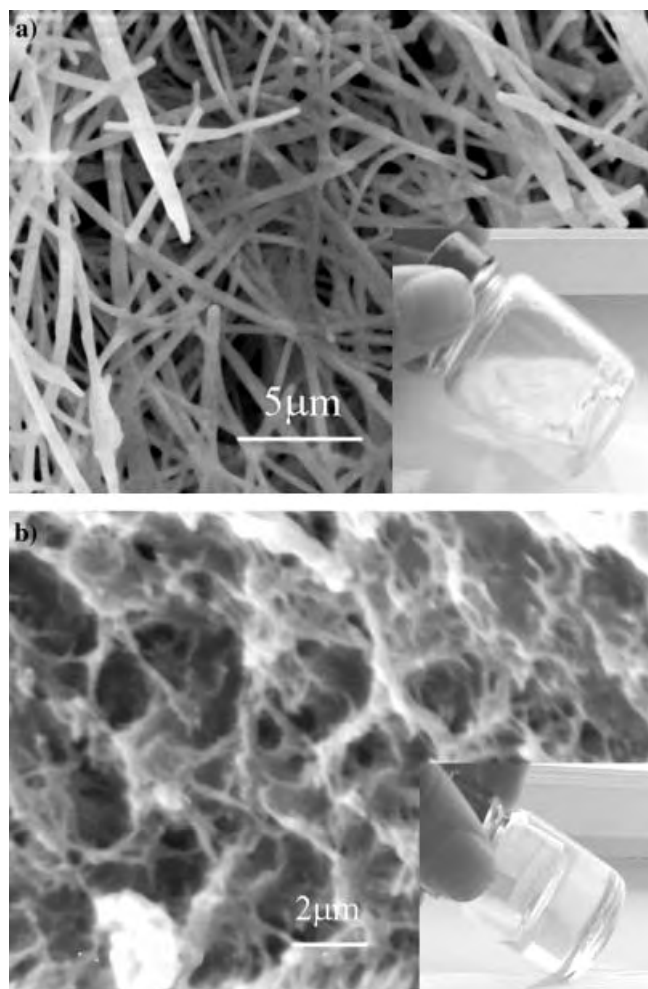


Figure 1. a) Separate fibers occurring in the 10 wt % L/DHL/DIOP system. An opaque paste is obtained, as shown in the inset. b) Interconnected fiber networks in the 10 wt % L/DHL/DIOP system after adding EVACP. A clear and tough gel was obtained, as shown in the inset.

conditions to those described above, a tiny amount of EVACP (0.006 wt %) is sufficient to create interconnecting self-organized microscopic networks of nanofibers in the L/DHL/DIOP system (Figure 1b), which results in the formation of a solid and self-supporting gel (Figure 1b; neat vinyl acetate exerts no effect on the branching).

To investigate the influence of such a structural change on macroscopic properties, the rheological properties of the system were measured (Figure 2). Instantaneous measurement of the applied stress and the resultant strain allows the calculation of the storage modulus (G' , which describes the elastic property) and the loss modulus (G'' , which describes the viscosity), which, in turn, gives the complex modulus G^* ($G^* = [(G')^2 + (G'')^2]^{1/2}$).^[7,9–11]

Figure 2a displays the change in G^* as a function of time for the L/DHL/DIOP system. The value of G^* increases abruptly at $t \geq t_g$ (t_g = gelation time), which indicates the formation of L/DHL fibrils. The value of G^* reaches its maximum $G^*_{\max}$ when the formation of the fiber network is complete, which occurs as $t \rightarrow \infty$. In comparison with the control sample, the $G^*_{\max}$ value is almost doubled after a small amount of EVACP is added. (Similar changes were also obtained for G' and G'' ,

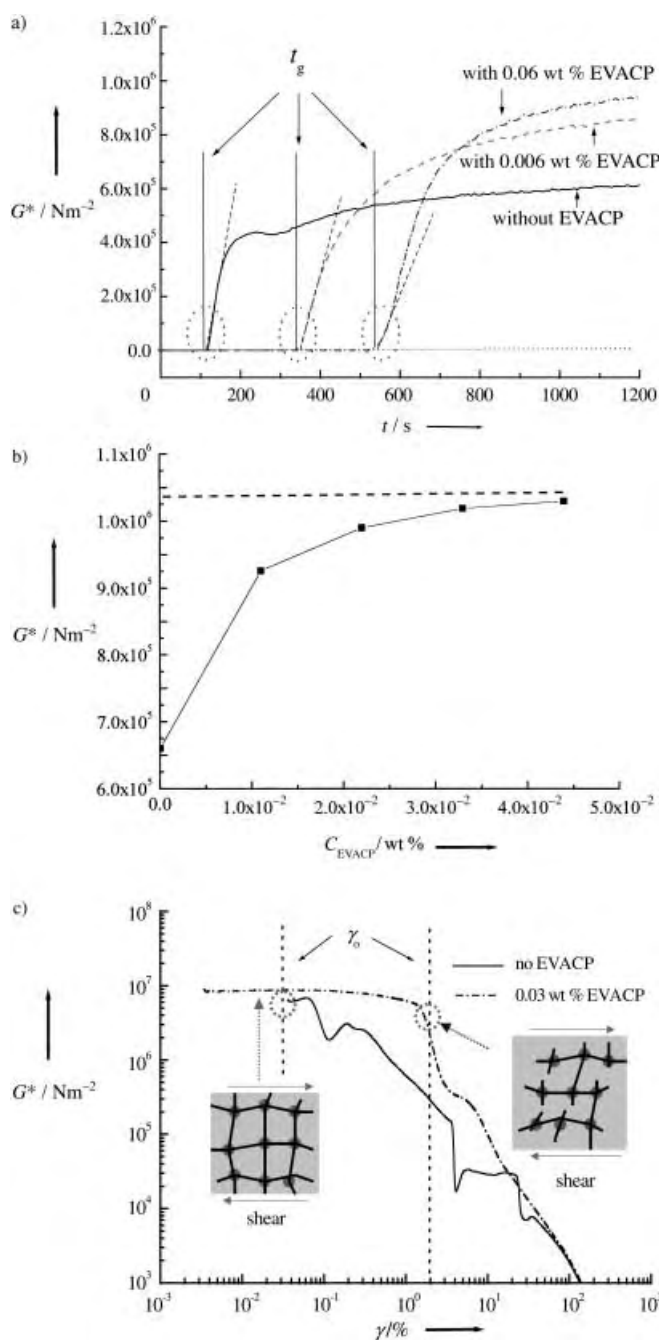


Figure 2. Changes in the rheological properties of the 10 wt % L/DHL/DIOP system, both with and without EVACP, as functions of time and strain.^[19] a) Dependence of the magnitude of complex modulus G^* on time. The amplitude of the oscillations was controlled to obtain a 0.1 % strain in the sample. (Under this strain limit, the structure of supramolecular materials will not be destroyed by the measurements.) The maximal G^* is almost doubled after adding EVACP. The slope of $G^* \sim t$ ($= dG^*/dt$) at $t \rightarrow t_g$ ($t > t_g$) represents the growth rate of L/DHL fibrils. b) Dependence of the magnitude of complex modulus G^* on the concentration of EVACP (C_{EVACP}) for the above system. c) Dependence of the storage modulus G' on strain. The linearity limit γ_0 is enhanced almost 100 times after adding EVACP.

respectively.) The change in G^* as a function of EVACP concentration (C_{EVACP}) is given in Figure 2b. As indicated, the value of G^* increases drastically at low C_{EVACP} values, which is as a consequence of greater interconnectivity between L/

DHL fibers. As C_{EVACP} increases further, G^* gradually reaches a constant level. This can be attributed to fine adjustment of the interconnecting fiber networks. The SEM micrographs suggest that the branching period of L/DHL fibers changes from approximately 1.2 to 0.8 μm as C_{EVACP} varies from 0.006 to 0.1 %. Within the same concentration range, the thickness of the fibers varies between approximately 30 and 60 nm, which is much thinner than that of L/DHL fibers without EVACP (approximately 800 nm).

Figure 2c shows the change in G' at various oscillating strain amplitudes (γ) at an angular frequency (ω) of $0.2\pi \text{ rads}^{-1}$. The strain corresponds to the deformation of the networks caused by the applied shear stress. The value of G' remains constant (linear) at small strains and decreases abruptly when γ exceeds a certain value, γ_o . The onset of nonlinearity (decrease in G') at γ_o indicates bond breakage within the networks.^[12] Figure 2c indicates that the addition of EVACP leads to a significant enhancement (approximately 100 times) of the limit of linearity γ_o . Since our experiments show that EVACP itself has no direct impact on the G' or γ_o values, the changes of G^* , G' , and γ_o must be attributed to the establishment of 3D interconnecting fiber networks.

To explore the network-promotion mechanism of EVACP, one must first understand the cross-linking mechanism. It is

believed^[2,4] that the formation of nanofibers of small molecules such as L/DHL occurs through molecular self-assembly. This process implies that the fibrils have only low-dimensional or liquid-crystalline ordering, and the formation of networks should be controlled by diffusion.^[2,4] However, X-ray diffraction (XRD) analysis shows that L/DHL powders, needles, and 3D interconnecting fibrils have identical crystalline characteristics (Figure 3a). The formation of L/DHL needles and 3D interconnecting fibrils is, therefore, essentially controlled by a nucleation-growth process. According to 3D nucleation models^[13] $\ln t_g$ is linearly dependent on $1/(\Delta\mu/kT)^2$. Here, $\Delta\mu$ is the difference in chemical potential between L/DHL molecules in the fibril and in the liquid phase, and can be given by Equation (1).

$$\frac{\Delta\mu}{kT} \cong \frac{\Delta H_{\text{diss}}}{kT_{\text{eq}}T} (T_{\text{eq}} - T) \quad (1)$$

ΔH_{diss} denotes the molar dissolution enthalpy of the nucleating phase, T_{eq} and T are the equilibrium temperature for a given concentration and the experimental temperature, respectively, and k is the Boltzmann constant.

On the basis of the above results (Figure 3) and the “trimmed Cayley tree” structure (Figure 1b), we propose that propagation of the interconnecting network of L/DHL after adding EVACP proceeds as follows: primary nucleation $\rightarrow$ fiber growth $\rightarrow$ crystallographic mismatch branching $\rightarrow$ fiber growth $\rightarrow$ crystallographic mismatch branching, etc. (Figure 4c).^[14] One of the key steps to building self-organized interconnecting fiber networks is the so-called crystallographic mismatch branching (CMB)^[14] induced by EVACP. This process occurs when crystal layers on the tips of the growing fibrils exert a certain degree of structural mismatch with respect to the crystallographic orientation of the parent fibers. This situation leads to the formation of new daughter fibers on the tips of the parent fibers (Figure 4b).

The formation of sharp crystalline needles or fibers arises from the rapid growth of the tips, which implies that the kinetic resistance of sharp fibril tips along the fibril axis is very low in comparison with other directions,^[13,15] and corresponds to a very low step-free energy (that is, the energy required to create a step at the crystal surface).^[15] Consequently, the growth of L/DHL fibrils is very likely to be controlled by either 2D nucleation “birth-and-spread growth” or “rough-growth” mechanisms.^[13,15] The birth-and-spread mechanism involves growth along the fibril axis by growing new crystal layers on top of an existing layer through 2D nucleation (Figure 4a).^[13]

For the growth of separate needlelike fibrils, integration of L/DHL molecules into the crystal structure of fibrils at the tip surface is much more rapid than the transport of molecules from the bulk to the surface.^[13,15] It follows that all growth units transported to the tip surface will be incorporated into the tip instantly.^[13] Therefore, the concentration of deposited material at the surface of the tips is very close to the equilibrium concentration (or supersaturation $\Delta\mu/kT \rightarrow 0$).

For a crystalline system, the probability of heterogeneous nucleation, which leads to the occurrence of new fibrils, depends on both the structural match between the substrate

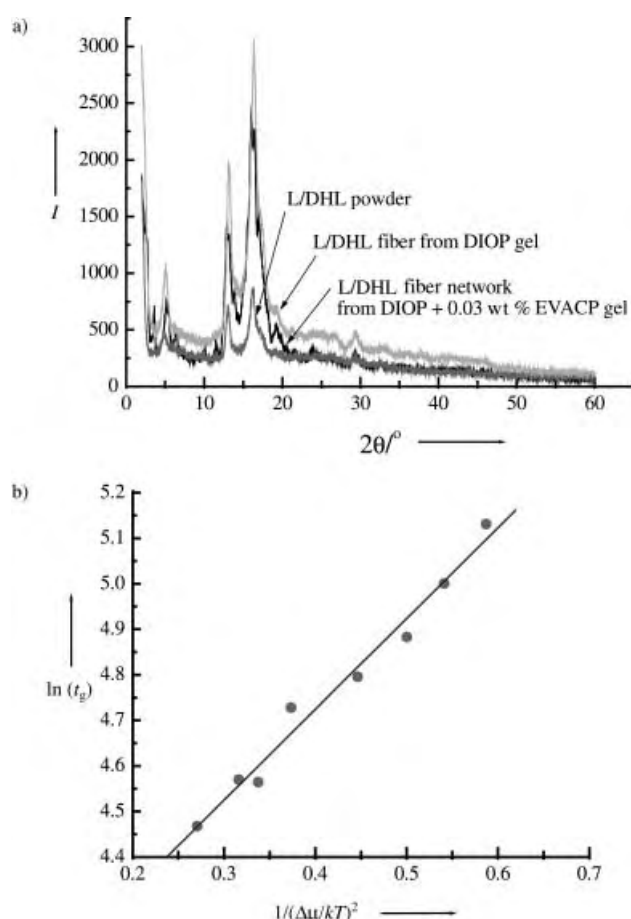


Figure 3. a) X-ray diffraction analysis for L/DHL crystalline powders and fibrils. All forms have crystalline order and an identical structure. b) Plots of $\ln t_g - 1$ versus $(\Delta\mu/kT)^2$ for the 10 wt % L/DHL/DIOP system. A linear relationship is obtained, which indicates the control of nucleation during fibril formation.^[13]

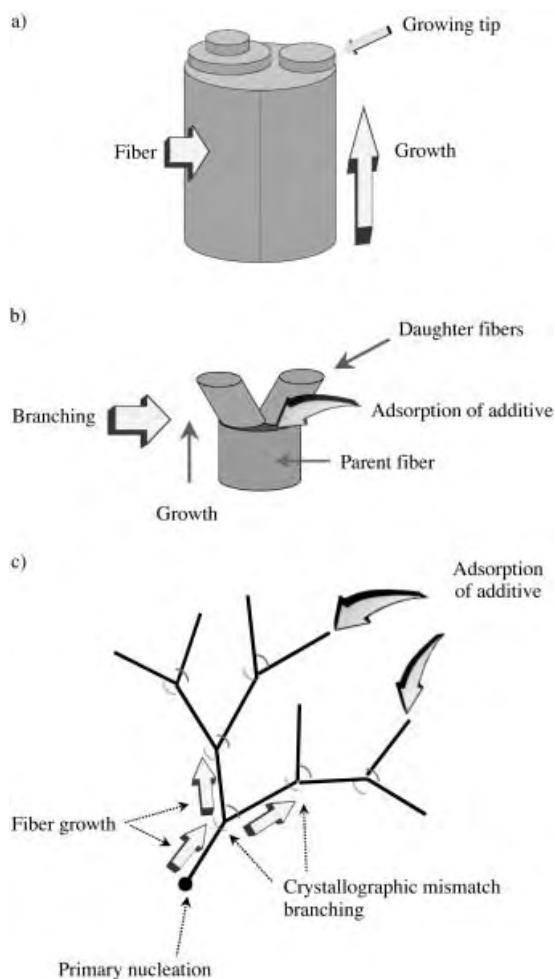


Figure 4. a) Growth of L/DHL fibrils controlled by the birth-and-spread two-dimensional nucleation mechanism.^[13,22] This process can take place at low supersaturation values, and correspondingly the structure of the new layers occurring at the tip of the fibrils exactly matches that of the crystal surface. b) The adsorption of EVACP causes mismatch nucleation at the tip of growing fibril, which leads to crystallographic mismatch branching. c) The formation of interconnecting fiber networks.

and the nucleating phase, as well as supersaturation.^[13] It is of note that the surface of existing fiber tips can also be a perfect substrate for self- or auto-epitaxial nucleation and growth.^[13b,16] For the growth of L/DHL needles, the deposition of new layers on the existing surface of growing tips requires a perfect structural match at very low levels of surface supersaturation (Figure 4a).^[13] As the surface supersaturation increases, the tendency for a mismatch of new layers on the existing surface of growing tips (Figure 4b) increases because of the lowering of the mismatch nucleation barrier.^[13] If structural mismatch occurs, new fiber branches will emerge from the tips of existing fibers, which leads to CMB (Figure 4b).

EVACP is an agent that will selectively adsorb on certain surfaces of organic crystals.^[17] The molecules can strongly adsorb on the tip of growing fibrils or the surface of foreign particles. As shown in Figure 2a, the value of t_g , which is proportional to the induction time of primary nucleation, changes from 1.2×10^2 to 3.4×10^2 and 5.4×10^2 s upon addition

of 0.006 and 0.06 wt% EVACP, respectively. These results suggest that the primary nucleation of L/DHL, which normally initiates from foreign particles,^[13] is suppressed by the adsorption of EVACP onto the surface of the particles.^[13,15] More importantly, the adsorption of EVACP on the tip of growing fibrils will hinder significantly the integration of surface L/DHL molecules into the crystal^[18] and, consequently, reduce the growth rate of the fibers. It can be seen from Figure 2a that the growth rate of the fibrils in the axial direction, R_g , changes from 9C to 3.3C and 1.2C ($C = \text{constant}$) when 0.006 and 0.06 wt% EVACP are added, respectively (see the legend of Figure 2a and ref. [23] for details). Consequently, the surface supersaturation is greatly enhanced to a level close to the bulk supersaturation.^[13] As mentioned above, high surface supersaturation promotes the formation of new fibrils on the tip of the parent fibril (Figure 4b), which leads to the onset of CMB. The experiments verify that the correlation between the branching distance and supersaturation $1/(\Delta\mu/kT)$ can be described quantitatively by the CMB mechanism when branching occurs.^[19]

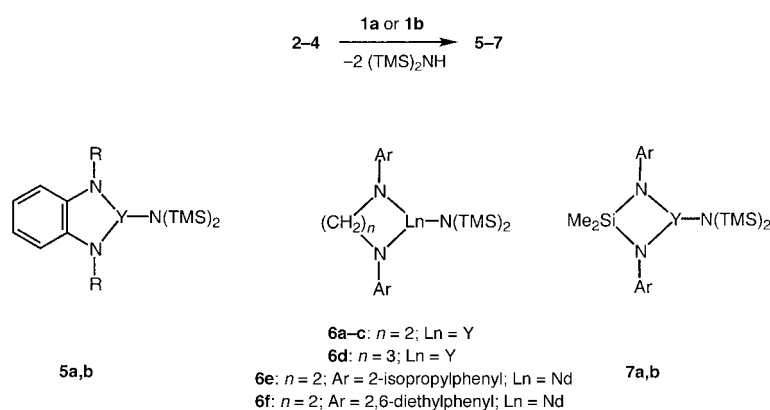
Otsubo^[20] reported that silica particle suspensions also form 3D networks on addition of polyacrylamide. The network is formed by the adsorption of one polymer chain onto two or more existing particles, which binds them together. In this case, the polymer molecules serve as bridging materials in the formation of the 3D network, and adsorption onto the surface of particles is an irreversible process. In contrast, the EVACP introduced into the L/DHL/DIOP system promotes the branching of lanosterol fibrils by affecting the kinetics of fiber formation, rather than through direct involvement by bridging different existing fibrils. This process completely alters the topology of the fiber networks, and leads to the formation of the Cayley tree type of 3D interconnecting network (Figures 1c and 4c). Therefore, in comparison with the bridging mechanism, additive-induced CMB requires a much lower quantity of polymer than the previous case (at least two magnitudes lower).^[21] The formation of 3D interconnecting nanofiber networks of L/DHL by the addition of EVACP is thermally reversible since the branching process is kinetically controlled. This is in contrast to the thermally irreversible 3D network formed by the bridging of polyacrylamide, and exemplifies the differences between these systems.^[20]

It is noticeable that the adsorption of additives on the growing tips may reduce the anisotropy of needlelike growth, and result in tip-splitting as a consequence of instability at the corners.^[15,22] The branching in our case is a special type of 3D nucleation (Figure 4d), whereas tip-splitting is essentially a diffusion-control growth process. As an important distinction, the split tips and the parent fiber belong to the same crystal, whereas the daughter fibers and the parent crystal in CMB belong to different crystallites (Figure 1b).

In conclusion, we have constructed a 3D interconnecting fibrous network of a supramolecular functional material at the micro/nanoscale level, by utilizing a "branching creator", EVACP. This novel approach can enable the creation and engineering of interconnecting 3D nanofiber networks with a desired structure and significantly modified rheological properties. Our experiments show that the architecture of the

(2.7 mol %) of **1a** or **1b** in C₆D₆ at 24 °C resulted in the immediate and apparently quantitative liberation of (TMS)₂NH with concomitant generation of the corresponding and presumably amine-ligated^[5] amido complexes. It is well established that the catalytic activity of group 3 metallocenes in alkene hydroamination is quite sensitive to steric perturbations about the metal center.^[2a–c] In light of this, we set out to determine the role that sterically hindered chelating diamide ligands might play in altering the reactivity profile of group 3 amido complexes (Scheme 2).

The ligand motifs that were selected for evaluation in this study fell into three categories corresponding to the easily accessible diamines **2–4**. The selection of these was based on the consideration that aryl amine moieties would be sufficiently acidic to be irreversibly metallated by bis(trimethylsilyl) amides such as **1a**.^[4] This proved to be the case as exposure of **2–4** to 1 equiv of **1a** in C₆D₆ or [D₈]toluene led to



Scheme 2. Formation of the complexes **5–7**.

smooth elimination of (TMS)₂NH with simultaneous formation of the yttrium chelates **5**, **6a–d**, and **7**.^[6,7] The neodymium complexes **6e** and **6f** were obtained from **1b** in an analogous manner.

The catalytic activity of these complexes relative to that of **1a** was first examined in the diastereoselective cyclization of the racemic amino alkene **8**. Whereas the cyclization of **8** to the pyrrolidines **9a** and **9b** in the presence of 5 mol % of **1a** at 60 °C was extremely slow, requiring 31 days to reach 95 % conversion (**9a:9b** = 9:1),^[8] cyclization was > 95 % complete in 15 min at 60 °C in the presence of 5 mol % of **6b** (**9a:9b** = 19:1). Related catalytic activity enhancements for the chelate complexes **5–7** were clearly apparent in an allied series of intramolecular hydroaminations. A compilation of reaction times and diastereoselectivities observed for the cyclization of amino alkene **8** in the presence of the yttrium chelates **5–7** appears in Table 1.

Several of the above results are worthy of comment. Five-membered chelates derived from the sterically hindered diamines **3a** and **3b** are clearly superior in activity relative to complex **5a**. The incorporation of secondary ligating domains, as in complex **5b**, results in decreased conversion rates but improved diastereoselectivities compared to those of chelate structures such as **5a** that possess simple alkyl

Table 1. Catalyzed cyclizations of 2-aminohept-5-ene (**8**).

Complex	<i>t</i> _{React.} [a]	d.r. (9a:9b)	Conv. [%] [b]
1a	744 h	9:1	> 95
5a	51 h	11:1	> 95
5b	84 h	19:1	> 95
6a	70 min	19:1	> 95
6b	15 min	19:1	> 95
6d	42 h	11:1	> 95
7a	11 h	19:1	> 95
7b	2 h	16:1	> 95

[a] All reactions were conducted at 60 °C. [b] Based on ¹H NMR integration.

substituents. Opening of the coordination sphere at the yttrium center by the use of diamines **4a,b** that form four-membered chelates results in catalysts (e.g., **7a,b**) possessing somewhat lower activity. Six-membered chelates (e.g., **6d**) reminiscent of the zirconium complexes reported by McConville and co-workers^[9] are comparatively inferior in terms of activity as well as stereoselectivity. Complexes **5a** and **6a–c** were next examined for the diastereoselective cyclization of amino alkene **10** to the piperidines **11a** and **11b** (Table 2). Although these reactions were in general slower and less stereoselective than those involving amino alkene **8**, similar trends in catalytic activity were observed, with **6a–c** showing the highest activities. The notable activity of complex **6c** as compared to **6a**

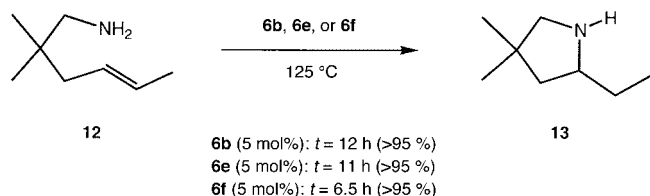
or **6b** in this transformation further emphasizes the sensitivity of intramolecular alkene hydroamination to steric perturbations within the ligand domain.

1,2-Disubstituted alkenes have been shown to be the least reactive carbon–carbon double bond substrates toward intramolecular hydroamination thus far.^[2c] Despite this, amino alkene **12**^[10] was efficiently converted into pyrrolidine **13** at 125 °C over 12, 11 and 6.5 hours, respectively, in the presence

Table 2. Catalyzed cyclizations of 2-aminohept-6-ene (**10**).

Complex	<i>t</i> _{React.} [a]	d.r. (11a:11b)	Conv. [%] [b]
5a	10 h	1:4	> 95
6a	45 min	1:4	> 95
6b	95 min	1:5	> 95
6c	< 15 min	1:4	> 95

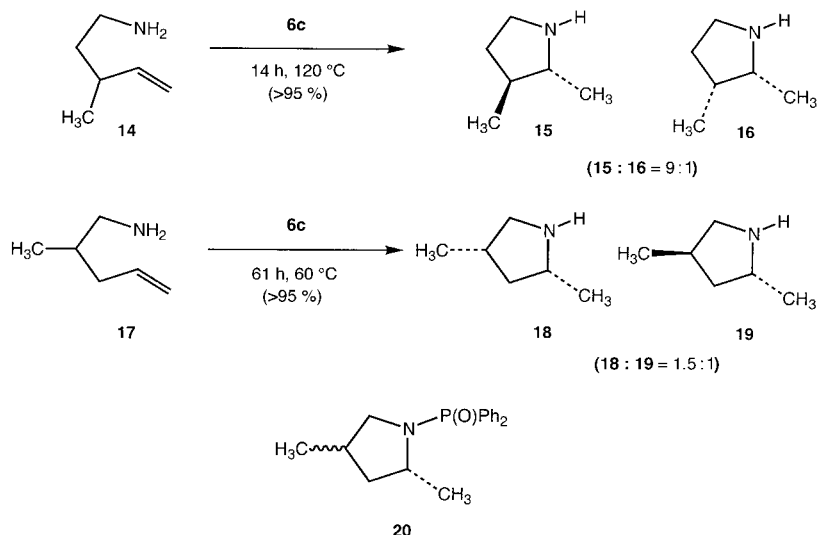
[a] All reactions were conducted at 120 °C. [b] Based on integration of the ¹H NMR spectrum.



Scheme 3. A 1,2-disubstituted alkene (**12**) as a substrate for the intramolecular hydroamination.

of 5 mol% of **6b**, **6e** or **6f** (Scheme 3). These results are noteworthy as the catalytic activities of these first-generation chelates are comparable, and in the case of **6f**, superior to those of the sensitive and more difficultly accessible metallocene complexes described by Marks and co-workers.^[2c]

To estimate the substrate control of diastereoselectivity during the formation of substituted pyrrolidines, the amino alkenes **14**^[11] and **17**^[11] were subjected to cyclization in the presence of 5 mol% of **6c** (Scheme 4).^[12] In the case of **14**, the



Scheme 4. Cyclizations of substituted 1-aminopent-4-enes.

2,3-disubstituted pyrrolidines **15** and **16** were formed in a ratio of 9:1 (>95% yield by NMR spectroscopy, 81% isolated as the *p*-toluenesulfonamides). As expected, the cyclization of **17** proved less selective, providing the pyrrolidines **18** and **19** with a *cis/trans* ratio of 1.5. In this case, the corresponding phosphonamides **20** were secured in 99% yield.^[13]

In conclusion, we have demonstrated that modification of the metal center in $[\text{Ln}\{\text{N}(\text{TMS})_2\}_3]$ ($\text{Ln} = \text{Y, Nd}$) is readily achieved by amine elimination in the presence of sterically hindered chelating diamines, in situ, to provide complexes possessing substantially augmented catalytic activities and improved stereoselectivities in intramolecular alkene hydroamination. The utilization of this strategy for the synthesis of chiral Group 3 amido complexes and their use in the asymmetric variation of this reaction in addition to its application to the construction of naturally occurring polyfused ring systems will be the topics of future accounts.

Experimental Section

General procedure for intramolecular alkene hydroaminations: In an argon-filled glove box, $[\text{Ln}\{\text{N}(\text{TMS})_2\}_3]$ ($1.6 \times 10^{-5}\text{ mol}$) and the appropriate diamine ($1.6 \times 10^{-5}\text{ mol}$) were introduced into an NMR tube (J. Young) equipped with a teflon screw cap, and then C_6D_6 or $[\text{D}_8]\text{toluene}$ (0.7 mL) was added. The homogeneous reaction mixture was heated to $120\text{ }^{\circ}\text{C}$ (C_6D_6) or $150\text{ }^{\circ}\text{C}$ ($[\text{D}_8]\text{toluene}$) to effect ligand exchange until the peak of $[\text{Ln}\{\text{N}(\text{TMS})_2\}_3]$ had disappeared with concomitant generation of free $(\text{TMS})_2\text{NH}$. The appropriate amino alkene ($3.2 \times 10^{-4}\text{ mol}$) was added to the resulting complex and the reaction mixture was subsequently heated at 60, 120, or $125\text{ }^{\circ}\text{C}$ in an oil bath. ^1H NMR spectroscopy (with a pulse delay of 10 s to avoid signal saturation) was employed to monitor the reactions.

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- [7] Metallation of the hindered diamines **3a,b** through amine elimination is comparatively slow relative to **2**.
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- [12] In these reactions, $[\text{D}_8]\text{toluene}$ was used as the solvent. Whereas the initial amine elimination reaction between **1a** and **3b** required 5 days at $120\text{ }^{\circ}\text{C}$ in C_6D_6 , the corresponding reaction at $150\text{ }^{\circ}\text{C}$ in $[\text{D}_8]\text{toluene}$ proceeded in only 5 h. Significantly, the present amido chelates exhibit superb thermal stability as contrasted with the metallocene complexes of Marks and co-workers.^[2c]
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Bispyrene-Conjugated 2'-O-Methyloligonucleotide as a Highly Specific RNA-Recognition Probe**

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In designing antisense molecules, it is crucial to detect the regions of the target RNA where the antisense molecule can hybridize.^[1] To date, several studies have focused on the detection of these regions. The studies include theoretical calculations,^[2] enzymatic digestion,^[3] and DNA arrays,^[4] and all of them have achieved a partial success. However, none of these methods have the potential to be applied to cells in which various endogenous molecules interact with RNA in a variety of manners.

Solution-based fluorescence methods should be suitable to deduce the RNA structure in vitro, because these methods primarily function without disturbing the RNA structure. One of the most useful fluorescence methods is based on fluorescence resonance energy transfer (FRET), which provides information about the distance between two chromophores. A three-dimensional structure of a ribozyme was revealed by such methods.^[5] A molecular beacon, which is based on FRET, was applied to the detection of RNA in living cells.^[6] In another method, various types of pyrene-conjugated oligonucleotides have been used for the detection of both RNA and DNA sequences.^[7] The methods were based on excimer formation upon the formation of hybrid molecules and could not discriminate RNA from DNA. As a final goal, we intend to elucidate the detailed structure of RNA in living cells, and have developed a novel bispyrene-conjugated 2'-O-methyloligonucleotide probe (OMUpy2; Figure 1). The probe is also expected to be feasible for use in analysis of intracellular RNA traffic and consequently to evaluate RNA functions.

OMUpy2 was synthesized and purified according to the reported procedure with slight modifications.^[8] To evaluate whether OMUpy2 can detect single-stranded regions of native-folded RNA molecules, we used *E. coli* 5S-rRNA, which contains 120 nucleotides (nt). 5S-rRNA is a component of the 50S ribosome subunit and the secondary structure has been reported (Figure 2).^[9] We chose the regions for probing with OMUpy2 as follows; OMUpy2-I was complementary to

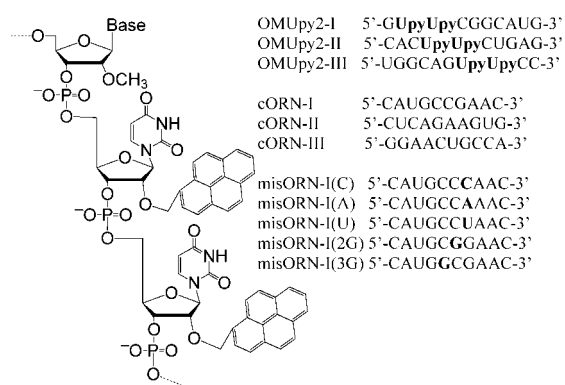


Figure 1. Structure of bispyrene-conjugated 2'-O-methyloligonucleotides and the sequence of OMUpy2 and target oligoRNA (ORN). Upy = 2'-O-(1-pyrenylmethyl)uridine. The mismatch bases are shown in bold.

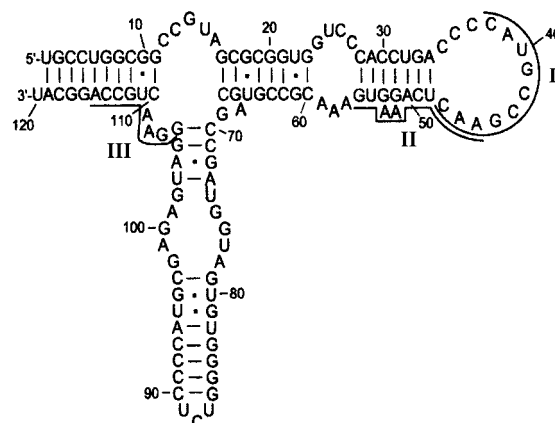


Figure 2. Secondary structure of 5S-rRNA and the region for probing by OMUpy2.^[10]

region I (38–47 nt), and OMUpy2-II and III were complementary to regions II (45–56 nt) and III (106–115 nt), respectively.

The fluorescence characteristics of OMUpy2 in the absence and presence of the equimolar solution of its complementary oligodeoxyribonucleotide (cODN) or oligoribonucleotide (cORN) are shown in Figure 3. Compared with 1-pyrenylmethanol, the structured emission caused by the pyrene of the OMUpy2-I around 380 nm was largely quenched, and a weak, broad, and structureless emission around 480 nm was observed. It is likely that the monomeric pyrene emission was quenched by the intercalation of the pyrene between nucleobases.^[8,10] On the other hand, when the OMUpy2-I was hybridized with cORN, the broad structureless fluorescence band around 480 nm was increased by 43.7-fold compared with the corresponding single-stranded OMUpy2-I, and the structured emission around 380 nm was substantially unchanged. The mechanism of the increment in fluorescence intensity around 480 nm is not known. However, it is rational to assume that two pyrenes would participate in the emission and that the pyrene would interact with each other, forming a defined complex upon hybridization. In most cases reported, the broad, strong, structureless emission around 480 nm is attributed to the pyrene excimer. As another explanation, we are verifying the possibility that the emission is from the ground state dimer of pyrenes. At this stage, we cannot

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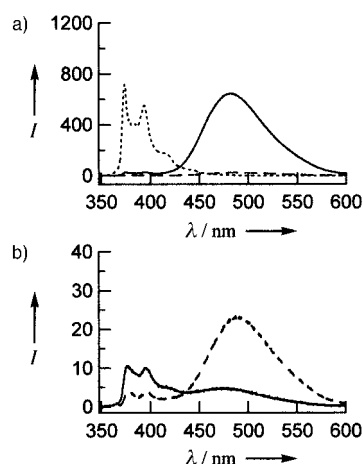


Figure 3. a) Fluorescence spectra of 1-pyrenylmethanol (••••) and OMUpy2-I (—), equimolar mixture of OMUpy2-I and cORN (—), b) fluorescence spectra of OMUpy2-I (---) and equimolar mixture of OMUpy2-I and cODN (—). [OMUpy2-I] = [cORN] = [cODN] = 6 μ M, λ_{ex} = 342 nm, 10 mM phosphate buffer (pH 7.0), 0.1M NaCl, 11 °C

conclude whether the emission around 480 nm is attributed to the excimer, to the dimer, or to both. The detailed features of the complex are now under investigation. When OMUpy2-I was hybridized with cODN, the emission around 480 nm could barely be observed, and the structured emission around 380 nm was slightly increased (Figure 3b). These results suggest that the pyrene remained intercalated between nucleobases when OMUpy2-I formed a hybrid with the cODN. Then, the fluorescence enhancement was further studied using several ORNs with a single-point mutation. When OMUpy2-I was mixed with the ORNs containing the mismatch sequence whose mismatch positions were next to the UpyUp core region, the fluorescence enhancement could scarcely be observed. As the mismatch positions were moved further away from the UpyUp core regions, there was some fluorescence enhancement. These results clearly demonstrate that the firm hybrid formation of the UpyUp core region is essential for fluorescence enhancement. OMUpy2-II and III showed very similar characteristics to OMUpy2-I. These results suggest that OMUpy2 increases the fluorescence intensity around 480 nm only when hybridized with the cORN and that the manner of probing is highly sequence specific.

OMUpy2 was then studied for its ability to detect single-stranded regions of naturally folded 5S-rRNA from *E. coli*. X-ray crystallographic analysis of 5S-rRNA^[11] from *E. coli* suggested that region I of 5S-rRNA is in the region that gave an obscure diffraction pattern and that the regions II and III are in the firm-stem regions. Also, X-ray crystallography of the large ribosomal subunit from *Haloarcula marismortui* suggested that there were several non-Watson-Crick base pairs in region I of the 5S-rRNA.^[12] When OMUpy2-I was added to 5S-rRNA, an emission around 480 nm was observed, which indicates that OMUpy2-I hybridized with 5S-rRNA. On the other hand, when OMUpy2-II and III were added to 5S-rRNA, the fluorescence did not change appreciably, which indicates that the OMUpy2-II and III did not hybridize with 5S-rRNA. These results (Table 1) suggest that region I is an

Table 1. Relative fluorescence intensity of OMUpy2 and the duplex with oligoRNA and oligoDNA and oligoRNA with single-point mutation and melting temperatures (260 nm)

Oligomer	Relative fluorescence intensity at 480 nm ^[a]	m.p. [°C] ^[b]
OMUpy2-I	1.0	
+ cORN-I	45.7	48.2
+ cODN-I	0.3	45.1
+ misORN-I(C)	0.4	33.9
+ misORN-I(A)	0.9	33.9
+ misORN-I(U)	0.6	34.2
+ misORN-I(2G)	9.3	34.8
+ misORN-I(3G)	38.1	27.3
+ 5S-rRNA	32.3	
OMUpy2-II	3.5	
+ cORN-II	43.9	42.0
+ 5S-rRNA	4.0	
OMUpy2-III	0.4	
+ cORN-III	38.9	51.4
+ 5S-rRNA	0.4	

[a] Fluorescence spectra of OMUpy2 were obtained under the same conditions as shown in Figure 3. [b] Measurements were carried out at 260 nm for the equimolar mixture of OMUpy2 and oligonucleotide in 10 mM phosphate buffer (pH 7.0) with 0.1M NaCl.

accessible site of the antisense molecule, and that regions II and III are not accessible.

In conclusion, bispyrene-conjugated 2'-O-methyloligoribonucleotide was a useful probe to detect the hybridization with complementary RNA and to evaluate the accessibility of the native folded RNA for oligonucleotides. As this probe is highly specific to RNA, it might be useful for a variety of purposes including the detection of endogenous RNAs in living cells.

Experimental Section

Synthesis of bispyrene-conjugated 2'-O-methyloligoribonucleotides: Synthesis of OMUpy2 was carried out by standard phosphoramidite chemistry using DMT-2'-O-methyloligoribonucleotide and 5'-DMT-Upy amidite (DMT = 4,4'-dimethoxytrityl).^[9] OMUpy2 was purified by reverse-phase HPLC with a linear gradient of acetonitrile in 0.1M triethylammonium acetate (pH 7.0) at a flow rate of 0.8 mL min⁻¹.

Physical Measurements: The fluorescence measurements were performed on a fluorescence spectrophotometer (RF-5300PC, Shimadzu Co.) with an excitation wavelength of 342 nm. No attempt was made to eliminate dissolved oxygen in the buffer solution (10 mM phosphate buffer with 0.1M NaCl) for the fluorescence measurements. UV-melting curves of the duplexes were acquired from an equimolar mixture of OMUpy2 and oligonucleotide with an increase in temperature from 0 to 90 °C, at a rate of 1.0 °C min⁻¹.

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Self-Assembly Using Organometallogligands as Spacers in the Controlled Formation of Isomeric 1D and 2D Supramolecular Quinonoid Networks**

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Metal-coordination-directed self-assembly of polymers and discrete nanostructures is a very active research area.^[1] The construction of predictable architectures having useful electronic, catalytic, or host–guest properties is the driving force behind this work. To date, the vast majority of reported compounds have metal centers connected by simple organic molecules that serve as multifunctional ligands or spacers.^[1] We recently demonstrated, however, that the π -bonded

organometallic complex ion $[(\eta^4\text{-benzoquinone})\text{Mn}(\text{CO})_3]^-$ (**1**) can serve as a bifunctional ligand (“organometallogligand”) by coordinating through the quinone oxygen atoms in the presence of divalent transition-metal ions.^[2a] M^{2+} ions ($\text{M} = \text{Mn}, \text{Cd}, \text{Zn}$) and **1** were found to self-assemble into crystalline organometallic quinonoid polymers, whose dimensionality and geometry can be controlled by the choice of added metal ion.

Herein, we report that the organometallogligand $[(\eta^4\text{-benzoquinone})\text{Mn}(\text{CO})_3]^-$ reacts with Mn^{2+} ions to form two isomeric coordination networks. Figure 1 illustrates the two architectures possible when **1** links to the Mn^{2+} centers. Either a 2D pseudoplanar quinonoid array (Figure 1 a) or 1D “string” arrays (Figure 1 b) can be formed. A representation

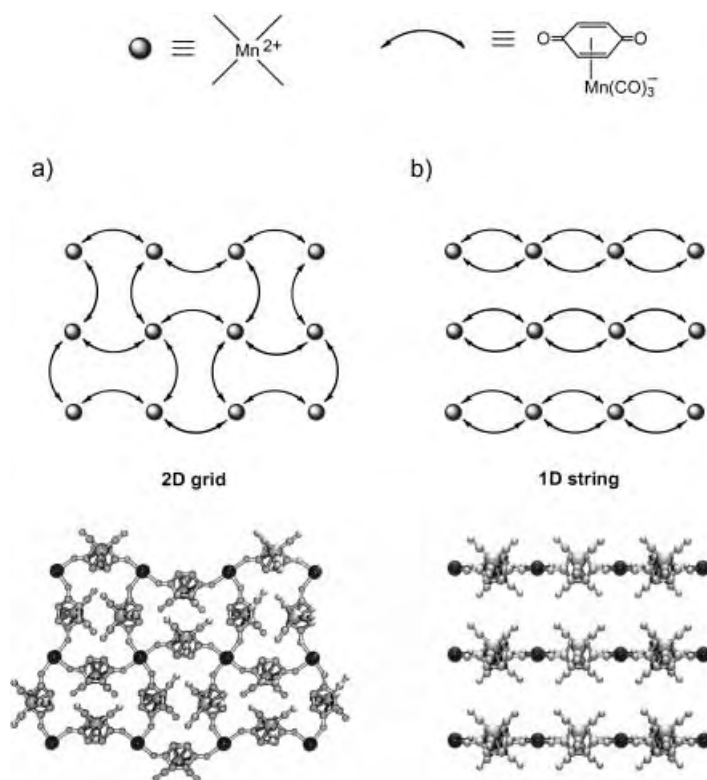
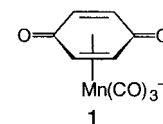
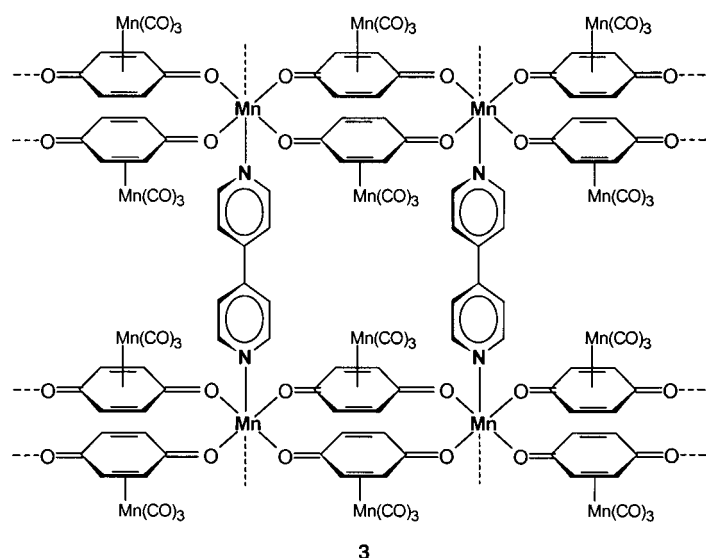


Figure 1. Representation of the self-assembly of Mn^{2+} ions with the η^4 -quinone complex **1** to form neutral a) 2D grid and b) 1D string networks.

of these two networks with $[\text{Mn}(\text{CO})_3]$ moieties attached to the constituent quinone molecules is also given in Figure 1. One would expect that bifunctional spacer molecules could be used to join together the planes in Figure 1 a, or the strings in Figure 1 b. Indeed, we recently demonstrated that **1**, Mn^{2+} ions, and 4,4'-bipyridine self-assemble in dimethyl sulfoxide (DMSO) to afford a polymer (**2**), which contains a 2D planar network linked by bipyridine spacers.^[2a] We now report that self-assembly of the same components, but with the Mn^{2+} ions maintained at a very low concentration, results in the formation of the isomeric polymer **3**, consisting of the 1D strings linked by bipyridine spacers. It is noteworthy that polymers **2** and **3** both contain rectangular grid networks. Typically, the isomer distribution found in supramolecular

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structures is dictated by the presence of guest molecules that serve as templates for self-assembly.^[1e,3] In our studies, however, the isomer formed is determined not by guest molecules but rather by the concentration of the metal ion that coordinates to the organometallogand and the bipyridine spacers.

When **1** and 4,4'-bipyridine react in DMSO in air at 70 °C for two days in ambient room light, there is a slow photo-generation of Mn^{2+} ions and concomitant formation of polymer **3**. In contrast, when several equivalents of $\text{Mn}(\text{OAc})_2$ are present in the reaction mixture, polymer **2**, which contain a 2D pseudoplanar quinonoid network, is formed exclusively. In reactions with lower Mn^{2+} concentrations, the 1D string analogue **3** appears, and becomes dominant when no $\text{Mn}(\text{OAc})_2$ is added at the commencement of the reaction. Table 1 lists the distribution of polymers **2** and **3** as a function

Table 1. Distribution of polymeric isomers **2** and **3** in the self-assembly of **1**, 4,4'-bipyridine, and Mn^{2+} ions as a function of the number of added equivalents of $\text{Mn}(\text{OAc})_2$.^[a]

Equivalents of $\text{Mn}(\text{OAc})_2$	Products
8	2 only
2	2 only
0.5	2 (major) and 3
0.25	2 and 3 (major)
0	3 only

[a] In the presence of 1.0 equiv of **1** and 20 equiv of 4,4'-bipyridine in DMSO at 70 °C.

of the amount of added $\text{Mn}(\text{OAc})_2$.^[4] An examination of the disposition of the organometallogand spacers in Figure 1 suggests that the quinone oxygen donors are more likely to be "trapped" in a 2D planar network where there is an abundance of available Mn^{2+} ions. Formation of the 1D string architecture would be more likely when the concentration of Mn^{2+} ions is maintained at a low level. Support for this hypothesis was obtained by treating **1** with excess $\text{Mn}(\text{OAc})_2$ in dimethylacetamide (DMA), from which crystalline polymer $[[(\eta^4\text{-benzoquinone})\text{Mn}(\text{CO})_3]_2\text{Mn}(\text{dma})_2]_n$ (**4**) was obtained (reaction in DMSO did not afford suitable crystals).

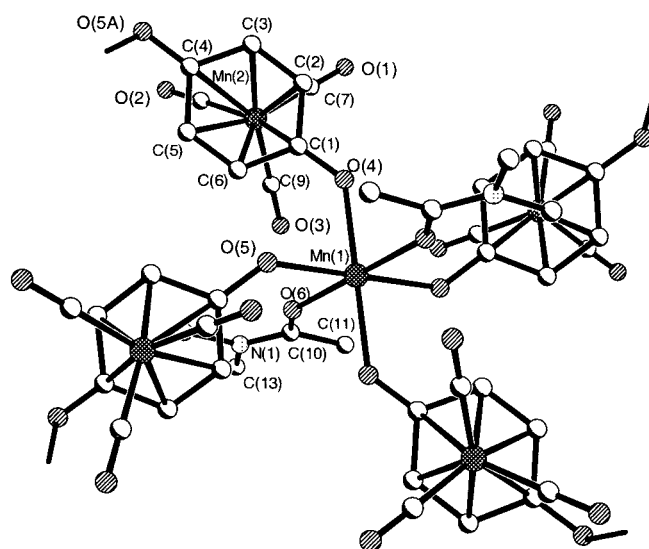


Figure 2. Crystal structure of polymer **4**, $[[(\eta^4\text{-benzoquinone})\text{Mn}(\text{CO})_3]_2\text{Mn}(\text{dma})_2]_n$.

The crystal structure of **4** (Figure 2) verified the anticipated 2D quinonoid network with each Mn^{2+} ion possessing two axial DMA ligands.

The crystal structure of **3** is shown in Figure 3 and a representation of one layer of the polymeric assembly is provided in Figure 4. The organometallogand in **3** adopts a boat conformation with the quinone carbon atoms bent out of the plane of the diene by 13°, so that the overall structure is best described as an η^4 -quinone. The rectangular grids in **3** have dimensions of approximately 10×12 Å. The pseudoplanar layers stack through noncovalent interactions to form the 3D material. As may be seen in Figure 5, the rectangular boxes in one layer are overlaid by $[\text{Mn}(\text{CO})_3]$ moieties in the next layer, so that the crystal does not contain open channels. Two DMSO molecules per box are located between adjacent

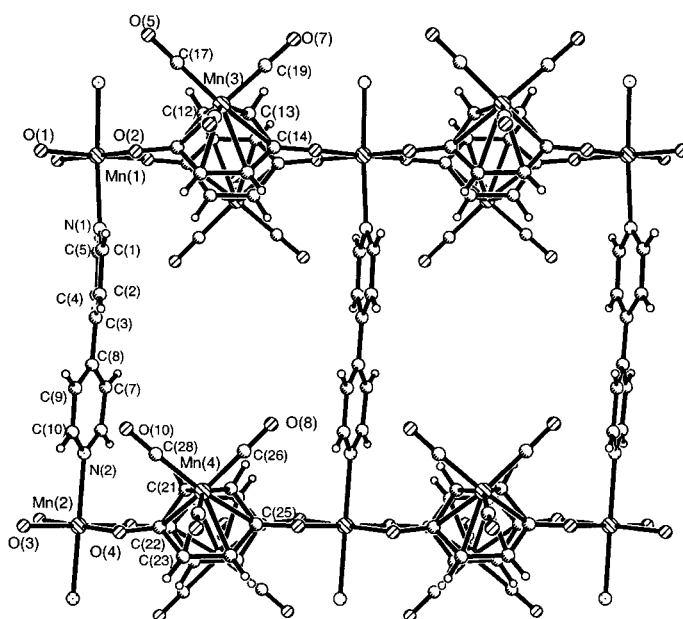


Figure 3. Crystal structure of polymer **3**, $[[(\eta^4\text{-benzoquinone})\text{Mn}(\text{CO})_3]_2\text{Mn}(4,4'\text{-bipyridine})]_n$.

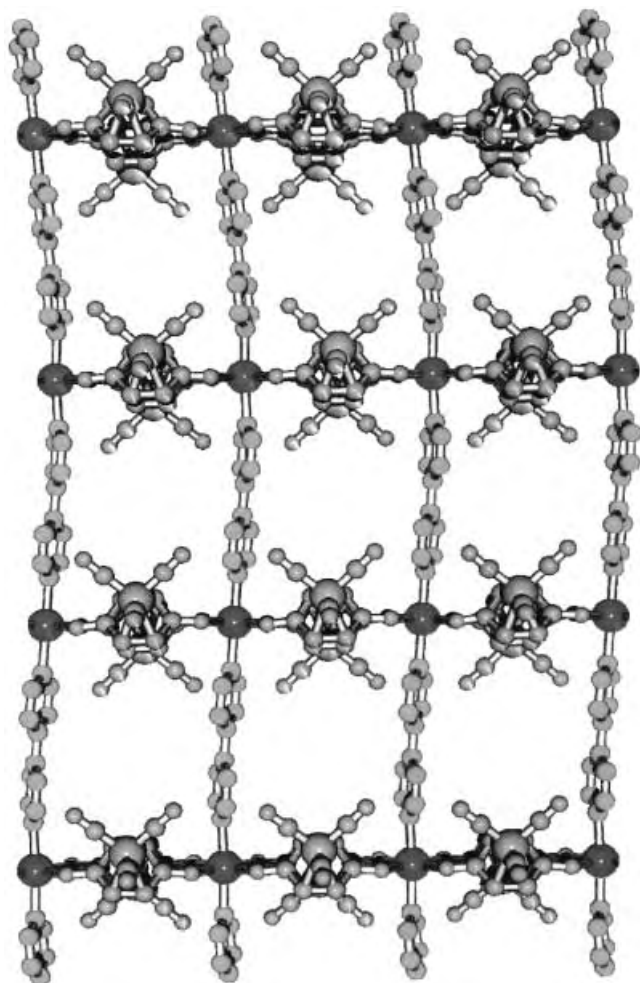


Figure 4. Representation of one layer of polymer **3**.

layers, with a third DMSO molecule situated within each box (Figure 5). Suspending **3** in CD_2Cl_2 at room temperature for 2 h resulted in the complete and quantitative loss of all three

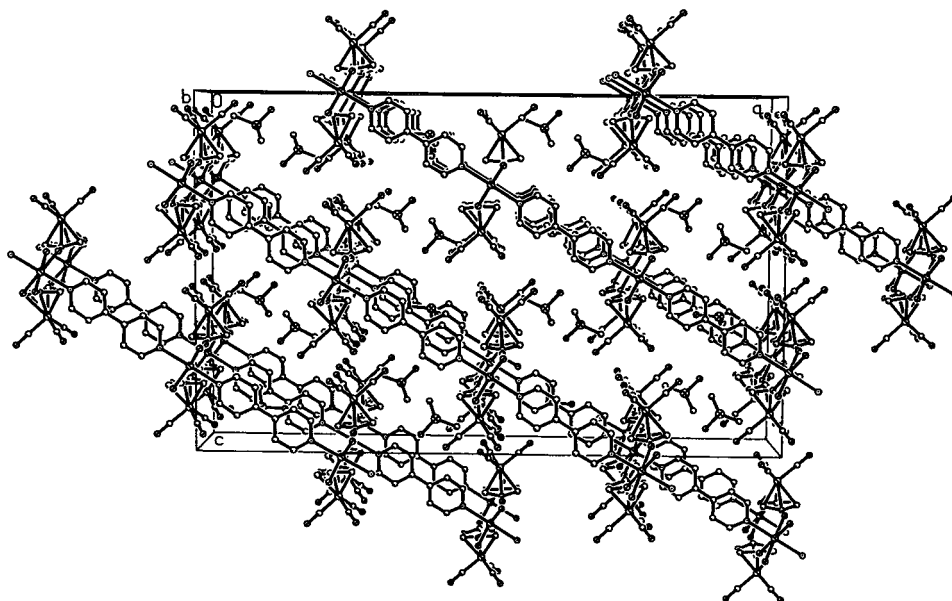


Figure 5. Packing diagram of polymer **3** showing the relative disposition of the layers and the presence of two DMSO molecules located between the layers and a third DMSO molecule located in each rectangular box.

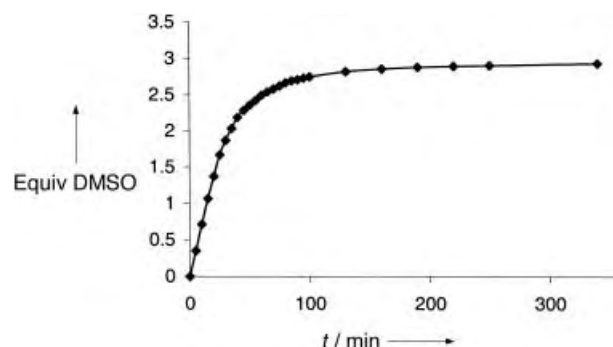


Figure 6. Equivalents of DMSO displaced at room temperature from polymer **3**:3DMSO when suspended in CD_2Cl_2 .

DMSO molecules (Figure 6). Significantly, an X-ray rotation photograph taken after removal of DMSO indicated that this process occurs without affecting the crystallinity.

In conclusion, we have demonstrated the selective polymerization of π -bonded quinone complexes to afford 1D and 2D networks which can be subsequently linked by bipyridine spacers to generate isomeric polymers containing rectangular grids.^[5] This chemistry constitutes a rare example of the use of a π -bonded organometallic complex to function as a spacer (organometallogand) in the coordination-directed self-assembly of a supramolecular structure. It is reasonable to suppose that organometallogand spacers may find general application in supramolecular chemistry. They offer the possibility of novel structural features, as well as novel applications based on through-bond metal–metal interactions between organometallic and inorganic metal centers.

Experimental Section

Syntheses of polymers 3 and 4: The complex $[(\eta^5\text{-1,4-semiquinone})\text{Mn}(\text{CO})_3]^{[2b]}$ (12 mg, 0.048 mmol) and excess 4,4'-bipyridine (10 equiv) were combined in DMSO (0.5 mL) at 70 °C in ambient room light. The bipyridine rapidly converted the manganese complex into the quinone complex **1**. After 2 days, crystals of polymer **3** suitable for X-ray studies were obtained in 77 % yield. IR (KBr): $\tilde{\nu}_{\text{CO}} = 2027$ (s), 1960 (s), 1929 (s), 1603 (w), 1567 (s), 1521 (s) cm^{-1} ; elemental analysis calcd (%) for **3**:3DMSO, $\text{C}_{34}\text{H}_{34}\text{Mn}_3\text{N}_2\text{O}_{13}\text{S}_3$: C 43.46, H 3.65, N 2.98, S 10.24; found: C 43.09, H 3.56, N 2.88, S 10.01. Polymer **4** was synthesized by combining $[(\eta^5\text{-1,4-semiquinone})\text{Mn}(\text{CO})_3]$ (12 mg, 0.048 mmol) and $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (2 equiv) in dimethylacetamide (DMA, 0.5 mL) at 70 °C. After 2 days, crystals of **4** suitable for X-ray studies were obtained in 75 % yield. IR (KBr): $\tilde{\nu}_{\text{CO}} = 2026$ (s), 1949 (s), 1929 (s), 1558 (s), 1510 (s) cm^{-1} .

Crystal structures of 3 and 4: Crystals of **3** suitable for X-ray studies were grown from a solution in DMSO. X-ray data collection with $\text{MoK}\alpha$ radiation was carried out at 298 K by using a Siemens P4 diffractometer equipped with a CCD area-detector. The structure was determined by direct methods and refined on F^2 using SHELXTL version 5. All hydrogen atoms were inserted in ideal

positions, riding on their carbon atoms. Crystal data for **3**: $C_{17}H_{17}Mn_{1.5}NO_{6.5}S_{1.5}$, $M_r = 469.82$, monoclinic, space group $C2/c$, $a = 39.700(3)$, $b = 8.3664(6)$, $c = 24.390(2)$ Å, $\beta = 90.128(2)^\circ$, $V = 8101.0(11)$ Å³, $Z = 16$, $\rho_{\text{calcd}} = 1.541$ g cm⁻³, $\mu = 1.139$ mm⁻¹, $F(000) = 3832$, θ range $1.03\text{--}26.40^\circ$, 520 variables refined with 8304 independent reflections to final R indices [$I > 2\sigma(I)$] of $R_1 = 0.0676$ and $wR_2 = 0.1892$, and $GOF = 1.025$. Crystals of **4** suitable for X-ray studies were grown from a solution in DMA. Crystal data for **4**: $C_{26}H_{26}Mn_3N_2O_{12}$, $M_r = 723.31$, monoclinic, space group $P2_1/c$, $a = 12.939(2)$, $b = 10.0886(15)$, $c = 12.9121(19)$ Å, $\beta = 90.128(2)^\circ$, $V = 1510.0(4)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.591$ g cm⁻³, $\mu = 1.299$ mm⁻¹, $F(000) = 734$, θ range $2.68\text{--}26.36^\circ$, 206 variables refined with 12 734 independent reflections to final R indices [$I > 2\sigma(I)$] of $R_1 = 0.0570$ and $wR_2 = 0.1397$, and $GOF = 0.979$. CCDC-182869 and -186586 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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Reversible Photoinsertion of Ferrocene into a Hydrophobic Semiconductor Surface: A Chemionic Switch**

Masahiro Muraoka, Stephen L. Gillett, and Thomas W. Bell*

Molecular devices are currently of intense interest,^[1] but functional supramolecular devices are shorter term candidates for various applications including signal processing^[2] and separation.^[3] Control of the self-assembly^[4] of photonic, electronic, and ionic supramolecular, or “chemionic”,^[2a,5] devices remains an important challenge. We have devised a surprisingly simple, self-reversing, photoredox system that functions as a chemionic switch (Figure 1). This bi-stable

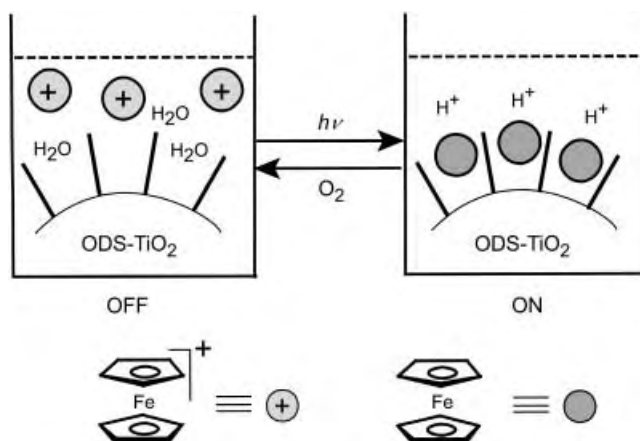


Figure 1. Illustration of the self-reversing chemionic switch. “ODS-TiO₂” describes TiO₂ particles surface-functionalized with octadecyltrichlorosilane (ODS). Holes generated by near-UV illumination oxidize the solvent to generate hydrogen ions, while photogenerated electrons reduce solution ferrocenium (Fc⁺) to ferrocene (Fc), which dissolves into the hydrophobic monolayer on the surface of the TiO₂. After storing the sample in the dark for several hours the ferrocene spontaneously reoxidizes by reaction with atmospheric O₂.

supramolecular device can be switched “on” by light and “off” by chemical oxidation. Light is an attractive agent for mediating self-assembly, and this has led us to base our chemionic switch on a photoredox reaction driven by an illuminated semiconductor.^[6] Electron–hole pairs formed near the surface of the semiconductor by the absorption of

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photons that have energy greater than its band-gap are highly active "reagents" for driving redox reactions.

Titanium dioxide (TiO₂) is a well-known semiconductor for photoinduced redox reactions,^[7] and is indefinitely stable when in contact with aqueous solutions. Its threshold band-gap energy lies in the near-UV (ca. 390 nm). Ferrocene (Fc) was employed as the redox-active species because of the well-known stability of the ferrocene/ferrocenium (Fc/Fc⁺) redox couple.^[8] The ferrocene moiety has also been incorporated into a vast number of derivatives, which suggests that more elaborate redox-active molecular systems based on ferrocene might be achieved. Ferrocenium (Fc⁺) salts are soluble in polar solvents, but reduction produces a nonpolar species (Fc). We formed a covalently bonded hydrophobic monolayer on the TiO₂ particles by treating them with octadecyltrichlorosilane (ODS) to produce "ODS-TiO₂".^[9]

Solutions of ferrocenium tetrafluoroborate in various solvents containing suspensions of ODS-TiO₂ particles were subjected to near-UV radiation (details in Supporting Information). In most cases, UV irradiation resulted in a striking visual change: the blue Fc⁺ solution became colorless, while the suspended, white TiO₂ particles turned yellowish beige. UV/Vis absorption spectroscopic analysis showed that decolorization of the blue Fc⁺ solution corresponded to a decrease in the intensity of the Fc⁺ absorption at 618 nm (Figure 2).

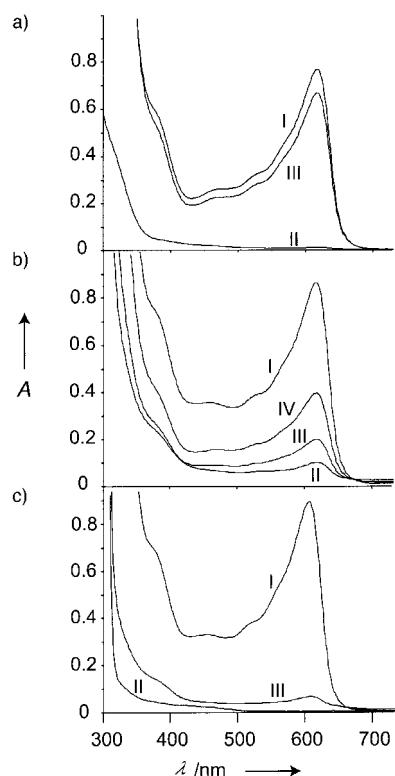


Figure 2. UV/Vis absorption spectra of supernatant solutions from suspensions of ODS-TiO₂ showing the redox-switching of ferrocene/ferrocenium (Fc/Fc⁺); initial [Fc⁺BF₄⁻] = 2 mM. a) 1M HCl solution in ethanol. I: Initial Fc⁺ solution; II: after UV-irradiation for 25 min; III: after stirring in the dark for 14 h. b) 0.1M HCl solution in ethanol. I: Initial Fc⁺ solution; II: after UV-irradiation for 60 min; III: after stirring in the dark for 40 h; IV: after stirring in the dark for 70 h. c) 0.01M HBF₄ solution in ethanol. I: Initial Fc⁺ solution; II: after UV-irradiation for 40 min; III: after stirring in the dark overnight (ca. 14 h).

After illumination, the mixtures were then stirred in the dark at room temperature for varying lengths of time. Over the course of 10–20 minutes, a 1M HCl solution containing the yellow-beige particles became pale blue, while the ODS-TiO₂ particles became white.

These observations are interpreted as follows: the holes generated by UV absorption react with water to yield hydrogen ions (e.g., Eq. (1)). Holes produced in TiO₂ are known to react quickly with the surrounding solvent.^[10] While in contrast, electrons are relatively slow to react and thus are available for reduction of solution species such as dyes^[11] and metal ions.^[12] In this case, the electrons reduce the Fc⁺ ions in solution to Fc [Eq. (2)], which is consistent with its standard reduction potential (versus a normal hydrogen electrode (NHE)) of 0.4 V.^[13] The nonpolar Fc was then extracted into the hydrophobic layer on the TiO₂, which accounts for the color change of the TiO₂ particles. In the dark, the Fc in the Fc/ODS/TiO₂ system was evidently reoxidized slowly to form Fc⁺ ions, which in turn redissolved into the supernatant, as is shown by UV/Vis spectroscopy (Figure 2a). The oxidation is presumably because of the presence of atmospheric O₂ and the strongly acidic conditions. The overall process is shown in Figure 1.



This mechanism is supported by three lines of evidence. First, Fc was extracted by dichloromethane from the yellowish beige ODS-TiO₂ particles and identified by ¹H NMR spectroscopy. ODS-TiO₂ particles that are yellowish beige because of ferrocene dissolved in the ODS layer will be termed "Fc-ODS-TiO₂". The ODS-TiO₂ particles became white after this extraction was carried out.

Second, when the suspension was saturated with O₂ prior to UV illumination, not all of the Fc⁺ ions were reduced (Figure 3a). In contrast, saturation with air or N₂ led to complete or near-complete photoreduction (Figure 3b, c). Reoxidation in the dark (described below) also proceeded more quickly with O₂ than with air (Figure 3b) but was almost completely inhibited under N₂.

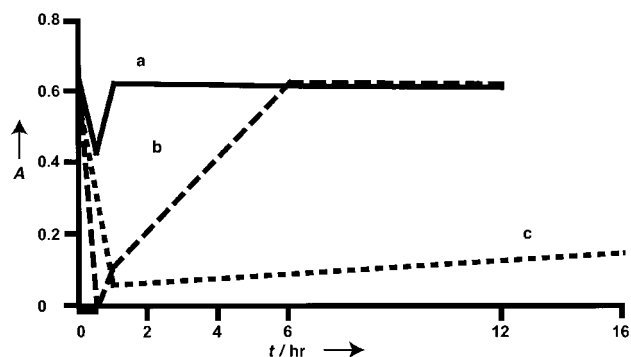


Figure 3. Change in the intensity of the ferrocenium absorption band (618 nm) upon UV illumination for 30 min (marked by bar along abscissa) followed by the bubbling of gases through the TiO₂ suspension in darkness (see text). a) —: O₂; b) ---: air; c) ----: N₂.

Third, a roughly quantitative decrease in the pH value of the solution was detected upon irradiation in a separate experiment. An aqueous solution of FcBF_4 (10^{-3} M) in which unfunctionalized P25 TiO_2 had been suspended was adjusted to pH 6.4 with NaOH and subjected to UV irradiation for 30 min. The pale-blue solution again turned colorless while the TiO_2 particles became yellowish beige. The pH value of the supernatant, after separation from the TiO_2 by centrifugation, was 3.7. Full reduction of Fc^+ should yield a final pH value of approximately 3, but competing reactions such as those shown in Equations (3) and (4) probably account for this discrepancy.^[14] Although oxidation of chloride ions may also occur^[15] in 1M HCl, similar results were found when experiments were conducted in 1M HBF_4 , so reduction does not depend on the nature of the anion.



As the experiment above shows, the same set of photo-reactions also proceeded quickly in mixtures of plain (that is, non-ODS-functionalized) TiO_2 in near-neutral aqueous solution. However, no reduction of Fc^+ species was observed in reaction mixtures of plain TiO_2 in 1M HCl. Presumably under such conditions, reoxidation of Fc to Fc^+ by atmospheric O_2 occurs so swiftly that no Fc accumulation takes place. Strongly acidic conditions are known to facilitate the oxidation of Fc by O_2 [Eq. (5)].^[16] Fc accumulation (indicated by the color change of the TiO_2 particles) is observed with ODS- TiO_2 because dissolution of Fc into the hydrophobic ODS layer hinders this reoxidation. Moreover, chloride adsorption at the plain TiO_2 surface may inhibit electron transfer,^[17] while the ODS layer will drastically alter the adsorption properties of the TiO_2 surface.



When acetonitrile was used as solvent, the photoreduction of Fc^+ by ODS- TiO_2 was very slow (16 h) as compared with combinations that included water as a cosolvent, in which reactions took less than 1 h. These results further suggest that water facilitates the reduction of Fc^+ on irradiated ODS- TiO_2 suspensions by acting as a hole scavenger [Eq. (1)]. Furthermore, the Fc in Fc-ODS- TiO_2 was not completely reoxidized to Fc^+ in 0.1M HCl (Figure 2b) and 0.01M HBF_4 (Figure 2c) solutions in ethanol even after more than two days in the dark. Presumably the pH value of these solutions is too high for re-oxidation to occur. Remarkably, and contrary to our initial expectations, photogenerated holes also do not oxidize Fc to Fc^+ on continued irradiation of Fc-ODS- TiO_2 . This is probably a result of the large difference in oxidation potential between Fc and the holes.

We have demonstrated a remarkably simple chemionic switch involving the reduction of ferrocenium (off) to ferrocene (on) and reoxidation to ferrocenium. Reduction is driven by near-UV light and the spontaneous reversion by atmospheric oxygen (Figure 1). This spontaneously reversing system is an attractive model for a light-driven “self-eluting” adsorbing surface for the particularly promising application of

solute extraction. Photoreduction of a redox-active solution species causes its precipitation, with elution occurring on reoxidation by atmospheric O_2 . A spontaneously reversing system for the extraction of Cu^{2+} ions has been demonstrated, but in contrast to our system, the photoreduction does not work in air.^[18] Although recovery of metals by semiconductor-mediated photoreduction has been the subject of much study,^[19] the difficulty of eluting the precipitated metal has so far prevented practical applications.

In addition, although metallocene–metallocenium couples have been widely used in determining photopotentials,^[20] our system also seems to be the first quantitative out-of-solution photoreduction of a metallocenium species. Finally, this chemionic switch further indicates how light can be utilized to drive molecular organization, in this case through photoreduction, which induces the insertion of the hydrophobic Fc into the ODS layer on the TiO_2 surface.

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Gram-Scale Synthesis of Suspension-Polymerized Styrene–Divinylbenzene-Based Resins Using an Oscillatory Baffled Reactor

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The use of spherical particulate cross-linked vinyl polymer beads or resins produced by free-radical suspension polymerization is now widespread in both synthetic and screening methodologies.^[1–3] Increasingly, however, they are also being exploited as the basis of heterogeneous reagents, catalysts, and scavengers to facilitate the synthesis of target molecules in solution.^[4,5] The work-horse species are styrene–divinylbenzene-based resins, which are synthesized on a large industrial scale (ca. 1000 kg) by using a batch polymerization procedure carried out in steel, stirred-tank reactors (STR).^[6] Laboratory-scale syntheses are performed similarly by using a glass reactor typically of 0.5–2.0 L in volume.^[7] A major technical challenge is to avoid particle aggregation, and this is usually achieved by dissolving a suitable suspension stabilizer in the aqueous phase, coupled with efficient stirring. In practice, stabilization conditions are usually optimized by experimentation, and no universal procedure is available that

is suitable for all polymerization mixtures. Since aggregation is associated primarily with surface phenomena, that is, particle–particle, particle–reactor, and particle–stirrer interactions, and since the surface/volume ratio increases as the scale of the process is reduced, aggregation becomes more problematic. Suspension polymerization to produce high-quality beads in good yield on a gram scale is therefore difficult to achieve. This situation is unfortunate because an attractive strategy for synthesizing complex functional resins is to use an appropriate functional (for example, styryl) monomer in a suspension polymerization to produce resin beads with a predetermined loading, cross-link ratio, and morphology. Since laboratory resin synthesis is problematic below the 10–20 g scale, and some optimization program is almost always necessary for each functional comonomer, there is a considerable deterrent to investing in complex monomer synthesis in view of the likely wastage that will ensue in implementing successful suspension polymerization.

We have now developed a robust suspension polymerization procedure by using a small oscillatory baffled reactor (OBR) capable of providing good yields of high-quality resin beads, of both gel-type and various macroporous morphologies, and operating on a gram scale. We have also shown that a functional styryl co-monomer can be employed in the system with no deterioration in the yield nor physical quality of the resin beads obtained.

The design and underlying principles of the OBR have been reported by Mackley and co-workers,^[8–10] and the appropriate choice of the dimensions of the reactor and the oscillating baffles, together with the frequency and amplitude of oscillation, leads in effect to each baffled cell acting as if it were a continuously stirred tank.^[9,10] Ni et al. have reported the results of remarkable flow-visualization experiments^[11] and computational fluid-dynamic simulations^[12] which confirm this picture. The successful application of OBRs in suspension polymerization by the same group^[13–16] prompted us to investigate the possibility of scaling down the reactor size to carry out gram-scale suspension polymerizations.

Accordingly, the glass OBR shown in Figures 1 and 2 was constructed. The reactor consists of a vertical glass tube 25 mm in diameter and 137 mm tall (ca. 70 mL volume) with a water jacket 53.5 mm in diameter and 158 mm tall. The top of the reactor is a conventional glass flange arrangement that allows the use of an N₂ supply and a condenser. The oscillatory motion in the reaction mixture is achieved by moving a set of stainless steel baffles up and down. The set consists of two or three orifice baffles (with orifice diameters of 11 mm) and an upper coupling plate into which is located the driving con-rod. The latter is 6.3 mm in diameter and 190 mm in length and is connected non-centrally to a rotating wheel which thus provides the oscillatory vertical motion. The con-rod moves within a long teflon bearing in the glass flange lid so as to maintain a vertical alignment of the baffles within the reactor. The baffles are made of 3-mm thick stainless-steel plate, and are connected to each other and the coupling plate by two 1.5-mm stainless-steel rods. The distance between the lower baffle and the reactor bottom is 6 mm (at full extension) and the oscillation amplitude is set at 21 mm. The free baffle area ratio (defined as the ratio of baffle orifice area to the tube

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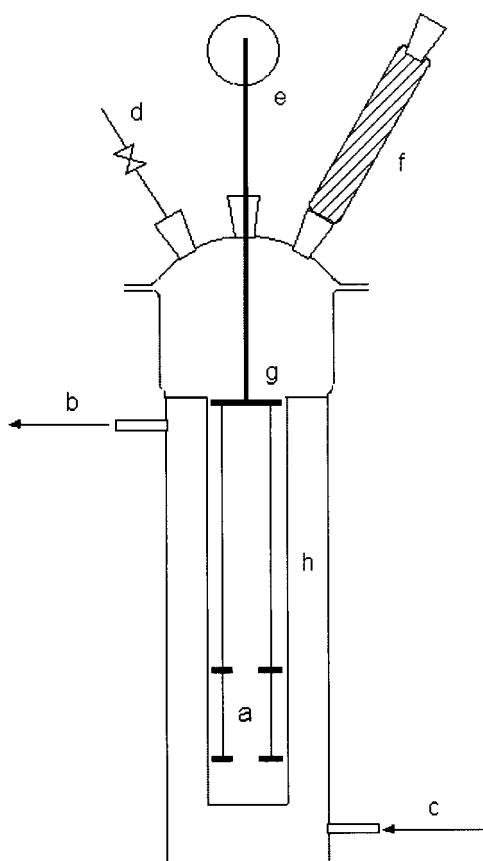


Figure 1. Schematic representation of small-scale oscillatory baffled reactor (OBR): a) orifice baffles; b) port to water bath; c) port from water bath; d) N₂ supply; e) off-centered drive coupled to con-rod; f) condenser; g) coupling plate; h) water jacket.

area) is fixed at 19 %, with a baffle spacing of 32 mm. Perhaps somewhat counter intuitively, optimum suspension conditions are provided by low frequency oscillation, typically about 2–8 Hz.

Data for the synthesis of representative macroporous resins are shown in Table 1. Earlier experiments utilized 40–65 mL of aqueous phase and 10 mL of organic phase (5 mL of comonomer and 5 mL of porogen) with the triple baffle set

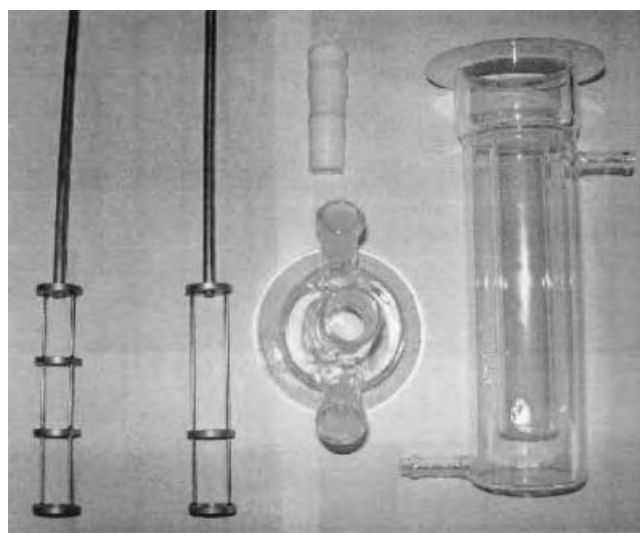


Figure 2. Actual OBR reactor, flange top, con-rod teflon guide, and 3 × orifice baffle arrangement/2 × orifice baffle arrangement.

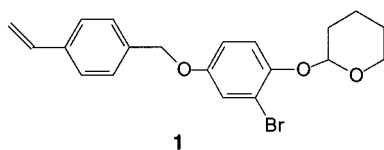
arrangement. The yields of high-quality spherical beads are generally good or very good, and this is consistent with the results obtained using a laboratory-scale stirred-tank-type reactor,^[7] where it is normally found that high-quality macroporous resins are easier to produce than gel types. Oscillation frequencies in the range 2.5–6 Hz were found to be suitable with tylose MH1000 (methyl cellulose) as the suspension stabilizer. Excessive foaming and particle aggregation occurred above 6.5 Hz, and likewise particle aggregation started to occur at 2.5 Hz. Particle diameters fall in a similar range to those found using a laboratory-scale stirred-tank reactor^[7] and the breadth of the distribution also seems similar. Additional fractionation by sieving would be necessary to achieve narrower distributions than those indicated in Table 1. The nature of the stabilizer did not prove to be too crucial, with good quality products also being obtained using poly(vinyl alcohol) (PVA, 88 % hydrolyzed, M_w = ca. 125 000) or xanthan gum (kelzan) as the primary stabilizer. Both toluene and 2-ethylhexan-1-ol were employed as porogens. The former interacts quite well (relatively thermodynamically “good”

Table 1. Macroporous styrene/DVB based beads prepared by suspension polymerization in a small oscillatory baffled reactor (OBR).^[a]

Resin	Co-monomer composition			Porogen [mL] ^[d]	Aqueous phase (mL, stabilizer)	Set of baffles	Oscillation frequency [Hz]	Reaction time [h]	Reaction temper- ature [°C]	Yield [%] ^[e]	Bead characteristics	
	[mL, vol %]										diameter [μm]	analysis [%] found/calcd
	styrene	DVB ^[b]	CMS ^[c]									
M1	2.00, 40	3.00, 60	–	T (5)	40, 0.44 % tylose MH1000	3	6	8	70	95	106–710 ^[f]	–
M2	2.00, 40	3.00, 60	–	T (5)	65, 0.44 % tylose MH1000	3	6	7	80	84	–	–
M3	2.00, 40	3.00, 60	–	T (5)	40, 0.44 % tylose MH1000	3	5	8	70	96	106–710 ^[f]	–
M4	2.00, 40	3.00, 60	–	T (5)	40, 0.44 % tylose MH1000	3	4	8	70	89	106–710 ^[f]	–
M5	2.00, 40	3.00, 60	–	T (5)	40, 0.44 % tylose MH1000	3	3	8	70	92	212–710 ^[f]	–
M6	2.00, 40	3.00, 60	–	T (5)	40, 0.44 % tylose MH1000	3	2.5	8	70	91	300–710 ^[f,g]	–
M7	–	1.00, 100	–	T (1)	25, 0.75 % PVA/3.3 % NaCl ^[i]	2	6	5	70	85	99–147 ^[h]	–
M8	4.80, 87	0.70, 13	–	EH (4.5)	40, 0.44 % tylose MH1000	3	3	8	70	71	106–710 ^[f]	–
M9	0.88, 88	0.20, 12	–	EH (1)	25, 0.75 % PVA/3.3 % NaCl ^[i]	2	6	5	70	71	119–257 ^[h]	–
M10	3.65, 73	0.60, 12	0.75, 15	EH (5)	65, 0.44 % tylose MH1000	3	3	7	80	75	–	Cl, 3.8/4.1
M11	3.65, 73	0.60, 12	0.75, 15	EH (5)	65, 0.75 % PVA/3.3 % NaCl	3	3.5	7	80	67	62–151 ^[h]	Cl, 3.9/4.1
M12	4.55, 77 ^[k]	0.76, 10 ^[k]	0.81, 13 ^[k]	EH (5)	65, 0.44 % tylose, MH1000	3	3.5	7	80	78	85–191 ^[h]	Br, 2.4/2.7

[a] 1 wt % azobisisobutyronitrile (AIBN), relative to monomer. [b] DVB, 80 % grade. [c] CMS = chloromethylstyrene (mixed isomers). [d] T = toluene; EH = 2-ethylhexan-1-ol. [e] Yield of isolated high-quality spherical beads. [f] By sieving into fractions. [g] Larger fractions aggregated. [h] Optical microscopic observation. [i] functional comonomer, (1), replacing CMS. [j] Additional 5 mL added during reaction. PVA = poly(vinyl alcohol). [k] g, wt %.

solvent) with polystyrene-based resins and is known to generate high surface area macroporous resins when used with relatively large levels of divinylbenzene.^[17] In this instance resin M7 (Figure 3a) has a dry-state surface area of 659 m² g⁻¹ as determined from a BET analysis of N₂ sorption data (Micromeritics ASAP 2000), and so the morphology of this species is totally as anticipated. 2-Ethylhexan-1-ol is, in contrast, a relatively thermodynamically “poor” solvent and is known to generate macroporous resins with modest surface area when used with rather low levels of divinylbenzene.^[17] Here resin M9 (Figure 3b) has a dry-state surface area of 64 m² g⁻¹, and so again this is consistent with similar resins prepared in a stirred-tank reactor. Replacement of part of the styrene feed with chloromethylstyrene (M10 and M11; Figure 3c) or with functional co-monomer **1**^[18] (M12; Fig-



ure 3d) does not disturb the suspension system and good yields of high-quality resins are obtained in each case. Elemental microanalysis of the resins confirmed the incorporation of these monomer residues at a level close to the feed composition and we anticipate that the distribution and accessibility of functional groups will be similar to that in analogous resins prepared in a stirred-tank reactor. Finally it is important to note that high quality macroporous beads can be obtained in good yield on a one-gram scale (M7 and M9) by reducing the volume of the aqueous phase to 25 mL and employing the double baffle set arrangement.

Data for the synthesis of representative gel-type resins are shown in Table 2. In general, high-quality lightly cross-linked spherical gel-type resins are more difficult to synthesize in good yield than are macroporous species. This is because gel-type species show a higher tendency to aggregate and the suspension conditions required to avoid this are somewhat more rigorous. Our initial attempts to produce 2% cross-linked styrene/DVB resins in our small OBR are exemplified by entries G1 and G2 in Table 2 using xanthan gum as a primary stabilizer. Though beads were obtained (with this and

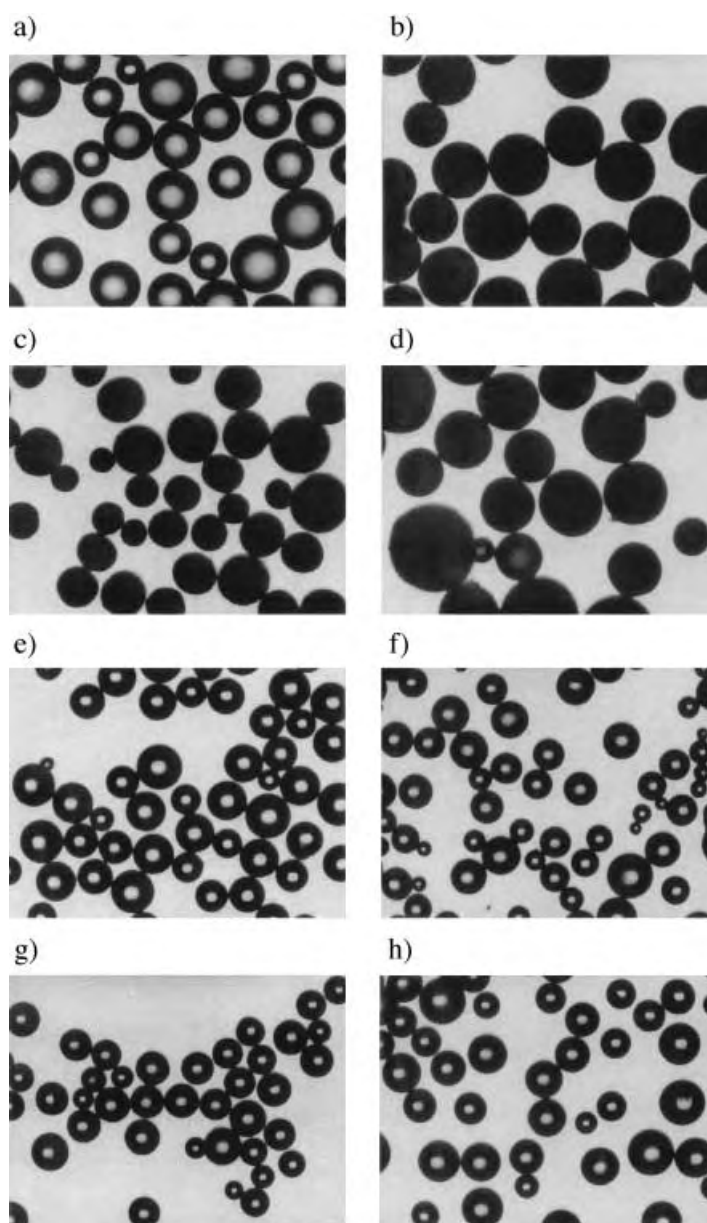


Figure 3. Optical micrographs: a) macroporous resin M7; b) macroporous resin M9; c) macroporous resin M11; d) macroporous functional resin M12; e) gel-type resin G4; f) gel-type resin G7; g) gel-type resin G8; h) gel-type functional resin G9. (Typical diameters ca. 150 μm.)

Table 2. Gel-type styrene/DVB-based beads prepared by suspension polymerization in small oscillatory baffled reactor (OBR).^[a]

Resin	Co-monomer composition [mL, vol %]			Aqueous phase [mL, stabilizer]	Set of baffles	Oscillation frequency [Hz]	Reaction time [h]	Reaction temperature [°C]	Yield [%] ^[c]	Bead characteristics	
	styrene	DVB ^[b]	functional monomer							diameter [μm] ^[d]	analysis found/calcd
G1	4.92, 98	0.08, 2	–	65, xanthan gum ^[e]	3	8	7	80	36	62–136	
G2	3.40, 68	0.08, 2	1.52, 30 ^[f]	65, xanthan gum ^[e]	3	8	7	80	44	–	Cl, 9.9/7.9
G3	1.90, 95	0.10, 5	–	25, ^[i] 0.75 % PVA/3.3 % NaCl	2	6	5	70	67	–	–
G4	1.90, 95	0.10, 5	–	25, ^[i] 0.75 % PVA/3.3 % NaCl	2	6	5	70	77	129–248	–
G5	1.90, 95	0.10, 5	–	25, ^[i] xanthan gum ^[e]	2 ^[g]	6	5	70	53	59–110	–
G6	1.90, 95	0.10, 5	–	25, ^[i] 0.75 % PVA/3.3 % NaCl	2	6	5	70	60	–	–
G7	1.96, 98	0.04, 2	–	25, ^[i] 0.75 % PVA/3.3 % NaCl	2	6	5	70	70	83–248	–
G8	1.98, 99	0.02, 1	–	25, ^[i] 0.75 % PVA/3.3 % NaCl	2	6	5	70	54	101–202	–
G9	1.17, 59 ^[h]	0.05, 2 ^[i]	0.78, 40 ^[h,j]	25, ^[i] 0.75 % PVA/3.3 % NaCl	2	6	5	70	74	119–257	Br, 8.8/8.0

[a] 0.7 wt % AIBN. [b] 80% grade DVB; figure quoted refers to actual DVB isomers. [c] Yield of isolated high-quality spherical beads. [d] Optical microscopic observation. [e] 1.6 wt % boric acid, 0.01 wt % cellosize, 0.08 wt % xanthan gum, 16 wt % NaCl. [f] Chloromethylstyrene, mixed isomers. [g] Oscillation frequency, 8 Hz. [h] Functional co-monomer (**1**). [i] Additional 5 mL added during reaction; PVA = poly(vinyl alcohol). [j] g, wt %.

other stabilizers), the yield of the isolated high-quality spherical resin was rather low, too low to allow economic adaptation for use with complex functional co-monomers. However, it was realized that a major contribution to the seeding of aggregation was irregular agitation at the liquid–gas interface, especially when this interface was located too close to one of the oscillating baffles. Accordingly, therefore the two baffle set arrangement was designed, built, and commissioned and the volume of the total liquid phase adjusted to be sufficiently remote from the upper baffle to allow for efficient suspension within the bulk of the liquid and yet to avoid induction of particle aggregation at the surface. Since evaporative losses were also significant with an aqueous phase volume of only 25 mL, the level of liquid was maintained during the reaction by gradual addition of more aqueous phase (5 mL). These simple design and operational changes led to a significant improvement in the yields of the isolated high quality beads, despite the polymerization being performed with only approximately 2 g of comonomers (for example, G4, G7, and G8, Figure 3e–g). The most robust stabilizer used was poly(vinyl alcohol) (PVA, 88% hydrolyzed, M_{wt} = ca. 125 000 Aldrich) at 0.75 wt %, with 3.3 wt % of NaCl in the aqueous phase, and with a baffle oscillation frequency of 6 Hz. Xanthan gum was also a useful stabilizer (G5) but a higher oscillation frequency, 8 Hz, was required because of the larger viscosity of this aqueous solution. By using the optimized procedure 2% cross-linked gel-type resin G9 was prepared using functional co-monomer **1**, with a good yield of isolated quality beads of about 1.5 g (ca. 75%; Figure 3h). Resins G1–G9 are all lightly cross-linked ($DVB \leq 5$ vol %) and have been prepared in the absence of any porogen. Each would therefore be expected to have a gel-type morphology and a correspondingly very low dry-state surface area. This was confirmed for resin G8 whose dry-state surface area is less than $5 \text{ m}^2 \text{ g}^{-1}$. The volume swelling of G4, G7, and G8 with cross-link ratios of 5, 2, and 1 %, respectively, in toluene are 3.05, 4.52, and 7.59 mL g^{-1} , which is again consistent with the gel-type morphology of these species. Interestingly the corresponding swelling figure for the 2% cross-linked functional resin G9 is 3.37 mL g^{-1} , which suggests that the presence of the residues from the functional co-monomer **1** reduces somewhat the ability of toluene to solvate this resin.

In summary, we have developed a robust small-scale experimental procedure for synthesizing both macroporous and gel-type high-quality spherical particulate styrene–divinylbenzene resins in good yield. The methodology is tolerant to the use of functional co-monomers, and now offers the prospect of exploiting complex, structurally well-characterized monomers in suspension polymerization to produce resins for use in high-throughput discovery programs.

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An Azulene Dimer as a Near-Infrared Quencher**

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Highly sensitive, efficient, and quenched fluorochromes have become essential for acquiring genomic and proteomic data from biological samples.^[1] Fluorescent compounds also have many other useful applications in medicine, biotechnology, and biological science.^[2,3] Specifically, fluorochromes attached to various ligands have been used for detecting nucleic acid hybridization (molecular beacons),^[4,5] in drug discovery,^[6] for sensing molecular interactions,^[7,8] and for deciphering biological pathways.^[9] Typically, molecular DNA beacons^[4,5] and enzyme-sensing probes^[10] primarily rely on the fluorescence resonance energy transfer (FRET) between

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a fluorochrome and a quencher. The vast majority of sensors fluoresce in the visible light range (400–650 nm) and commonly consist of organic fluorochrome or semiconductor materials.^[11] The most commonly used quencher to pair with those fluorochromes is 4-(4'-dimethylaminobenzeneazo)benzoic acid (DABCYL), which has a broad absorption spectrum between 360 and 560 nm.

More recently fluorochromes fluorescing in the near-infrared (NIR) range have been developed to either 1) extend the number of color probes available for simultaneous sensing or encoding,^[12,13] or 2) to image molecular interactions in vivo.^[14–21] Most reported near-infrared fluorochromes contain bi- or tricyanocyanine rings and exhibit fluorescence between 650 and 900 nm.^[20–22] One particular challenge, however, is the development of efficient, biocompatible, and conjugatable quenchers, analogous to DABCYL but with absorptions in the near-infrared range. We describe here the synthesis and properties of a generic type of compound that efficiently quenches NIR fluorescence. We furthermore show how derivatives of this model compound can be used for protease sensing in the near-infrared spectrum.

Based on prior observations that certain azulene precursors of antibacterial and anti-inflammatory agents^[23] have strong absorption in the 500 to 600-nm range,^[24] we hypothesized that it should be feasible to extend the conjugated π system to a linked bicyclic system resulting in higher wavelength absorption. We furthermore postulated that such compounds should be stable, biocompatible, and suitable for either solid-phase or aqueous chemistry, and also have a single attachment moiety for bioconjugation. Another consideration for constructing a bis-azulenyl compound was that the chemical reactivity of azulene has been studied extensively.^[25–29] Absorbance of derivatives can be fine-tuned by replacing the substituents on the azulene rings.^[24]

The synthesis of a nonfluorogenic near-infrared quencher (NIRQ) started from 1,4-dimethyl-7-isopropylazulene (**1**, Scheme 1). First a carboxylic acid handle was attached to the cycloheptatriene ring prior to condensation. The methyl group at the 4-position was deprotonated by the method developed by Schrott et al.^[30] The nucleophilic moiety was generated by *n*BuLi at -40°C in the presence of diisopropylamine. The subsequent in situ nucleophilic substitution was

carried out by reaction with bromoacetic acid to make the carboxylic acid intermediate **2**. Two moles of **2** were then condensed with one mole of squaric acid by refluxing in the presence of BuOH. The dominant product of this reaction was the desired monosubstituted dimer NIRQ. Under the optimized conditions a disubstituted by-product was formed in less than 4% yield and was removed conveniently by flash column chromatography.

As expected, upon dimerization we observed a significant shift in absorption from 550 nm for **2** to a broad peak around 700–800 nm for NIRQ (Figure 1). The absorption maximum changed little with different solvents; however, the extinction coefficient was solvent dependent (Table 1).

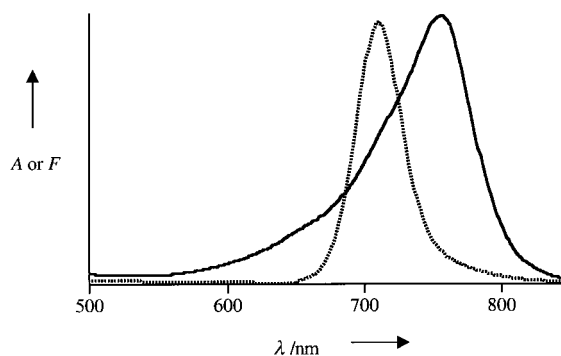


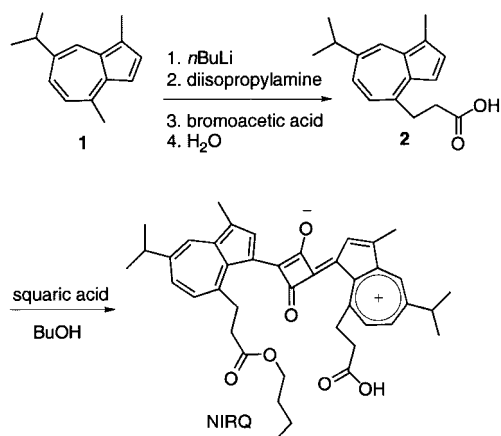
Figure 1. Absorption spectrum of quencher NIRQ (solid line) and emission spectrum of fluorochrome Alexa-680 (dashed line).

Table 1. Absorption maximum and extinction coefficient of NIRQ.

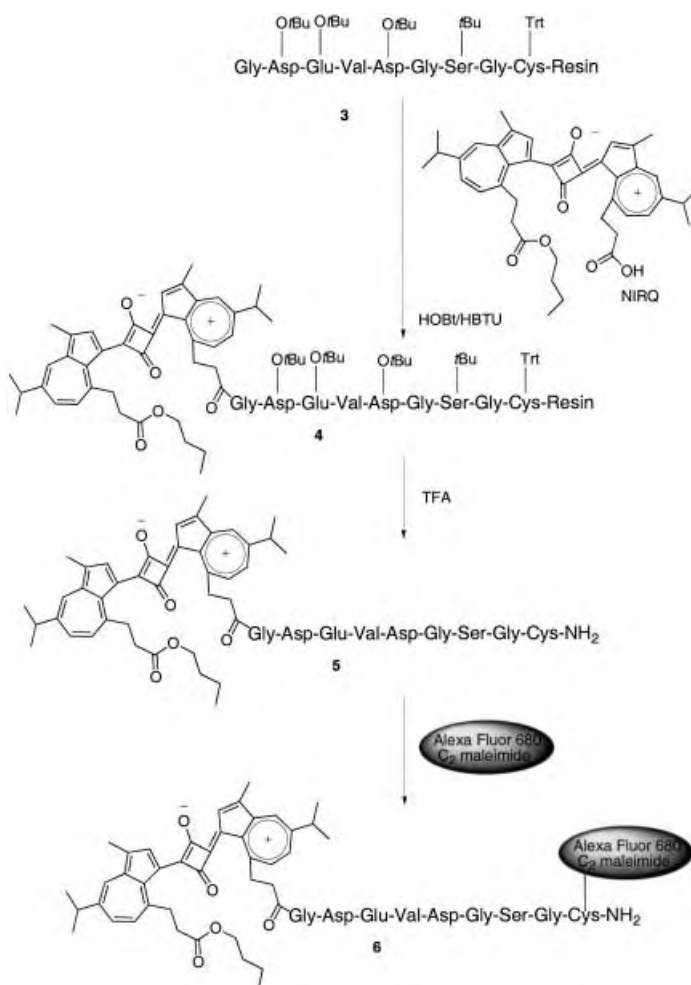
Solvent	λ_{max} [nm]	ϵ [$\text{M}^{-1}\text{cm}^{-1}$]
acetonitrile	760	69 000
MeOH	757	82 000
DMF	768	50 000
DMSO	773	41 000

In order to test the utility of the NIR quencher we designed an activatable NIR-fluorescent caspase-3 substrate. NIRQ activated with HBTU/HOBt was directly anchored to the N-terminus of a caspase-3 cleavable peptide substrate *GDEVDGSGC* (cleavage site in italics, Scheme 2). The labeled peptide was then cleaved from the solid support and purified by reversed-phase HPLC. NIRQ retained its optical property despite the harsh acid treatment during peptide cleavage and deprotection. Thereafter, a near-infrared fluorochrome, Alexa-680 C_2 maleimide ($\lambda_{\text{ex}} = 679$ nm and $\lambda_{\text{em}} = 702$ nm), was reacted with the cysteine residue of the opposite end of the peptide chain. Alexa-680 was chosen as the fluorescence donor because its emission spectrum overlaps with the absorption spectrum of NIRQ (Figure 1). Two other probes containing Alexa-680, either without the quencher (**7**) or with DABCYL (**8**), were also prepared as controls (Figure 2a).

The HPLC-purified NIRQ probes were tested against caspase-3 with and without an inhibitor of the enzyme in pH 7.2 buffer (20 mM PIPES, 100 mM NaCl, 10 mM DTT, 1 mM EDTA, 0.1% CHAPS, 10% sucrose).^[31] Within 180 min the



Scheme 1. Preparation of the azulene-based NIR quencher NIRQ.



Scheme 2. Synthesis of NIR-fluorescent caspase-3 substrates. HBTU = *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, HOBt = 1-hydroxy-1*H*-benzotriazole, TFA = trifluoroacetic acid.

fluorescence signal of **6** had increased about fourfold while no activation was observed when the caspase-3 specific inhibitor was present (Figure 2b). Since DABCYL is not an ideal quencher in this range of wavelengths, the fluorescence signal of probe **8** was only increased by 2.4-fold (Figure 2c, Experiment E). As expected, the fluorescence signal of both negative controls, probe **7** with enzyme (Experiment D) and probe **6** without enzyme (Experiment A), were unchanged. The result indicates that these probes are stable in DTT-containing buffer. An initial study relying on a Stern–Volmer plot suggests that fluorescence quenching is caused by resonance energy transfer.^[2]

Overall, our results show that the bis-azulenyl compound developed is an extremely stable and efficient generic NIR-quenching molecule. Its maximum absorption is in the range around 700 to 800 nm, the best window for in vivo imaging.^[32] Transformation of the carboxylic acid group into a hydroxysuccinimide ester allows ready conjugation to peptides, oligonucleotides, and potentially other target ligands. The material can be synthesized in 53 % yield, and synthesis can be scaled up easily. Additional modifications to side chains and unsaturated spacers are conceivable to further fine-tune absorption maxima and/or shift them further into the near-

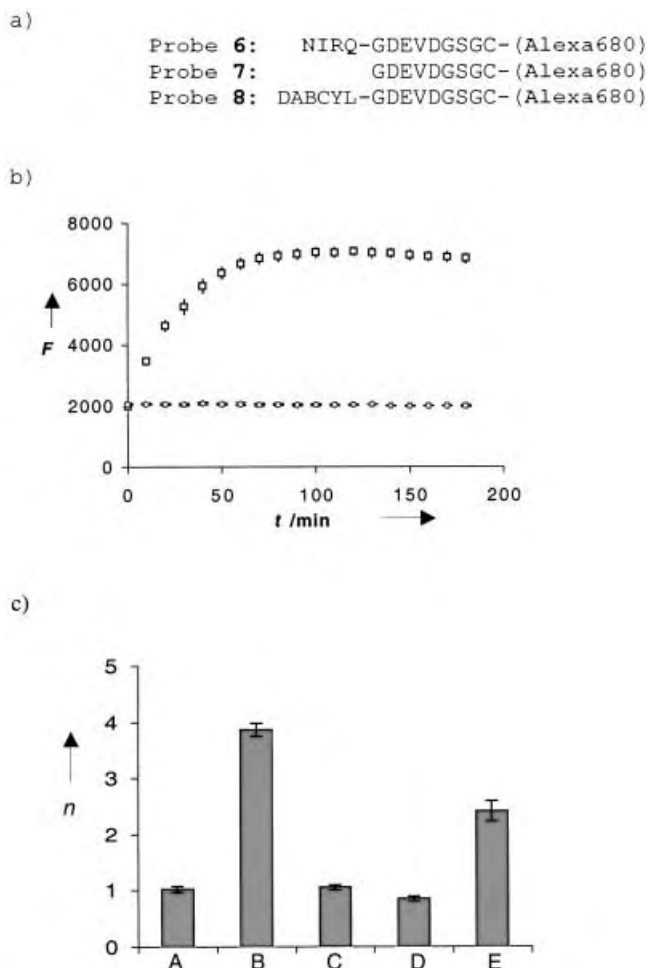


Figure 2. Activation of various NIR probes with caspase-3. a) List of tested probes. b) Fluorescence observed on activation of probe **6** with (square) and without (circle) specific caspase-3 inhibitor. c) Changes (*n*-fold) in the intensity of the NIR fluorescence signal at 180 min for a series of experiments: A) **6**, B) **6** + caspase-3, C) **6** + caspase-3 + inhibitor, D) **7** + caspase-3, E) **8** + caspase-3.

infrared region. While the current compound was designed to be lipophilic (primarily for solid-phase coupling), additional modification of side chains (e.g. by sulfonation, pegylation, hydroxylation) could render the material hydrophilic. With the extension of fluorochromes into the near-infrared spectrum for broader coverage and in vivo applications this quencher should find widespread use in imaging molecular targets in vivo and in multiwavelength sensing.

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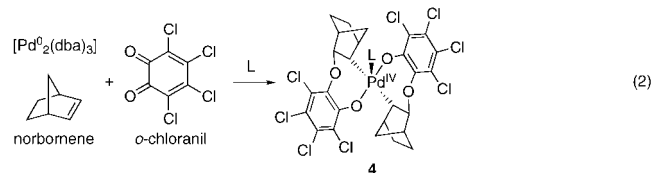
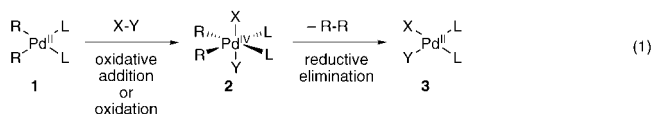
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Single-Step Assembly of a C₂-Symmetrical Palladium(IV) Spirocyclic Complex

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Palladium is an extensively studied transition element in organometallic chemistry as a versatile promoter of various stoichiometric and catalytic organic transformations.^[1] Although palladium generally prefers low oxidation states 0, +1, and +2, the involvement of organopalladium(IV) intermediates have been claimed in important catalytic processes.^[2,3] In contrast to platinum, which has an extensive organometallic chemistry in the +4 oxidation state,^[4] organopalladium(IV) complexes had hardly been studied until the first unequivocal trialkylpalladium(IV) complex, [PdMe₃(bpy)], was isolated and characterized by X-ray analysis.^[5] Since this report, various polyalkylpalladium(IV) complexes **2** were synthesized from dialkylpalladium(II) precursors **1** by oxidative addition of alkylhalides, or oxidation by H₂O, halogens, dichalcogenides, etc., and most of them are thermally labile with the reductive elimination of an alkane readily occurring at or below room temperature to produce the corresponding palladium(II) fragments **3** [Eq. (1)].^[6] In striking contrast, we found that the reaction of a readily available palladium(0) complex, [Pd₂(dba)₃ (dba = *trans,trans*-dibenzilideneacetone)], with tetrachloro-1,2-benzoquinone (*o*-chloranil) and bicyclo[2.2.1]hept-2-ene (norbornene) directly produced a novel spirocyclic palladium(IV) dialkyl complex **4** in high yield [Eq. (2)].



Quinones have received considerable attention in coordination chemistry as redox-active, strongly electron-accepting ligands. Various transition metals have been shown to coordinate to *p*-quinones at their localized ring olefinic bonds.^[7] On the other hand, *o*-quinones usually form complexes containing semiquinone or hydroquinone chelate ligands with the concomitant oxidation of transition-metal centers.^[8] This was the case for palladium. The reaction of the Pd⁰-phosphane complex [Pd(PPh₃)₄] with *o*-chloranil has already been reported to furnish a palladium(II) catecholate complex [(Ph₃P)₂Pd(O₂C₆Cl₄)].^[9] Remarkably, the treatment

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of the Pd⁰ complex [Pd₂(dba)₃] with *o*-chloranil (5 equiv) and norbornene (5 equiv) at ambient temperature in acetone followed by addition of diethyl ether produced the palladium(IV) spirocyclic complex **4a** (L = Et₂O) in 81 % yield [Eq. (2)]. The absence of the intact *o*-quinone in **4a** was confirmed by its IR spectrum which showed no C=O absorption. The ¹H NMR (300 MHz, CDCl₃) spectrum showed signals at δ = 1.0–5.0 ppm which were assigned to norbornyl ligands and coordinated diethyl ether. The diethyl ether complex **4a** is readily soluble in acetone, THF, and CHCl₃, but it slowly decomposed to deposit black materials in CHCl₃. Complex **4a** was quantitatively converted into a thf complex **4b** (L = thf) upon treatment with THF at ambient temperature. To obtain further structural information we characterized **4b** since it is stable in degassed THF at room temperature. The ¹³C NMR (125 MHz, [D₈]THF) spectrum of **4b** showed four signals (δ = 117.84, 122.49, 124.87, and 128.20 ppm) which were assigned to the aromatic C–Cl carbon atoms, and two lower-field signals (δ = 144.76 and 157.24 ppm) were assigned to the aromatic C–O carbon atoms. These observations are indicative of an unsymmetrical tetrachlorocatecholate moiety being present in **4b**. In addition, seven signals observed at higher field (δ = 24–100 ppm) are assigned to norbornane rings in an unsymmetrical environment. The structure of **4b** was unambiguously confirmed by a single-crystal X-ray diffraction study.^[10] As shown in Figure 1, **4b** is a dialkylpalladium(IV) complex with a trigonal bipyramidal geometry. Two molecules each of *o*-chloranil and norbornene were coupled on the palladium center to form a pair of unprecedented seven-membered chelete rings. Their O- and C-termini occupy the axial and equatorial positions, respectively. The third equatorial position accommodates a thf molecule. The Pd–O1 and Pd–O3 bonds of 2.0004(13) and 2.0012(13) Å, respectively, are slightly shorter than those in the known Pd^{II} tetrachlorocatecholate complex (2.028(5) and 2.039(5) Å), which are elongated by the *trans* influence of PPh₃ ligands.^[11] The four

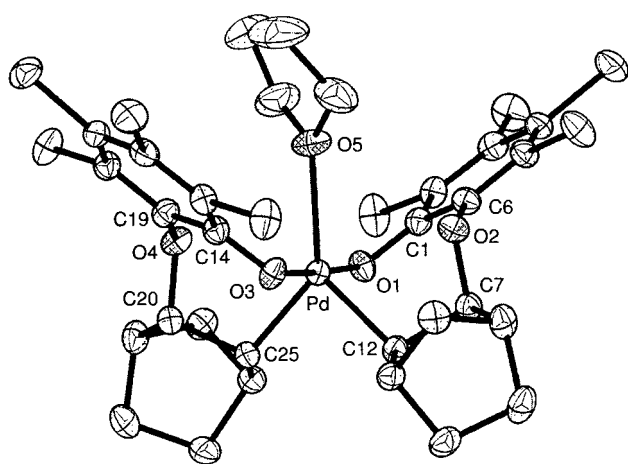


Figure 1. ORTEP diagram of **4b**. All hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Pd–O1 2.0012(13), Pd–O3 2.0004(13), Pd–C12 2.0361(17), Pd–C25 2.0405(17), Pd–O5 2.3751, O1–C1 1.321(2), O3–C14 1.320(2), O2–C6 1.377(2), O4–C19 1.378(2), O2–C7 1.463(2), O4–C20 1.462(2); O1–Pd–O3 177.02(5), C12–Pd–C25 88.98(7), O5–Pd–C12 136.36(6), O5–Pd–C25 134.67(6).

C–O bonds in the hydroquinone moieties at 1.320–1.378 Å are close to that expected for a C_{sp²}–O single bond (1.34 Å).^[12] The C_{sp²}–C_{sp²} bonds within the benzene rings (1.390(3)–1.407(2) Å) show no evidence of residual benzoquinone character. The Pd–C bonds of 2.0361(17) and 2.0405(17) Å are similar to those of Pd^{IV}–Me bonds in the precedent examples.^[6] All isolated examples of polyalkylpalladium(IV) complexes to date are confined to octahedral complexes containing bidentate or tripodal donor supporting ligands which prevent the formation of the five-coordinate intermediates that are required for facile reductive elimination of an alkane.^[6] On the other hand, the trigonal bipyramidal complex **4b** is stable in the solid state without any bidentate or tripodal donor spectator ligands. The complete decomposition of **4b** in THF requires several days at ambient temperature. This observation is in contrast to dialkylpalladium(IV) complexes possessing Pd–O₂CAr bonds which are unstable at or below 20 °C even though they have tris(pyrazol-1-yl)borate or 2,2'-bipyridyl donor ligands.^[13] The remarkable stability of **4** can probably be ascribed to the formation of a chelete ring connecting the labile tetrachlorocatecholate and norbornyl ligands.

It is noteworthy that the palladaspirocyclic framework was possibly assembled through a tandem oxidative cyclization between *o*-chloranil and norbornene on the palladium(0) center. The formation of both the Pd–C and O–C bonds selectively occurred at the less hindered *exo* face of norbornene. The combination of *o*-chloranil and norbornene is quite essential for this process: Employing 3,5-di-*tert*-butylbenzoquinone or 9,10-phenanthrenequinone in place of *o*-chloranil failed to form the corresponding analogues. No product was obtained when less-strained cyclopentene was used as an olefin component. These results show that both the strong oxidizing ability of *o*-chloranil and the ring strain of norbornene play critical roles in the oxidative cyclization.

Figure 2a shows the ORTEP diagram of **4b** projected down the O5–Pd axis. Interestingly, the palladaspirocyclic framework in **4b** has C₂ symmetry and this is illustrated by a schematic representation in Figure 2b. The sterically demanding tetrachlorophenyl rings occupy gray quadrants and, as a result, the thf molecule occupies the vacant site in such a way that it is placed along less-hindered colorless quadrants. Such a coordination mode is frequently involved in the enantioface differentiation mechanisms of C₂-chiral asymmetric catalysts.^[14] The palladaspirocyclic fragment is a potential C₂-symmetrical Lewis acid acceptor bearing the electron-deficient palladium(IV) center. A diethyl ether ligand L in **4** can be replaced by other Lewis basic molecules. In fact, the diethyl ether complex **4a** was dissolved in dry degassed pyridine at ambient temperature to form a new *cis*-bispyridine complex **5**. Figure 3 shows the ORTEP diagram of **5**.^[10] To our surprise, **5** has a distorted octahedral geometry with an O1–Pd–O2 angle of 165.32(5)°. Two pyridine molecules are incorporated in the equatorial positions. It is interesting to note that the two tetrachlorophenyl rings are turned away from the coordination sites in the same direction as the norbornane rings. Therefore, the palladaspirocyclic framework has a considerable flexibility to adjust the coordination space to the nature of the coordinated molecules. The coordination number seems to

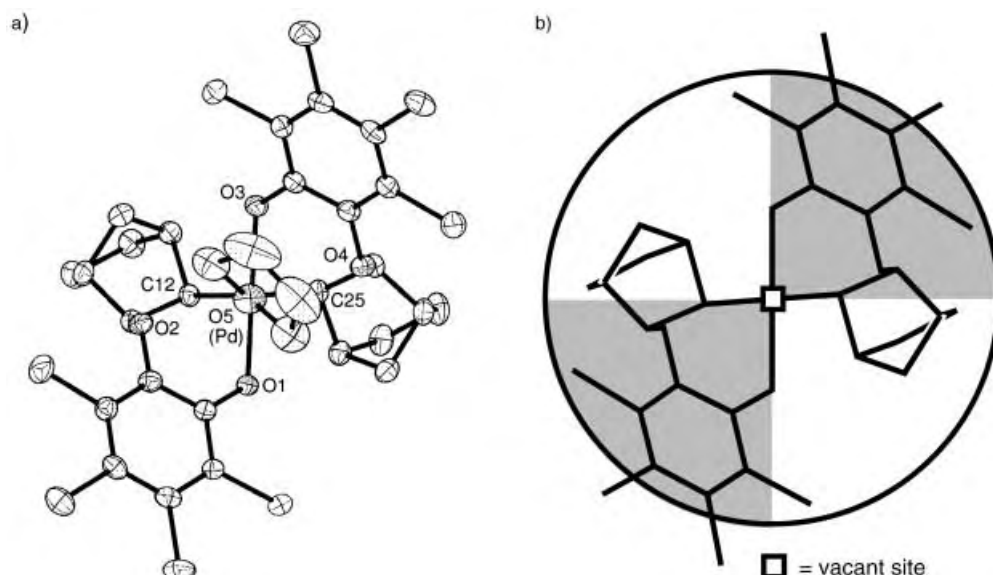


Figure 2. a) ORTEP diagram of **4b** projected down the O5–Pd axis and b) schematic representation of palladSpirocyclic framework.

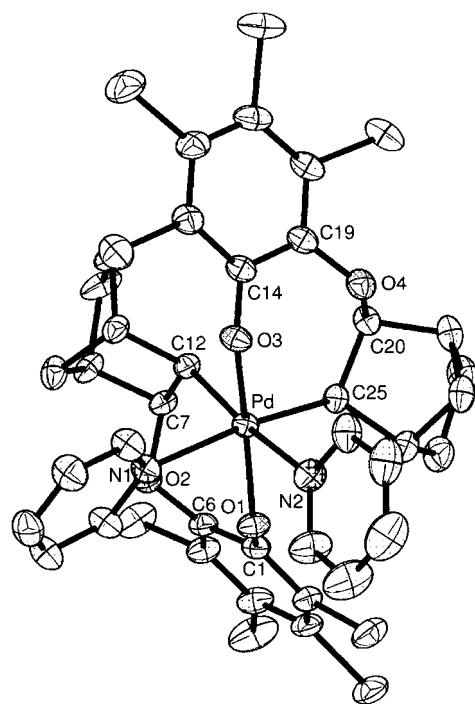


Figure 3. ORTEP diagram of **5**. All hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Pd–O1 2.0248(11), Pd–O3 2.0301(11), Pd–C12 2.0753(15), Pd–C25 2.0741(15), Pd–N1 2.2480(14), Pd–N2 2.2391(15), O1–C1 1.3133(19), O3–C14 1.312(2), O2–C6 1.3630(18), O4–C19 1.356(2), O2–C7 1.4475(18), O4–C20 1.453(2); O1–Pd–O3 165.32(5), C12–Pd–C25 84.51(6), N1–Pd–N2 85.46(5), N1–Pd–C12 95.54(6), N2–Pd–C25 95.59(6).

vary depending on the electron-donating ability of the Lewis base molecules; that is, it increased from five for the weaker thf donor to six for the stronger pyridine donor. In accordance with this observation, the Pd–C12 and Pd–C25 bonds in **5** are longer than those in **4b** by 0.0392 and 0.0336 Å, respectively, as a result of the *trans* influences of the stronger electron-donor pyridine.

In conclusion, we have identified an unprecedented single-step assembly of dialkylpalladium(IV) complex having a novel palladSpirocyclic framework from commercially available $[\text{Pd}_2(\text{dba})_3]$, *o*-chloranil, and norbornene. The palladSpirocyclic fragment has C_2 symmetry and functions as a Lewis acid acceptor. The ligand exchange from thf to pyridine caused a geometrical transformation to afford a bispyridine complex with a distorted octahedral geometry. The elucidation of the mechanism for the palladSpirocyclic formation and its application to Lewis acid catalysis are now under way.

Experimental Section

4a: A solution of $[\text{Pd}_2(\text{dba})_3]\cdot\text{CHCl}_3$ (155.3 mg, 0.150 mmol), *o*-chloranil (245.9 mg, 0.750 mmol), and norbornene (94.2 mg, 0.750 mmol) in dry degassed acetone (10 mL) was stirred at room temperature for 30 min. The initial purple suspension turned into a red homogeneous solution within 10 min. The resultant solution was filtered through a glass frit and the filtrate was concentrated to 3 mL, diluted with dry degassed diethyl ether (50 mL), and cooled overnight at about -15°C . The orange crystals obtained were collected on a glass frit and dried under vacuum at room temperature for 48 h. The yield was 209.9 mg (81 %): m.p. 117.3–118.3°C (decomp); ^1H NMR (300 MHz, CDCl_3): δ = 1.00–1.15 (m, 1H), 1.21 (t, J = 7.0 Hz, 3H), 1.35–1.46 (m, 1H), 1.48–1.75 (m, 3H), 2.66 (d, J = 4.5 Hz, 1H), 2.84 (d, J = 4.5 Hz, 1H), 3.01 (d, J = 11.5 Hz, 1H), 3.48 (q, J = 7.0 Hz, 3H), 4.08 (d, J = 4.5 Hz, 1H), 4.84 ppm (dd, J = 4.5, 2.0 Hz, 1H); elemental analysis calcd (%) for $\text{C}_{30}\text{H}_{30}\text{Cl}_8\text{O}_5\text{Pd}$ (860.60): C 41.87, H 3.51; found: C 41.60, H 3.53.

4b: The diethyl ether complex **4a** (86.1 mg, 0.10 mmol) was dissolved in dry degassed THF (5 mL) and stirred at room temperature for 30 min. The solution was filtered through a glass frit and the filtrate was concentrated to 1 mL, diluted with dry degassed pentane (10 mL), and cooled overnight at about -15°C . The orange crystals obtained were collected on a glass frit and dried under vacuum at room temperature for 48 h. The yield was 82.4 mg (96 %): m.p. 109.8–110.0°C (decomp); ^1H NMR (500 MHz, $[\text{D}_8]\text{THF}$) δ = 1.20–1.27 (m, 1H), 1.43–1.49 (m, 1H), 1.54 (tt, J = 12.5, 5.0 Hz, 1H), 1.65 (d, J = 11.0 Hz, 1H), 1.76–2.66 (m, 4H), 2.66 (d, J = 4.5 Hz, 1H), 2.75 (d, J = 5.0 Hz, 1H), 2.94 (d, J = 11.0 Hz, 1H), 3.60–3.64 (m, 4H), 4.10 (d, J = 4.5 Hz, 1H), 4.42 ppm (dd, J = 5.5, 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $[\text{D}_8]\text{THF}$) δ = 24.73 (CH_2), 26.39 (CH_2), 27.98 (CH_2), 36.67 (CH_2), 44.44 (CH), 45.83 (CH), 68.22 (CH_2), 78.12 (CH), 98.92 (CH), 117.85, 122.49, 124.87, 128.20, 144.76, 157.24 ppm; FAB-MS m/z (%) 541

(44) $[M^+ - \text{thf} - \text{C}_6\text{Cl}_4\text{O}_2]$, 446 (100) $[MH^+ - \text{thf} - \text{C}_6\text{Cl}_4\text{O}_2 - \text{C}_7\text{H}_{12}]$; elemental analysis calcd for $\text{C}_{30}\text{H}_{28}\text{Cl}_8\text{O}_3\text{Pd}$ (858.58): C 41.97, H 3.29; found: C 42.27, H 3.43.

5: The diethyl ether complex **4a** (86.1 mg, 0.10 mmol) was dissolved in dry degassed pyridine (1 mL) and stirred at room temperature for 30 min. The solution was filtered through a glass frit and the filtrate was diluted with dry degassed pentane (30 mL) before being cooled overnight at about -15°C . The obtained brown crystals were collected on a glass frit and dried under vacuum at room temperature for 48 h. The yield was 76.7 mg (75.6%): m.p. 99.2–99.5 $^\circ\text{C}$ (decomp); ^1H NMR (300 MHz, CDCl_3): δ = 1.16–1.32 (m, 1H), 1.34–1.46 (m, 1H), 1.54–1.80 (m, 3H), 2.71 (d, J = 3.8 Hz, 1H), 2.75 (d, J = 3.8 Hz, 1H), 3.00 (d, J = 10.2 Hz, 1H), 4.03 (s, 2H), 7.25 (dd, J = 7.8, 4.2 Hz, 4H), 7.67 (tt, J = 7.8, 1.5 Hz, 1H), 8.51 ppm (d, J = 4.2 Hz, 4H); MS (FAB) m/z (%) 541 (34) $[M^+ - 3\text{Py} - \text{C}_6\text{Cl}_4\text{O}_2]$, 446 (100) $[MH^+ - 3\text{Py} - \text{C}_6\text{Cl}_4\text{O}_2 - \text{C}_7\text{H}_{12}]$; elemental analysis calcd (%) for $\text{C}_{41}\text{H}_{35}\text{Cl}_8\text{N}_3\text{O}_3\text{Pd}$ (1023.78): C 48.10, H 3.45, N 4.10; found: C 47.93, H 3.41, N 3.91.

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R_1 = 0.0302, wR_2 = 0.0811 [$I > 2\sigma(I)$], and GOF = 0.733 (for all data, R_1 = 0.0320, wR_2 = 0.0832). CCDC-186953 (**4b**) and CCDC-186954 (**5**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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Direct Assembly of Large Arrays of Oriented Conducting Polymer Nanowires**

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Recently, oriented carbon nanotubes, and nanowires of semiconductors, oxides, and metals have attracted wide attention. However, there have been few reports on the direct growth of oriented polymer nanostructures such as oriented polymer nanowires. Oriented conducting polymer nanostructures will be very useful for many applications,^[1–3] which range from chemical and biological sensing and diagnosis to energy conversion and storage (photovoltaic cells, batteries and capacitors, and hydrogen-storage devices), light-emitting display devices, catalysis, drug delivery, separation, microelectronics, and optical storage.

Several methods, which include electrospinning^[4,5] and polymer-templated electrochemical synthesis,^[6] have been used for preparing conducting polymer nanofibers. Highly porous, conducting polymer films based on techniques such as dip coating on porous supports have been widely investigated for separation and sensing,^[7] but the random pore structures and misalignment of the polymers are not ideal for high efficiency and faster kinetics. Controlled orientation is more critical for applications such as in light-emitting and micro-

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electronic devices. To date, oriented conducting polymer nanostructures, including oriented polypyrrole or polyaniline nanorods or nanotubes, were mostly obtained with a porous membrane as the template.^[8–13] Recently, Gao et al.^[14] used oriented carbon nanotubes as the template to deposit a thin polyaniline-polymer coating on the surface of the carbon nanotubes electrochemically. In the templated approach, the dimensions and the morphology of the polymer structures are defined (or limited) by the porous support. The formation of arrays of oriented polymer rods or tubes involves carefully etching away the membrane without disturbing the conducting polymer structure. Published results indicate that oriented structures were only obtained for rods and tubes with a large diameter.^[15] Etching away the membrane supports for nanorods or tubes with a diameter smaller than 100 nm caused the polymer to collapse into structures without preferred orientation.^[15]

Herein, we report the direct electrochemical synthesis of large arrays of uniform and oriented nanowires of conducting polymers with a diameter much smaller than 100 nm, on a variety of substrates (Pt, Si, Au, carbon, silica), without using a supporting template. Compared with membrane-templated synthesis, it is easier to prepare oriented conducting polymer nanostructures on complicated surfaces (such as on a micro-electrode surface) through direct electrochemical deposition, therefore opening up new opportunities for designing devices. We first observed that if polyaniline were deposited under a galvanostatic current density of 0.08 mA cm^{-2} , a value higher than that reported in the literature (0.017 mA cm^{-2} , for example),^[16] polyaniline nanoparticles, rather than continuous films, were observed on the substrate under our experimental conditions. We hypothesized that we could use these polyaniline particles as the nucleation sites to grow extended polymer nanostructures by adding a second or a third deposition step with a reduced current density. Therefore, we designed a three-step electrochemical deposition procedure. In the first step, a large current density was used to create the nucleation sites on the substrate. The initial stage was followed by continued polymerization with reduced current density. A typical procedure involves electrochemical deposition in an aniline-containing electrolyte solution, by using the substrate as the working electrode. This process involves: 0.08 mA cm^{-2} for 0.5 h, followed by 0.04 mA cm^{-2} for 3 h, which was then followed by another 3 h at 0.02 mA cm^{-2} . The stepwise growth produced uniform, oriented nanowires on a variety of flat and rough surfaces. The amount of aniline polymerized is estimated to be $1.1 \times 10^{-3} \text{ mmol monomer cm}^{-2}$ ($0.1 \text{ mg aniline cm}^{-2}$) for the first step, $4.5 \times 10^{-3} \text{ mmol monomer cm}^{-2}$ (or 0.42 mg cm^{-2}) for the second step, and $2.2 \times 10^{-3} \text{ mmol monomer cm}^{-2}$ (or 0.21 mg cm^{-2}) for the third step, respectively.

The polyaniline films prepared by the above method appear to be fairly uniform by visual inspection. The color is intensely black and nonreflective. The morphology of the film was examined under a field emission-scanning electron microscope (SEM). When viewed from an angle perpendicular to the surface at a low magnification (Figure 1a), the film appears to contain uniform white dots all across the surface. At a higher magnification (Figure 1b), it is revealed that the

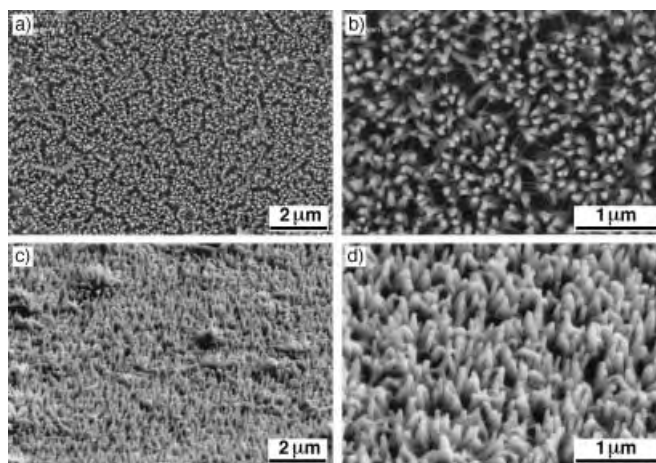


Figure 1. SEM micrographs of oriented polyaniline on Pt: a) low magnification face-on; b) high magnification face-on; c) tilted view, low magnification; d) tilted view, high magnification.

white dots are actually the tips of uniform nanowires, mostly oriented perpendicular to the substrate. The diameters of the tips range from 50 nm to 70 nm. There are also some thin filament structures, approximately 20 nm in diameter, at the base of the oriented nanowires. When the sample is tilted, the morphology and the orientation of the nanowires are clearly revealed (Figure 1c and d). The oriented nanowires are fairly uniform in length and diameter, but the diameter is slightly smaller at the tip position than at the base position. From the tilt angle (about 40°), the nanowires are estimated to be $0.8 \mu\text{m}$ in length.

To investigate how the oriented nanowires were formed, we examined a sample after the first step (0.08 mA cm^{-2} for 0.5 h) (Figure 2a). At this stage the polymer was deposited on the

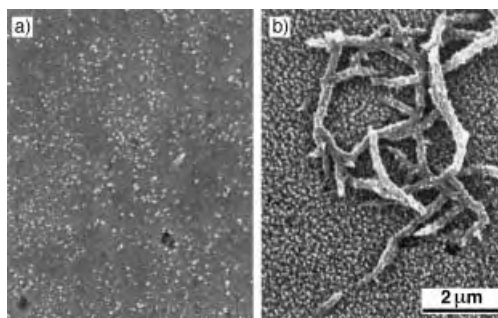


Figure 2. Growth stages of polyaniline on Pt: a) polyaniline particles after 0.5 h at 0.08 mA cm^{-2} ; b) polyaniline particles and fibers after 3 h at 0.08 mA cm^{-2} .

surface as small particles about 50 nm in diameter. If the electrochemical deposition was extended for several hours under the same current density (0.08 mA cm^{-2}), a much higher density of polymer was deposited (Figure 2b), but long, oriented nanowires were not observed. In addition, thick-branched polymer fibers of hundreds of nm in diameter began to form at many locations. Only when the current density was successively reduced were uniform and oriented nanowires formed (Figure 1). We suggest that the nanowires are formed by the following mechanisms (Figure 3a): 1) nucleation on the

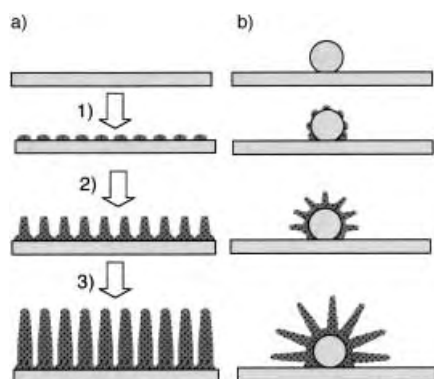


Figure 3. Schematic illustration of the nucleation and growth of polyaniline nanowires, a) on a flat substrate, and b) on a colloidal particle.

substrate at a high current density, and 2) continued nucleation and growth at the low current density.

Understanding how the oriented nanowires are formed suggests useful approaches to control the orientation of the polymers. We first deposited a monolayer of closely packed silica spheres on the substrate and expected that the polymer nanowires would grow with an orientation perpendicular to the particle surfaces (not to the substrate surface; Figure 3b). To illustrate how the polymer grows from the silica particles, we show the results in an area where the particles were not closely packed. Figure 4a shows the surface roughness induced by the presence of silica particles, which follow the contours of the individual particles. The radial growth of the polymer wires around the particles is clearly illustrated. Figure 4b shows the morphology of the polymers across the edge of the silica monolayer. Close to the edge where there are no silica particles, the polymers are oriented vertically, but on top of the silica particles the polymer orientation is disrupted and randomly connected. In the area occupied by a monolayer of densely packed silica spheres, the radial growth of polymer nanowires overlap and form 3D-interconnected polymer networks (Figure 4c and 4d). Such morphologies

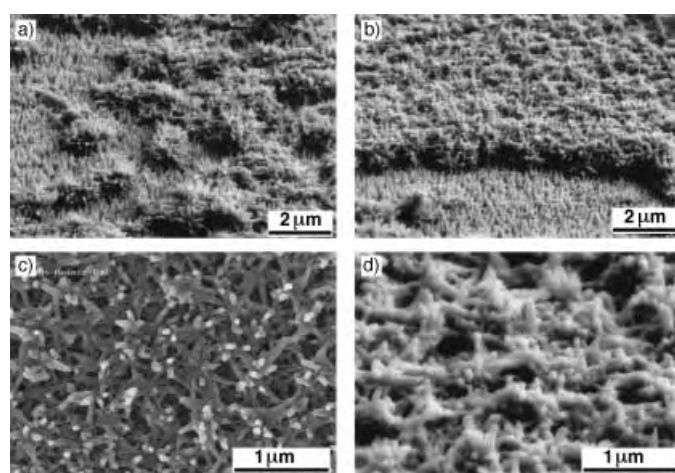


Figure 4. Interconnected conducting nanofibers with colloidal silica. a) Radial growth of the nanowires from single silica particles; b) the morphology of nanofibers on the edge of the colloidal silica monolayer; c) top view of the interconnected nanofibers; d) tilted view of the oriented nanofibers.

may be useful for applications such as active filtration membranes.

The electrochemical properties of different morphologies deposited on Pt plates were investigated by cyclic voltammetry using Hg/HgCl₂ as the reference electrode in 1M HClO₄ and at a sweep rate of 50 mVs⁻¹. Figure 5 shows the voltammograms of samples corresponding to the vertically

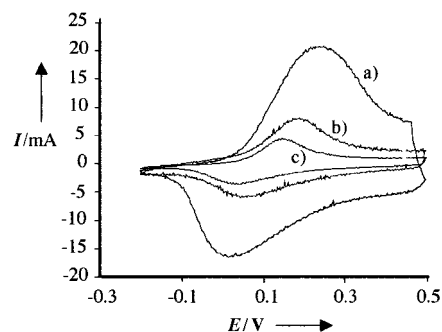


Figure 5. Cyclic voltammograms of different polyaniline morphologies: a) oriented polymer nanowires on Pt; b) interconnected polymer fibers on Pt with silica spheres; c) polymer deposited without stepwise control of the current density.

oriented nanowires (see Figure 1), samples deposited at constant current density (see Figure 2b), and interconnected nanofibers deposited with colloidal silica (see Figure 4). All samples demonstrated electrochemical activity, which is characterized by the typical reduction and oxidation responses.^[17,18] However, the oriented nanowires have considerably higher redox current than the interconnected nanofibers, which in turn have a higher redox current than the samples prepared with a constant current. The difference in the redox currents reflects the effective active surface areas that are accessible to the electrolytes. Apparently, the oriented nanowires have the highest effective surface area, which is desirable for high efficiency and sensitivity of many devices.

In summary, we were able to deposit directly large arrays of oriented conducting polymer nanowires on a variety of substrates without a porous membrane support. This is a very novel approach for synthesizing oriented polymer nanostructures and we believe that it will have great potential for microsensors and other microelectronic and optical devices.

Experimental Section

Oriented nanowires on Pt and other substrates: A Pt plate was washed thoroughly with ethanol and dried in air. The Pt foil was further rinsed in a 1 wt.% sodium dodecyl sulfate (SDS) solution to improve the wetting behavior with water and dried in air. Electrochemical deposition of polyaniline was performed by immersing the Pt plate into the aqueous solution containing 0.5M aniline and 1.0M perchloric acid (HClO₄). The effective area of the immersed Pt plate is 4.5 cm². Polyaniline was grown from the surface of the platinum plate by redox polymerization using an EG&G Princeton Applied Research Model 273 potentiostat/galvanostat controlled by a personal computer with EG&G Princeton Applied Research Model 270 electrochemical software. A one-compartment cell was used with another platinum plate as the counter electrode. The same instrument was used for the voltammetry measurements. Besides Pt, other substrates, including Ti, Au, Si, were investigated and yielded similar results.

Preparation of polyaniline with a monolayer of colloidal silica: To control the morphology of the polymer, a monolayer of close packed colloidal silica (0.5 μm diameter standard silica spheres obtained from Duke Scientific, Palo Alto, California) was first deposited on the Pt substrate. After the Pt plate was rinsed with the SDS solution, a droplet of a colloidal silica solution containing 0.4 wt. % silica particles was placed on the Pt substrate. The SDS treatment improved the wetting behavior of the silica colloidal solution and allowed the droplet to spread over the whole surface of the Pt plate. The excess solution was removed from the substrate by positioning the Pt plate vertically to allow the excess water to flow off. After drying, the Pt plate with the silica particles was heated in an oven at 110°C for 0.5 h. Electrochemical deposition of polyaniline was conducted using the same procedure.

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A New Generation of Air Stable, Highly Active Pd Complexes for C–C and C–N Coupling Reactions with Aryl Chlorides**

Anita Schnyder, Adriano F. Indolese,*
Martin Studer,* and Hans-Ulrich Blaser

Palladium-catalyzed coupling reactions such as the Suzuki coupling, the Heck reaction, and the Buchwald–Hartwig amination or arylation of ketones are now standard transformations in both academic and industrial laboratories.^[1] While simple palladium salts are excellent catalysts for reactive substrates, such as aryl iodides, activated aryl bromides, or aromatic diazo compounds, the less reactive but commercially very interesting aryl chlorides require palladium catalysts activated and stabilized by additional ligands. A crucial factor for a successful catalyst is the choice of the right ligand, most frequently an electron-rich, bulky tertiary phosphane, and in recent years a number of very effective ligands have been developed for the reactions mentioned above.^[2]

However, these customized phosphanes are usually expensive and their synthesis can be difficult, often involving multistep syntheses using air-sensitive substances. An interesting alternative could be secondary phosphanes, many of which are available in bulk quantities at a relatively low price. Even though their application in transition-metal catalysis is rare,^[3] we recently found that secondary dialkyl phosphanes such as HP(*tert*-butyl)₂ and HP(adamantyl)₂ can indeed be applied successfully for the palladium-catalyzed Heck reaction even with notoriously unreactive, electron-rich aryl chlorides.^[4]

This result encouraged us to investigate other palladium-catalyzed reactions (Scheme 1) using a combinations of palladacycles and secondary phosphanes. Palladacycles have recently been described as versatile catalyst precursors for a number of coupling reactions^[5] and they can be regarded as stable, easily accessible aryl palladium species. Catalyst libraries with high diversity could readily be prepared with this strategy since a wide variety of palladacycles and secondary phosphanes are available.

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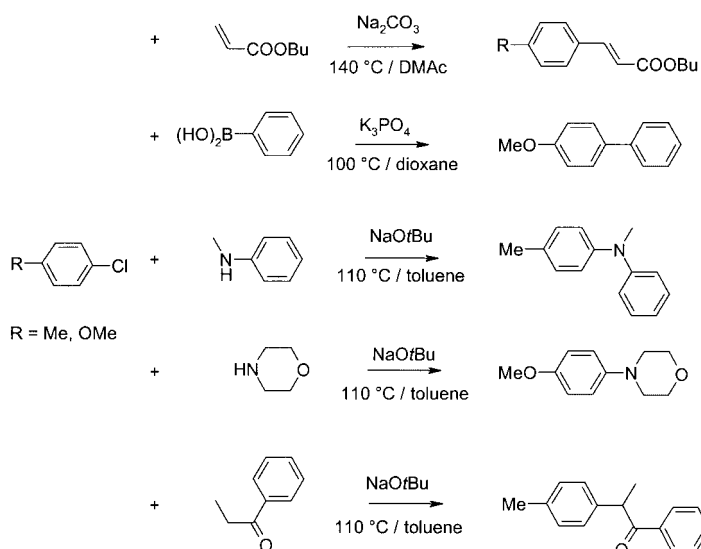
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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.



Scheme 1. Substrates and conditions used for coupling reactions catalyzed by palladacycle/secondary phosphane catalysts.

Herein we report very active catalysts obtained in situ from palladacycles and secondary phosphanes for the Heck and Suzuki reaction, the Buchwald–Hartwig amination, and the α -arylation of ketones with aryl chlorides as the arylating agent. In addition, the isolated and well-characterized palladacycle/HPR₂ complexes are stable, easy to handle, and versatile catalysts for these transformations.

For a first screening we selected the reaction of phenylboronic acid with 4-chloroanisole, and assembled a small catalyst library prepared in situ by mixing the five palladacycles **1–5** and three sterically demanding dialkyl phosphanes (Scheme 2; HPCy₂, HPNor₂ and **6**^[6]). The palladacycles are easily accessible by orthometalation of substituted benzenes containing a coordinating N or O atom to form five- or six-membered chelating rings.^[5] All combinations gave active catalysts, thus showing the basic suitability of our approach, whereas the palladacycles alone yielded less

than 2% coupling product (Figure 1 and Table 1^[7]). Some trends were clearly visible: Conversions generally improved going from the least demanding ligand **6** to the bulkiest phosphane HPNor₂; the highest yields (> 90%) were ob-

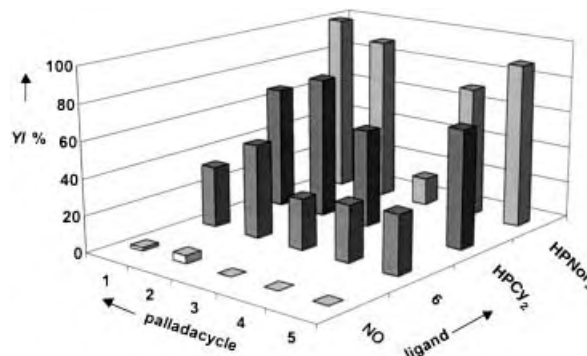


Figure 1. GLC yields (YI [%]) of the Suzuki coupling of 4-chloroanisole with phenylboronic acid in the presence of palladacycles **1–5** and selected secondary phosphanes.^[7]

Table 1. GLC yields for the Suzuki and Heck reaction for various combinations of Pd precursors and secondary phosphanes.^[7]

Entry	Ligand	Suzuki 1 (1 %)	Heck 1 (0.5 %) ^[a]	Heck 3 (0.5 %)	Heck 4 (0.5 %)	Heck ^[4] PdCl ₂ (1 %)	Heck ^[4] Pd(OAc) ₂ (0.5 %)
1	–	2%	0%	0%	0%	0%	0%
2	PCy ₃	53%	19%	24%	22%	40%	15%
3	HPCy ₂	67%	32%	30%	35%	39%	17%
4	HPNor ₂	100%	41%	40%	45%	77%	34%
5	HPAd ₂	84%	58%	74%	65%	78%	52%
6	HP(<i>t</i> Bu) ₂	94%	46%	71%	77%	77%	53%
7	6	33%	4%	15%	0%	n.a.	n.a.
8	7	61%	20%	37%	18%	n.a.	n.a.
9	P(<i>t</i> Bu) ₃	n.a.	61	70%	71%	98%	49%

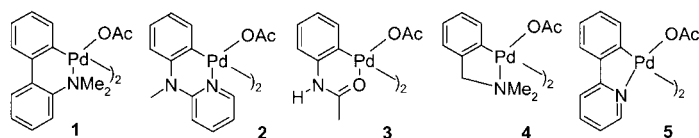
Conditions: See Scheme 1, reaction time 20 h; [a] average of 2 runs. n.a. = not available.

tained with **1**, **2**, and **5** in combination with HPNor₂. The combination **1**/HPNor₂ rendered a particularly active catalyst where 95% of the starting material reacted within the first hour, while conversion with all other catalytic systems after 1 h never exceeded 50%.

Similar screening experiments with palladacycles **1**, **3**, and **4**, PdCl₂, and Pd(OAc)₂ were also carried out for the Heck reaction of 4-chloroanisole with *n*-butyl acrylate, and gave similarly encouraging results (Table 1). For both the Suzuki and the Heck reaction, these in situ catalysts have similar activity as the [Pd₂(dba)₃]/P(*t*Bu)₃ (dba = *trans,trans*-dibenzylideneacetone) catalysts developed by Littke and Fu.^[8] It is interesting to note that whereas HPNor₂ is the preferred ligand for the Suzuki coupling, HPAd₂ and H(*t*Bu)₂ give the highest conversion for the Heck reaction. It is precisely this catalyst specificity which makes the combinatorial approach attractive because it guarantees access to a broad range of different Pd complexes and enables the optimal one to be found as fast as possible.

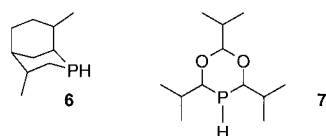
While the in situ approach is very useful for catalyst screening, for preparative purposes it would be more attractive to have one or at most a few one-component catalysts with high activities for as many C–C and C–N coupling

Palladacycles



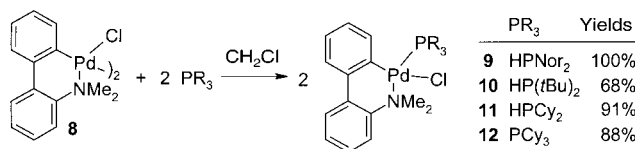
Secondary phosphanes

HPCy₂ Cy = cyclohexyl
HP(*t*Bu)₂ *t*Bu = *tert*-butyl
HPAd₂ Ad = 1-adamantyl
HPNor₂ Nor = 2-norbornyl



Scheme 2. Structures and numbering of palladacycles and secondary phosphanes.

reactions as possible. On the basis of our screening results and some additional experiments, we decided that palladacycle **1** in combination with the phosphanes depicted in Scheme 2 would give us a fair chance to reach this goal. Indeed we succeeded in developing a simple procedure to obtain isolated complexes **9–12** by treating the chloride-bridged palladacycle **8** with several basic phosphanes in high yields^[9] (Scheme 3).



Scheme 3. Structure, yield, and numbering of the isolated palladacycles.

Table 2 summarizes the results of the screening program with the four isolated palladacycles **9–12** in the five model reactions depicted in Scheme 1. Complex **12** was included as a reference because PCy₃ has been shown to be one of the most

Table 2. GLC yields for various coupling reaction using isolated palladacycles **9–12**.^[7]

Complex	Ligand	Suzuki (1 %)	Heck (1 %)	Heck (0.25 %)	Arylation (0.5 %)	Amination ^[a] (0.5 %)	Amination ^[b] (2 %)
9	HPNor ₂	95	100	48	100	100	100
10	HP(<i>t</i> Bu) ₂	45	100	46	60	94	100
11	HPCy ₂	91	100	89	69	98	82
12	PCy ₃	99	95	42	99	66	38

Reaction conditions: See Scheme 1, reaction time for Suzuki and Heck: 20 h; for arylation and amination 15 h. [a] *N*-methylaniline substrate. [b] Morpholine substrate.

effective ligands known for these reactions.^[10] Without discussing these results in too much detail, it is important to note that in each reaction one of the new complexes—but not always the same one—gives either comparable or better results than the PCy₃ complex. In the Suzuki reaction with 0.1 mol% **9**, 660 turnovers were achieved in 20 h; these catalytic activities are comparable to screening results recently described by Bedford and Cazin^[11] using a combination of a palladacycle of type **4** in combination with PCy₃. This publication appeared during the course of our work and also reported that catalysts formed in situ have a similar performance as the isolated complexes. In addition, it was shown that under optimal reaction conditions (especially replacement of K₃PO₄ with the more expensive Cs₂CO₃) this catalyst type is capable of achieving up to 8000 turnovers with 4-chloroanisole. For the Heck reaction, our palladacycles are comparable or more active than the most active catalysts reported in the literature, [Pd(*dba*)₂]/P(*n*Bu)Ad₂^[12] and Pd(OAc)₂/HPAd₂.^[4] An interesting result was recently published using oxime-derived palladacycles which catalyzed Heck reactions between nonactivated aryl chlorides and methyl acrylate or styrene in the absence of any phosphane with turnovers around 100.^[13] Our results for the arylation and amination reactions also compare well with those obtained by Buchwald and co-workers^[14] and Kawatsura and Hartwig^[15] using electron-rich tertiary phosphanes with a biphenyl and ferrocenyl backbone, respectively.

The mode of action and the nature of the active species of the palladacycle/secondary phosphane catalysts are not yet known.^[4] In a stoichiometric reaction of palladacycle **1** with HPCy₂ we obtained low yields of 2-dimethylamino-2'-dicyclohexylphosphanyl biphenyl, previously described by Buchwald and co-workers^[14a] as a very effective ligand for both the Suzuki coupling and the Buchwald–Hartwig amination. However, we doubt that the catalytic activity of our novel catalysts is really a consequence of this species because—among other observations—we found that this ligand is not active for the Heck reaction.^[16]

In conclusion, we have developed a new type of highly active Pd catalysts consisting of a palladacycle and a secondary phosphane with broad applicability for various coupling reactions. Very high yields can be obtained for the Suzuki coupling, the Heck reaction, the Buchwald–Hartwig amination as well as the ketone arylation by using aryl chlorides as starting materials. The catalysts can either be prepared in situ starting from a palladacycle and a secondary phosphane thereby allowing a combinatorial screening approach or the isolated preformed complex can be used which is very convenient for preparative purposes and also in chemical production. We believe that palladacycle **9**^[17] is at the moment the most practical catalyst, with the broadest application range, for use in the laboratory, but in principle it is possible to prepare complexes with any combination of palladacycle and secondary phosphane.

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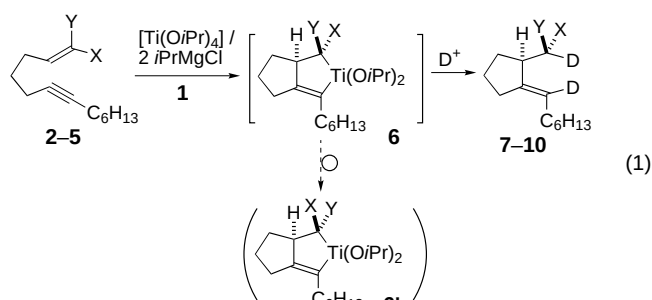
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- [9] General procedure: Complexes **9–12** were easily prepared by adding the appropriate phosphane to a degassed suspension of the dimeric palladacyclic chloride **8** in dichloromethane under argon. The resulting complexes are soluble and the solutions are stable against hydrolysis and oxidation by air. Some metallic palladium was removed by filtering the solution through a plug of silica. The solutions were concentrated to a minimal volume and the complexes precipitated with hexane. Complexes **9–12** were obtained as yellow to brownish yellow powders in medium to high yields that were completely odorless and air stable for at least several months. (For details see the Supporting Information).
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Sulfur-Functionalized Olefins for Titanacycle Formation: Tandem Asymmetric Cyclization and the Pummerer Reaction Based on Sulfoxides Promoted by Titanium(II)-to-Titanium(IV) Relay**

Miho Narita, Hirokazu Urabe, and Fumie Sato*

Sulfur functional groups such as sulfides, sulfoxides, and sulfones have found numerous and pivotal applications in organic synthesis.^[1] When enynes having a sulfur functional group are subjected to cyclization mediated by (stoichiometric) group-four transition metals,^[2,3] the formation of new sulfur-functionalized metallacycles is expected and their behavior should be of considerable interest. Considering that study along this line is so far notably limited,^[4] we report here new aspects of the use of vinylic sulfur functional groups in the titanium alkoxide-mediated enyne cyclization.

First, the viability of the cyclization of enynes having a vinylic sulfide, sulfone, or sulfoxide moiety with a Ti^{II} alkoxide reagent, [Ti(O*i*Pr)₄]/2 *i*PrMgCl (**1**),^[3] was briefly surveyed [Eq. (1)].



The *E*- and *Z*-vinyl sulfides **2** and **3** underwent clean and, more importantly, stereospecific and stereoselective cyclization to the most likely titanacycles **6**, which underwent deuterolysis to give the isomeric deuterated products **7** and **8**, respectively [Eq. (1) and entries 1 and 2, Table 1].^[5,6] Analogously, the *E*-vinyl sulfone **4** afforded **9** (entry 3) upon deuterolysis, which suggests the selective generation of the titanacycle **6**. Contrarily, the *Z*-vinyl sulfone **5** gave a mixture of **10** (minor constituent) and **9** (as a major component; entry 4), which indicates that the stereochemical integrity of **5**

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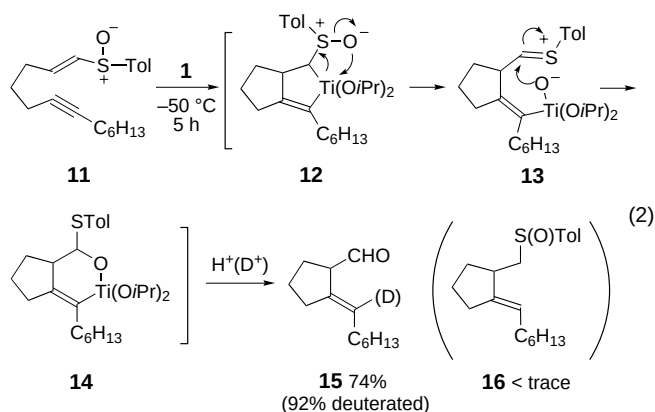
Table 1. Stereospecificity in the cyclization of sulfides and sulfones according to Eq. (1).^[a]

Entry	X	Y	Enyne	E/Z	Yield [%] ^[b]	Product	D [%] ^[c,d]	Isomers	Ratio ^[d]
1	SMe	H	2	pure <i>E</i>	7	73	97	7/8	> 99: < 1
2	H	SMe	3	8:92	8	76	99	8/7	93:7 (100:0 ^[e])
3	SO ₂ Ph	H	4	pure <i>E</i>	9	98	94	9/10	94:6
4	H	SO ₂ Ph	5	2:98	10	79	98	10/9	23:77

[a] The reaction temperatures were -50°C for sulfides and -20°C for sulfones; these were essential to complete the cyclization. [b] Combined yield of isomers. [c] Total deuterium incorporation at the carbon atom α to X and Y. (The olefinic position was also deuterated to a high degree.) [d] Determined by ^1H NMR spectroscopic analysis. [e] Corrected to pure *Z*-vinyl sulfide.

was lost, probably caused by the isomerization of **6** to the less sterically congested **6'** under these reaction conditions.^[7] Stereodefined titanacyclopentenes such as those generated as shown in entries 1–3 of Table 1 should find use for the stereoselective construction of cyclic systems.^[7]

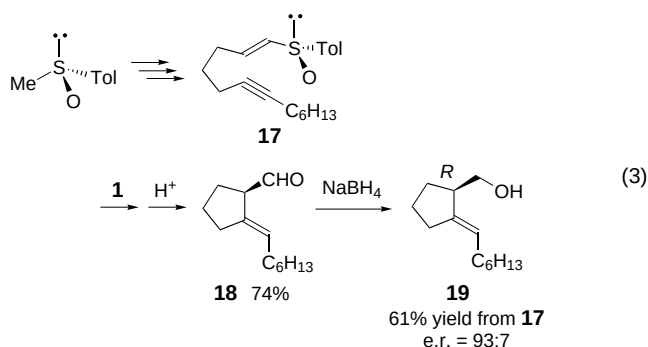
In contrast to the two above-mentioned sulfur compounds, the corresponding sulfoxide **11** did not afford the expected cyclization product **16** but, instead, the cyclic aldehyde **15** [Eq. (2); Tol = *p*-tolyl].



The formation of **15** could be rationalized by the **1**-mediated cyclization of **11** giving the titanacycle **12**, followed by the subsequent Pummerer-type rearrangement (**12**→**13**→**14**)^[8] to furnish the aldehyde **15** after aqueous workup. In fact, the presence of the remaining carbon–titanium bond in **14** was confirmed by deuteriolysis experiments and may be used for further synthetic elaboration.^[9] Surprisingly, this Pummerer reaction proceeded at a very low temperature compared to other standard procedures.^[8] The presence of an anionic moiety α to the sulfoxide, and the Lewis acidity of this proximate titanium(IV) center,^[10] may account for this extremely facile rearrangement even at a low temperature.

We then proceeded to the next stage, an asymmetric cyclization, taking advantage of a chiral sulfoxide moiety.^[11] Equation (3) illustrates this transformation, showing a high chirality induction at the cyclization step.^[12]

The enantiomeric ratio (e.r.), as well as the absolute configuration of aldehyde **18**, was unambiguously determined by derivatization to **19** and further correlation to a known compound. Additional results are summarized in Table 2. The stereochemistry of the exocyclic, trisubstituted double bond of the produced aldehydes was established as *E* by an NOE study in a representative case. When the terminal substituent



of acetylenes is more sterically demanding (**20** and **21**→**17**→**22**), the enantiomeric ratio of the products is slightly lowered (**24** and **25**→**18**→**26**). In contrast to the *E*-vinyl sulfoxides (entries 1–4), the less readily available *Z*-vinyl sulfoxide (**23**, entry 5) has no advantageous feature with respect to the chemical yield or enantiomeric ratio (with reversal of the absolute configuration as predicted from the following considerations). Scheme 1 shows a proposed mechanism for the production of *R*-aldehydes from *E,R*-vinyl sulfides. The sulfoxide oxygen atom coordinates to the titanium center to fix the structure as depicted, and the titanium–acetylene moiety approaches the carbon–carbon double bond on a reaction path that minimizes the steric repulsion (that is, the favored path, above in Scheme 1) to show the high degree of observed asymmetric induction.

In summary, by taking advantage of sulfur functional groups, we disclose herein the generation of new functionalized titanacycles and their subsequent reaction. Functional-group manipulation on a metal template, as illustrated by the Pummerer reaction on the titanacycle, may lead to new utility of metallocycles in organic synthesis.

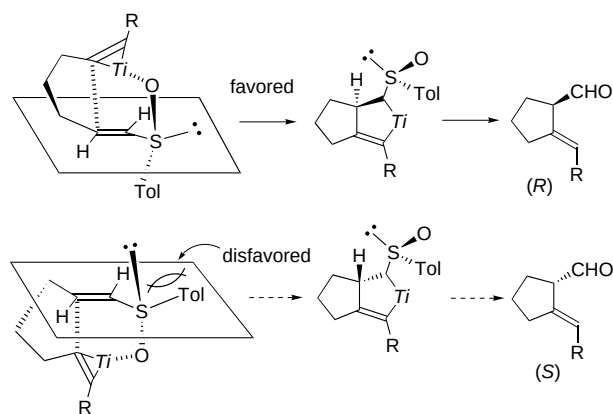
Experimental Section

Typical procedure for 18: To a stirred solution of **17** (100 mg, 0.316 mmol) and $[\text{Ti}(\text{O}i\text{Pr})_4]$ (0.117 mL, 0.395 mmol) in 5 mL of Et_2O was added $i\text{PrMgCl}$ (1.34 M in Et_2O , 0.590 mL, 0.790 mmol) at -78°C under argon. After stirring for 30 min, the solution was allowed to warm to -50°C over 30 min and kept at this temperature for 5 h. Then, the reaction was quenched by the addition of aqueous 1 N HCl at -50°C . The organic layer was separated and washed with aqueous NaHCO_3 solution, dried over Na_2SO_4 , and concentrated to leave an oil, ^1H NMR spectroscopic analysis of which revealed the crude yield of **18** to be 74%. The crude product was chromatographed on silica gel to afford **18** (43 mg, 70%) which was slightly contaminated by an unknown impurity (ca 10%). Further purification on TLC plates (Merck article no. 1.05554, 1% EtOAc in hexanes) afforded **18** (26.5 mg, 43%) as a colorless oil, which was fully characterized by ^1H NMR, ^{13}C NMR and IR spectroscopic analysis, and elemental analysis.

Table 2. Tandem cyclization and the Pummerer reaction of vinyl sulfoxides.

Entry	Enyne	Aldehyde ^[a]	Yield [%] ^[b]	e.r. ^[c]
1			40 ^[d] (60)	95:5
2			56 (66)	95:5
3			70, ^[e] 43 ^[f] (74)	93:7
4			(62) ^[g]	92:8
5			(30)	79:21

[a] While the absolute configurations of **18** and **27** have been established, others were assigned by analogy, based on the sign of $[\alpha]_D$. [b] Yield isolated after purification. Values in parentheses were determined by ^1H NMR spectroscopic analysis of a crude sample with an internal standard. [c] Enantiomeric ratio was assessed after reduction to the alcohol [see Eq. (3)]. [d] The low yield may reflect the volatility of this compound. [e] This sample contains a small amount (ca. 10%) of unknown impurity. [f] Pure sample after repeated purification. [g] This aldehyde is very unstable and its attempted purification was not successful. Characterization was performed after reduction of crude **26** to the corresponding alcohol.



Scheme 1. Proposed reaction course from *E,R*-vinyl sulfoxides to *R*-aldehydes. $\text{Ti} = \text{Ti}(\text{O}i\text{Pr})_2$.

The enantiomeric ratio was determined after derivatization to the alcohol **19**. $[\alpha]_D^{27} = -94.0$ ($c = 0.2$ in CHCl_3) for a sample of 93:7 enantiomeric ratio.

Typical procedure for **19** [Eq. (3)]: A crude sample of **18**, prepared from **17** (100 mg) as above, was reduced with sodium borohydride (10.4 mg, 0.174 mmol) in 6 mL of MeOH at 0°C . After 10 min, the solution was allowed to warm to RT and was stirred for 1 h. After the addition of water and diethyl ether, the organic layer was separated, dried over Na_2SO_4 , and concentrated to an oil. The crude product was chromatographed on silica gel to afford **19** (37.8 mg, 61% overall from **17**) as a colorless oil, which was fully characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopic analysis, and elemental analysis. The enantiomeric ratio was determined by the formation of the Mosher ester. $[\alpha]_D^{27} = -18.5$ ($c = 0.4$ in CHCl_3) for a sample of 93:7 enantiomeric ratio.

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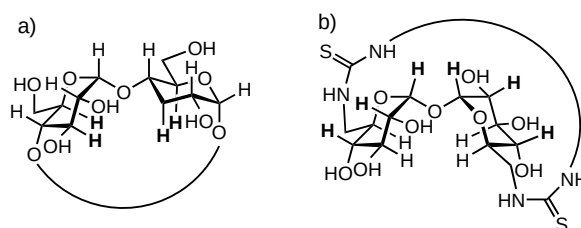
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Cyclotrehalins: Cyclooligosaccharide Receptors Featuring a Hydrophobic Cavity**

Juan M. Benito, José L. Jiménez Blanco, C. Ortiz Mellet,* and José M. García Fernández*

Dedicated to Dr. Jacques Defaye

Interactions between carbohydrates and other biomolecules play a prominent role in many biological recognition processes.^[1] The complexity of such phenomena has stimulated the use of model systems to gather information about their nature (hydrophobic, polar, hydrogen bonds) and to unravel the factors influencing the binding specificity and the stability of carbohydrate-containing supramolecular entities.^[2] Among sugar-derived model hosts, the commercially available cyclodextrins (CDs) have been by far the most extensively investigated for this purpose,^[3] as they feature a hydrophobic cavity that can accommodate a guest molecule of appropriate size. The study of the resulting inclusion complex, by techniques such as NMR spectroscopy, is facilitated by the high symmetry and the rigidity of the CD structure. Yet, this strait-jacketed host has an intrinsic limitation: Exclusively contacts involving the inner α face of the D-glucopyranose units (i.e., H-3 and H-5) are observable (Scheme 1a).



Scheme 1. Representation of a) cyclodextrins (CDs) and b) trehalose cyclotrehalins (CTs) incorporating thiourea intersaccharide bridges. The CH protons directed toward the inside of the corresponding cavities are in boldface.

Although much effort has been directed towards the preparation of synthetic CD analogues bearing a cavity of designed shape, size, and electrostatic potential,^[4,5] no cyclooligosaccharide hosts suitable for the analysis of specific interactions involving the β face of the monosaccharides have been reported so far.

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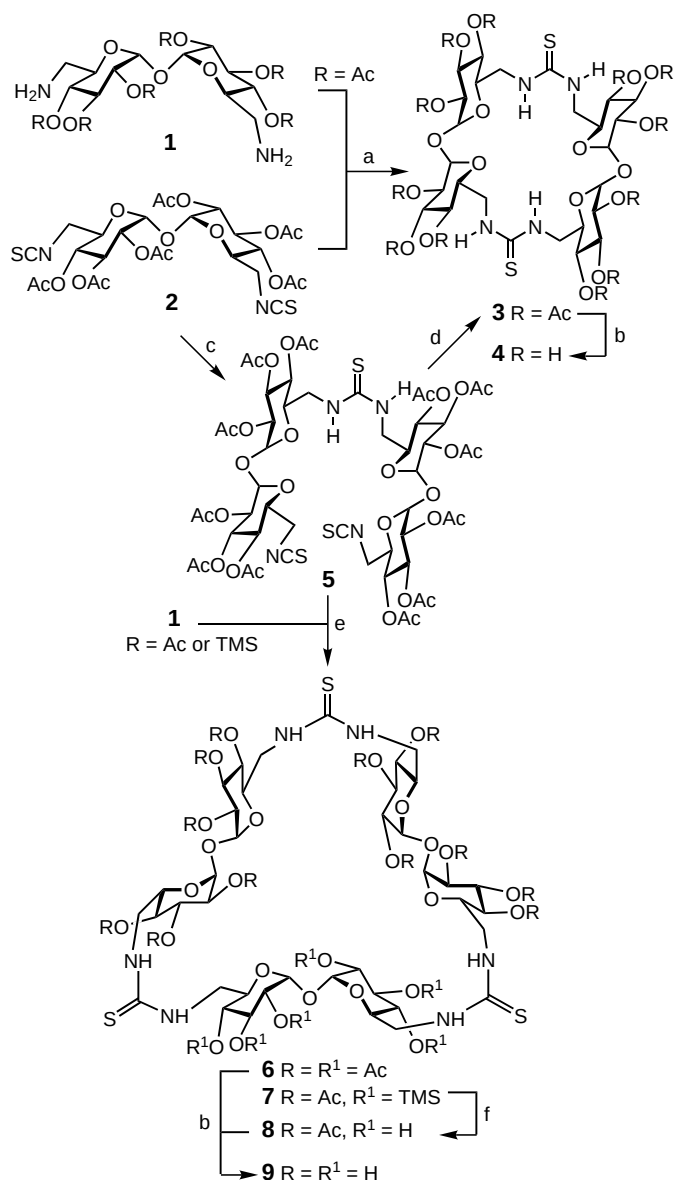
In principle, “reversed CDs”, in other words cyclooligosaccharides in which the β face of the monosaccharide constituents is oriented toward the inside of a convex cavity, are deemed to exhibit inclusion capabilities analogous to those of the original CDs. To prove this concept, we have focused on the potential of cyclic arrays of desired ring size and defined secondary structure composed of alternating (6 $\rightarrow$ 6)-linked α,α' -trehalose moieties and thiourea groups as novel artificial receptors (Scheme 1 b). Preliminary modeling studies suggested that the inner wall in these macrocycles (cyclo-trehalins, CTs)^[6] would expose the H-1, H-2, and H-4 protons for contacts with an included guest, provided that the conformation about the interglycosidic bonds of the trehalose segments remains identical to that of the parent disaccharide, in other words, fitting the *exo*-anomeric effect.^[7] Moreover, the presence of thiourea segments in the structure might provide additional chelation points for molecular recognition and catalysis.^[8]

Replacement of the classical O-glycosidic intersaccharide linkages in cycloglucans with achiral thiourea functional groups permits a convergent retrosynthetic analysis for CTs, involving the coupling reaction of C_2 -symmetric diamine and diisothiocyanate precursors. Actually, this approach proved successful in the preparation of dimer **3** from the hexa-*O*-acetylated derivatives **1** (R = Ac) and **2** (Scheme 2).^[9] Confirmation of the reversed CD conformation of the unprotected receptor **4** was, however, prevented by the limited dimensions of the cavity.

A similar strategy for the synthesis of the trimer homologue requires prior desymmetrization of the trehalose building blocks. Our solution to this problem involved the water-promoted self-condensation of diisothiocyanate **2**, directly affording the linear pseudotetrasaccharide **5** in which the α,α' -trehalose subunits are already desymmetrized and appropriately functionalized.^[10] Compound **5** can be cyclized in situ to give the cyclic dimer **4** or, alternatively, coupled with the per-*O*-acetylated diamine **1** to give the cyclic pseudohexasaccharide **6** in modest (25 %) yield. When the silyl ether derivative (**1**, R = TMS) was used the corresponding cyclic trimer **7** was obtained in 70 % yield.

The NMR spectra of the per-*O*-acetate **6** exhibit signals for a single D-glucopyranose subunit, as expected for a D_3 -symmetric structure. The symmetry is reduced to C_2 in the case of compound **7** and its desilylated derivative **8** which results in the presence of three distinct spin systems in their NMR spectra. NOE experiments indicate close contacts between the H-1/H-1', H-1/H-5', and H-5/H-1' protons of the magnetically nonequivalent D-glucopyranose moieties of the acetylated trehalose fragments (Figure 1 a). This points unequivocally to a rigid conformation about the glycosidic linkages dictated by the *exo*-anomeric effect in agreement with our original hypothesis.

The three-dimensional model of the D_3 -symmetric, unprotected CT **9** depicts a truncated-cone structure with the hydroxy groups located at both rims, reminiscent of the CDs (Figure 1).^[11] Contrary to the dimeric CT **4**, for which the macrocyclic ring imposes a *Z,E* configuration about the NH–C(=S) bonds, in **9** the possibility of both *Z,E*- and *Z,Z*-rotameric dispositions at the semirigid thiourea segments



Scheme 2. Modular and convergent synthesis of cyclotrehalins **4** and **9** from symmetric trehalose precursors: a) pyridine, 40 °C, 48 h (40 %); b) NaOMe, MeOH, then H₂O, room temperature (96–99 %); c) pyridine/H₂O (15:1), 40 °C, 6 h (43 %); d) pyridine/H₂O (10:1), 60 °C, 48 h (38 % overall from **2**); e) from **1** (R = Ac), pyridine, 40 °C, 24 h (25 %); from **1** (R = TMS), CH₂Cl₂, 12 h (70 %); f) H₂O/AcOH (10:1) in CHCl₃/MeOH/H₂O (4:3:1), 60 °C, 15 h, (89 %). TMS = trimethylsilyl.

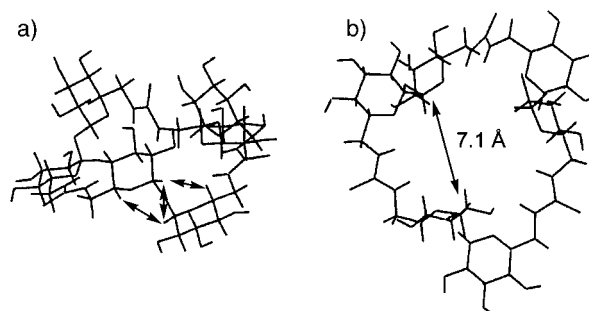
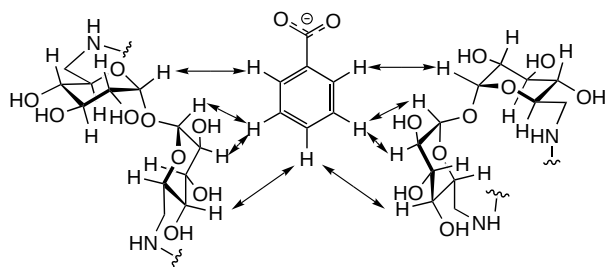


Figure 1. Structure of receptor **9** according to MM2 calculations in water: a) side view showing the intramolecular ROE contacts (observable in the C_2 -symmetric derivatives **6** and **7**); b) top view (narrower rim).

provides the structure with limited flexibility. However, this flexibility does not affect significantly either the topology or the size of the internal cavity (medium internal diameter 7.1 Å), which is estimated to be intermediate to that of α - and β -CDs (5.7 and 7.8 Å, respectively). Accordingly, receptor **9** binds benzoate anion in water. We determined the 1:1 stoichiometry for the complex (Job plot)^[12] and an association constant (K_{ass}) of $8 \pm 2 \text{ M}^{-1}$ by ^1H NMR titration.^[13] The high-field shift of the H-1, H-2, and H-4 protons upon addition of tetrabutylammonium benzoate suggests that the aromatic ring is bound in the cavity through hydrophobic interactions involving the β face of the monosaccharide subunits, while the carboxylate group is still solvated. There are a number of intermolecular ROE contacts, which indicate the mutual orientation of both complexation partners. The result is exactly as predicted: The phenyl ring is located inside the cavity, and the carboxylate group protrudes through the wider rim of the cone, remaining in contact with bulk water (Scheme 3). It is noteworthy that this situation is significantly different from that reported for the corresponding inclusion complexes of α - and β -CDs and benzoate: Whereas the association constants are in the same range ($10\text{--}11 \text{ M}^{-1}$),^[3a] the CD structure does not induce a precise orientation of the guest in the cavity.^[14]



Scheme 3. Intermolecular ROE interactions in the complex formed between host **9** and benzoate anion. The thiourea linkers and one of the three α,α' -trehalose subunits are omitted for clarity.

For further information about the dimensions of the cavity and the inclusion capabilities of CT **9**, 2-naphthalene sulfonate (NS) and 1-adamantanecarboxylate (AC) were investigated as guests. In both cases the 1:1 complex stoichiometry was confirmed, indicative of a size-matched host–guest combination, with K_{ass} values of 235 ± 15 and $4.6 \pm 0.4 \times 10^4 \text{ M}^{-1}$, respectively.^[13] The CT complex with the NS guest is more stable than that with benzoate, a finding parallel to that encountered in the corresponding complexes with α -CD (K_{ass} for α -CD:NS $363 \pm 8 \text{ M}^{-1}$)^[3a] and can be ascribed to the naphthalene hydrophobic part of NS being deeply embedded in the hydrophobic cavity in the longitudinal direction. The much higher stability of the **9**:AC complex, even more stable than the corresponding β -CD:NS complex ($K_{\text{ass}} = 3.9 \pm 0.3 \times 10^4 \text{ M}^{-1}$),^[3a] is in accord with the size-fit concept and the symmetric complementarity between host and guest.

In summary, we have designed new carbohydrate-based receptors for the study of specific interactions between the β face of the constituent saccharides and guest molecules. This

class of cyclic oligomers could become versatile tools for ligand binding and molecular recognition.

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Generation of Libraries of Pharmacophoric Structures with Increased Complexity and Diversity by Employing Polymorphic Scaffolds

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During the last decade we have witnessed the emergence of combinatorial chemistry as a tool for the discovery of new lead compounds.^[1] Outstanding examples of sophisticated directed libraries have been reported, including pharmacophoric scaffolds,^[2] bioactive metabolites,^[2] designed “unnatural”, diversity-oriented, pharmacophore-like, rigid, and versatile structures,^[3] and even natural products with highly complex architectures.^[4] The state-of-the-art in this field combines three main features: 1) suitably functionalized druglike “privileged structures”^[5] having specific spatial architecture and rigidity, 2) short synthetic pathways comprising reliable, clean, and high-yielding reactions, and 3) an overall “diversification strategy” resulting ideally in “libraries

of libraries”^[6] of scaffolds resembling evolution-selected molecules like natural products or drugs.

Libraries are mainly based on a core molecule that is subjected to functional group manipulation which leads to a number of derivatives with the same central structure. Several versatile molecules that were key intermediates used by traditional medicinal chemists, for example, Corey's lactone, the Wieland–Miescher ketone, and the Prelog–Djerassi lactone, could lead to a variety of apparently unrelated pharmacophoric frameworks. These starting materials are small molecules equipped with many reactive sites and functionalities, which can undergo both skeletal rearrangements and functional group interconversions. The use of such a polymorphic compound as the cornerstone of a library would be of great advantage since: 1) Many known synthetic key intermediates lead to medicinally important or “privileged” scaffolds; 2) they possess high potential for both structural and functional diversification; 3) their chemical transformations and modifications in solution are well docu-

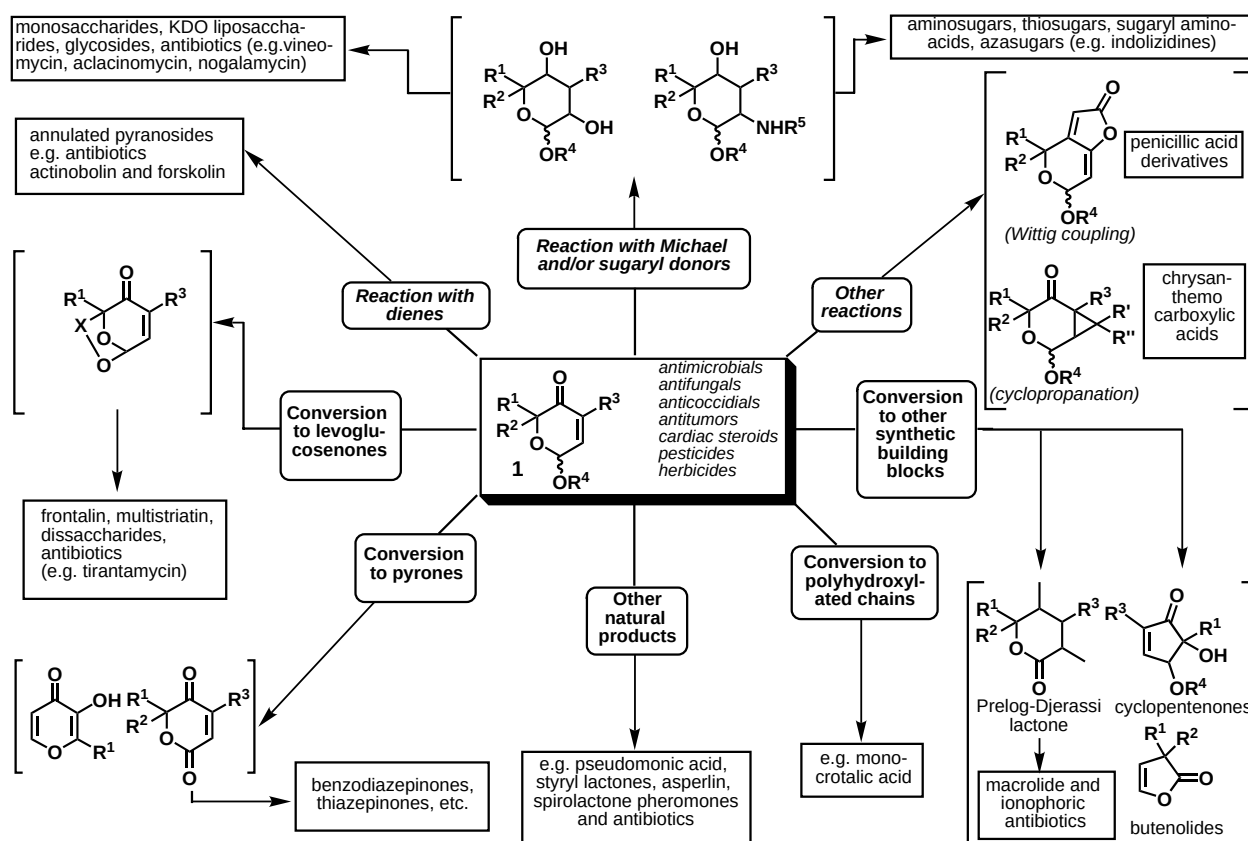


Figure 1. Representative reported derivatizations and applications of pyranone 1.

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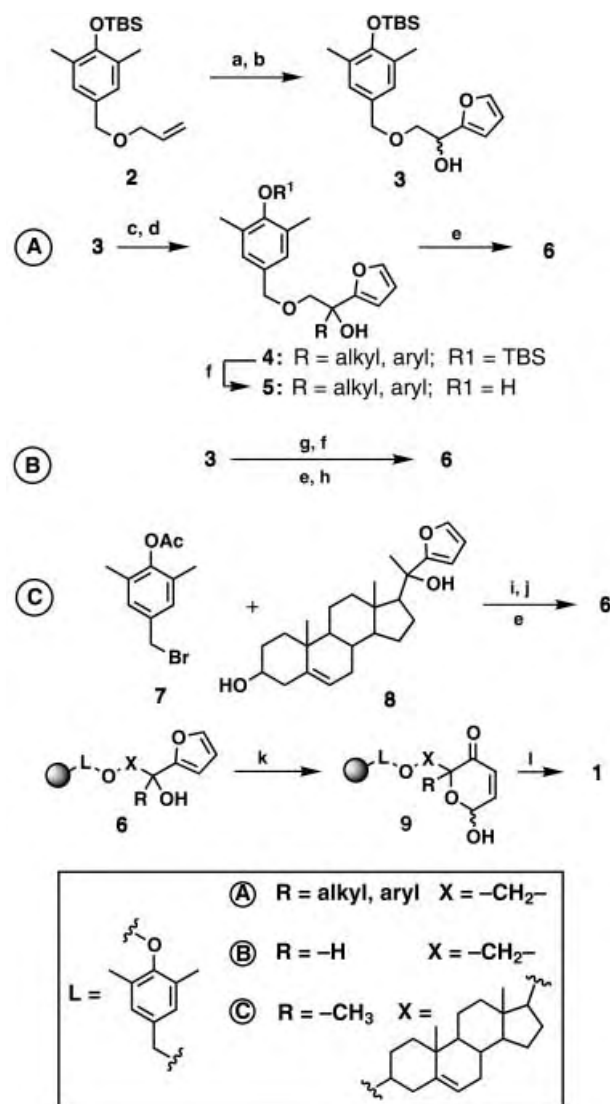
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mented; and 4) the pharmacological activity of their descending structures is well precedented.

To demonstrate the above concept, 2*H*-pyran-3(6*H*)-one (**1**)^[7,8] was selected from among several synthetic key intermediates listed in the literature. As shown in Figure 1, derivatives of pyranone **1** exhibit significant biological activities, including antibacterial, antifungal, anticoccidial, antiinflammatory, and anticancer properties. Besides serving as intermediates in several natural product syntheses, such

compounds have also acted as templates for the synthesis of monosaccharides and glycosides. In addition, they undergo skeletal rearrangements to yield a wide range of structures ranging from polyhydroxylated chains and benzodiazepines to butenolides and anthraquinones.

The primary concern and prerequisite for the effective use of this molecule in combinatorial chemistry is the identification of a suitable linker to attach the pyranone core on the resin (**9**, Scheme 1). This linker should be able to withstand a variety of chemical transformations, be cleavable under specific, relatively mild conditions, and be compatible with many functionalities. We tested several possibilities before we



Scheme 1. Loading of pyranone precursors on resin. Reagents and conditions: a) OsO₄/NaIO₄, THF/H₂O 1:1; b) furyllithium, Et₂O, 0 °C; c) SO₃·py, DMSO/Et₃N/CH₂Cl₂, 0 °C; d) RMgX, Et₂O, 0 °C; e) Merrifield resin, Cs₂CO₃, Bu₄NI, CH₂Cl₂, 5 d; f) TBAF, THF, 0 °C; g) Ac₂O, Et₃N, DMAP, CH₂Cl₂; h) MeONa, THF/MeOH 4:1, 25 °C, 8 h; i) Cs₂CO₃, Bu₄NI, 60 °C, DMF; j) LiOH_(aq)/THF/MeOH 1:1:1; k) NBS, THF/H₂O 4:1, 0 → 25 °C, 1 h; l) DDQ, CH₂Cl₂/H₂O 18:2, 25 °C, 2–3 h, then aqueous ascorbic acid or CH₂Cl₂/TFA 6:1, 25 °C, 8–10 h. TBS = *tert*-butyldimethylsilyl, py = pyridine, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TBAF = tetrabutylammonium fluoride, DMAP = 4-dimethylaminopyridine, NBS = *N*-bromosuccinimide, TFA = trifluoroacetic acid.

selected an oxidatively cleavable aromatic ether (linker L, Scheme 1). This linker was designed^[9] to tolerate basic and mildly acidic or oxidative conditions and be cleaved rapidly upon treatment with DDQ or TFA. In the optimum loading procedure the respective furyl alcohol (pyranone precursor) was coupled with the linker and then loaded on Merrifield resin by using Cs₂CO₃ (Scheme 1). Thus, furyl alcohol **3** was prepared by conversion of allyl ether **2** into the corresponding aldehyde, followed by addition of furyllithium. This alcohol, after oxidation and subsequent derivatization with Grignard reagents, was transformed into tertiary alcohols **4** (route A). The latter, after desilylation, were loaded on the resin to afford supported furyl alcohols **6**, which were oxidized to 2*H*-pyran-3(6*H*)-ones **9** in high yields following a slightly modified reported protocol.^[7c] Secondary alcohol **3** could also be loaded on the resin in the same fashion after protection of the hydroxy group (route B). Complicated substrates could also be loaded by using an additional “handle” on the side chain (e.g., route C). Most of the compounds were cleaved efficiently and isolated in satisfactory yields and purity; cleavage conditions, yields, and purity are presented in Table 1.

For the practical demonstration of the use of 2*H*-pyran-3(6*H*)-ones **9** as key intermediates with great potential for diversification we carried out a significant number of derivatizations and transformations (Scheme 2). Upon treatment with isocyanates they were converted into carbamates **10**, scaffolds known to show anticoccidial and antimicrobial activities.^[8a,b] These carbamates were treated with further alcohols to give bioactive ethers **11** by using catalytic HClO₄ or, under alkaline conditions, quantitatively converted into pharmacophoric oxazolidiones **12**.^[10] A patented procedure was applied to convert substrates **12** into angiogenesis inhibitor **13**,^[8k] albeit in low yield.

Further oxidation of substrate **9** with the Dess–Martin reagent afforded pyrones **14**, which were transformed, after reduction with NaBH₄, into lactones **15**. The latter may serve as the core structures for the generation of new libraries since they have many reactive sites for derivatization with either nucleophilic or electrophilic reagents, as well as with dienes. Moreover, pyrone **14**, after treatment with several binucleophiles,^[11] was transformed into medicinally important heterocycles such as thiazinones **16**, benzothiazinones **17**, and diazepinones **18**. Pyranone **9** was also directly esterified (to give **19**) or etherified (to give **21**). These classes of compounds are known for their antimicrobial (against both Gram-positive and Gram-negative bacteria), antifungal, pesticidal, and anticoccidial activities.^[8] Acetate **19** (R³ = CH₃) served as a model glycosyl acceptor and was efficiently glycosylated with 6-*O*-methyl-2,3,4-triacetylglycopyranoside.^[12] Methyl ether **21** (R⁵ = CH₃) was used as a Michael acceptor to yield deoxy-sugar derivatives **22** and **23**. The same substrate (**21**) was reduced with NaBH₄ and subsequently epoxidized to afford epoxide **24**, which was further derivatized to give sugar derivatives **25**.^[7b,8l]

Application of additional known transformations already listed in Figure 1 should lead efficiently to further structurally diversified substrates. Furthermore, new reactions and novel transformations might be applied on these highly reactive

Table 1. Structures, cleavage conditions, yields, and purity of selected members of the library.

Substrate	Cleavage ^[a]	Structure	Substituents	Yield [%] (Purity [%]) ^[b]
9	A		R = Ph	95 (95)
9	A		R = (CH ₂) ₉ CH ₃	85 (80)
11	A		R = Ph, R ² = CH ₃	90 (85)
11	A		R = Ph, R ² = Bn	75 (80)
11	A		R = Ph, R ² = (CH ₂) ₇ CH ₃	85 (85)
11	A		R = (CH ₂) ₉ CH ₃ , R ² = CH ₃	85 (85)
12	A		R = Ph, R ⁹ = Bn	90 (90)
12	A		R = Ph, R ⁹ = CH ₃	90 (90)
12	A		R = (CH ₂) ₉ CH ₃ , R ⁹ = CH ₃	90 (90)
16	B		R = Ph	75 (pur.)
16	B		R = (CH ₂) ₉ CH ₃	65 (pur.)
17	B		R = Ph	70 (pur.)
17	B		R = (CH ₂) ₉ CH ₃	67 (pur.)
19	A		R = Ph, R ³ = C ₆ H ₅	95 (95)
19	A		R = Ph, R ³ = pNO ₂ C ₆ H ₄	95 (95)
19	A		R = Ph, R ³ = CH ₃	95 (95)
19	A		R = (CH ₂) ₉ CH ₃ , R ³ = pNO ₂ C ₆ H ₄	80 (85)
19	A		R = (CH ₂) ₉ CH ₃ , R ³ = C ₆ H ₅	80 (85)
21	A		R = Ph, R ⁵ = CH ₃	95 (95)
21	A		R = Ph, R ⁵ = CH ₂ CH ₃	90 (95)
21	A		R = (CH ₂) ₉ CH ₃ , R ⁵ = CH ₃	85 (95)
22	A		R = Ph, R ⁵ = CH ₃ , R ⁶ = S(CH ₂) ₃ CH ₃	90 (95)
22	A		R = (CH ₂) ₉ CH ₃ , R ⁵ = CH ₃ , R ⁶ = S(CH ₂) ₃ CH ₃	90 (95)
23	A		R = Ph, R ⁵ = CH ₃ , R ⁶ = N ₃	70 (80)
26	B		R = Ph, R ⁵ = CH ₃	80 (pur.)

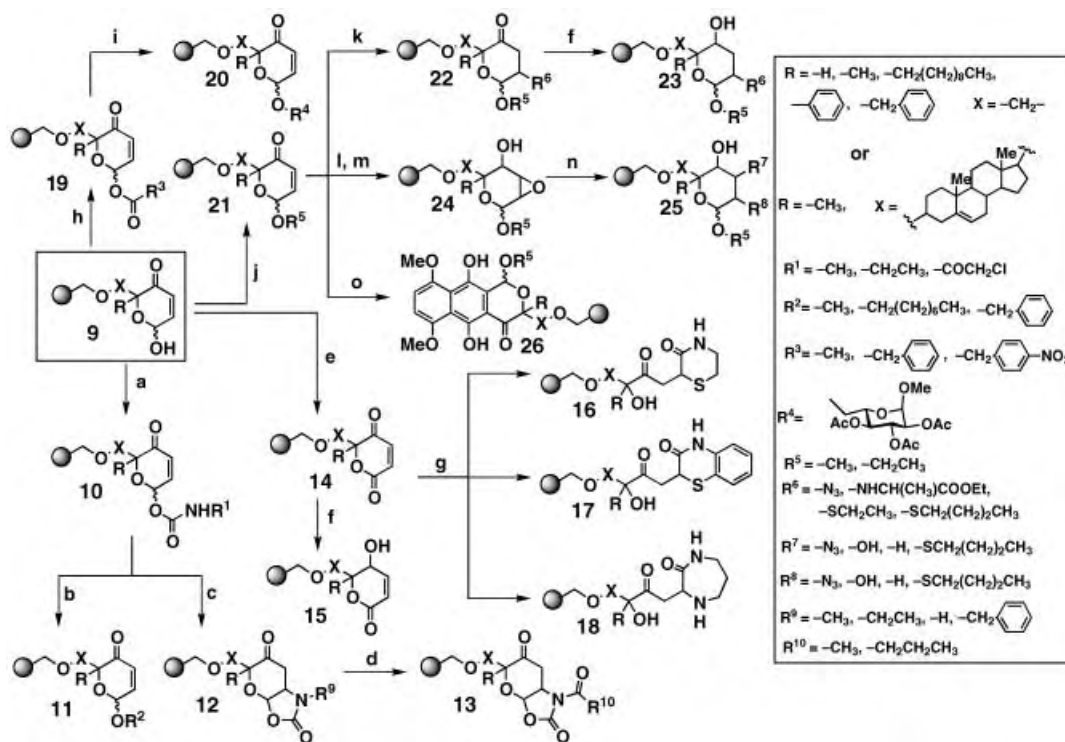
[a] For details on the cleavage conditions and compound characterization see the Supporting Information. Method A: DDQ, CH₂Cl₂/H₂O 18:2, 25 °C, 2–3 h; then ascorbic acid. Method B: CH₂Cl₂/TFA 6:1, 25 °C, 8–10 h. [b] Yields and purities (HPLC) pertain to the mixture after cleavage before any purification unless (purity) is stated.

molecules, thus expanding the range of targeted chemical classes. For example, 2*H*-pyran-3(6*H*)-ones (**21**) were efficiently transformed into pharmacophoric naphthoquinones **26** upon treatment with a dipole equivalent (Scheme 2).^[13]

In conclusion, we have demonstrated that a polymorphic synthetic key intermediate can be used as the core structure of a directed library leading through structural modifications to well-defined classes of compounds, each of which may subsequently serve as the intermediate for the construction of new directed libraries of medicinally important molecules.

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Scheme 2. Construction of a library from **9**. Reagents and conditions: a) R^1NCO , Et_3N , $0 \rightarrow 25^\circ C$, 2 h; b) R^2OH , THF, cat. $HClO_4$ 70 %, $25^\circ C$, 1 h; c) DBU, CH_2Cl_2 , $25^\circ C$, 12 h; d) for $R^9 = H$: $R^{10}COCl$, Et_3N , CH_2Cl_2 , $25^\circ C$, 6 h; e) Dess–Martin reagent, CH_2Cl_2 , $25^\circ C$, 12 h; f) $NaBH_4$, THF/ H_2O 1:4, $25^\circ C$, 0.5 h; g) binucleophile, CH_2Cl_2 , $25^\circ C$, 10 h; h) R^3COCl , Et_3N , $25^\circ C$, 12 h; i) glycosyl donor, $BF_3 \cdot Et_2O$, CH_2Cl_2 , $5^\circ C$, 6 h; j) $CH(OR^5)_3$, $BF_3 \cdot Et_2O$, THF, $0^\circ C$, 1 h; k) R^6SH , Et_3N , CH_2Cl_2 , $25^\circ C$, 2 h or $NaN_3(aq)$, CH_3COOH , pH 5, $25^\circ C$, 1 h; l) $NaBH_4$, THF/ H_2O 1:4, $25^\circ C$, 2 h; m) *m*CPBA, CH_2Cl_2 , $25^\circ C$, 6 h; n) nucleophile, CH_2Cl_2 , $25^\circ C$, 8 h; o) 4,7-dimethoxy-3-oxodihydroisobenzofuran-1-carbonitrile, LDA, THF, $-78 \rightarrow 0^\circ C$, 4 h. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, *m*CPBA = *m*-chloroperoxybenzoic acid, LDA = lithium diisopropylamide.

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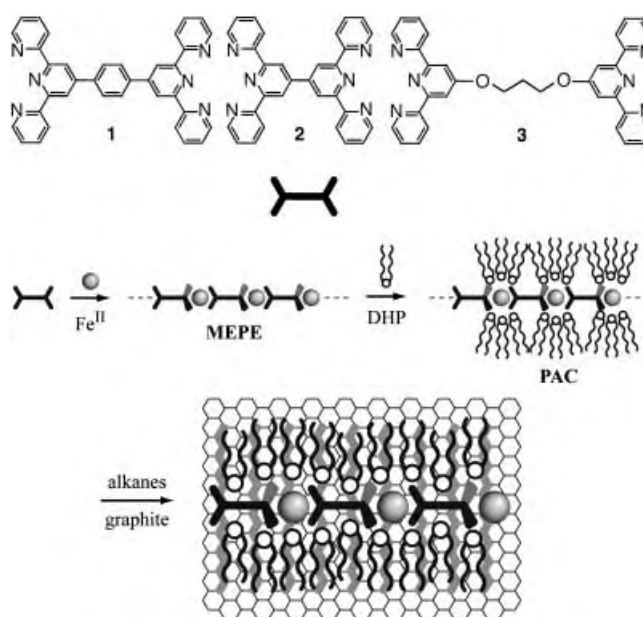
Perfectly Straight Nanostructures of Metallosupramolecular Coordination-Polyelectrolyte Amphiphile Complexes on Graphite**

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The progression of structural hierarchy from the atom to the molecule, the supermolecule, and the supramolecular assembly corresponds to an increase in diversity and complexity.^[1] At each level of the hierarchy, characteristic structural or functional features emerge that do not exist at lower levels. Multistep auto-assembly of architectures with structures of different length scales has, therefore, become a central objective in supramolecular chemistry and materials science.^[2] Important advances toward this goal were reported, particularly in the domain of metal-ion-induced superstructures.^[3] The intriguing prospects of supramolecular devices and materials have, in addition, stimulated research in this area recently.^[4] To address, manipulate, and operate functional devices individually at the nanoscopic level it is particularly interesting to assemble them on a surface.^[5]

We have developed a modular approach based on metallosupramolecular coordination polyelectrolytes (MEPEs)^[6] and the corresponding polyelectrolyte–amphiphile complexes (PACs)^[7] that provides a facile entry towards hierarchical architectures. These materials are readily self-assembled from metal ions, ditopic ligands, and amphiphiles as shown in Scheme 1. The composition of PAC-1 formed under the particular assembly conditions is such that six dihexadecyl phosphate molecules (DHPs) bind per repeat unit.^[8] Presumably, DHPs form a charged hydrogen-bonded network, which binds to the MEPE through electrostatic interactions as schematically depicted in Scheme 1. In contrast, the composition of PAC-2 and PAC-3 are such that two DHPs bind per repeat unit. The association of MEPE and DHP has a profound impact on the properties of the final material. PACs dissolve in common organic solvents spread at the air–water interface^[8] and form thermotropic liquid-crystalline mesophases.^[9] Herein we describe the self-assembly of perfectly straight and epitaxially oriented nanostructures of PACs based on the multicomponent sequential self-assembly process depicted in Scheme 1.

In a first series of experiments, submonolayers of PACs were spin-coated on bare graphite. Tapping-mode scanning



Scheme 1. Metal-ion-induced self-assembly of iron acetate and ditopic bisterpyridines, **1**, **2**, and **3**, results in metallosupramolecular coordination polyelectrolytes (MEPEs). A linear, positively charged macromolecule is formed as a consequence of the octahedral coordination geometry (indicated by the wedges). Sequential self-assembly of MEPE and dihexadecyl phosphate (DHP) gives the polyelectrolyte–amphiphile complex (PAC). Finally, PAC and alkanes auto-assemble on graphite. The bottom part schematically depicts the proposed model for the resulting nanostructures (simplified representation, not to scale). The alkanes (thick rods) adsorb epitaxially on the lattice of the basal plane of the underlying graphite surface. This alkane monolayer serves as a template for orienting the rigid rods of type PAC-1 and PAC-2.

force microscopy (SFM) images (not shown) revealed 2D objects with an average diameter of about 100 nm which one could ascribe either to single long coiled polymers or, alternatively, to aggregates of a few shorter polymer molecules. The objects made from PAC-1 and PAC-2 exhibit relatively short (< 50 nm) straight chain segments, while PAC-3 is completely coiled, which indicates that the flexible spacer in **3** hinders the formation of straight rods. Spin-coating a dilute solution of a mixture of PAC and a long chain alkane at a mass ratio around 1:10 then leads to perfectly straight nanostructures of PAC-1 and PAC-2, with lengths up to 200 nm being obtained. Figure 1 shows SFM images of a submonolayer of PAC on top of an alkane monolayer. Imaging the bottom layer reveals regular highly ordered lamellae, which are characteristic for self-assembled monolayers of alkanes on graphite (Figure 1b, inset).^[10] The long chain alkanes seem to preferentially wet the graphite surface, while the PACs assemble on top of the interface and became oriented parallel to the alkane lamellae axis and, therefore, 30° relatively to a graphite lattice axis.^[11] We note that the distance between the PAC rods is always (5.5 ± 0.3) nm, irrespective of the length of the alkanes utilized, which indicates that the alkane layer orients and straightens the PAC, but does not determine the distances between adjacent PACs. The width of the PAC can be as large as 6 nm if the alkyl chains are fully extended. We, therefore, conclude that the imaged objects correspond to individual PAC rods.

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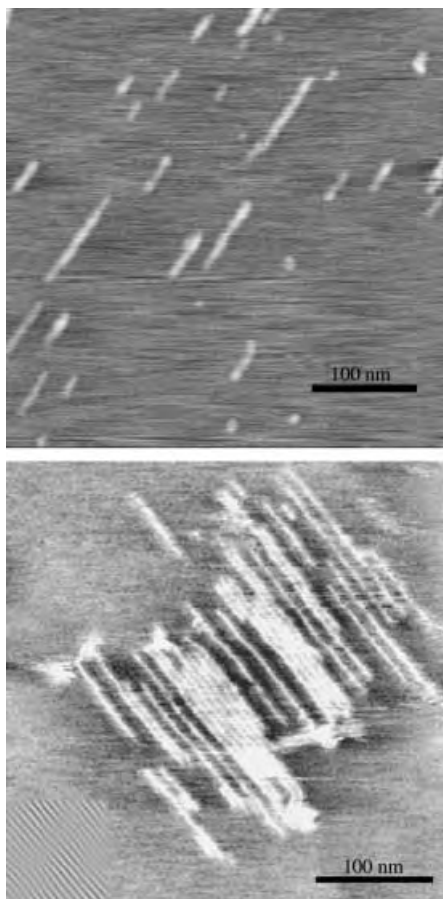


Figure 1. Top: Representative SFM image of PAC-1 adsorbed in the presence of $C_{32}H_{66}$ on the basal plane of graphite. Bottom: SFM image of a sample prepared from about twice the concentration and recorded with harder tapping than usual. The bottom layer consists of regular ordered lamellae of the self-assembled alkane monolayer (inset shows a filtered image of a part of the surface with the pure alkane monolayer). Perfectly straight PAC rods are observed on top of the alkane template layer.

The distributions of rod lengths P of PAC-1 and PAC-2 are displayed in Figure 2 for rods which were longer than 30 nm. The error bars indicate the statistical error of each data point. If an association equilibrium is assumed, the length distribution P of assemblies is given by $P \approx C_n = e^{-\alpha n} (C_1 e^{\alpha})^n$, where n is the number of repeat units in an assembly, α is the binding energy per repeat unit in units $k_B T$, and C_n is the concentration of assemblies consisting of n monomers.^[12] The resulting total concentration is then given by $C = \sum_{n=1}^{\infty} C_n = \frac{C_1}{(1 - C_1 e^{\alpha})^2}$. By combining the two equations, one can solve for the binding energy α since the concentration C is known and C_n is determined experimentally. The resulting binding energies are $(21.5 \pm 1)k_B T$ (53.4 kJ mol^{-1}) for PAC-1 and $(19 \pm 1)k_B T$ (47.2 kJ mol^{-1}) for PAC-2.^[13] We propose that coordination of the metal ion is the major contributor to the overall binding energy for two reasons: first, the cohesive energy of alkanes is much smaller compared to metal ion coordination and, second, it is further reduced because two or six DHPs per repeat unit cannot form a continuous close-packed structure. Additional evidence is provided by the observation that ordering by the amphiphiles is not strong enough to induce

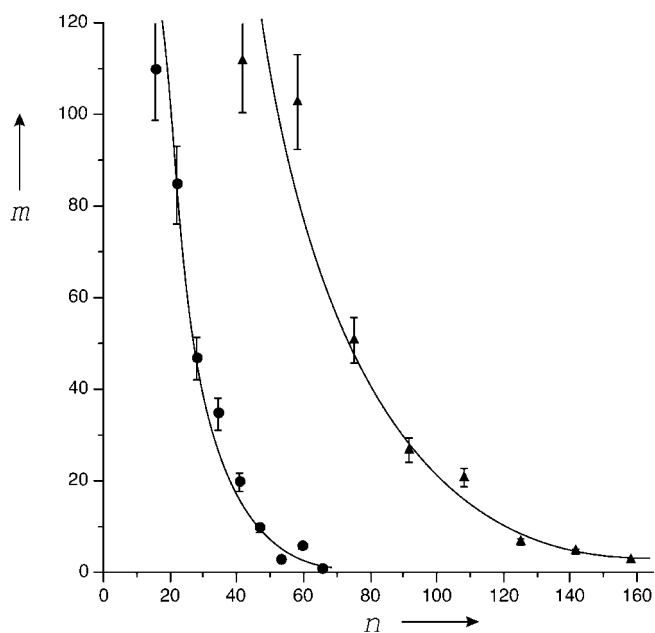


Figure 2. Experimental length distribution of PAC-1 ($\blacktriangle$) and PAC-2 ($\bullet$) determined by SFM and calculated length distribution (—) based on binding energies of $21.5 k_B T$ (53.4 kJ mol^{-1} , PAC-1) and $19 k_B T$ (47.2 kJ mol^{-1} , PAC-2). n = number of repeat units, m = occurrence.

orientation of the flexible PAC-3. A possible contribution of DHP to the overall binding energy might be reflected in the fact that PAC-1 (6DHPs) has a slightly higher binding energy than PAC-2 (2DHPs). Within the experimental error, the binding energies of both PACs are in agreement with that of mononuclear bisterpyridine Fe^{II} complexes in solution, which suggests that the assumption of an association equilibrium proposed above is reasonable.^[14]

The observations can be explained by the following model. In the absence of alkanes, PACs are not oriented because the potential ripple of the graphite surface is very small.^[11b] Immediately after spin-coating, the PACs are still mobile—since traces of remaining solvent facilitate molecular diffusion—which results in interfacial reorganization including polymerization and/or aggregation up to a point when all the solvent has evaporated. The PACs are now immobilized and can be visualized with SFM. In contrast, co-adsorption of PAC and alkanes results in perfectly straight PAC rods because the alkane molecules can form a stable, highly ordered monolayer at the solid/liquid interface^[10] and the surface potential ripple of an alkane monolayer is larger than that of a graphite surface (see also ref. [11d]). We, therefore, propose that the PAC and alkane molecules co-assemble at the interface such that the alkane molecules act as a template to orient the PACs.

It is interesting to note that the lengths of the PACs directly adsorbed on graphite are much longer than if they are co-adsorbed with alkanes, which reflects a higher concentration of PAC at the surface than in solution. In fact, the average length of self-aggregating macromolecules with a binding energy of $21.5 k_B T$ or $19 k_B T$ at the same concentration as observed at the surface should be around 560 and 270 nm, respectively, which is indeed of the order of the total contour lengths of PAC-1 and PAC-2 on bare graphite. On the other hand, at the solution concentration the equilibrium chain

lengths are expected to be 56 and 27 nm for PAC-1 and PAC-2, respectively, which correspond approximately to the actual average PAC lengths adsorbed in the presence of alkanes. Therefore, we suggest that the length distribution of PACs in solution is preserved upon co-adsorption of PAC and alkanes. Apparently, PACs and alkanes co-assemble at the interface without interfacial reorganization.

In summary, almost perfectly straight and epitaxially oriented chains of metallosupramolecular coordination-poly-electrolyte-amphiphile complexes formed from rigid ditopic metal ion receptors are self-assembled on the basal plane of graphite by using long chain alkanes as an orienting template layer. Through a sequence of molecular recognition steps comprising metal ion coordination, electrostatic interactions, and amphiphilic self-assembly the adsorption of nanoscopic assemblies can be performed at an interface in a predictable manner. Controlling the correlation of position and orientation is of paramount importance for encoding new properties and functions.^[15] On-going research in our laboratories indicates that this approach is of general utility. The modularity of this approach provides an entry to encode the value-adding physicochemical properties of metallosupramolecular devices into nanoscopic architectures that can be addressed and manipulated individually by scanning probe techniques.

Experimental Section

Ligands **1**, **2**, and **3** were prepared according to literature procedures.^[16] The assembly of MEPE and PAC was carried out according to previously published procedures.^[8] Alkanes ($C_{32}H_{66}$, $C_{44}H_{90}$, $C_{50}H_{102}$, Aldrich) were used as received. Solutions of neat PACs ($1.3 \times 10^{-3} \text{ g L}^{-1}$) or mixtures of PAC ($1.3 \times 10^{-3} \text{ g L}^{-1}$) with $C_{32}H_{66}$, $C_{44}H_{90}$, $C_{50}H_{102}$ ($1.3 \times 10^{-2} \text{ g L}^{-1}$) were spin-coated onto the basal plane of highly oriented pyrolytic graphite (HOPG, Advanced Ceramics Co., USA, quality ZYH at 40 rps). The coated graphite samples were dried for 10 min at 40 °C before SFM investigations were carried out with a Nanoscope IIIa (Digital Instruments, Santa Barbara, CA) in the tapping mode. An E-scanner over a range of scan lengths from 5 to 0.3 μm , and commercial Si cantilevers (length 125 μm and width 30 μm) with spring constants between 17 and 64 N m^{-1} were used.

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($\text{C}_2\text{H}_{10}\text{N}_2$)[Cr(HPO_3) F_3]: The First Organically Templated Fluorochromium(III) Phosphite**

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In recent years the search for new open-framework materials with transition metal elements has become the focus of much interest due to the potential application of these materials as absorbents, ion exchangers, solid-state electrolytes, and catalysts in heterogeneous catalysis.^[1] Such applications are not possible with main group systems of tetrahedral framework zeolites. The syntheses of these materials usually involve organic templates, for example organic diamines, for generating large cavities and are performed under mild hydrothermal conditions to avoid the formation of dense phases.

Microporous behavior has been successfully extended to the phosphate and arsenate systems of at least 14 elements of the periodic table, but examples dealing with chromium have not been reported.^[1b,2] The pattern of behavior of these kinds of compounds is underpinned by the strength of the P–O

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bond, which is broadly comparable with that of Si–O and Al–O bonds. Therefore, the relative stabilities within this family of M–P–O materials are probably determined by the M–O bond strengths. However, less work has been carried out on the anionic part of the inorganic network. The possibility of incorporating the pyramidal $(\text{HPO}_3)^{2-}$ hydrogen phosphite group into extended structures templated by inorganic alkaline earth cations was explored a few years ago.^[3] Recently we prepared several phosphite compounds templated by alkyldiamine molecules,^[4] which incorporate 3d transition metal cations.

At a first glance it appears that the Cr^{III} –P–O system would surely show excellent kinetic and thermodynamic stability, given the large ligand field stabilization energy of the octahedrally coordinated Cr^{III} cation. However, the particular behavior of Cr^{III} in solution, with many condensation steps between the octahedra, can make the attainment of Cr^{III} phosphate systems difficult.^[5] Recently, a chromium(III) dicarboxylate compound exhibiting a microporous structure was formed.^[6] To date, neither inorganic–organic hybrid phosphate nor phosphite materials containing the Cr^{III} cation have been reported. Here we describe the synthesis and crystal structure of $(\text{C}_2\text{H}_{10}\text{N}_2)[\text{Cr}(\text{HPO}_3\text{F}_3)]$, the first organically templated M–P–O compound containing Cr^{III} .

The crystal structure of $(\text{C}_2\text{H}_{10}\text{N}_2)[\text{Cr}(\text{HPO}_3\text{F}_3)]$ consists of $[\text{Cr}(\text{HPO}_3\text{F}_3)]^{2-}$ chains running along the $[001]$ direction, in which the fluoride anions stabilize the +3 oxidation state of chromium. The ethylenediammonium cations are in the cavities of the structure delimited by three different chains (Figure 1). These organic cations establish both ionic interactions and hydrogen bonds with the anionic chains.

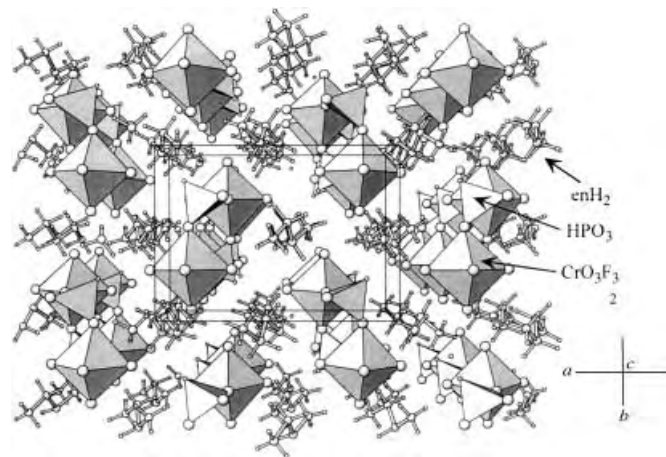


Figure 1. Crystal structure of $(\text{C}_2\text{H}_{10}\text{N}_2)[\text{Cr}(\text{HPO}_3\text{F}_3)]$.

The $[\text{Cr}(\text{HPO}_3\text{F}_3)]^{2-}$ chains are constructed from isolated CrO_3F_3 octahedra and pseudopyramidal $(\text{HPO}_3)^{2-}$ phosphite oxoanions (Figure 2). The CrO_3F_3 octahedra share the *trans* O(1) and O(3) atoms with the HPO_3 tetrahedra, forming an infinite chain of alternating octahedra and tetrahedra. Each octahedron also shares its O(2) atom with another HPO_3 tetrahedron belonging to a parallel chain, giving rise to infinite double chains as shown in Figure 2. A remarkable feature of this compound is the absence of covalent Cr–O–Cr intrachain interactions.

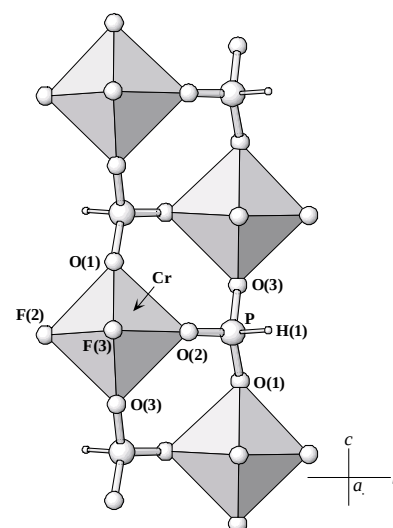


Figure 2. Representation of the chains in $(\text{C}_2\text{H}_{10}\text{N}_2)[\text{Cr}(\text{HPO}_3\text{F}_3)]$. The Cr–O and Cr–F distances range from 1.880(3) to 1.974(4) Å. The *cis* and *trans* angles are between 86.3(2)–94.7(2)° and 175.7(2)–176.4(2)°, respectively. The Cr^{III} – Cr^{III} intrachain bond distances are 4.883(2) and 6.508(2) Å. The mean P–O bond distance is 1.55(8) Å.

The reflectance diffuse spectrum of $(\text{C}_2\text{H}_{10}\text{N}_2)[\text{Cr}(\text{HPO}_3\text{F}_3)]$ is characteristic of Cr^{III} with octahedral coordination.^[7] The values of the D_q and Racah parameters are $D_q = 1535 \text{ cm}^{-1}$, $B = 720 \text{ cm}^{-1}$, and $C = 3280 \text{ cm}^{-1}$. The B parameter is approximately 75% of that corresponding to the Cr^{III} ion (918 cm^{-1}), which indicates the existence of significant covalent character in the Cr–O bonds.

The molar magnetic susceptibility χ_m increases with decreasing temperature in the range studied (Figure 3). The

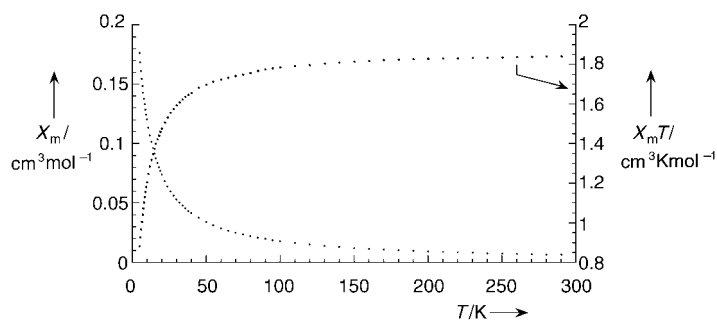


Figure 3. Thermal evolution of the molar magnetic susceptibility χ_m and the product $\chi_m T$ for $(\text{C}_2\text{H}_{10}\text{N}_2)[\text{Cr}(\text{HPO}_3\text{F}_3)]$. The arrow in the figure indicates that the curve corresponds to the $\chi_m T$ versus T representation.

thermal evolution of χ_m follows the Curie–Weiss law at temperatures above 10 K, with $C_m = 1.88 \text{ cm}^3 \text{ K mol}^{-1}$ and $\theta = -5.4 \text{ K}$. The value for $\chi_m T$ decreases from $1.84 \text{ cm}^3 \text{ K mol}^{-1}$ at 300 K to $0.88 \text{ cm}^3 \text{ K mol}^{-1}$ at 5.0 K, indicating the existence of antiferromagnetic interactions.

Experimental Section

$(\text{C}_2\text{H}_{10}\text{N}_2)[\text{Cr}(\text{HPO}_3\text{F}_3)]$: A mixture of $\text{Cr}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (1.00 g, 2.51 mmol), H_3PO_3 (1.23 g, 15.00 mmol), HF (1.0 mL, 27.59 mmol), and ethylenediamine (up to pH 2.0) in 20 mL of water/ethanol (1/1) was stirred until homogeneous, and sealed in a PTFE-lined (PTFE = poly(tetrafluoroethy-

lene) stainless-steel pressure vessel (fill factor 75%). The reagents were heated at 170 °C for 5 d, and then the mixture was slowly cooled to room temperature. The pH value did not show any appreciable change during the hydrothermal reaction. Small, well-formed, green single crystals were formed. Elemental analysis calcd for $C_2H_{11}CrF_3N_2O_3P$: C 9.5, H 4.3, N 11.1, P 12.2, Cr 20.5, F 22.5; found: C 9.3, H 4.1, N 10.8, P 12.0, Cr 20.1, F 22.0. The IR spectrum does not show any bands above 3500 cm^{-1} , in accordance with the absence of $(OH)^-$ groups.^[8] A density of $2.11(1)\text{ g cm}^{-3}$ was measured by flotation in $CHCl_3/CHBr_3$ (60/40).

Physical measurements: The diffuse reflectance spectrum was recorded at room temperature on a Cary 2415 spectrometer from 210–2000 nm. Magnetic measurements on powdered samples were performed at temperatures between 5.0–300 K, using a Quantum Design MPMS-7 SQUID magnetometer. The magnetic field was 0.1 T, a value in the range of linear dependence of magnetization vs. magnetic field, even at 5.0 K.

Structure determination of $(C_2H_{10}N_2)[Cr(HPO_3)_3F_3]$: $0.08 \times 0.035 \times 0.03\text{ mm}$, $M_r = 251.10$, orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 12.801(2)$, $b = 9.337(1)$, $c = 6.508(1)\text{ Å}$, $V = 777.9(2)\text{ Å}^3$, $Z = 4$, $\mu = 1.703\text{ mm}^{-1}$, $\rho_{\text{calcd}} = 2.144\text{ g cm}^{-3}$, $F(000) = 508$. The data were collected on a BRUKER SMART-APEX CCD automated diffractometer (graphite-monochromated MoK_{α} radiation, $\lambda = 0.71073\text{ Å}$, $T = 100\text{ K}$). Of 4588 measured reflections ($2.70^\circ \leq \theta \leq 28.45^\circ$), 1176 were independent ($R_{\text{int}} = 0.0521$) and 1100 observed ($I > 2\sigma(I)$). An absorption correction based on symmetry-equivalent reflections was applied using SADABS.^[9] The structure was solved by direct methods (SHELXS 97)^[10] and refined by the full-matrix least-squares method based on F^2 , using the SHELXL 97 computer program^[11] belonging to the WINGX V1.63.02 software package.^[12] All non-hydrogen atoms were assigned anisotropic thermal parameters. The atomic coordinates of the hydrogen atoms of the phosphite anions were calculated from difference Fourier maps, the hydrogen atoms of the ethylenediammonium cations were geometrically placed. Final R factors: $R1 = 0.088$ (all data), $wR2 = 0.127$; max./min. electron density $0.673/-0.976\text{ e Å}^{-3}$; goodness of fit on F^2 : 0.879. Further details on the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, 76344 Eggenstein-Leopoldshafen, Germany (fax: (+49)7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-412497. A simulation based on the single-crystal structure of $(C_2H_{10}N_2)[Cr(HPO_3)_3F_3]$ was in excellent agreement with the X-ray powder data, indicating phase purity and high crystallinity.

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Tuning Electronic Behavior of Carbonyl Metal Clusters by Substitution of Interstitial and Capping Atoms**

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Ligand-stabilized, nanosized metal clusters have been proposed as an ultimate solution for nanolithography and microelectronics.^[1] In this context metal carbonyl clusters could also play a role as they are potential nanocapacitors. However, for the cluster to truly function as a capacitor, its CO shell should effectively insulate the metal core, and it should be able to reversibly accept and donate electrons. At present there is no evidence of intermolecular exchange of electrons between differently charged carbonyl clusters, at least on the EPR timescale. They act as quantum dots, in which the cluster valence electrons are confined.^[2] However, most metal carbonyl clusters displaying redox behavior have fortuitously been obtained.^[3]

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To develop clusters as molecular capacitors, it would be desirable to know how to tailor their geometry and composition in order to modulate their electronic behavior and tune their redox potentials. Complementary work carried out by Dahl and co-workers^[4] and our research groups^[5] on non-centered icosahedral Ni_{10}E_2 and Ni-centered $\text{Ni}_{10}\text{E}_2(\mu_{12}\text{-Ni})$ carbonyl clusters ($\text{E} = \text{Ge}, \text{Sn}, \text{P}, \text{As}, \text{Sb}, \text{Bi}, \text{Se}, \text{Te}$) showed that the presence of an interstitial Ni atom alters the number of cluster valence electrons and triggers reversible redox behavior and multivalence in otherwise electron-precise clusters.^[5] Therefore, it appeared possible that substitution of the interstitial atom of a given cluster could allow modulation of its electronic behavior. To prove this assumption, we started a systematic investigation of bimetallic Ni–Rh carbonyl clusters with the aim of obtaining body-centered cubic clusters related to either $[\text{Rh}_{14}(\text{CO})_{25}]^{4-}$ (**1**)^[6] or $[\text{Rh}_{15}(\text{CO})_{30}]^{3-}$,^[7] but featuring Ni as the interstitial atom. Previously reported Ni–Rh carbonyl clusters—for example, $[\text{Ni}_{10}\text{Rh}(\text{CO})_{19}]^{3-}$, $[\text{Ni}_9\text{Rh}_3(\text{CO})_{21}]^{3-}$, $[\text{Ni}_6\text{Rh}_3(\text{CO})_{17}]^{3-}$, and $[\text{Ni}_6\text{Rh}_5(\text{CO})_{21}]^{3-}$ ^[8,9]—were obtained by reaction of $[\text{Ni}_6(\text{CO})_{12}]^{2-}$ with 0.25–1 equiv of $[\text{Rh}(\text{cod})\text{Cl}]_2$ (cod = cyclooctadiene) or $[\text{Rh}(\text{CO})_2\text{Cl}]_2$.

We now report that the addition of 1.5–1.7 equiv of $[\text{Rh}(\text{cod})\text{Cl}]_2$ to $[\text{Ni}_6(\text{CO})_{12}]^{2-}$ in acetone leads to a mixture of $[\text{NiRh}_{13}(\text{CO})_{25}]^{5-}$ (**2**), $[\text{Ni}_2\text{Rh}_{12}(\text{CO})_{25}]^{4-}$ (**3**), and $[\text{Ni}_3\text{Rh}_9(\text{CO})_{25}]^{3-}$ (**4**). Owing to similar solubilities of the $[\text{NEt}_4]^+$ salts, the complexes were roughly separated by subsequent extractions with acetone. Monitoring by IR spectroscopy indicated that the initial extraction portions contained **4** as the prevalent species, whereas the final portions gave mainly a mixture of **2** and **3**. Upon precipitation with hexane, pure $[\text{NEt}_4]_3[\textbf{4}]$ (30–35% yield based on rhodium) crystallized from the first fraction, and cocrystallized mixtures (20–25% yield) of $[\text{NEt}_4]_5[\textbf{2}]$ and $[\text{NEt}_4]_4[\textbf{3}]$ separated from the second fraction (see the Experimental Section).

These new tetradecanuclear bimetallic Ni–Rh clusters were shown by X-ray diffraction studies^[10] to be isostructural with **1**. In Figure 1 we present the structure of **4** as an example. The major differences between **2–4** and **1** (Table 1) are a shrinkage of the central Rh_8 cube, which contains an interstitial Ni atom in **2–4** rather than a Rh atom, and a shortening of the M–M interactions involving Ni or the disordered Ni/Rh cap (see below). In detail the four side caps of **4**, which are related by an idealized C_4 axis, are orderly occupied by Ni atoms, whereas the unique cap contained within the C_4 axis is made up of Rh. In contrast, in the cocrystallized mixture of **2** and **3** all the caps of the Ni-centered Rh_8 cube are made up of Rh atoms with the exception of one side cap, whose electron density could be refined as arising from substitutionally disordered Ni/Rh atoms (0.35/0.65, that is, Ni could substitute Rh in some molecules). Accordingly, the unit cell of the cocrystallized mixture contains five $[\text{NEt}_4]^+$ cations; however, one cation shows a refined occupancy fraction of 0.65, evidently because it is unnecessary when the cap in question is Ni. Monitoring of several single crystals from different preparations by IR spectroscopy and ESI mass spectrometry confirmed the above result by showing the presence of both **2** and **3** in each examined crystal.

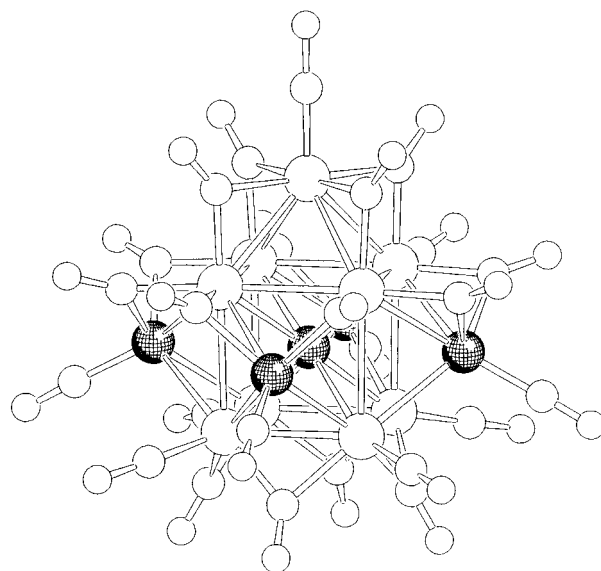


Figure 1. Crystal structure of **4**, as an example of the isostructural clusters **1–5**.

Table 1. Selected average M–M distances [Å] in complexes **1**, **2/3**, **4**, and **5** (M = Ni, Rh).^[a]

	1	2/3	4	5
$\text{M}_{\text{interstitial}}\text{--Rh}_{\text{cube}}$	2.64	2.53	2.49	2.46
$\text{M}_{\text{interstitial}}\text{--Rh}_{\text{top cap}}$	3.38	3.43	3.37	3.39
$\text{M}_{\text{interstitial}}\text{--M}_{\text{side cap}}$	3.08	3.34	3.15	3.13
Rh–Rh _{cube} (top square)	3.00	2.95	2.90	2.88
Rh–Rh _{cube} (bottom square)	2.80	2.82	2.80	2.75
Rh–Rh _{cube} (intersquare)	3.32	2.99	2.92	2.88
Rh _{top cap} –Rh _{cube}	2.79	2.85	2.84	2.84
$\text{M}_{\text{side cap}}\text{--Rh}_{\text{cube}}$	2.74	2.83	2.67	2.65
Ni/Rh _{side cap} –Rh _{cube}		2.77		

[a] Data for **1** are taken from reference [6d].

A substitution of Rh with Ni that is limited to the side caps of **1** is in keeping with the lower degree of CO coordination at these sites with respect to the top cap. On the contrary, it may appear surprising that Ni could replace Rh as the interstitial atom in the architecture of **1**. Indeed, Ni possesses a lower heat of atomization than Rh^[13] and the Ni–CO bond is energetic.^[14] Probably, the M–M energy loss upon Ni-centering of a $\text{Rh}_{14-x}\text{Ni}_x$ cluster is overcome by the gain in energy of the remaining Rh–Rh interactions arising from the contraction of the Rh_8 cube, as well as from substitution of Ni–CO with Rh–CO interactions.

The most striking feature of compounds **1–4** is that they are isostructural but not isoelectronic. Figure 2 presents the EHMO diagrams of the frontier region of **1–4** obtained with CACAO.^[15] These show that two additional MOs (which for **1** are relatively high in energy and fall in the antibonding region) are progressively stabilized as the interstitial Rh and then the side caps are replaced by Ni atoms.

Compounds **1–4** display electrochemically reversible redox properties. In particular, **4** can be chemically or electrochemically oxidized in reversible steps to the corresponding congeners $[\text{Ni}_5\text{Rh}_9(\text{CO})_{25}]^{2-}$ (**5**, $E_{1/2} = -0.34$ V) and $[\text{Ni}_3\text{Rh}_9(\text{CO})_{25}]^{-}$ (**6**, $E_{1/2} = -0.18$ V). Complex $[\text{NEt}_4]_2[\textbf{5}]$

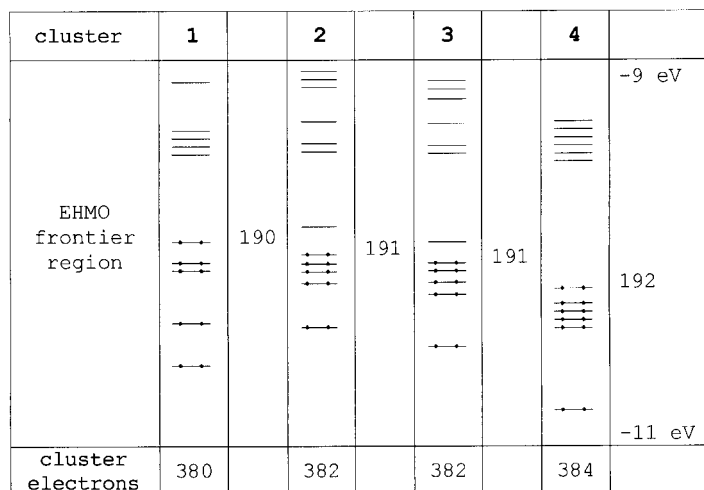


Figure 2. The frontier region between -11 and -9 eV of the EHMO diagram of **1–4**. The number of cluster electrons is obtained with the following formula: $N_{\text{Ni}} \times 10 + N_{\text{Rh}} \times 9 + N_{\text{CO}} \times 10 + N_{\text{negative charges}}$

($\bar{\nu}_{\text{CO}}$ (MeCN) = 2027 s, 1984 m, 1895 m, 1868 s cm^{-1} ; $g = 2.07$) has been isolated and characterized by X-ray structure analysis.^[10c] As expected, **5** is isostructural with **4**, with the major difference being a further contraction of the Rh_8 cube (see Table 1).

In contrast to complex **1**, compounds **2–4** do not readily afford the corresponding hydride derivatives upon protonation. The hydride atom of $[\text{HRh}_{14}(\text{CO})_{25}]^{3-}$ is fluxional in solution^[16] and swells the Rh_8 cube in the solid state.^[6b] Such an effect could justify the lack of propensity for protonation of **2–4**, since it would destabilize the observed structures.

In conclusion, **1–5** show that progressive Rh/Ni exchange modulates the electronic as well as chemical properties of this cluster architecture and prompts multivalence. As a direct consequence, such an exchange provides a further clue for obtaining more effective molecular capacitors by tailoring the metal cluster composition, as well as for tuning their redox and chemical behavior. This stems from the fact that, in contrast to the situation for main group elements,^[17] interstitial metal atoms should not only be regarded as an internal source of electrons. As a function of the relative energies of their valence orbitals, they may alter the number of cluster valence MOs.

Experimental Section

$[\text{NET}_4]_2[\text{Ni}_6(\text{CO})_{12}]$ (2.08 g, 2.19 mmol) was dissolved in anhydrous THF (50 mL) in a 250-mL flask under a nitrogen atmosphere. $[\text{Rh}(\text{cod})\text{Cl}]_2$ (1.61 g, 3.27 mmol) was added in portions under stirring over a period of 2 h. The resulting brown suspension was dried under vacuum, and the brown precipitate was washed with water (20 mL), THF (20 mL), and methanol (20 mL). The residue was extracted with five portions of acetone (10 mL each). The first two portions were combined, and isopropyl alcohol (30 mL) was diffused into the solution to precipitate 0.59 g of $[\text{NET}_4]_3[\text{4}]$ as black crystals. Elemental analysis calcd for $[\text{NET}_4]_3[\text{4}]$: Ni 12.71, Rh 40.10, C 25.46, N 1.82, H 2.60; found: Ni 12.4, Rh 40.3, C 25.27, N 1.76, H 2.67; $\bar{\nu}_{\text{CO}}$ (MeCN) = 2006 s, 1958 m, 1869 m, 1840 s, 1808 cm^{-1} .

The last three portions were also combined and treated to diffusion of isopropyl alcohol (50 mL) to precipitate 0.35 g of a cocrystallized mixture (ca. 2:1) of $[\text{NET}_4]_3[\text{2}]$ ($\bar{\nu}_{\text{CO}}$ = 1966 s, 1813 cm^{-1}) and $[\text{NET}_4]_4[\text{3}]$ ($\bar{\nu}_{\text{CO}}$ = 1983 s, 1820 s cm^{-1}).

Cyclic voltammetry measurements were performed at a platinum electrode in MeCN containing $[\text{NET}_4]\text{PF}_6$ (0.1 mol dm^{-3}) as the supporting electrolyte. The potentials are referred to that of the standard calomel electrode (SCE). Under the present experimental conditions the one-electron oxidation of ferrocene occurs at $E^\circ = +0.38$ V.

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- a) Crystal data for 0.65 $[\text{NET}_4]_3[\text{2}]/0.35[\text{NET}_4]_4[\text{3}]$: orthorhombic, space group $P2(1)2(1)2$, $a = 22.9818(12)$, $b = 26.5796(14)$, $c = 13.4220(7)$ Å, $V = 8198.8(7)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 2.177$ g cm^{-3} , graphite-monochromated $\text{MoK}\alpha$ radiation ($\lambda = 0.71073$ Å); the final R value was 0.0457 ($wR = 0.0804$) for 17837 independent reflections having $I > 2\sigma(I)$. b) Crystal data for $[\text{NET}_4]_3[\text{4}]$: tetragonal, space group $P4/ncc$, $a = 12.7817(3)$, $c = 45.3444(16)$ Å, $V = 7408.0(4)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 2.072$ g cm^{-3} , graphite-monochromated $\text{MoK}\alpha$ radiation ($\lambda = 0.71073$ Å); the final R value was 0.0735 ($wR = 0.2162$) for 4056 independent reflections having $I > 2\sigma(I)$. c) Crystal data for $[\text{NET}_4]_3[\text{5}]$: tetragonal, space group $P4(1)2$, $a = 12.9563(4)$, $c = 17.8804(7)$ Å, $V = 3001.51(18)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 2.413$ g cm^{-3} , graphite-monochromated $\text{MoK}\alpha$ radiation ($\lambda = 0.71073$ Å); the final R value was 0.0388 ($wR = 0.1077$) for 4423 independent reflections having $I > 2\sigma(I)$. The data were collected at 298 K and corrected for Lorentz polarization and absorption effects (empirical absorption SADABS^[11]). The structures were solved by

direct methods and refined with full-matrix least squares (SHELX97^[12]). CCDC-185351 for [NEt₄]₃[4], CCDC-185352 for [NEt₄]₂[5], and CCDC-185353 for 0.65 [NEt₄]₃[2]/0.35 [NEt₄]₄[3] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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Synthesis, X-ray Structure, and Properties of a Tetrabenzannelated 1,2,4,5-Cyclophane**

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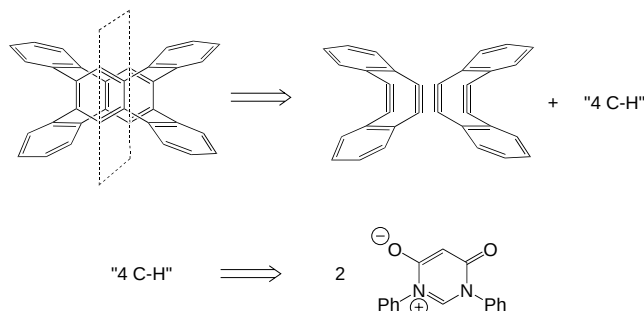
Parylene is the most frequently used material in the protective encapsulation of modern electronic components and medical implants.^[1] This high-performance polymer is produced by the pyrolytic decomposition of [2.2]paracyclophane.^[1c] Another high-performance organic material with even stronger C–C bonds would be produced if another highly strained, all-aromatic cyclophane could be pyrolyzed, thus resulting in a “superparylene”. However, contrary to the mode of pyrolytic decomposition of [2.2]paracyclophane, where scission of the C_{sp³}–C_{sp³} bond is the important first step leading to a p-xylylene monomer, in the case of a molecule such as **1** (Scheme 2), cleavage of a biaryl bond would produce a very reactive diradical monomer.

Angle and bond strain in organic molecules and their effect on properties also continue to be an active field of research.^[2]

Over the last five decades, a substantial number of chemists have prepared many fascinating, strained saturated and unsaturated molecules.^[2,3] The most notable of the strained unsaturated molecules are those of the fullerene C₆₀^[4] and the cyclophane families.^[5] In the former, the hexagons are essentially cyclohexatrienes^[6] and in the latter, the hexagons, while considerably distorted, still retain their benzenoid character. Since the first synthesis of [2.2]paracyclophane diene by Dewhirst and Cram,^[7] a variety of [2.2]paracyclophanes with unsaturated or benzannelated bridges have been synthesized.^[8] The influence of the bridges on the trans-annular benzene interactions and the geometry of the strained cyclophanes has been widely investigated.^[9] To date, only a few unsaturated bridged and benzannelated cyclophanes are known,^[9] but no benzannelated [2_n]cyclophane with more than two bridges (*n* > 2) has been reported.^[10] One would expect that, as the number of *o*-phenylene bridges increased, the total strain would also increase.

To prepare a superparylene and to test the effect of benzo bridges in place of the alkyl bridges of cyclophanes one needs a rapid, reasonably high-yield synthetic entry. A priori, based on existing cyclophane synthetic methodology, the preparation of a symmetrical tetrabenzannelated [2_n]cyclophane tetraene would appear to be rather difficult and lengthy. However, careful consideration of the molecular symmetry of the target revealed that the synthesis could be easily achieved. Herein, we describe the synthesis, X-ray structure, and some of the properties of the symmetrically benzannelated [2₄]cyclophane tetraene **1**. In future publications we will report on the results of its pyrolytic decomposition.

In Scheme 1 we depict the retrosynthetic analysis with a rather unusual disconnection leading to two dibenzocyclooctadiene-dynes and four methine units. As shown, the latter can originate from a *meso*-ionic precursor.



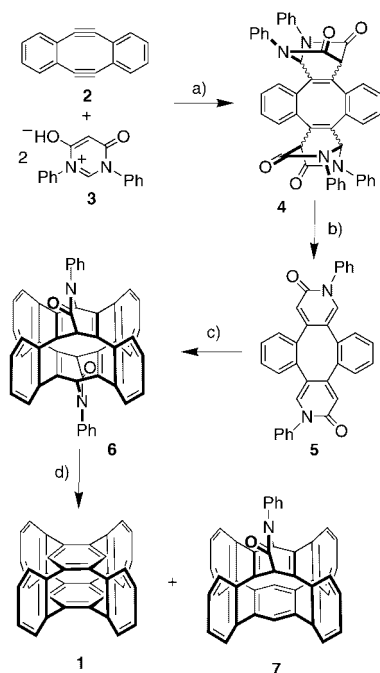
Scheme 1. Retrosynthetic analysis of **1**.

The synthesis of the tetrabenzocyclophane **1** is based on the known Diels–Alder reactivity of diene **3**^[11] to afford **4** (as a mixture of *syn* and *anti* isomers),^[12] followed by thermal extrusion of phenyl isocyanate, which leads to a new reactive diene **5** (Scheme 2).^[13] The twofold addition of **2**^[14] to **3** afforded the bisadduct **4** in 70% yield; the monoadduct does not form even with a 1:1 ratio of reagents. Pyrolysis of **4** gave reactive diene **5** quantitatively. Compound **5** has absorption maxima at 252 and 333 nm, and exhibits a weak blue fluorescence at 406 nm (in THF). It reacts with an excess of

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Scheme 2. Synthesis of cyclophane **1**. a) *o*-dichlorobenzene (ODCB), 110°C, 1 day; b) neat, 250°C, 1 h; c) **2**, ODCB, 150°C, 3 d; d) neat, 350°C, 4 h.^[13]

dienophile **2** to give compound **6** in 25% yield, without polymerization but accompanied by decomposition products of diyne **2**. The absence of polymerization is the result of: 1) the high dilution conditions and 2) the preorganization, arising from the boat conformation of the intermediate that results from the intramolecular cycloaddition to form **6**. Pyrolysis of **6** afforded a mixture of **1** (50% isolated) and **7** (30% isolated), which co-sublime at this temperature. In contrast to **4**, cyclophane precursor **6** is less willing to extrude its phenylisocyanate bridges. Thermogravimetric analysis (TGA) of **4** showed that the loss of the isocyanate occurred between 200 and 250°C, whereas with **6** a temperature of 350°C is required (see Supporting Information).

The thermally stable cyclophane **1** was isolated by column chromatography and characterized by ¹H and ¹³C NMR spectroscopy. Slow evaporation of a solution of **1** in CS₂ at 40°C afforded colorless platelike crystals suitable for X-ray structural analysis (Figure 1).^[15] To assess the electronic structure of **1** we performed quantum mechanical density functional theory calculations^[16] at the B3LYP/6-31G(d) level of theory^[17] (used for discussion of structural features) as well as ab initio calculations at the HF/3-21G* level^[18] (used for discussion of orbital energies).^[19,20]

The independent unit in the crystal is located at an inversion center and forms layers. The benzene moiety is significantly bent with deviation from planarity for the carbon skeleton of 0.133–0.139 Å (calcd 0.153 Å) and a C18'–C9–C8–C7 dihedral angle of 12.7–13.7° (calcd 14.6°) between the C–C bonds in the benzene moiety. A very significant strain is reflected in a large angle between the C6–C7 bond and the C7–C8–C17' plane (19.8–21.4°). The sum of three linear angles around C7 is 355.4–356.0° (calcd 355.8°), which reflects its partial sp³ character. The C–C–C angles (e.g., C1–C6–C7) in the

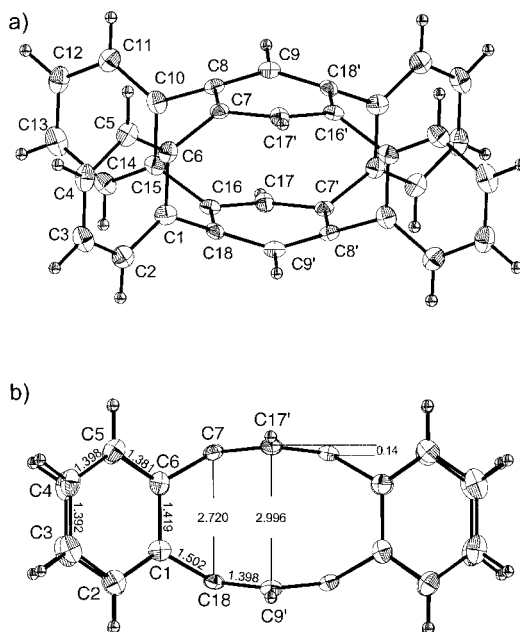


Figure 1. The X-ray structure of **1**. ORTEP view and numbering scheme of the independent molecule located on an inversion center (with 50% probability displacement ellipsoids). Selected bond angles [°]: C10–C15–C16 116.3(3), C17–C16–C18 118.5(4), C17–C16–C15 117.8(3), C18–C16–C15 119.6(3), C18'–C9–C8–C7 12.7(3).

benzo bridges are distorted to 115.3–116.3° (calcd 116.2°) and the C–C bond in the bridges is elongated to 1.419–1.424 Å (calcd 1.427 Å). The C9–C17 bond between the central carbon atoms of the cyclophane rings is 2.996 Å (calcd 3.060 Å), while the calculated distance between the two strained ring protons is shorter,^[21] at 2.912 Å.^[22] Consequently, in NMR experiments the C9 carbon atoms of the strained rings resonate at low field (δ : 139.3 ppm)^[23] and the adjacent protons resonate at higher field (δ : 6.57 ppm).

The UV/Vis spectrum, with two absorptions at 225 and 285 nm, is comparable to that of previously reported cyclophanes,^[24] but with an important exception: the broad “cyclophane band” appears at 330 nm, which is the most red-shifted position of this band recorded to date. Electrochemical experiments show an irreversible oxidation at $E_{\text{p.c.}} = +1.49$ V versus the ferrocene/ferrocenium couple^[25] and a reversible reduction wave at $E^0 = -2.80$ V for **1**. This observation should be contrasted with the oxidation wave for [2.2]paracyclophane ($E_{\text{p.c.}} = 1.10$ V, no reduction peak was observed down to -3.0 V) under the same conditions. At first sight, the large negative value observed for **1** is contrary to expectations based on strain arguments in fullerene chemistry, where the electron-accepting property was related to strain (hybridization).^[26] However, results of ab initio calculations indicate that although the LUMO (2.45 eV, Figure 2b) is lower lying than that of benzene (4.12 eV), it is higher than that of anthracene (1.81 eV), which reduces at a less negative potential ($E^0 = -2.47$ V). On the other hand, the larger value for the oxidation wave of **1** relative to [2.2]paracyclophane is consistent with increased strain in **1** compared with [2.2]paracyclophane; C₆₀ is also easier to reduce than to oxidize.^[27] The HOMO of cyclophane **1** (−8.21 eV Figure 2a) is relatively high, lying between that of benzene (−9.22 eV) and anthra-

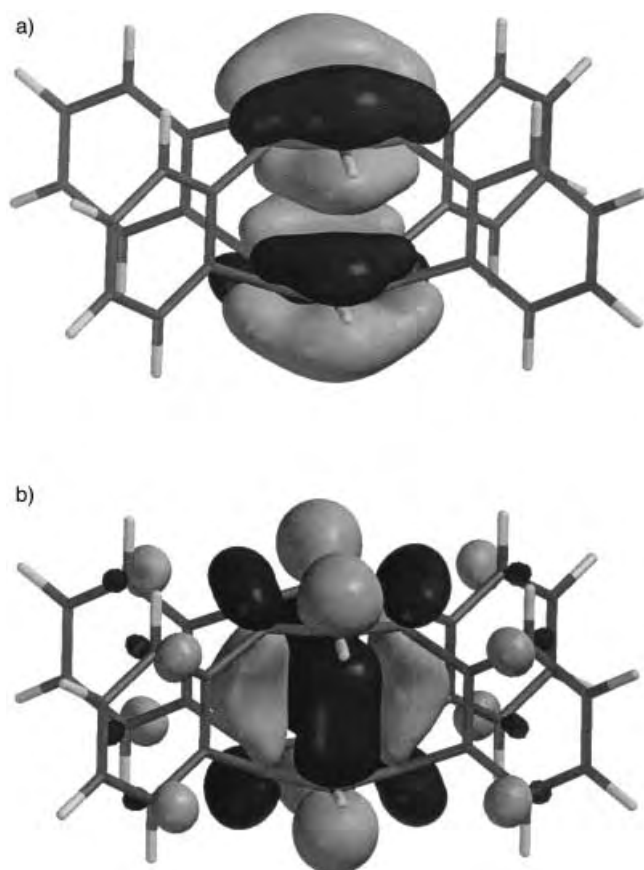
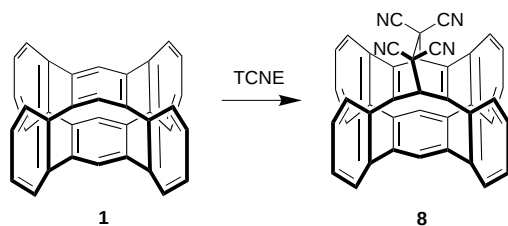


Figure 2. a) The HOMO and b) LUMO of **1** as calculated at HF/3-21G**/HF/3-21G* level, generated with Spartan 5.0.3.

cene (−7.16 eV). These low LUMO and high HOMO energies are further evidence of molecular strain.

As a result of the high HOMO energy, **1** is expected to be very reactive as a diene in Diels–Alder reactions. Indeed, the unusual electronic properties of the strained rings in **1** are manifested in their high reactivity towards tetracyanoethylene (TCNE).^[28] The published cyclophane (closest in structure to **1**), [2₄](1,2,4,5)cyclophane,^[29] forms a blue charge-transfer (CT) complex which lasts “a few seconds”,^[30] followed by formation of the Diels–Alder adduct. In addition, a highly strained pyrene belt cyclophane^[28] is converted at first into a green CT complex with a lifetime of minutes.^[31] In comparison, **1** reacts with TCNE directly, without the detection of a CT band (either visual or spectrophotometric) to produce adduct **8** in almost quantitative yield (Scheme 3). The disappearance of the “cyclophane” band, without the appearance of a CT band, can be followed spectroscopically (see Supporting Information).



Scheme 3. Addition of TCNE to cyclophane **1**.

In conclusion, we have described a simple, symmetry-driven synthesis of a strained, very thermally stable cyclophane. The distorted aromatic rings are more reactive with TCNE than those in [2.2]paracyclophane. Another consequence of heightened strain is a bathochromic shift of the cyclophane band to 330 nm, the longest wavelength absorption observed for this band to date. By using this methodology other benzo-ring-substituted cyclophanes should now be accessible through functionalized dibenzocyclooctadienediyne.^[32]

Experimental Section

All syntheses were performed under argon. See Supporting Information for detailed characterization of **4–6** and details of the reaction of **1** with TCNE.

4: A solution of **2** (100 mg, 0.500 mmol) and **3** (315 mg, 1.05 mmol) in *o*-dichlorobenzene (ODCB, 6 mL) was stirred at 110 °C until full conversion of **2** was indicated by thin-layer chromatography (TLC, 1 day). The red reaction mixture was evaporated in vacuo, and purified by column chromatography on silica (eluting with hexane/ethyl acetate, 1:1 v/v) to yield compound **4** (250 mg, 70%), which can be further purified by recrystallization from chloroform, m.p. 250 °C (decomp).

5: Compound **4** (50 mg, 0.069 mmol) was heated to 250 °C for 1 h in vacuo and then purified by column chromatography on silica (eluting with hexanes/ethyl acetate, 1:1 v/v) to give **5** as a light-orange powder (32 mg, 95 %), m.p. > 350 °C.

6: A solution of **5** (50 mg, 0.10 mmol) in ODCB was slowly added (16 h, using syringe pump) to a solution of **2** (20 mg, 0.10 mmol) in ODCB (5 mL) at 150 °C. The reaction mixture was stirred at 150 °C until full consumption of **5** (3 days, TLC monitoring), then ODCB was distilled in vacuo and the solid residue was purified by column chromatography on silica (eluting with chloroform) to give **6** as a powder (17 mg, 25 %), m.p. 350 °C (decomp).

1: Compound **6** (30 mg, 0.043 mmol) was heated in a sublimation apparatus to 350 °C for 4 h and the sublimed material was purified by column chromatography on silica (eluting with chloroform). The first fraction (*R_f* ca. 0.8) gave the target product **1** (10 mg, 50 %) as a white powder, m.p. > 350 °C (sublim). ¹H NMR (CDCl₃, 400 MHz): δ = 6.57 (s, 4H), 7.21 (q, *J* = 3.5 Hz, 4H), 7.38 ppm (q, *J* = 3.5 Hz, 4H); ¹³C NMR (Cl₂(CD)₂Cl₂, 125 MHz): δ = 124.6, 127.0, 139.3, 143.4, 144.3 ppm; UV/Vis (c-C₆H₁₂, λ_{max}, ε) = 225 (30300), 285 (3020), 330 nm (110); IR (DRIFT): ν̄ = 3060, 3024, 2924, 1444, 1234, 916, 750, 516 cm^{−1}; *m/z* (EI): 452 (*M*⁺, 100). HRMS (EI): calcd for [C₃₆H₂₀]: 452.1565; found: 452.1556. The second fraction afforded an intermediate **7** (7.4 mg, 30 %), m.p. > 350 °C, which can be converted into **1** under the conditions described for **6**.

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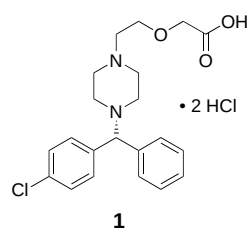
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- [13] Although a single isomer is shown for compounds **5** and **6**, one cannot say with certainty if it is the *anti* isomer (as shown). Chromatographic isolation of **5** and **6** produces a single isomer, as evidenced by NMR spectroscopy. However, final structural determination will have to rest with X-ray crystallography. It is possible that recrystallization of **4**, prior to pyrolysis, allowed selection of only one isomer, which could then only produce a single isomer of **5** (and hence **6**).
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Asymmetric, Catalytic Phenyl Transfer to Imines: Highly Enantioselective Synthesis of Diarylmethylamines**

Nina Hermanns, Stefan Dahmen, Carsten Bolm, and Stefan Bräse*

Enantiomerically pure diarylmethylamines are important intermediates in the synthesis of biologically active compounds.^[1] Cetirizine hydrochloride (**1**) stands out from several drug candidates as a commercially important non-sedating antihistamine agent. Binding studies indicate that the *R* enantiomer displays a better pharmacological profile than the racemate.^[2] Despite the importance of enantiopure diarylmethylamines, synthetic accesses and especially asymmetric (catalytic) processes for their synthesis are rather limited.^[3] While there are several synthetic routes to, for example, enantiopure cetirizine



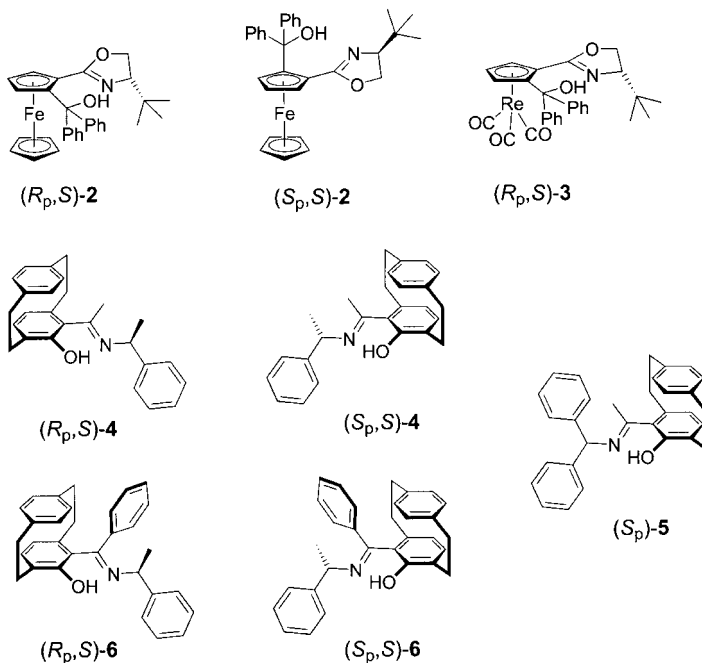
that utilize resolution techniques,^[4] stoichiometric amounts of chromium complexes,^[5] or diastereoselective approaches with chiral auxiliaries,^[6] to the best of our knowledge there is only a single report on an asymmetric catalytic addition of an organometallic arylation agent to an imine derivative. Hayashi and Ishigedani described a highly enantioselective rhodium-catalyzed process for the arylation of *N*-sulfonylimines with aryl stannanes (up to 96 % *ee*).^[7]

For quite some time we have been engaged in the asymmetric transfer of a phenyl group from organozinc reagents and have developed a protocol for the highly enantioselective transfer of a phenyl group to aldehydes using ferrocene (*R_p,S*)-**2** and cyrhetrene (*R_p,S*)-**3**.^[8] However, a major difficulty in the development of asymmetric processes for the transfer of a phenyl group remains the much higher reactivity of diphenylzinc relative to dialkylzinc and the concomitant rapid uncatalyzed background reaction.

Recently, we developed a catalytic procedure for the enantioselective addition of diethylzinc to masked *N*-formylimines by employing catalytic amounts of [2.2]paracyclophane-based ketimines.^[9,10] We now report on the combination of both methods, which leads to the first highly

enantioselective addition of phenylzinc to imines and gives rise to optically active diarylmethylamines in very high enantiomeric excesses.

At the outset of our study we examined the use of different N,O-ligands (Scheme 1) in the phenylation of *N*-[*p*-tolylmethyl-(toluene-4-sulfonyl)]formamide (**7a**, Table 1). This class of *N*-acylimine precursors is readily available in a one-pot



Scheme 1. N,O-Ligands employed in the asymmetric transfer of a phenyl group to imines.

synthesis from benzaldehyde, amide, and *p*-tolylsulfonic acid.^[11] The addition to the imine then proceeds by deprotonation of amide **7a**, followed by elimination of the sulfinic acid to form *N*-formylimine **8a**. Addition of the zinc reagent gives rise to the *N*-formylamine **9a**. We started out by employing the reaction conditions developed for the enantioselective transfer of a phenyl group to aldehydes using a mixed zinc reagent formed in situ from diphenylzinc and diethylzinc. This reagent selectively transfers only the phenyl moiety to the substrate to afford *N*-formylamine **9a** in very high yield without formation of the corresponding ethylation product.^[12]

The ligand screening (Table 1) showed that ferrocene (*R_p,S*)-**2** and cyrhetrene **3**, which represent the best ligands for the enantioselective transfer of a phenyl group to aldehydes (up to 99 % *ee*) so far, gave only moderate enantioselectivities in the addition to imine **8a** (entries 1 and 3). The catalysis with diastereomeric ferrocene (*S_p,S*)-**2** did not lead to any improvement (entry 2). In contrast, the use of [2.2]paracyclophane-based ketimines **4–6**^[13] gave rise to *N*-formyl-diarylmethylamines in good to excellent enantioselectivities (up to 97 % *ee*, entry 11). Ketimine (*R_p,S*)-**6** showed the best results in the ligand screening and was chosen for further optimization studies. Interestingly, (*S_p*)-**5** bearing only the element of planar chirality, also gave rise to the product amine in very high enantioselectivity (entry 6). Within our ongoing study of [2.2]paracyclophane-based N,O-ligands, this

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Table 1. Ligand screening for the transfer of a phenyl group to imines.^[a]

Entry	Ligand (10 mol %)	<i>T</i> [°C]	ZnPh ₂ /ZnEt ₂ [equiv]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	(<i>R</i> _p , <i>S</i>)- 2	0	2/2	98	54 (–)
2	(<i>S</i> _p , <i>S</i>)- 2	0	2/2	99	48 (–)
3	(<i>R</i> _p , <i>S</i>)- 3 ^[d]	–20	2/2	98	41 (–)
4	(<i>R</i> _p , <i>S</i>)- 4	0	2/2	99	89 (+)
5	(<i>S</i> _p , <i>S</i>)- 4	0	2/2	97	72 (–)
6	(<i>S</i> _p)- 5	0	2/2	94	91 (–)
7	(<i>S</i> _p , <i>S</i>)- 6	0	2/2	98	71 (–)
8	(<i>R</i> _p , <i>S</i>)- 6	0	2/2	99	93 (+)
9	(<i>R</i> _p , <i>S</i>)- 6	–10	2/2	99	95 (+)
10	(<i>R</i> _p , <i>S</i>)- 6	–10	1.2/1.2	96	92 (+)
11	(<i>R</i> _p , <i>S</i>)- 6	–20	1.5/1.5	98	97 (+)
12	(<i>R</i> _p , <i>S</i>)- 6	–20	1.2/1.2	85	87 (+)
13	(<i>R</i> _p , <i>S</i>)- 6	–20	2.5/–	99	92 (+)
14	(<i>R</i> _p , <i>S</i>)- 6	–40	2/2	51	67 (+)

[a] Reactions were carried out in toluene for 12 h with 0.25 mmol of imine precursor **7a**. [b] Determined by ¹H NMR spectroscopy. [c] Determined by HPLC on a chiral stationary phase (see Supporting Information). [d] 9 mol % of (*R*_p,*S*)-**3** was used.

is the first example of a ligand in which the combination of both planar and central chirality is not required to achieve high enantioselectivity.

Toluene proved to be the solvent of choice; in hexane only moderate yields were obtained. The amount and ratio of zinc reagents was varied and found to be optimal with respect to yield and enantioselectivity when 1.5 equivalents of both ZnPh₂ and ZnEt₂ were used (entries 9–12). If diphenylzinc was used alone, the *ee* value was slightly lower relative to that obtained with the mixed reagent (entries 11 and 13). This

observation can be explained by a faster and, therefore, more competitive uncatalyzed background reaction of diphenylzinc occurring relative to when the modified reagent formed from diphenylzinc and diethylzinc was used.

The reaction temperature had a significant impact on the stereochemical outcome of the process as well. With **7a** as the substrate, the highest *ee* value of 97 % was obtained at –20 °C. At –40 °C not only did the *ee* value drop significantly, but the yield was also diminished (entry 14).

A wider range of substrates was applied in the title reaction to demonstrate the broad applicability of the method (Table 2). The results reveal that aromatic imine precursors with different electronic properties as well as different substitution patterns are equally well tolerated. The substrates can be electron rich or electron poor, and even sterically hindered imines with a double *ortho* substitution gave excellent results (95 % *ee*, entry 8). Only a *meta*-substituted starting material gave a product with a slightly lower *ee* value (89 % *ee*, entry 7). Interestingly, the same effect was observed in the addition of diethylzinc to imines using (*R*_p,*S*)-**4** and (*R*_p,*S*)-**6**.^[9] A decrease in the catalyst loading resulted in the formation of products with slightly

or significantly lower enantiomeric excesses depending on the substrate (entries 2, 4, and 5).

The deprotection of *N*-formylamines **9** to the free amines can easily be achieved by acidic methanolysis (Scheme 2). The deprotection of *N*-formylamine **9b** proceeds quantitatively and without racemization. The absolute configuration of **9b** was assigned to be *R* by comparison of the specific optical rotation of free amine (–)-**10b** with the literature value.^[14,15] This configuration is consistent with the asymmetric induction observed in the addition of diethylzinc to imines in the presence of (*R*_p,*S*)-**4** and (*R*_p,*S*)-**6**.^[9] The *ee* value of *C*-(4-chloro-phenyl)-*C*-phenylmethanimine **10b** was determined by HPLC analysis of *N*-[(4-chlorophenyl)phenylmethyl]acetamide (**11b**) obtained by treatment of **10b** with acetic anhydride and triethylamine.^[16]

In summary, we have presented the first catalytic and highly enantioselective process for the asymmetric addition of a phenylzinc reagent to imines that gives rise to diarylmethyl-

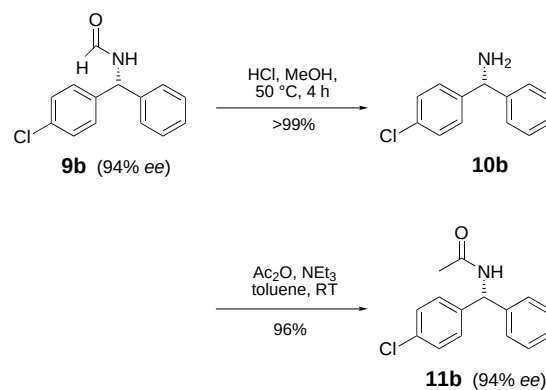
Table 2. Substrate spectrum for the transfer of a phenyl group to imines.^[a]

Reaction scheme for Table 2:

Starting material **7a-g** (R-substituted benzylideneformaldehyde) reacts with ZnEt_2 and ZnPh_2 to form intermediate **8a-g** (R-substituted benzylideneformaldehyde zinc complex). Intermediate **8a-g** then reacts with ZnEt_2 and ZnPh_2 catalyzed by $(R_p, S)\text{-6}$ to form product **9a-g** (R-substituted 1-phenyl-2-phenylmethanimine).

Entry	R	Product (R_p, S)- 6 [mol %]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]	
1	4-MeC ₆ H ₄	9a	10	99 (85)	97 (+)
2	4-MeC ₆ H ₄	9a	5	99	94 (+)
3	4-ClC ₆ H ₄	9b	10	99 (82)	94 (+)-(R)
4	4-ClC ₆ H ₄	9b	5	99	81 (+)-(R)
5	4-ClC ₆ H ₄	9b	1	98	69 (+)-(R)
6	4-MeOC ₆ H ₄	9c	10	99 (75)	97 (+)
7	3-MeC ₆ H ₄	9d	10	98	89 (+)
8	2,6-Cl ₂ C ₆ H ₄	9e	10	99 (89)	95 (+)
9	4- <i>t</i> BuC ₆ H ₄	9f	10	98 (81)	96 (+)
10	4-COOMeC ₆ H ₄	9g	10	99 (80)	95 (–)

[a] Reactions were carried out in toluene at –20 °C for 12 h, 1.5 equiv ZnPh₂, 1.5 equiv ZnEt₂, with 0.25 mmol of imine precursor **7a–g**. [b] Determined by ¹H NMR spectroscopy. Yields in parenthesis refer to yields after column chromatography. [c] Determined by HPLC on a chiral stationary phase (see Supporting Information).



Scheme 2. Deprotection of *N*-formylamine **9b**.

amines in excellent yields and enantioselectivities. Further optimizations and applications of this methodology as well as a detailed mechanistic study are in progress.

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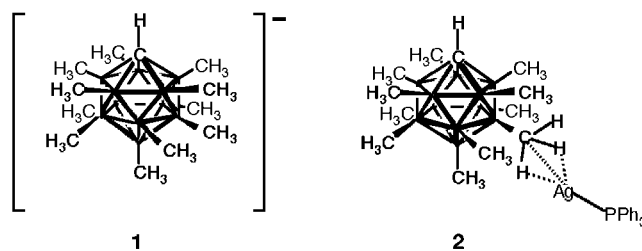
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[(PPh₃)Ag(HCB₁₁Me₁₁)][−]: A Complex with Intermolecular Ag...H₃C Interactions**

Michael J. Ingleson, Mary F. Mahon, Nathan J. Patmore, Giuseppe D. Ruggiero, and Andrew S. Weller*

Dedicated to Professor Thomas P. Fehlner on the occasion of his 65th birthday

The “least-coordinating” peralkylated monoanionic carboranes based around [1-*closo*-CB₁₁R₁₂][−] (R = alkyl)^[1,2] are of significant technological interest. They can form stable, lipophilic, free radicals that are also strong oxidants,^[3] novel electrolytes,^[2] act as partners with lithium ions as catalysts for pericyclic rearrangements,^[4] or can be used to isolate reactive cations such as [nBu₃Sn]⁺^[5] or Me⁺.^[6] They constitute some of the weakest nucleophiles within the family of icosahedral mono-carborane anions,^[7] and also have the attractive properties of being relatively chemically robust^[8] and available in gram quantities. Given that much of the interest in least-coordinating anions, such as the perfluorinated tetraaryl borates, is based around the generation of cationic Lewis acidic metal centers that show enhanced catalytic properties,^[9] analogous complexes partnered with peralkylated carborane anions are of significant interest. The fact that peralkylated anions such as **1** can be considered as being negatively charged “alkane



balls” is of particular relevance as there is considerable interest in the isolation and structure of metal–alkane complexes.^[10] The structures of simple alkali-metal salts of [1-*closo*-CB₁₁Me₁₂][−] have been reported,^[11] while the main-group-metal complex [nBu₃Sn][1-*closo*-CB₁₁Me₁₂] is a closely associated ion-pair in the solid state, a structure that is thought to be retained in solution.^[5] However, no analogous transition-metal complexes have been described. We have a current interest in the chemistry of metal–ligand complexes partnered with monoanionic carborane anions^[12] and report here the first example of a d-block-metal complex containing

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a peralkylated carborane, $[\text{PPh}_3\text{Ag}][1\text{-}closo\text{-HCB}_{11}\text{Me}_{11}]$ (**2**), that displays unprecedented intermolecular $\text{Ag}\cdots\text{H}_3\text{C}$ interactions between the silver center and the carborane periphery in both the solid and solution state.

The addition of a solution of triphenylphosphane in CH_2Cl_2 to $\text{Ag}[1\text{-}closo\text{-HCB}_{11}\text{Me}_{11}]$ ($[\text{Ag}]\mathbf{1}$)^[13] affords a colorless solution from which crystalline $[\text{PPh}_3\text{Ag}][1\text{-}closo\text{-HCB}_{11}\text{Me}_{11}]$ (**2**) can be isolated in good yield. The solid-state structure of **2** is shown in Figure 1.

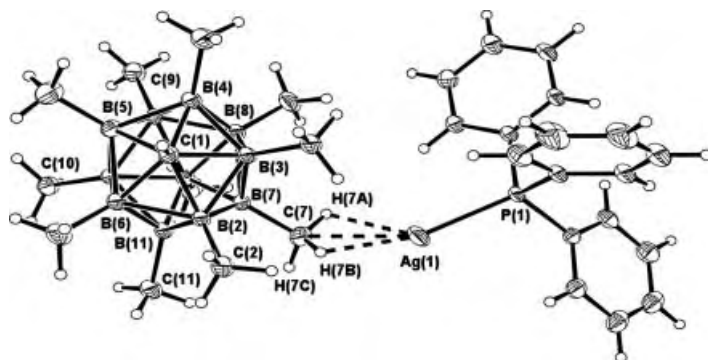


Figure 1. ORTEX diagram^[27] of complex **2** showing thermal ellipsoids at the 30% probability level. Selected bond lengths [Å] and angles [°]: Ag(1)–H(7A) 2.19(3), Ag(1)–H(7B) 2.20(3), Ag(1)–H(7C) 3.033, C(7)–H(7A) 0.93(3), C(7)–H(7B) 0.93(3), C(7)–H(7C) 0.93(4), Ag(1)–C(7) 2.544(2), Ag(1)–P(1) 2.3871(5); C(7)–Ag(1)–P(1) 152.21(4), H(7A)–C(7)–B(7) 109(1), H(7B)–C(7)–B(7) 109(1), H(7C)–C(7)–B(7) 112(2).

In the solid state, the asymmetric unit shows that the silver-phosphane fragment is in close contact to one of the methyl groups (C(7)) on the lower pentagonal belt of the cage. The interactions between the $\{\text{Ag}(\text{PPh}_3)\}^+$ fragment and the C(7) methyl group are significant, as judged by the Ag(1)···C(7) separation (2.544(2) Å) being longer than that found for a Ag–C single bond (for example, 2.144(5) Å in $[(\text{PPh}_3)\text{AgCH}_2\text{C}_6\text{F}_5]]$ ^[14] but much shorter than the sum (3.29 Å) of the van der Waals radius of a methyl group (2.00 Å) and the ionic radius of an Ag^I ion (1.29 Å).^[15] Moreover, the Ag(1)···C(7) separation is only slightly longer than those found in silver–arene complexes (2.47 Å) in which significant silver–carbon interactions are suggested to occur.^[16] The hydrogen atoms on C(7) were located in the penultimate Fourier difference map and refined freely. There are two close H···Ag contacts (Ag(1)···H(7A) 2.19(3) and Ag(1)···H(7B) 2.20(3) Å) in the asymmetric unit; the separation from the third methyl hydrogen atom (Ag(1)···H(7C) 3.033 Å) is significantly longer resulting in a B(7)–C(7)–Ag(1) angle of 138.9(2)°. While acknowledging the limitations of X-ray diffraction in the accurate location of hydrogen atoms, it is reasonable to say that there is no lengthening of the C–H bonds for the hydrogen atoms in close proximity to Ag(1) in **2**. The structural motif in **2** is similar on first inspection to that reported for the zwitterionic complexes $[[1,3\text{-(Si-Me)}_2\text{C}_5\text{H}_3]_2\text{ZrMe}(\mu\text{-Me})\text{B}(\text{C}_6\text{F}_5)_3]$ (**A**)^[17] and $[(1,2\text{-Me}_2\text{Cp})_2\text{ZrCH}_3(\mu\text{-Me})\text{B}(\text{C}_6\text{F}_5)_3]$ (**B**)^[18] in which Zr···H₃C agostic interactions are suggested to be present. In the extended lattice (Figure 2) there are two further, significantly longer, Ag···C contacts from permethylated cages proximate

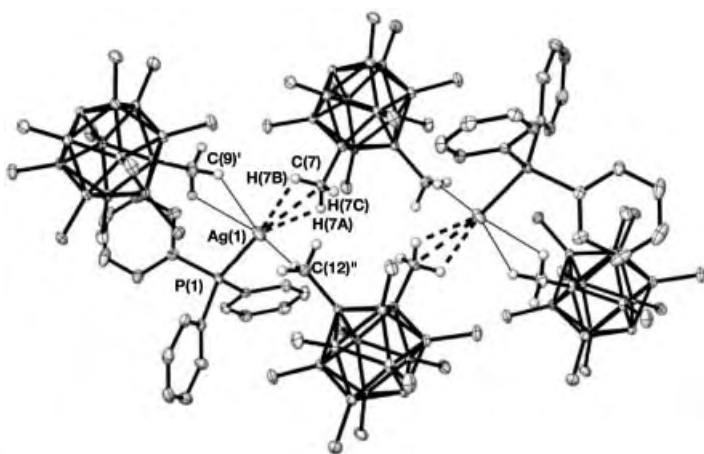


Figure 2. Packing diagram for **2** showing the extended $\{\text{BCH}_3\}\cdots\{\text{Ag}\}$ interactions in the solid state. Only the hydrogen atoms on C(7), C(9)', and C(12)'' are shown for clarity. Selected bond lengths [Å]: Ag(1)–C(9)' 3.154(2), Ag(1)–C(12)'' 3.336(2).

in the lattice: Ag(1)···C(9)' 3.154(2), Ag(1)···C(12)'' 3.336(2) Å. The associated hydrogen atoms were located and refined; one methyl group (C(9)') is bidentate with respect to the Ag···H interactions, while the other (C(12)') is monodentate. The overall structural motif is reminiscent of that found for $\text{Li}[\text{B}(\text{CH}_3)_4]$, in which extended tridentate and bidentate $\text{CH}_3\cdots\text{Li}$ interactions are observed in the solid state.^[19]

Energy minimization at the B3LYP/DZVP level for $[\mathbf{1}]^-$ and the three possible isomers of **2** shows that there is a small energy difference between the isomers (Table 1), with the metal fragment favoring interaction with the (7)–(11) vertices as observed experimentally, very closely followed by vertex (12). This observation is consistent with the distribution of charge on the three chemically different $\{\text{B}(\text{CH}_3)\}$ moieties in the free anion, $[\mathbf{1}]^-$ (Table 1) and is similar to that previously reported for $[n\text{Bu}_3\text{Sn}][1\text{-}closo\text{-CB}_{11}\text{Me}_{12}]$.^[5]

Table 1. Comparison of the charges (from natural bond orbital (NBO) analysis) on $[1\text{-}H\text{-}closo\text{-}1\text{-CB}_{11}\text{Me}_{11}]^-$, $[\mathbf{1}]^-$, and the relative energies of the isomers of $[1\text{-}H\text{-}closo\text{-}1\text{-CB}_{11}\text{Me}_{11}][\text{AgPPh}_3]$ (**2**), all calculated at the B3LYP/DZVP level.

Vertex/isomer	$[\text{HCB}_{11}\text{Me}_{11}]^-$		$[\text{HCB}_{11}\text{Me}_{11}][\text{AgPPh}_3]$ energy [kJ mol ^{−1}]
	CH ₃	B(CH ₃)	
(12)	−0.28	−0.09	+6
(7)–(11)	−0.28	−0.13	0
(2)–(6)	−0.29	+0.07	+24

In solution the Ag···H₃C interactions are still present and significant, as shown by NMR spectroscopy. The ¹H{¹¹B} NMR spectrum of **2** shows a 5:1:5 pattern for the cage methyl groups. These signals are considerably broadened compared with those of $[\text{Me}_4\text{N}][1\text{-}closo\text{-HCB}_{11}\text{Me}_{11}]$ ($[\text{Me}_4\text{N}]\mathbf{1}$) (Figure 3), which is indicative of interaction with $\{\text{Ag}(\text{PPh}_3)\}$, while other peaks in the spectrum were sharp and well-resolved. ¹H{¹¹B-selective} NMR experiments were used to assign the methyl resonances, and demonstrate that the signal for the unique C(12) methyl carbon atom is shifted by

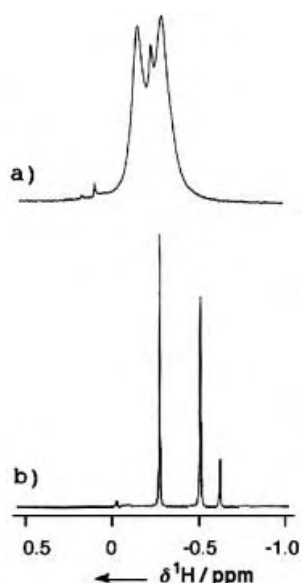


Figure 3. ^1H NMR spectra of **2** (a) and **1**[NMe₄]^[13] (b). Peak assignments (downfield to upfield) for **2**: C(7)–C(11), C(12), C(2)–C(6) and for **1**[NMe₄]: C(2)–C(6), C(7)–C(11), C(12).

the cage in solution (1:5:5 pattern), while in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum a single phosphorus environment reveals coupling to both ^{109}Ag and ^{107}Ag nuclides ($J(\text{Ag}_\text{av}\text{P})$ 824 Hz). No significant change was observed in either the ^1H or the $^{31}\text{P}\{^1\text{H}\}$ NMR spectra on cooling the solution to -60°C . Progressive heating of the sample ($\text{C}_2\text{D}_2\text{Cl}_4$, 20 – 70°C) resulted in gradual decomposition to unidentified species.

The $\text{Ag}\cdots\{\text{H}_3\text{CB}\}$ interactions in **2** may be switched off by addition of one equivalent of $[\text{NBu}_4][1\text{-closo-CB}_{11}\text{H}_6\text{Br}_6]$ ^[23] to a solution of **2** in CD_2Cl_2 , which results in rapid exchange of the permethylated carborane for the hexabromocarborane anion at the silver(I) center. The ^1H NMR spectrum of the resulting solution shows sharpening of the methyl signals, and chemical shifts identical to pure $[\text{NMe}_4]\textbf{1}$, while the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum shows evidence for the clean formation of $[(\text{PPh}_3)\text{Ag}(1\text{-closo-CB}_{11}\text{H}_6\text{Br}_6)]$.^[12] $[1\text{-closo-HCB}_{11}\text{Me}_{11}]$ can thus be considered to be less nucleophilic than $[1\text{-closo-CB}_{11}\text{H}_6\text{Br}_6]$, which itself is one of the least-coordinating anions known.^[17]

Metal–alkane complexes are of considerable current interest,^[10,24] but complexes isolated under standard laboratory conditions are rare.^[25] Complexes such as **A**–**C**, which possess methyl groups that coordinate in an intermolecular fashion, are models for alkane complexes of the early transition metals. However, to our knowledge, no later d-block-metal complexes showing analogous interactions are known. Complex **2** represents the first example of a silver metal center interacting with an alkyl (CH_3) group in either an intra- or intermolecular fashion, and is thus a model for an interaction between a d^{10} metal center and an alkane.^[24] The fact that these interactions are readily observed by ^1H NMR spectroscopy suggests that they will provide a useful spectroscopic

marker in the development of the transition-metal chemistry of peralkylated carborane anions.

0.41 ppm downfield relative to that of **1**[NMe₄].^[13,20] There is also a comparable downfield shift observed for the methyl groups on the lower pentagonal belt (0.37 ppm), while C(2)–C(6) are not shifted significantly. These results are consistent with the metal fragment interacting mostly with the C(7)–C(12) unit in solution. Similar downfield shifts have been reported for the BeCH_3 protons in $[(\eta^5\text{-C}_5\text{Me}_5)_2\text{Yb}(\mu\text{-Me})\text{Be}(\eta^5\text{-C}_5\text{Me}_5)]$ (**C**) in which the $\text{Yb}\cdots\{\text{H}_3\text{CBe}\}$ interaction may be considered more electrostatic.^[21] In contrast, in related complexes such as **A** and **B**, where agostic $\text{Zr}\cdots\{\text{H}_3\text{CB}\}$ interactions are proposed,^[9] upfield shifts of the BCH_3 group are observed.^[22] The $^{11}\text{B}\{^1\text{H}\}$ NMR spectrum of **2** confirms C_{5v} symmetry for

the cage in solution (1:5:5 pattern), while in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum a single phosphorus environment reveals coupling to both ^{109}Ag and ^{107}Ag nuclides ($J(\text{Ag}_\text{av}\text{P})$ 824 Hz). No significant change was observed in either the ^1H or the $^{31}\text{P}\{^1\text{H}\}$ NMR spectra on cooling the solution to -60°C . Progressive heating of the sample ($\text{C}_2\text{D}_2\text{Cl}_4$, 20 – 70°C) resulted in gradual decomposition to unidentified species.

Experimental Section

2: Triphenylphosphane (60 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (5 mL) and added dropwise to a Schlenk flask charged with $[\text{Ag}(\text{CB}_{11}\text{Me}_{11}\text{H})]^{[13]}$ (92 mg, 0.23 mmol). The resulting solution was stirred in the dark for 16 h, cannula filtered, and the solvent removed in vacuo. The resultant white solid was redissolved in the minimum volume of CH_2Cl_2 , layered with hexanes, then placed in a freezer overnight at -30°C to afford colorless crystals (122 mg, 81 %).

$^1\text{H}\{^{11}\text{B}\}$ NMR (300 MHz, CD_2Cl_2 , 22°C , assignments from $^1\text{H}\{^{11}\text{B}\}$ -selective experiments): $\delta = 7.66$ – 7.36 (15 H, m, Ph), 1.26 (1 H, s, $\text{C}_{\text{cage}}\text{-H}$), -0.14 (15 H, brs, BCH_3 , B(7) CH_3 –B(11) CH_3), -0.22 (3 H, brs, B(12) CH_3), -0.28 ppm (15 H, brs, BCH_3 , B(2) CH_3 –B(6) CH_3). ^{11}B NMR (96 MHz, CD_2Cl_2 , 22°C , assignments from ^{11}B – ^{11}B COSY): $\delta = -1.3$ (1 B, s, B(12)), -9.0 (5 B, s, B(7)–B(11)), -11.9 ppm (5 B, s, B(2)–B(6)). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CD_2Cl_2 , 22°C): $\delta = 133.9$ (s, C_{phenyl}), 132.3 (s, C_{phenyl}), 130.0 (s, C_{phenyl}), 128.2 (d, C_{phenyl} , $J(\text{CP}) = 37$ Hz), 61.3 (s, C_{cage}), -0.7 – -6.0 ppm (br, CH_3). $^{31}\text{P}\{^1\text{H}\}$ (122 MHz, CD_2Cl_2 , 22°C): $\delta = 17.5$ ppm (dd, $J(\text{Ag}^{109}\text{P})$ 853 Hz, $J(\text{Ag}^{107}\text{P})$ 794 Hz). IR (KBr): $\tilde{\nu} = 2921$, 2895, 2829, 2736 cm^{-1} (CH_3); elemental analysis calcd for $\text{C}_{30}\text{H}_{49}\text{Ag}_2\text{B}_{11}\text{P}_1$: C 54.0, H 7.35 %; found: C 53.4, H 7.30 %.

Crystal data for **2**: triclinic, space group $P\bar{1}$, $a = 9.18400(10)$, $b = 13.6170(2)$, $c = 15.1520(3)$ Å, $\alpha = 111.6370(10)$, $\beta = 95.0050(10)$, $\gamma = 100.3360(10)^\circ$, $V = 1708.23(5)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.298$ Mg m^{−3}. Data were collected at 173(2) K on a Nonius kappaCCD diffractometer, MoK_α radiation (0.71073 Å), 9965 measured reflections to $2\theta_{\text{max}} = 60.12^\circ$, giving 7255 unique reflections ($R_{\text{int}} = 0.0417$). The structure was solved by direct methods, and refined against F^2 using all data.^[26] The final discrepancy indices were $R_1 = 0.0378$, $wR_2 = 0.0941$. CCDC-187180 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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A Simple, Reliable, Catalytic Asymmetric Allylation of Ketones**

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The asymmetric allylation of carbonyl groups to furnish homoallylic alcohols is a fundamental transformation in synthetic organic chemistry.^[1–3] Several catalysts will promote the asymmetric allylation of aldehydes to give secondary homoallylic alcohols with excellent enantioselectivities.^[4–15] The catalytic asymmetric allylation of ketones, however, has proven to be a more challenging transformation owing to the significant difference in reactivity between aldehydes and ketones. Thus, with one exception,^[16] catalysts that promote the enantioselective allylation of aldehydes fail to catalyze the analogous reaction with ketones. In general, the enantioselective formation of quaternary stereocenters, as generated in the asymmetric allylation of ketones, is of considerable difficulty.^[17,18]

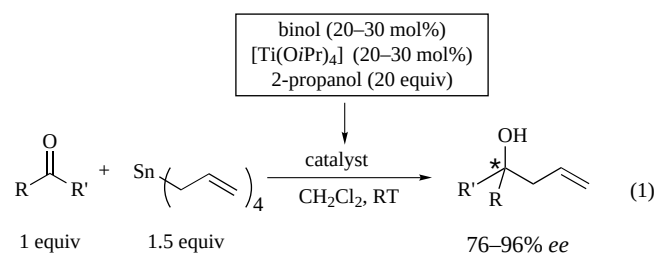
To compensate for the reduced reactivity of ketones, a more reactive allylating agent was needed. Baba and co-workers found that tetraallylstannane added to ketones in the presence of methanol and 200 mol % binol to give the homoallylic alcohol in up to 60 % *ee*.^[19] An important discovery in the asymmetric allylation of ketones was recently reported by Casolari, D'Addario, and Tagliavini.^[20] Their catalyst preparation involved the reaction of $[\text{Cl}_2\text{Ti}(\text{OiPr})_2]$ and binol with allyltributylstannane. After mixing for one hour, tetraallylstannane and the substrate ketone were added.

They observed the formation of the ketone allylation product with up to 65 % *ee* at 20 mol % binol (80 % *ee* with 40 mol % binol).

Based on the results of the Italian team,^[20] Maruoka and co-workers^[16] recently reported a system for the catalytic asymmetric allylation of aldehydes with a catalyst that is based on titanium, binol, and an achiral diamine spacer (2:2:1 ratio). This catalyst (60 mol % titanium and binol) was examined in the asymmetric allylation of only two ketones, acetophenone and methyl 2-naphthyl ketone, which underwent allylation with 90 and 92 % *ee*, respectively.^[16] More recently, Cunningham and Woodward^[21] demonstrated that monothioBINAP will promote the allylation of acetophenone derivatives with a mixture of $[\text{RSn}(\text{allyl})_3]/[\text{Sn}(\text{allyl})_4]$ ($\text{R} = \text{Et}, \text{Bu}$) with *ee* values as high as 92 % (51 % yield).

The ketone allylation reaction of Casolari, D'Addario, and Tagliavini^[20] attracted our attention because of our interest in the mechanisms of titanium-based asymmetric Lewis acid catalysts^[22–24] and the need for a more versatile and enantioselective catalyst for this important process. While investigating the catalyst structure of the Tagliavini system, we made several key observations that allowed us to develop the most general and enantioselective catalyst for the asymmetric allylation of ketones to date.

We repeated the catalyst preparation of Tagliavini^[20] described above in CDCl_3 to probe the nature of the (binolate)Ti species by NMR spectroscopy. Like Tagliavini and co-workers,^[20] we observed the production of tributyltin chloride. However, we were surprised to find that the major titanium-containing product was $[(\text{binolate})\text{Ti}(\text{OiPr})_2]$, which is dimeric in solution and trimeric in the solid state.^[25,26] We prepared this compound on a gram scale simply by mixing titanium tetraisopropoxide and binol followed by removal of the solvent and liberated 2-propanol.^[26] Using the isolated $[(\text{binolate})\text{Ti}(\text{OiPr})_2]$, we found that the enantioselectivities in the allylation reaction were about the same as those reported by Tagliavini and co-workers.^[20] An important breakthrough was made when the catalyst was prepared directly from titanium tetraisopropoxide and binol (1:1, 20 or 30 mol %) *without removal of the liberated 2-propanol*. When we employed this catalyst preparation, the *ee* of the product formed from 3-methylacetophenone rose from 51 % to 73 %. These results suggested that the liberated 2-propanol had a beneficial impact on the enantioselectivity of the catalyst. We therefore prepared the catalyst with additional 2-propanol and observed a significant increase in the catalyst enantioselectivity [Eq. (1)].



The advantageous effect of the 2-propanol on the enantioselectivity of the catalyst reached a maximum when 20 equiv

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(relative to the ketone) of 2-propanol were added. A further increase in 2-propanol to 100 equiv resulted in a slight decrease in the enantioselectivity of the tertiary homoallylic alcohol. Using this combination of binol, titanium tetraisopropoxide, 2-propanol, and tetraallylstannane [Eq. (1)], the *ee* value of 3-methylacetophenone rose to 96%! The results of our catalytic asymmetric allylation of ketones are displayed in Table 1. Only a marginal electronic influence with substituted

Table 1. Asymmetric allylation of ketones [Eq. (1)].

Entry	Ketone	[mol %]	Yield [%] ^[b]	<i>ee</i> [%] ^[a]
1	X = 3-Me	20	82	96
2	X = 4-OMe	30	99	89
3	X = 3-CF ₃	30	93	92
4	X = 2-Me	30	77 ^[c]	84
5		30	96	95
6		30	88	90
7		30	99	90
8		30	96	80
9		30	99	76
10		30	67	84

[a] Enantiomeric excesses determined by GC or HPLC (see Supporting Information). [b] Yields of isolated products. [c] 7% recovered substrate after 4.5 d.

acetophenones was observed, as 4-methoxyacetophenone and 3-trifluoromethylacetophenone formed products with 89 and 92% *ee*, respectively (Table 1, entries 2 and 3). Substitution of the acetophenone with a 2-methyl group resulted in a lower *ee* value (84%) and turnover frequency, with the allylation product formed in 77% yield after 4.5 days (Table 1, entry 4).

The ketone α -tetralone often forms products of aldol condensation/dehydration in the presence of basic reagents.^[27] However, under the conditions of the allylation reaction [Eq. (1)], this substrate gave 95% *ee* with 96% yield (Table 1, entry 5).

Allylation of conjugated enones gave exclusive 1,2-allylation in high yield and with high enantioselectivity (Table 1, entries 6 and 7). Interestingly, while *trans*-4-phenyl-3-buten-2-one underwent allylation with 90% *ee*, the saturated derivative reacted to give the homoallylic alcohol with 80% *ee*. Nonetheless, 80% *ee* in entry 8 is impressive, given that the catalyst must differentiate between a methyl and an alkyl group.

The functionalized 3-chloropropiophenone exhibited moderate enantioselectivity (76%). The reaction of the heteroaromatic substrate acetylfuran under the conditions described

in [Eq. (1)] furnished the homoallylic alcohol with 84% *ee*. As a cautionary note, care must be used during work-up and chromatography to avoid racemization of tertiary alcohols.

Although we have not yet studied the catalyst structure or the mechanism of the allylation reaction in detail, preliminary experiments do provide meaningful information about the catalyst. When reactions were performed with binol of varying enantiopurity, a strong positive nonlinear effect was observed (see Supporting Information). Several possible catalyst structures and mechanisms could explain the nonlinear effects, including the formation of hetero- and homo-chiral (binolate)₂Ti species or [(binolate)TiX₂]₂ dimers (X = OiPr or X₂ = O). In such cases, the dimers could dissociate to reactive monomers, or the dimers themselves could be the active catalysts.^[28] Interestingly, reaction of 3-methylacetophenone under conditions in Eq. (1) with a 1:1 or 2:1 ratio of binol to [Ti(OiPr)₄] gave products with the same *ee* values.

Like other carbonyl allylations with tin reagents, we have found that our allylation procedure [Eq. (1)] exhibited an induction period. Reactions run with binol (20 mol %) and [Ti(OiPr)₄] (20 mol %), with no added 2-propanol, were complete after 2 h (73% *ee*). Our procedure with 2-propanol [Eq. (1)] resulted in increased initiation times (3% conversion at 2 h) with completion in under 6 h (96% *ee*). Premixing the binol (20 mol %), [Ti(OiPr)₄], tetraallylstannane, and 2-propanol for 22 h followed by addition of 3-methylacetophenone virtually eliminated the induction period (95% conversion in 1 h, 96% *ee*).

While the addition of alcohol is important in obtaining high enantioselectivity, the nature of the alcohol additive did not affect the *ee* value, as identical enantioselectivities were obtained from catalysts prepared from 2-propanol, cyclopentanol, cyclohexanol, and cycloheptanol. The use of as little as 0.25 equivalents of tetraallylstannane resulted in greater than 92% conversion and no decrease in enantioselectivity, indicating that each tetraallyltin complex can transfer at least three of its allyl groups to the substrate. These results suggest that the mechanism does not involve initial protonation of a tin allyl to generate a tin alkoxide that is the active allylating reagent. Furthermore, we have examined several sources of tetraallylstannane (homemade and from four vendors) and observed no differences in the *ee* values of the products.

In summary, we have developed a very practical enantioselective catalyst for the allylation of ketones that provides tertiary homoallylic alcohols. Homoallylic alcohols are versatile materials in organic synthesis and can be converted into β -hydroxy ketones, β -hydroxy aldehydes, γ -lactones (by hydroformylation), and can be epoxidized diastereoselectively.^[29] Our catalyst is prepared by simply mixing commercially available reagents at room temperature under nitrogen. This ketone allylation procedure is more reliable and experimentally simpler than the allylation of aldehydes.^[10,13,30] We are currently applying our catalyst system to other Lewis acid catalyzed processes.

Experimental Section

General procedure: [Ti(OiPr)₄] (98 μ L, 0.332 mmol, 20 mol % or 147 μ L, 0.498 mmol, 30 mol %) was added to a solution of (*R*)- or (*S*)-binol (95 mg, 0.332 mmol, 20 mol % or 142.5 mg, 0.498 mmol, 30 mol %) in dichloro-

methane (4.0 mL), and this orange solution was stirred for several minutes at room temperature. 2-Propanol (2.54 mL, 33.2 mmol) was added to this solution, followed by the ketone substrate (1.66 mmol) and tetraallylstannane (0.6 mL, 2.49 mmol). After an initial induction period, the color of the solution lightened from orange to yellow, indicating the commencement of the reaction. After stirring for 20 h, the reaction was quenched with saturated ammonium chloride and extracted with dichloromethane. After removal of the solvent under reduced pressure, the resulting oily orange residue was extracted with hexanes, dried over magnesium sulfate, filtered through celite, and purified by chromatography on silica, starting with hexanes to elute the majority of the tin species, and then with diethyl ether/hexanes (10–20%) to obtain the alcohol product (see Table 1 for yields and *ee* values). It is important to use ammonium chloride to quench the reactions instead of dilute hydrochloric acid, which resulted in partial racemization of the product. It is also best to run the column quickly, as some of the alcohol products racemize slightly when in contact with the silica for extended periods of time.

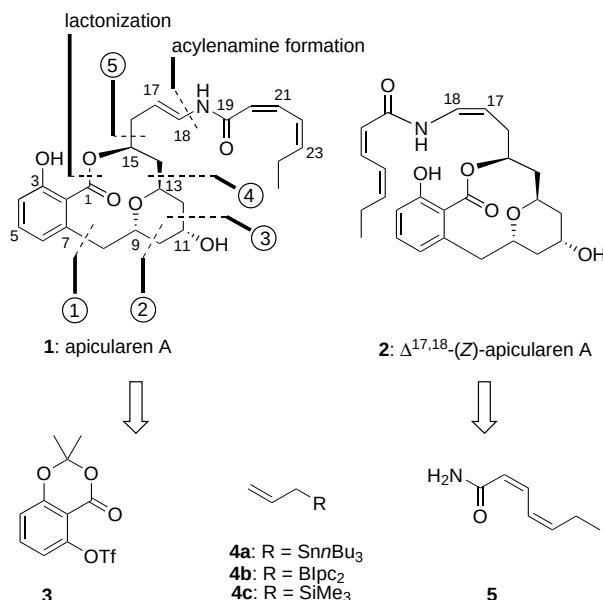
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Stereocontrolled Total Synthesis of Apicularen A and Its $\Delta^{17,18}$ Z Isomer**

K. C. Nicolaou,* David W. Kim, and Rachid Baati

Apicularen A (**1**, Scheme 1) is a polyketide natural product with a novel molecular architecture and impressive antiproliferative properties against a series of human cancer cells including a drug-resistant line.^[1,2] Recently isolated from



Scheme 1. Structures and retrosynthetic analysis of apicularen A (**1**) and its $\Delta^{17,18}$ Z isomer (**2**). ①–⑤: allylation–ozonolysis reiterations. Ipc = isopinocampheyl.

various strains of the myxobacterial genus *Chondromyces* (i.e., *C. apiculatus*, *C. lanuginosus*, *C. pediculatus*, and *C. robustus*),^[1] apicularen A possesses a structure characterized by a salicylic acid residue, a macrolide ring bridged by an oxygen atom in such a way as to form a tetrahydropyran system, and a 10-membered ring lactone bearing a side chain with a doubly unsaturated acylenamine moiety. Interestingly, biosynthetic studies revealed the incorporation of eleven

intact acetate units into the molecule of apicularen A that account for the entire natural carbon skeleton of the molecule except for C-17 (which stems from glycine), C-18, and C-25 (which is derived from methionine).^[2] Here we report a total synthesis^[3] of apicularen A (**1**) and its $\Delta^{17,18}$ Z isomer (**2**) inspired by its polyacetate-based biosynthesis.

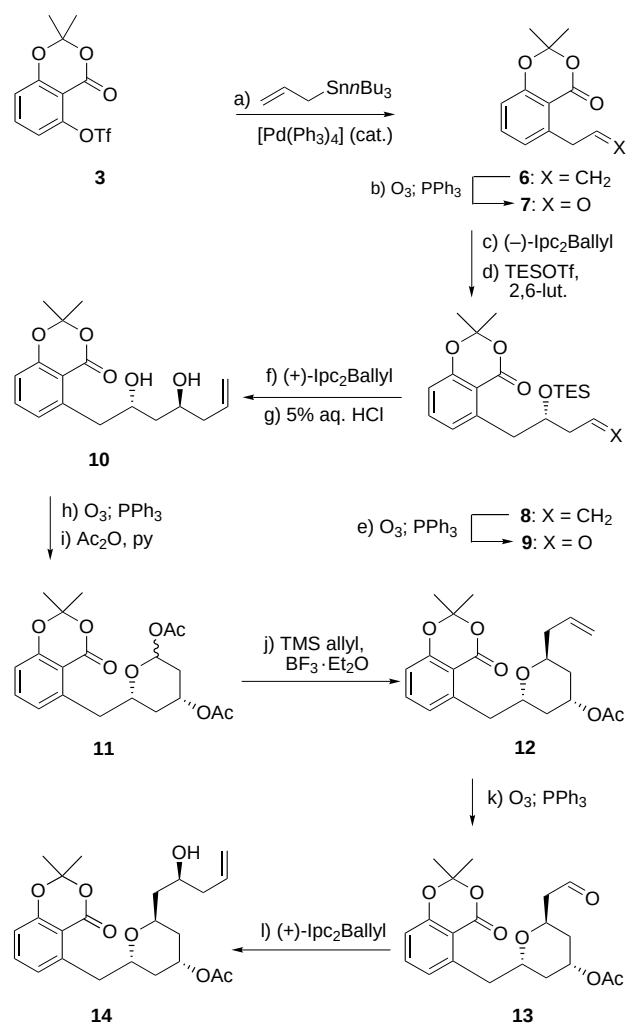
Scheme 1 traces retrosynthetically the origins of apicularen A (**1**) (and its isomer **2**) to key building blocks **3**, **4a–c**, and **5**, all of which are readily available.^[4–6] In this analysis, we equated the introduction of an acetate unit to a two-step procedure involving allylation followed by ozonolysis. The five projected reiterations of the allylation–ozonolysis sequence are indicated on the structure of **1** and were to be performed in the designated order (① to ⑤). These steps not only would “mimic” nature’s polyacetate biosynthetic pathway to **1**, but also would have the potential of yielding the correct stereochemistry at each chiral center of the target molecule through the judicious choice of appropriate reagents and conditions. Thus, while the first planned allylation^[7] with allyltributyltin and a palladium catalyst should provide the required extension from the salicylic acid residue, the second and third allylations with Brown’s reagent (Ipc₂Ballyl)^[5] should install the C-9 and C-11 hydroxy groups in their absolute stereochemistry through the use of the appropriate enantiomer. The fourth allylation calls upon allyltrimethylsilane as a reagent to further extend the growing chain with concomitant formation of the C-13 stereocenter in a diastereocontrolled manner. The fifth allylation would require, once more, the use of Brown’s reagent (Ipc₂Ballyl) for the construction of the final chiral center in its absolute stereochemical configuration. This strategy left the required ring-forming reactions and the stereoselective installment of the acylenamine side chain to be negotiated in the synthetic direction.

Scheme 2 details the construction of advanced intermediate **14** from which both **1** and **2** would be derived. Acetonide triflate **3**^[4] was coupled with allyltributyltin^[7] under the influence of catalytic [Pd(PPh₃)₄] to afford allyl compound **6** (99% yield) whose rupture with ozone led, upon reduction with PPh₃, to aldehyde **7** (92% yield). The addition of (–)-Ipc₂Ballyl to **7** in diethyl ether at –100°C produced the corresponding alcohol (70% yield, 95% *ee* by Mosher ester determination)^[8] which was protected as its triethylsilyl derivative **8** (83% yield). Reiteration of the above ozonolysis–allylation sequence, this time with the + enantiomer of Brown’s reagent ((+)-Ipc₂Ballyl), followed by mild acidic treatment (5% aqueous HCl) furnished diol **10** via intermediate aldehyde **9** (62% overall yield). Ozonolytic cleavage of the terminal olefin followed by acetylation of the resulting hydroxylactol resulted in the formation of diacetate **11** as a mixture of anomers (α : β ca. 3:1) in 83% yield. Anomeric allylation^[9] of **11** with allyltrimethylsilane in the presence of BF₃·Et₂O lead stereoselectively to allyl derivative **12** (97% yield) with the desired *anti* stereochemistry. Finally, another ozonolysis–allylation sequence employing (+)-Ipc₂Ballyl furnished the advanced intermediate **14** in 74% overall yield and in greater than 90% *de*.

Exposure of intermediate **14** to De Brabander’s conditions^[3a] (NaH, THF, 25°C) for 2 h followed by addition of

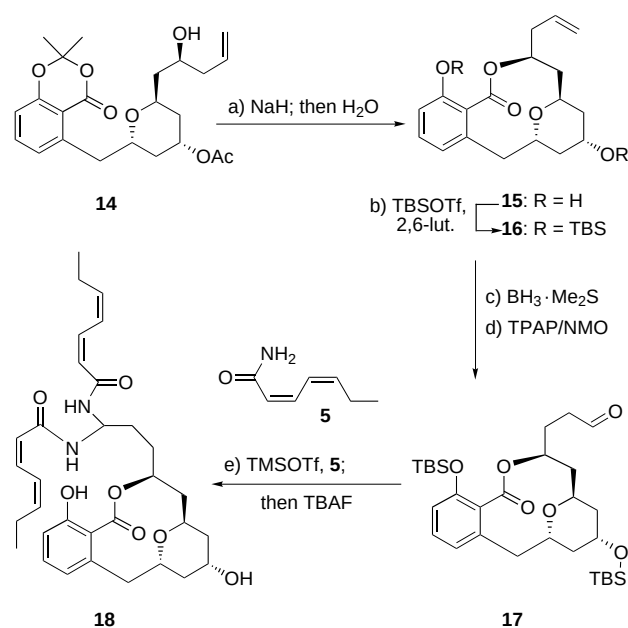
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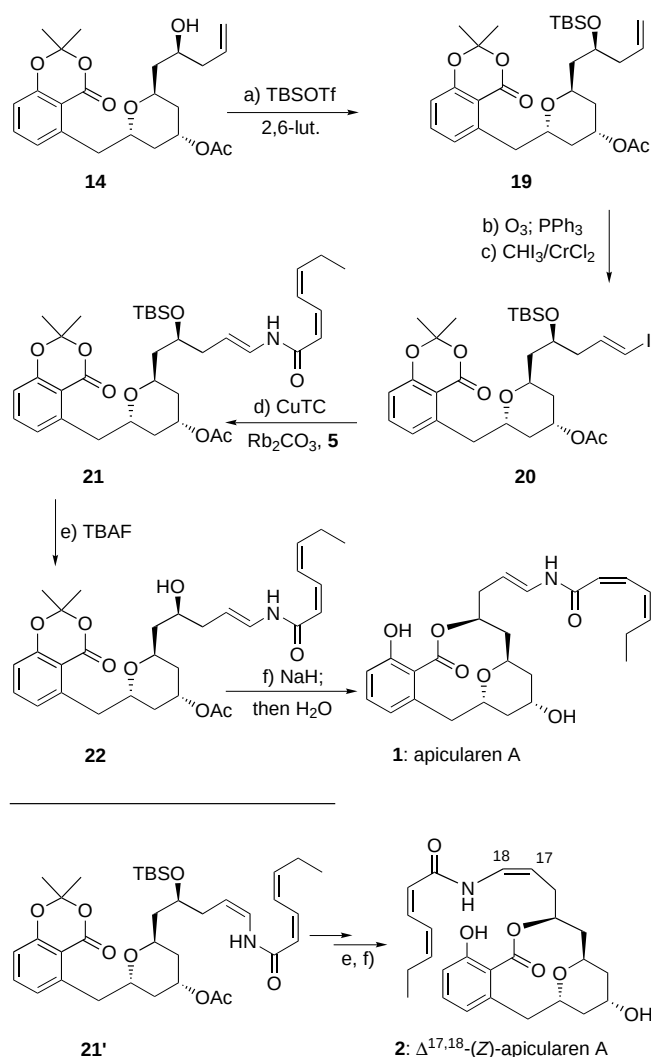
Scheme 2. Construction of advanced intermediate **14**. a) Allyltributyltin (1.2 equiv), LiCl (3.0 equiv), [Pd(PPh₃)₄] (0.02 equiv), THF, reflux, 12 h, 99%; b) O₃, CH₂Cl₂, -78°C, 1 h; then PPh₃ (4.0 equiv), 1 h, 92%; c) (-)-Ipc₂Ballyl (2.0 equiv), Et₂O, -100°C, 2 h, 70%; d) TESOTf (2.0 equiv), 2,6-lut (4.0 equiv), CH₂Cl₂, 25°C, 3 h, 83%; e) O₃, CH₂Cl₂, -78°C, 1 h; then PPh₃ (4.0 equiv), 1 h, 95%; f) (+)-Ipc₂Ballyl (2.0 equiv), Et₂O, -100°C, 2 h; g) 5% aq. HCl, 25°C, 4 h, 62% over 2 steps; h) O₃, CH₂Cl₂, -78°C, 1 h; then PPh₃ (4.0 equiv), 1 h; i) Ac₂O, py, 25°C, 1 h, 83% over 2 steps; j) allyltrimethylsilane (5.0 equiv), BF₃·Et₂O (1.1 equiv), CH₃CN, 0°C, 1 h, 97%; k) O₃, CH₂Cl₂, -78°C, 1 h, PPh₃ (4.0 equiv), 4 h, 98%; l) (+)-Ipc₂Ballyl (2.0 equiv), Et₂O, -100°C, 2 h, 74%. 2,6-lut = 2,6-lutidine; py = pyridine; TES = triethylsilyl; TMS = trimethylsilyl.

5.0 equiv of water and further stirring (8 h) at ambient temperature furnished the corresponding phenol–lactone **15** through ring closure, expulsion of acetone, and acetate cleavage, in 75% overall yield (Scheme 3). Compound **15** was then bis-silylated with TBSOTf in the presence of 2,6-lutidine to afford silyl derivative **16** (99% yield). Subsequent hydroboration to the corresponding primary alcohol (71% overall yield) followed by oxidation (99% yield) afforded aldehyde **17**. Finally, compound **17** reacted with unsaturated primary amide **5** in the presence of TMSOTf in 1,2-dichloroethane to furnish, upon addition of TBAF, the bis-amide derivative **18** in 75% overall yield. Attempts to convert this intermediate to apicularen A proved unsuccessful^[10] and therefore a new approach was sought.



Scheme 3. Total synthesis of apicularen A bis-amide derivative **18**. a) NaH (7.0 equiv), THF, 25°C, 2 h; then H₂O (5.0 equiv), 8 h, 75%; b) TBSOTf (4.0 equiv), 2,6-lut (8.0 equiv), CH₂Cl₂, 25°C, 4 h, 99%; c) BH₃·Me₂S (5.0 equiv), THF, 25°C, ultrasound, 30 min; then NaHCO₃, H₂O₂, 1 h, 71%; d) TPAP (0.1 equiv), NMO (2.0 equiv), 4 Å MS, CH₂Cl₂, 25°C, 2 h, 99%; e) TMSOTf (0.5 equiv), **5** (2.0 equiv), 1,2-dichloroethane, 25°C, 12 h; then TBAF (5.0 equiv), 25°C, 1 h, 75%. TBS = *tert*-butyldimethylsilyl; OTf = trifluoromethanesulfonate; TPAP = tetra-*n*-propylammonium perruthenate; NMO = 4-methylmorpholine *N*-oxide; 4 Å MS = 4 Ångström molecular sieves; TBAF = tetra-*n*-butylammonium fluoride.

Although the synthesis of the apicularen derivative **18** was of interest from the chemical biology point of view (see below), the task of synthesizing the natural product (**1**) remained unfinished. Completion of the total synthesis required retreat back to advanced intermediate **14** (see Scheme 4) which was now silylated to afford terminal olefin **19** (94% yield). Ozonolytic cleavage of **19** (89% yield) followed by Takai iodo-olefination^[11] (CHI₃/CrCl₂, 91% yield) led to (*E*)-vinyl iodide **20** contaminated with ca. 10% of its *Z* isomer. Coupling of this mixture with primary amide **5** under the influence of copper(I) thiophene carboxylate^[12] and Rb₂CO₃ furnished, stereospecifically, the sought-after Δ^{17,18}-(*E*)-enamide derivative **21** together with its *Z* isomer **21'** (90% yield, based on 50% conversion, ca. 10:1 ratio). The two enamide isomers **21** (see Table 1 for selected data) and **21'** were chromatographically separated and converted individually to their respective final products. Thus, removal of the silicon protecting group from **21** was effected with TBAF in THF at ambient temperature to furnish key intermediate hydroxy acylenamine **22** in 80% yield. Finally, and in one stroke, precursor **22** was converted to apicularen A (**1**) in 50% overall yield by initial exposure to NaH in THF followed by addition of 5.0 equiv of water at ambient temperature through ring closure and global deprotection. Δ^{17,18}-(*Z*)-Apicularen A (**2**, see Table for selected data) was prepared from **21'** similarly. Synthetic **1** exhibited identical chromatographic and spectroscopic data to those of an authentic sample.^[13] Biological assays^[14] revealed that whereas synthetic **1** exhibited



Scheme 4. Total synthesis of apicularen A (**1**) and its $\Delta^{17,18}$ isomer (**2**). a) TBSOTf (2.0 equiv), 2,6-lut (4.0 equiv), CH_2Cl_2 , 25 °C, 4 h, 94%; b) O_3 , CH_2Cl_2 , -78 °C, 1 h; then PPh_3 (4.0 equiv), 1 h, 89%; c) CHI_3 (4.0 equiv), CrCl_2 (12 equiv), THF, 25 °C, 12 h, 91%; d) CuTC (1.0 equiv), Rb_2CO_3 (3.0 equiv), amide **5** (3.0 equiv), DMA, 90 °C, 12 h, 90%; e) TBAF (5.0 equiv), THF, 25 °C, 8 h, 80%; f) NaH (7.0 equiv), THF, 25 °C, 1 h; then H_2O (5.0 equiv), 25 °C, 4 h, 50%. CuTC = copper(I) thiophene carboxylate; DMA = *N,N*-dimethylacetamide.

potent cytotoxicity against the 1A9 tumor cell line (IC_{50} = 0.42 nM), its bis-amide analogue **18** was devoid of such activity at concentrations up to 300 nM. The latter observation is not surprising given the fundamental importance of the enamide functionality of apicularen A (**1**) for biological activity. Interestingly, however, $\Delta^{17,18}$ -(Z)-apicularen A (**2**) maintained considerable cytotoxicity (IC_{50} = 92 nM) against the 1A9 tumor cell line.

The described chemistry demonstrates a chemical equivalent to the polyacetate biosynthetic pathway to polyketides, and establishes an entry into designed apicularen analogues. Applications of the developed synthetic technology to structure–activity relationship studies and chemical biology investigations within the apicularen family are anticipated.

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Table 1. Selected physical properties of compounds **2** and **21**.

2: white solid; R_f = 0.32 (silica, EtOAc/hexanes 1:4); $[\alpha]_{\text{D}}^{20}$ = 10.0 (c = 0.2, acetone); IR (thin film): $\tilde{\nu}_{\text{max}}$ = 3354, 2955, 2919, 2849, 1719, 1702, 1684, 1655, 1661, 1237, 1619, 1578, 1508, 1461, 1420, 1372, 1290, 1208, 1102, 1078, 1055, 1020 cm^{-1} ; ^1H NMR (500 MHz, $[\text{D}_6]$ acetone): δ = 8.80 (br d, J = 10.7 Hz, 1H), 8.45 (s, 1H), 7.49 (ddd, J = 11.4, 11.4, 1.1 Hz, 1H), 7.10 (dd, J = 8.4, 7.4 Hz, 1H), 6.86–6.80 (m, 2H), 6.77 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 7.4 Hz, 1H), 5.83 (d, J = 12.5 Hz, 1H), 5.82–5.76 (m, 1H), 5.47 (m, 1H), 4.81 (dt, J = 9.2, 7.5 Hz, 1H), 4.28–4.24 (m, 1H), 4.00–3.96 (m, 1H), 3.89–3.85 (m, 1H), 3.77 (d, J = 4.0 Hz, 1H), 3.35 (dd, J = 14.7, 10.3 Hz, 1H), 2.44–2.37 (m, 3H), 2.29–2.23 (m, 2H), 1.94–1.90 (m, 1H), 1.86–1.79 (m, 1H), 1.68–1.63 (m, 1H), 1.60–1.56 (m, 1H), 1.53–1.46 (m, 2H), 0.99 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $[\text{D}_6]$ acetone): δ = 169.3, 164.0, 154.2, 141.6, 140.2, 137.0, 130.2, 125.8, 125.4, 123.9, 122.2, 120.8, 114.3, 106.5, 73.8, 73.7, 67.7, 64.8, 40.1, 39.9, 39.5, 39.1, 32.1, 21.0, 14.3 ppm; HRMS (MALDI-FTMS), calcd for $\text{C}_{25}\text{H}_{31}\text{NO}_6$ [$M+\text{Na}^+$]: 464.2043, found: 464.2039

21: colorless oil; R_f = 0.50 (silica, hexanes/EtOAc 2:1); $[\alpha]_{\text{D}}^{20}$ = -7.1 (c = 2.8, acetone); IR (thin film): $\tilde{\nu}_{\text{max}}$ = 3450, 3319, 2955, 2931, 2861, 1731, 1713, 1642, 1584, 1455, 1373, 1242, 1208, 1088, 1044, 838, 779 cm^{-1} ; ^1H NMR (600 MHz, $[\text{D}_6]$ acetone): δ = 9.05 (br d, J = 10.8 Hz, 1H), 7.55–7.50 (m, 2H), 7.08 (d, J = 7.4 Hz, 1H), 6.89 (d, J = 7.9 Hz, 1H), 6.84 (dd, J = 11.9, 11.4 Hz, 1H), 6.77 (dd, J = 14.5, 10.6 Hz, 1H), 5.80–5.76 (m, 1H), 5.73 (d, J = 11.4 Hz, 1H), 5.25 (dt, J = 14.5, 7.4 Hz, 1H), 5.04–4.97 (m, 1H), 4.21–4.17 (m, 1H), 3.94–3.89 (m, 1H), 3.50–3.46 (m, 1H), 3.41 (dd, J = 12.7, 3.5 Hz, 1H), 3.15 (dd, J = 12.9, 8.6 Hz, 1H), 2.29–2.24 (m, 2H), 2.16–2.04 (m, 2H), 2.06–2.04 (m, 1H), 2.0 (s, 3H), 1.84–1.79 (m, 1H), 1.76–1.74 (m, 1H), 1.70–1.67 (m, 1H), 1.69 (s, 3H), 1.65 (s, 3H), 1.47–1.41 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H), 0.83 (s, 9H), -0.6 ppm (s, 6H); ^{13}C NMR (150 MHz, $[\text{D}_6]$ acetone) δ = 170.4, 163.5, 160.7, 157.8, 144.6, 141.3, 136.6, 135.8, 127.9, 125.8, 125.4, 120.9, 116.6, 113.4, 108.8, 105.8, 70.4, 70.0, 68.5, 68.0, 40.5, 39.5, 37.5, 35.4, 26.3, 26.2, 25.0, 21.2, 21.0, 18.5, 14.3, -4.4, -4.5 ppm; HRMS (MALDI-FTMS), calcd for $\text{C}_{36}\text{H}_{53}\text{NO}_8\text{Si}_2$ [$M+\text{Na}^+$]: 678.3432, found 678.3439

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Efficient and Simple Solid-Phase Synthesis of Short Cyclic Oligodeoxynucleotides Bearing a Phosphorothioate Linkage**

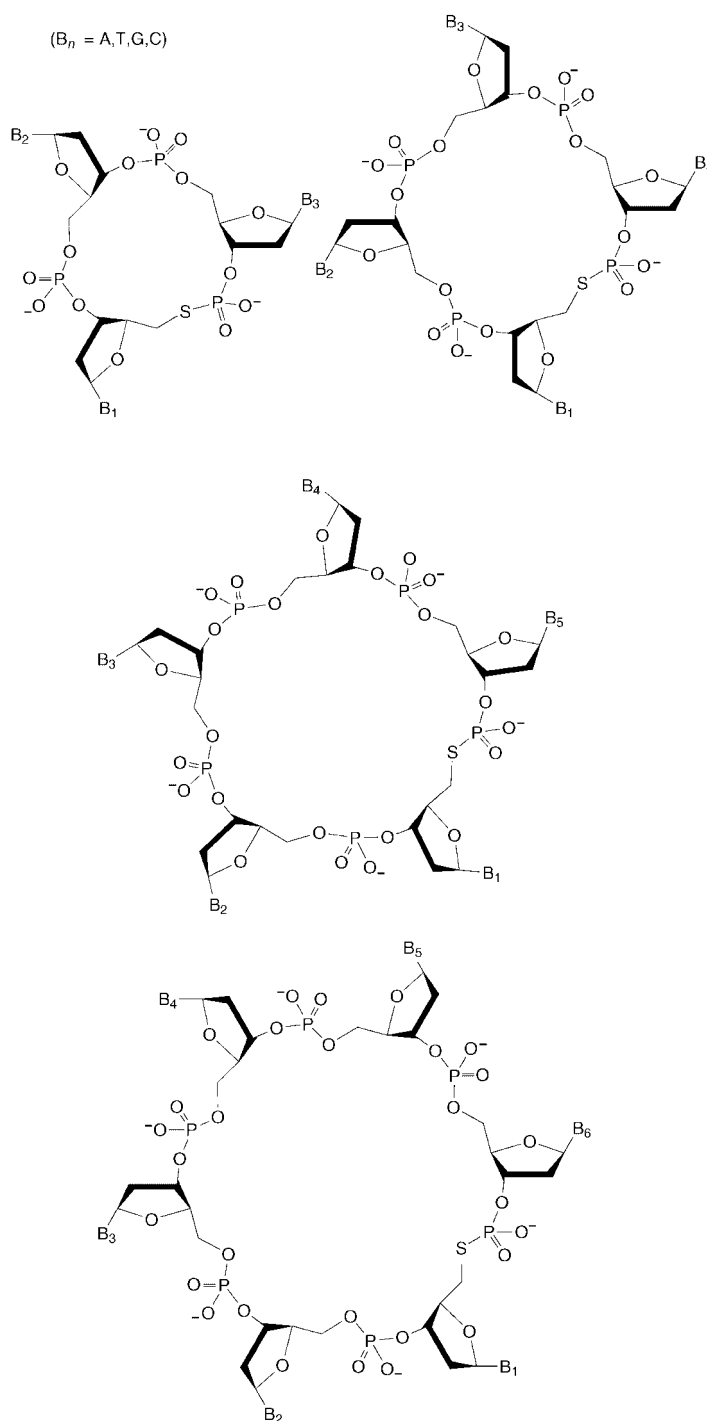
Michael Smietana and Eric T. Kool*

There has been an increasing interest of late in the unusual chemical and biological properties of synthetic cyclic DNAs and RNAs.^[1] Such molecules are distinct from standard linear oligonucleotides in several respects: they are often unusually good substrates for polymerase enzymes, they are remarkably stable in biological media, and they show unusual recognition abilities with other nucleic acids.^[2] Such properties have been reported for a wide range of such molecules, from larger cyclic sequences (e.g., > 100 nt in size),^[3] to intermediate-sized compounds (e.g., 18–72 nt in size),^[4] and even to the smallest ones (2–10 nt in size).^[5] As for this latter class of molecules, cyclic dinucleotides have been suggested as promising biological agents. For instance, *c*(GG) is an activator of cellulose synthase in *Acetobacter xilinum*,^[5c] and *c*(UU) and *c*(AU) are inhibitors of DNA-dependent RNA polymerase of *E. coli*.^[5d] The hypothesized application of short cyclic oligonucleotides in elucidating enzyme mechanisms and as lead structures for development of new drugs,^[6] calls for the definition of an easy and efficient production of such compounds.

So far, several methods have been proposed for the synthesis of short cyclic oligonucleotides, in solution using the phosphotriester^[7–9] or H-phosphonate^[10,11] method, or on polymeric support.^[12–14] Unfortunately, these procedures have two main drawbacks that limit their use: they are not compatible with the more common phosphoramidite chemistry, and they require additional protection and deprotection steps. Moreover, the yield for cyclization never exceeded 50 % using those approaches. De Napoli et al. wisely aimed to circumvent these problems by the use of a glass (CPG)

support for a general synthesis of cyclic oligonucleotides. However, cyclization yields were low (20 %) even in the case of very short oligomers (2–4 residues).^[15] The useful solid support developed by Pedroso et al.^[12] offers a moderate to good 50 % yield for the smallest cycles; however, only the T-support is commercially available.

In this study, we describe the first solid-phase synthesis of cyclic oligonucleotides using the standard β -cyanoethylphosphoramidite method. Oligodinucleotides **1** and larger cyclic oligomers (Scheme 1) bearing one 5'-bridging phosphorothioate linkage are obtained in good to excellent yields. The



Scheme 1. Cyclic oligonucleotides (trimer through hexamer).

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cyclization occurs spontaneously during deprotection of the oligonucleotide, and all four nucleobases can be used without restrictions.

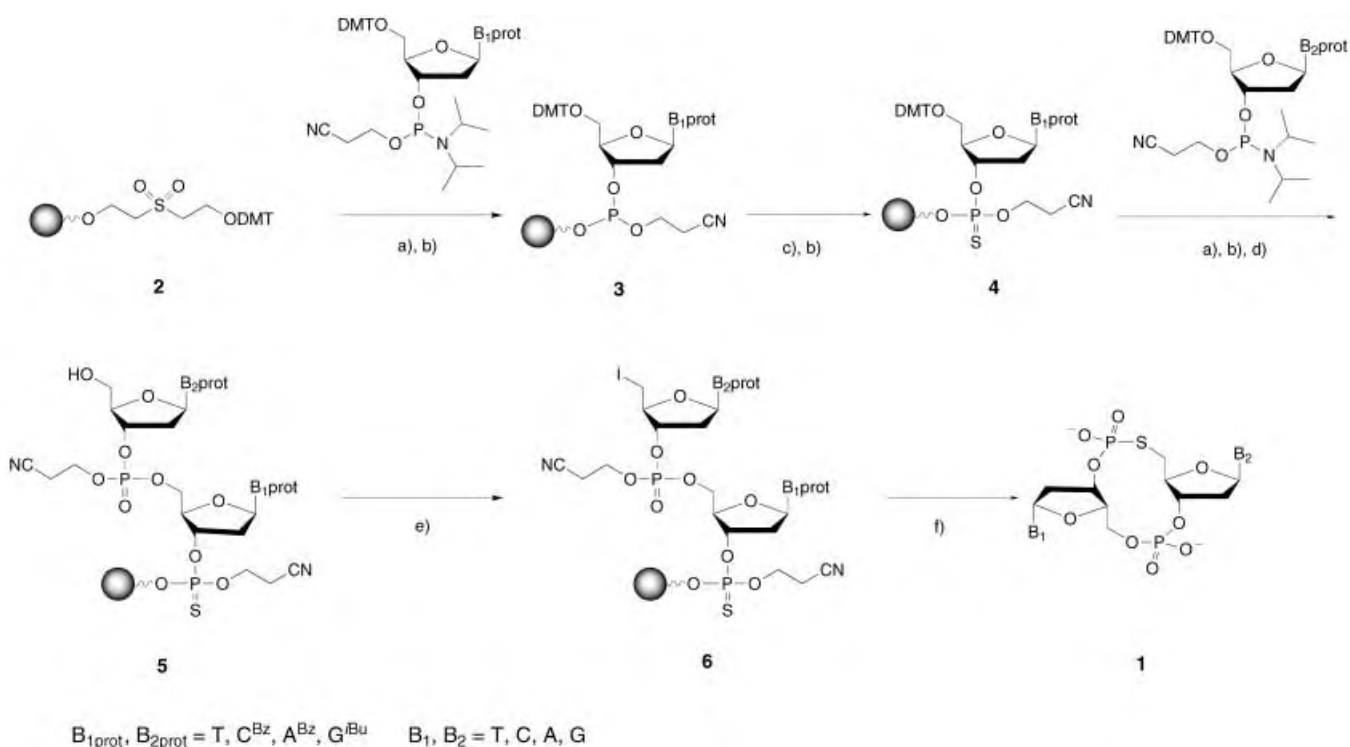
We have previously studied the nucleophilic displacement of 5'-iodo-nucleoside groups.^[16] This has proven to be a useful approach to nonenzymatic ligation of DNAs, involving the reaction of phosphothioates at the 3'-end of one strand with an iodide as leaving group on thymidine on another strand. Very recently, we described a rapid, inexpensive automated method to generate 5'-iodo-oligonucleotides directly on the DNA synthesis column in high yield using $(\text{PhO})_3\text{PCH}_2\text{I}$ as an iodination reagent.^[17] On the basis of these methodologies, we envisioned the formation of cyclic oligodinucleotides, with a sulfur atom replacing one of the bridging phosphodiester oxygen atoms. Of course it remains to be seen how this single sulfur-for-oxygen replacement affects biological activities; however, an earlier study revealed a number of enzymes that were unaffected by this difference in larger oligonucleotides,^[16b] and recent progress in medicinal development of phosphorothioate-containing oligonucleotides also suggests the benign nature of this replacement.^[18]

Starting with solid support **2**, the scheme for synthesis of cyclic oligodinucleotides was initiated on an automated DNA synthesizer on a 1 μmol scale, using two cycles of the standard DNA synthesis protocol that employed phosphoramidite chemistry (Scheme 2). The first nucleotide unit was added yielding the phosphite triester **3**. Oxidative sulfurization of **3** with the commercial reagent 3*H*-1,2-benzodithiol-3-one-1,1-dioxide (Beaucage reagent) led to the thiophosphotriester **4**.^[19] The second cycle was a standard DNA coupling cycle, and the terminal 5-dimethoxytrityl group was removed.

Iodination of the 5'-end of **5** was performed in one step, either on the synthesizer using the automated "iodo-cycle" or by following the manual procedure (see Experimental Section),^[17] leading to 5'-iodinated dinucleotides **6**. Deprotection of bases, release from the CPG support, and cyclization by $\text{S}_\text{N}2$ displacement, were all conducted in a single step by treatment with concentrated ammonium hydroxide for 24 h at room temperature. Overall, then, this procedure is virtually identical to the automated synthesis of a standard dinucleotide, but with a single additional step (the iodination step).

To test the generality of the method, a set of eleven cyclic oligodinucleotides **1** bearing a phosphorothioate linkage was prepared by using this approach. These dimers were characterized by ^1H and ^{31}P NMR spectroscopy and by electrospray mass spectrometry (see Table 1). They were purified by preparative reverse-phase HPLC and quantitated by UV absorbance.^[10] Phosphorus NMR analysis clearly revealed two signals, indicating the presence of one phosphorothioester and one phosphodiester bond. In particular the P(S) resonance signals observed ($\delta \approx 20$ ppm) clearly demonstrate the presence of a 5'-bridging phosphorothioate linkage, whereas unbridged P(S) linkages usually resonate at lower field ($\delta \sim 50$ ppm).^[19] In the ^1H NMR spectra, the signals corresponding to the different protons of each mononucleotide were well separated in the low-field regions, whereas some overlap occurred in the 4'-, 5'-, and 2'-sugar proton regions.

On the basis of a 1 μmol CPG column, the yields of the set of eleven cyclic dinucleotides ranged between 40 and 80 %, demonstrating the high efficiency of the method. The reaction time allowed for reaching these yields was routinely 24 h, although yields were approaching these values after only 16 h



Scheme 2. Synthesis of cyclic oligodinucleotides. a) coupling; b) capping; c) sulfurization: 3*H*-1,2-benzodithiol-3-one-1,1-dioxide, CH_3CN ; d) oxidation: I_2 , 0.02 M (H_2O , pyridine, THF); e) iodination: $(\text{PhO})_3\text{PCH}_2\text{I}$, DMF; f) cleavage: 28 % aq. NH_4OH , RT, 24 h.

Table 1. Analytical data for cyclic compounds.^[a] All contain one sulfur atom (replacing 5'-oxygen atom) immediately 5' to the first nucleotide listed.

Entry	Compound	³¹ P NMR [ppm] ^[b]		H-8	H-2	¹ H NMR [ppm]		H-1'	H-3'	[M + H] ⁺ ^[c]	RT [min] ^[d]	Yield [%]
		PS	PO			H-6	H-5					
1	c(TT)	20.24	−0.23			7.68 7.52		6.32 6.24	5.03	623.1	10.21	71
2	c(TC)	20.15	−0.20			7.93 7.79	6.07	6.29 6.21	5.00 4.91	608.1	9.07	78
3	c(TA)	20.22	−0.17	8.41	8.22	7.80		6.48 6.30	5.13 5.02	632.1	10.57	75
4	c(TG)	20.22	−0.14	8.04		7.50		6.16 5.03	5.15 5.03	648.1	9.65	77
5	c(GG)	20.39	−0.14	8.03 8.00				6.31	5.17	673.1	9.02	60
6	c(GA)	20.46	−0.17	8.41 8.01	8.24			6.50 6.31	5.23	657.1	9.88	55
7	c(CG)	20.31	−0.13	8.01		7.70	6.04	6.30	5.15 4.98	633.2	8.92	45
8	c(CC)	20.25	−0.21			8.25 7.93	5.88 5.79	6.14	4.98	593.1	8.12	65
9	c(CA)	20.36	−0.16	8.42	8.23	7.77	6.04	6.50 6.30	5.13 4.99	617.1	9.26	52
10	c(AA)	20.29	−0.18	8.42 8.40	8.24 8.22			6.50	5.02	641.1	10.65	36
11	c(AT)	20.28	−0.25			nd				632.1	10.64	50
12	c(T ₃)	19.58	−0.78 −1.11			7.76 7.75 7.59		6.39 6.36 6.27	4.88 4.83	927.1	13.31	70

[a] The NMR spectra were recorded in D₂O at 500 MHz. [b] ³¹P chemical shifts were measured with respect to 85 % H₃PO₄ as external standard. [c] Electrospray MS. [d] Retention time (RT) by analytical reverse-phase HPLC using a gradient of 0 to 20 % of acetonitrile over 20 min, at a flow rate of 1 mL min^{−1}. nd: not determined.

(by HPLC). A common feature of the HPLC profiles of all the crude cyclization/deprotection reactions is a single major peak representing the cyclic product (typically more than 70 % of the total integrated area) accompanied by only small impurities. Most of the sequences behaved similarly. However, particularly striking is the difference in yield between the two syntheses of c(TA) (Table 1, entry 3) and c(AT) (Table 1, entry 11): much lower yield was obtained from 5'-terminal iodo-dA. A possible explanation for this is the formation of a cyclonucleotide by N3 intramolecular attack either on the 5'-O-phosphonium Moffatt intermediate or on the subsequent 5'-iodo derivative.^[20]

Work is underway to apply a similar strategy to the preparation of short cyclic oligoribonucleotides. Such compounds, because of their greater reactivity, are commonly much more difficult to prepare than the corresponding 2'-deoxy analogues.^[13] Micura et al. recently developed a method for the synthesis of small cyclic RNAs by the use of 2'-O-triisopropylsilyloxymethyl (TOM)-protected amidites to circumvent the difficulties and limitations generally encountered.^[21] Preliminary results obtained in our laboratory show that 2'-O-methoxyribonucleotides are well iodinated on the 5'-end allowing the high-yield formation of mixed cyclic oligonucleotides (e.g. c(TU_(Ome)) (data not shown). However the synthesis of cyclic oligodi-(2'Ome)-ribonucleotides appears more difficult to achieve.

Finally, the synthesis of some larger cyclic oligodeoxynucleotides was undertaken to further evaluate the utility of the method. Although the formation of trimers appears to be as good as dimers (Table 1, entry 12), the cyclization yields decrease significantly, not surprisingly, as the size of the

oligomers increases (after 5 days at 50 °C, c(T₄) 50 %, c(T₅) 25 %, and c(T₆) 15 %). We noted that with the larger macrocycles these products appear with concomitant formation of an unexpected, apparently dethiophosphorylated by-product as indicated by mass spectrometry (data not shown), which apparently competes against formation of the desired cyclic product.^[22] Although the yield drops significantly as cyclic pentamers and hexamers are prepared, it is worth noting that these yields are still competitive with those obtained by previous approaches.

In conclusion, we present a very efficient procedure for the synthesis of short cyclic oligonucleotides using a standard commercial CPG support. Its suitability with standard DNA synthesizers and phosphoramidite chemistry, as well as the ease of execution, make the method quite attractive for general use. The higher final yields and shorter reaction times in comparison with previously described methods also speak for the utility of the approach. Elaboration of a library of cyclic molecules using modified nucleotides, as well as evaluation of such compounds against specific biological targets will be presented elsewhere.

Experimental Section

All cyclic oligonucleotides were prepared on a DNA synthesizer using standard phosphoramidite chemistry and standard synthesis cycles. After coupling the second nucleotide (DMT-off), columns were removed and 1 mL syringes were attached to both ends of the columns. (PhO)₃PCH₃I (1 mL, 0.5 M in anhydrous DMF) was then passed from one syringe, through the column, to the other syringe for 5 min before the sample was put on a shaker at room temperature for 25 min. The iodination reagent was then removed and the column washed with CH₂Cl₂ (10 mL), CH₃CN (10 mL), and CH₂Cl₂ (10 mL). Cleavage and cyclization of the nucleotides was



achieved by soaking the beads in concentrated ammonia at room temperature for 24 h. Cyclic compounds were purified by preparative reverse-phase HPLC using a gradient of 0–20% of acetonitrile over 20 min at a flow rate of 3 mL min⁻¹. Analytical data are given in Table 1.

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Kinetics of a Reversible Covalent-Bond-Forming Reaction Observed at the Single-Molecule Level**

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The examination of single molecules can reveal detail that is obscured in observations of ensembles. A great deal of recent work at the single-molecule level has focussed on biological problems;^[1–6] there has been less emphasis on chemistry, especially the making and breaking of covalent bonds. Seminal experiments have resulted in the observation of individual reaction steps catalyzed by enzymes^[7] and ribozymes.^[8] But, this work has employed optical techniques that are restricted to the use of fluorescent substrates or the investigation of nanoscale movements.^[9] We have previously used electrical recording, which does not suffer from these limitations, to visualize individual noncovalent interactions occurring in the lumen of a protein pore.^[10] Others have used electrical recording to study individual unidirectional covalent-bond-forming reactions^[11] and a reversible thermal isomerization.^[12] Herein, we demonstrate that reversible covalent-bond-forming chemistry can be observed by electrical detection. Reversible covalent-bond-forming chemistry at the single-molecule level has not been observed previously by any means.

To demonstrate our approach, we examined the reaction of organoarsenic(III) compounds with thiols, a reaction of considerable importance in the toxicology of environmental contaminants, chemotherapeutic agents, and chemical weapons.^[13–21] The reactions of organoarsenic(III) compounds with dithiols to form stable cyclic 1,3-dithia-2-arsolanes have been thoroughly investigated (Figure 1a, upper).^[22–25] Such reactions are essentially irreversible with formation constants of the order of $K_f = 10^7 \text{ M}^{-1}$.^[26,27] But, we reasoned that reactions with monothiols would be reversible (Figure 1a, lower); indeed, unstable adducts of organoarsenic(III) compounds with monothiols are known, although their chemistry has been hardly studied.^[28,29]

In our experiments, organoarsenic compounds were present in solution, while thiols were incorporated onto the luminal face of the α -hemolysin protein pore by site-directed muta-

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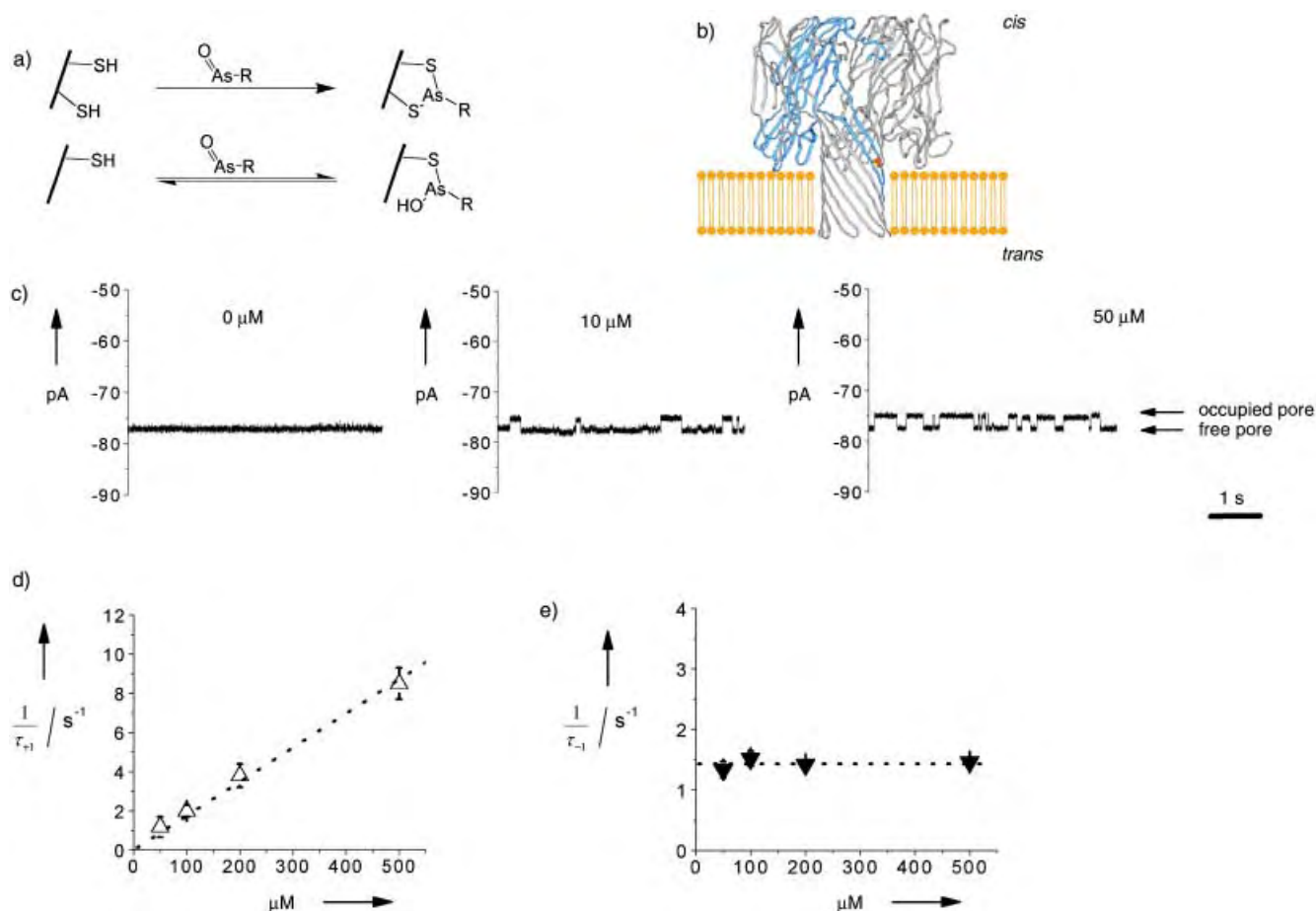


Figure 1. Reversible reactions in which covalent bonds are formed within a single protein pore. a) Upper: organoarsenic(III) compounds react with dithiols to form stable cyclic 1,3-dithia-2-arsolanes. Lower: organoarsenic(III) compounds react with monothiol adducts to form unstable adducts. b) Molecular graphics rendition of the P_{SH} pore. The α-hemolysin pore is a heptamer. In P_{SH}, one of the subunits has been replaced with a mutated subunit (blue) containing a cysteine residue (red, with S atom in yellow) in place of the naturally occurring threonine-117. The current flowing through single P_{SH} pores was measured by planar bilayer recording. Arsenic compounds were added to the *trans* side of the bilayer. c) Interaction of 4-sulfophenylarsane oxide with the P_{SH} pore. Single-channel recordings were carried out, samples are shown, at -50 mV with 2 M KCl, 80 mM 3-(4-morpholinyl)-1-propanesulfonic acid (MOPS), 100 μM ethylenediaminetetraacetate (EDTA), pH 8.4, in both chambers. Similar results were obtained with 2 M KCl, 80 mM sodium phosphate, pH 8.4. Current traces in the presence of 0, 10, and 50 μM 4-sulfophenylarsane oxide are shown. Current levels for the free and covalently modified pore are indicated. d) Plot of the reciprocals of the mean inter-event intervals (τ₊₁, Δ) versus 4-sulfophenylarsane oxide concentration. e) Plot of the reciprocals of the mean residence time (τ₋₁, ▼) versus 4-sulfophenylarsane oxide concentration. In d) and e), values of τ₊₁ and τ₋₁ were obtained by fitting dwell-time histograms to single exponential functions. For a simple bimolecular interaction: τ₋₁ = 1/k₋₁; τ₊₁ = 1/k₊₁[R], where [R] is the free reagent concentration.

genesis. For example, a version of the α-hemolysin pore (P_{SH}) was constructed in which the side-chain of a single cysteine residue at position 117 projects into the lumen of the transmembrane β-barrel (Figure 1b). The chemistry occurring at cysteine was observed by monitoring fluctuations in the ionic current flowing through a single P_{SH} pore in a planar bilayer (Figure 1c). P_{SH} itself had a unitary conductance of 1.54 ± 0.03 nS (*n* = 7, where *n* = the number of experiments performed) in 2 M KCl. In the presence of 4-sulfophenylarsane oxide,^[30] a model reactant, steps were observed during which the current was reduced by 2.5 ± 0.3 pA (*n* = 7). These events were not observed when 4-sulfophenylarsane oxide was added to a bilayer containing the wild-type α-hemolysin pore, which contains no cysteine residues. The events were eliminated either by replacing the arsenic-containing solution with buffer or by the addition of 2,3-disulfanypropanol (1.5 mM to 10 μM arsenic species).

The approach permits the rapid evaluation of kinetic constants under conditions of dynamic equilibrium.^[31] The

steps, which represent individual covalent couplings of 4-sulfophenylarsane oxide to form a noncyclic monothiol adduct (Figure 1a, lower), had a mean duration of 702 ± 38 ms (*n* = 6). Plots of the mean lifetime of the adduct (τ₋₁) and the mean inter-event intervals (τ₊₁) versus the concentration of 4-sulfophenylarsane oxide are suggestive of a simple bimolecular interaction (Figure 1d,e).^[31] Forward and reverse rate constants derived from the τ values (k₊₁ = 20 ± 3 × 10³ M⁻¹ s⁻¹; k₋₁ = 1.4 ± 0.1 s⁻¹) yielded a formation constant K_f = 1.4 ± 0.3 × 10⁴ M⁻¹ at 24 °C (*n* = 4).

Additional arsenic species were tested with the P_{SH} pore and they yielded signals with diverse amplitudes and mean dwell times. These data suggest that a wealth of chemical information should be accessible through the approach disclosed here. Because the observations are made under conditions of dynamic equilibrium, the time resolution is limited only by the sampling time of the system, which can be less than 50 μs. The approach is not limited by a requirement for a particular class of molecules, such as fluorophores.

Further, the geometry of the lumen of the α -hemolysin pore will allow the examination of several effects important in organic chemistry, such as the properties of neighboring groups introduced by mutagenesis or targeted chemical modification. Although the present system is restricted to aqueous chemistry on a protein surface, the general principle might be extended to alternative detection methods that work in different environments.

In addition, the electrical signals from reversible covalent-bond-forming reactions are rich in information and could be employed in stochastic sensing^[10] to detect organoarsenic species (such as the vesicant lewisite, 2-chlorovinylldichloroarsane) and other reactive molecules, such as nerve and mustard "gases". Because different patterns of residues can be engineered within the lumen of the α -hemolysin pore, the approach should be adaptable to a wide range of chemical systems. Finally, chemical modification at cysteine has played a major role in determining the structures of ion channels in different conformational states.^[32–34] It seems likely that reversible chemical modification at cysteine, during single-channel recording, will be valuable in this area too.

Experimental procedures for the preparation of the P_{SH} pore, the synthesis of 4-sulfophenylarsane oxide, and single channel recording are available in the Supporting Information.

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Hydroboration of Coordinated Dinitrogen: A New Reaction for the N₂ Ligand that Results in Its Functionalization and Cleavage**

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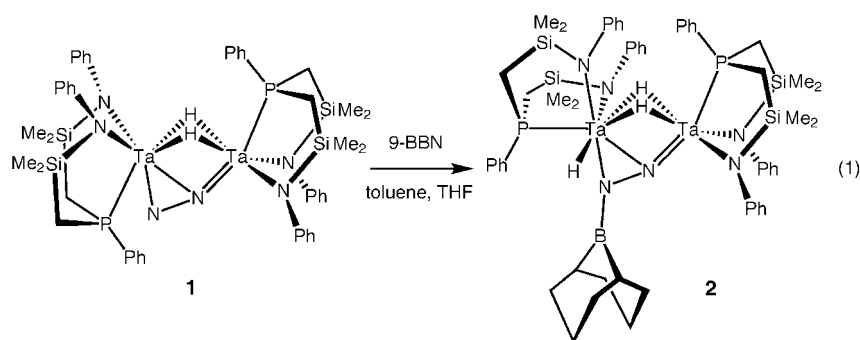
An essential process in nitrogen fixation is cleavage of molecular nitrogen.^[1] Several studies using model systems have confirmed that metal nitrides can be formed from coordinated dinitrogen providing that at least six electrons are available to formally reduce the N₂ unit to two N^{3–} ligands.^[2] To date, all well-characterized molecular examples of metal nitride formation from dinitrogen have involved intermediates containing multiple metal atoms. Therefore, comparisons have been made to the polymetallic FeMoco active site in nitrogenase enzymes, and activated iron surfaces in the Haber process.^[3] Herein we report a completely new way to form metal nitrides from coordinated dinitrogen that involves simple organoborane addition to a dinuclear tantalum dinitrogen complex. Because this result is quite unrelated to either biological or industrial nitrogen fixation, we suggest that a new paradigm for both cleaving and functionalizing coordinated dinitrogen is now available.

We have reported the facile preparation of [(NPN)Ta]₂-(μ-H)₂(μ-η¹:η²-N₂) (**1**; where NPN = (PhNSiMe₂CH₂)₂PPh),^[4] from the spontaneous reaction of N₂ gas with the dinuclear tantalum(IV)-hydride precursor [(NPN)Ta]₂(μ-H)₄. Equation (1) shows the 1:1 reaction between dark brown **1** and a THF solution of 9-borabicyclononane (9-BBN), which proceeds to completion over a few hours at room temperature to give orange [(NPN)Ta(H)](μ-H)₂(μ-N₂-BC₈H₁₄)[Ta(NPN)] (**2**), in almost quantitative yield.

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The $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of **1** and **2** each show the presence of a pair of inequivalent phosphane ligands, but the solution ^1H NMR spectrum of **2** indicates C_1 symmetry rather than the C_s symmetry exhibited by **1**. This finding is supported by the solid-state molecular structure of **2**, which was obtained by X-ray diffraction^[5] (Figure 1). The N–N bond of the dinitrogen moiety has been elongated from 1.319(4) Å in **1** to 1.411(15) Å in **2**. The B–N bond length is 1.40(2) Å, the sum of the angles around B1 atom is 360.0°, and the sum of angles around N1 is 354.6°. The ditantalum–dinitrogen core of the molecule is nearly planar, with an N1–Ta1–Ta2–N2 torsion angle of $-6.3(6)^\circ$. The NPN ligand bound to Ta1 appears to be occupying three facial sites with phosphane P1 *trans* to the Ta–Ta axis, amide N3 *trans* to the dinitrogen fragment, and amide N4 *cis* to N3 (angle N3–Ta1–N4 $95.3(5)^\circ$), which leaves one face of the Ta atom open. Thus, it is likely that the terminal hydride resides on this vacant face.^[6] The resonance signal of this hydride is clearly evident at $\delta = 15.31$ ppm in the ^1H NMR

spectrum of **2**. Surprisingly, no exchange is observed between the terminal hydride and the two bridging hydride ligands of **2**, either on the NMR timescale as explored by EXSY-NMR spectroscopy or on the chemical timescale in the di- μ -deuterio isotopomer $\mu\text{-D}_2\text{-2}$ (prepared from deuterated **1**). We have reported elsewhere^[4] that the HOMO of the $[\text{Ta}_2(\mu\text{-}\eta^1\text{:}\eta^2\text{-N}_2)]$ core of **1** has π -bonding character between Ta1 and N1 (numbering as in the structure of **2**), and therefore this reaction can be described as

the hydroboration of a metal–dinitrogen π bond. To our knowledge, this B–H addition across a metal–dinitrogen unit is unique, although simple borylations of coordinated dinitrogen have been reported.^[7]

The 9-BBN adduct **2** is thermally unstable and gradually undergoes further spontaneous rearrangement. Over four to six weeks in solution, **2** is transformed into the imide–nitride complex **3** (Figure 2) in 42 % yield. Like **2**, the imide–nitride **3** displays C_1 symmetry in solution, as shown by NMR spectroscopic experiments, and in the solid-state as demonstrated by the structure obtained by X-ray crystallography.^[5b] The numerous rearrangements leading to **3** include N–N bond scission accompanied by the loss of the three hydride ligands and one phenyl group from an amido donor (see below). Although the ancillary NPN ligand bound to Ta1 has clearly undergone an irreversible rearrangement, the other NPN ligand is unchanged. A highly organized square-planar Ta_2N_2 motif is present in the core of the molecule, with one bridging N atom bound to a Si atom of the rearranged ligand. The borylamido unit of **2** has been transformed into a borylimido fragment with a Ta1–N1 bond of 1.818(5) Å. The solution ^1H NMR spectrum of **3** shows no resonances indicative of hydride ligands, and the observation of D_2 gas (detected by GCMS) in the headspace above solutions of **3** derived from μ -

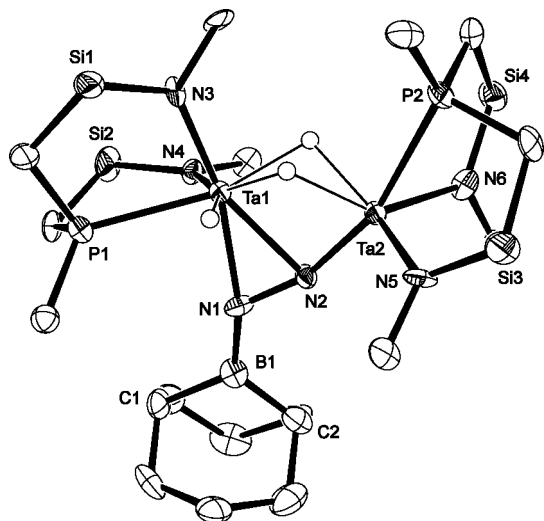


Figure 1. ORTEP drawing of the molecular structure of **2** as determined by X-ray crystallography (thermal ellipsoids set at the 50 % level). Silyl methyl and phenyl ring carbon atoms, other than the ipso carbon atoms, are omitted for clarity. Hydrides were placed using X-HYDEX. Selected bond lengths [Å], bond angles [°], and torsion angles [°]: N1–N2 1.411(15), Ta1–N1 2.123(12), Ta1–N2 2.200(12), Ta2–N2 1.833(11), N1–B1 1.40(2), Ta1–P1 2.583(4), Ta1–N3 2.076(13), Ta1–N4 2.110(11), Ta2–P2 2.606(4), Ta2–N5 2.022(11), Ta2–N6 2.019(12), Ta1...Ta2 2.8483(8); Ta1–N1–N2 $73.9(7)^\circ$, $68.0(7)^\circ$, Ta1–N2–Ta 2 $89.4(5)^\circ$, Ta1–N1–B1 $163.1(10)^\circ$, N1–Ta1–N3 $162.0(5)^\circ$, N3–Ta1–N4 $95.3(5)^\circ$, N3–Ta1–P1 $81.0(3)^\circ$, P1–Ta1–Ta2 $152.17(10)^\circ$, N2–Ta2–P2 $163.8(4)^\circ$, N5–Ta2–N6 $106.0(5)^\circ$; Ta1–N1–N2–Ta2 $6.3(6)^\circ$, P1–Ta1–Ta2–P2 $-117.8(2)^\circ$, P2–Ta2–Ta1–N2 $-174.7(5)^\circ$, P2–Ta2–Ta1–N3 $-4.4(4)^\circ$, P2–Ta2–Ta1–N4 $106.2(4)^\circ$, B1–N1–N2–Ta1 $-168.8(18)^\circ$.

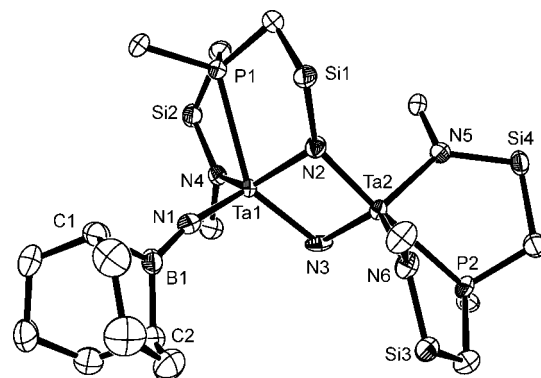


Figure 2. ORTEP drawing of the molecular structure of **3** as determined by X-ray crystallography (thermal ellipsoids set at the 50 % level). Silyl methyl groups and phenyl ring carbons, other than the ipso carbons, are omitted for clarity. Selected bond lengths [Å], bond angles [°], and torsion angles [°]: Ta1–N1 1.818(5), N1–B1 1.404(9), Ta1–N2 2.121(5), N2–Ta2 1.968(5), Ta2–N3 1.826(5), N3–Ta1 1.995(5), N2–Si1 1.717(5), Ta1–N4 2.052(5), Ta1–P1 2.672(2), Ta2–N5 2.062(5), Ta2–N6 2.076(5), Ta2–P2 2.683(1); Ta1–N2–Ta2 $99.5(2)^\circ$, N2–Ta2–N3 $89.0(22)^\circ$, Ta2–N3–Ta1 $99.5(2)^\circ$, N3–Ta1–N2 $80.5(2)^\circ$, Ta1–N1–B1 $167.0(5)^\circ$, N1–Ta1–P1 $102.9(2)^\circ$, N1–Ta1–N4 $111.4(2)^\circ$, Ta1–N2–Si1 $125.4(3)^\circ$, N3–Ta2–N5 $116.3(2)^\circ$, N3–Ta2–N6 $116.3(2)^\circ$, N3–Ta2–P2 $93.0(2)^\circ$; Ta1–N2–Ta2–N3 $-0.5(2)^\circ$, Ta1–Ta2–N2–Si1 $174.9(6)^\circ$, N1–Ta1–N2–Ta2 $-110.9(2)^\circ$, P1–Ta1–Ta2–P2 $143.15(6)^\circ$, Ta2–N2–Ta1–N4 $97.1(3)^\circ$.

D_2 -**2** indicates the reductive elimination of bridging D groups as D_2 and thus, elimination of bridging hydrides as H_2 from the non-deuterated compounds. The parent dinitrogen complex **1** tolerates several days of reflux in toluene with no elimination or rearrangement of any kind; therefore this intricate transformation is triggered by addition of the organoborane.

The atoms of the dinitrogen unit of **2** apparently correspond to N1 of the boryl imide and bridging nitride N3 of **3**, which implies that the bridging amide N2 is derived from the ancillary NPN ligand by loss of its phenyl substituent. However, the transformations leading to **3** are in fact more complicated. It is relatively simple to prepare $^{15}N_2$ -**1** from enriched $^{15}N_2$ and the hydride precursor $[(NPN)Ta]_2(\mu-H)_4$, which allows the synthesis of $^{15}N_2$ -**2** and $^{15}N_2$ -**3**. While ^{15}N NMR spectroscopy is not helpful in exploring the conversion of **2** into **3**, comparison of the ^{29}Si -DEPT NMR spectra of **3** and labeled $^{15}N_2$ -**3** unequivocally establishes that a silicon migration occurs during formation of **3**. Unlabeled **3** (top spectrum, Figure 3) gives rise to four doublets in the NMR spectrum (a small two-bond coupling to ^{31}P is observed in all ^{29}Si spectra of the NPN ligand), in agreement with C_1 symmetry which results in four distinct silicon environments. In $^{15}N_2$ -**3** (bottom spectrum, Figure 3) one of these signals changes to an AMX doublet of doublets consistent with additional coupling to ^{15}N ($I=1/2$). Therefore N2 of **3** originates in the dinitrogen ligand of **2**, and the NPN silicon atom Si1 has migrated to it from an NPN-ligand amide. Although there is precedent for intramolecular silicon migration between nitrogen and oxygen atoms of differing nucleophilicity,^[8] this is an instance of an amide and a nitride competing for an electrophilic silyl group.

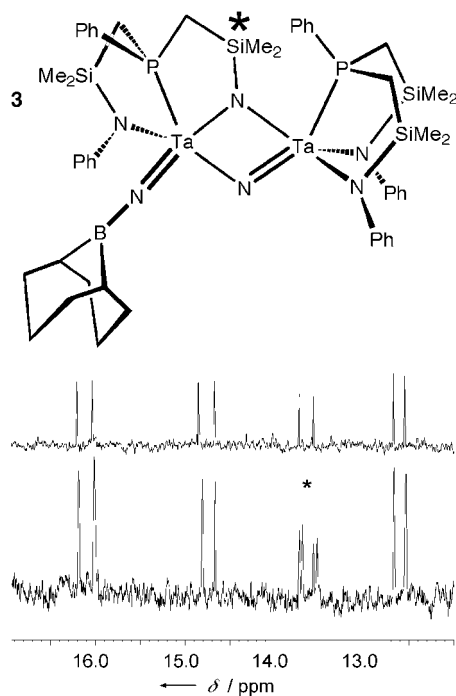


Figure 3. ^{29}Si -DEPT NMR spectra of complex **3** (top) and the isotopomer $^{15}N_2$ -**3** (bottom). Additional splitting in the peak at $\delta = 13.64$ ppm (*) is a result of ^{15}N coupling ($I=1/2$, $J_{N,Si}=3.2$ Hz).

The discovery of an intermediate in the conversion of **2** into **3** supports this assessment and provides further insight into this process. Judicious concentration and cooling of a THF solution of **2** left in a glove box at $15^\circ C$ for three weeks produced a crystalline material unlike **2** or **3** by its ^{31}P NMR spectrum. The solid-state molecular structure of **4**^[5b] is shown in Figure 4, and, like **3**, it shows the square imide–nitride motif associated with N–N bond cleavage, substantial rearrangement of one NPN ligand, and the absence of hydride ligands bridging the Ta–Ta unit. Although structural parameters for the square Ta_2N_2 motif in **4** are not significantly different from those of **3**, there are two key features of **4** that are not shared with **3**. First, the geometry at B1, which is trigonal planar in **3**,

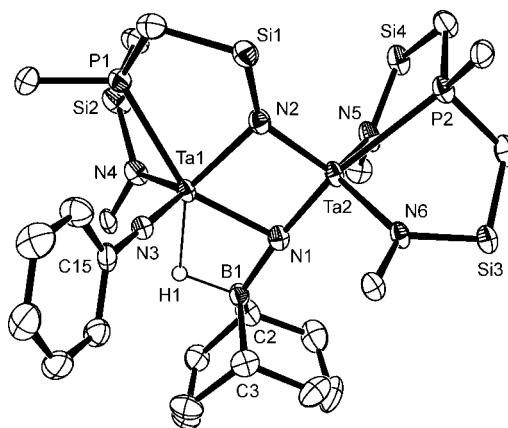
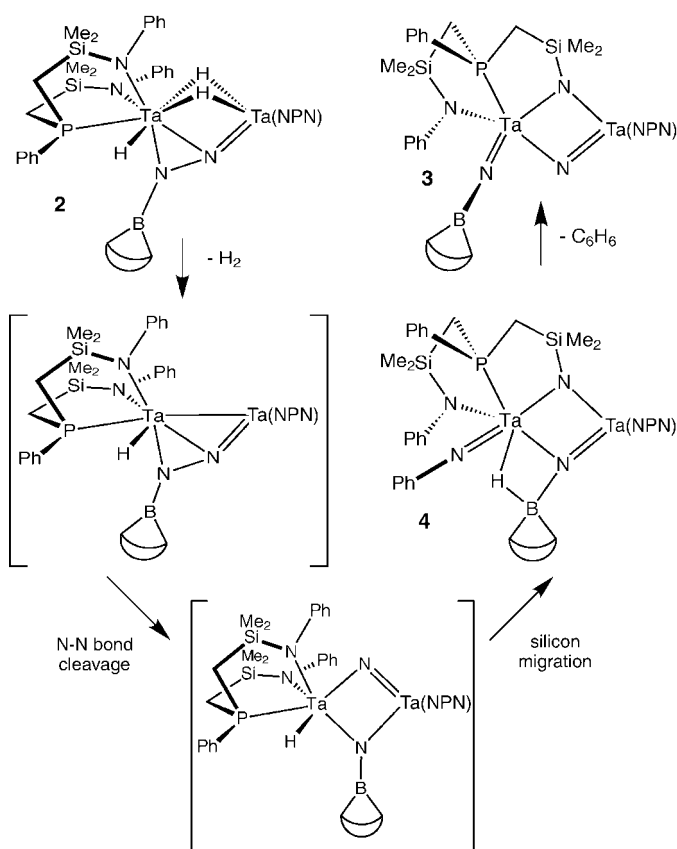


Figure 4. ORTEP drawing of the solid-state molecular structure of **4** as determined by X-ray crystallography (thermal ellipsoids set at the 50% level). Silyl methyl groups and phenyl ring carbon atoms, other than the ipso carbons, are omitted for clarity. Selected bond lengths [Å], bond angles [°], and torsion angles [°]: Ta1–B1 1.92(6), Ta1–N1 2.184(5), Ta1–N2 2.175(5), Ta1–N3 1.793(5), Ta1–N4 2.123(5), Ta1–P1 2.5900(15), N1–B1 1.517(8), B1–H1 1.33(6), Ta1–H1 1.92(6), N2–Si1 1.737(5), N1–N2 2.737(4), Ta2–N5 2.049(5), Ta2–N6 2.111(5), Ta2–P2 2.7831(15); N1–Ta1–N2 77.76(17), Ta1–N2–Ta2 93.66(18), N2–Ta2–N1 92.3(2), Ta2–N1–Ta1 96.20(19), Ta1–N1–B1 88.0(3), N1–B1–H1 101(3), N1–Ta1–N3 113.74(19), N1–Ta1–N4 109.26(18), N1–Ta1–P1 148.57(12), N1–Ta2–N5 101.93(19), N1–Ta2–N6 99.84(19), N1–Ta2–P2 167.80(15); Ta1–N2–Ta2–N1 $-2.7(2)$, P1–Ta1–Ta2–P2 $346.9(1)$, N1–Ta1–N2–Si1 $163.2(3)$, N2–Ta1–N1–B1 $-170.8(3)$.

is roughly tetrahedral in **4** as a result of the presence of the bridging hydride H1, which was located in the diffraction experiment and gives a resonance signal at $\delta = 4.56$ ppm in the ^1H NMR spectrum of **4**. H1 is presumably involved in an agostic interaction with Ta1 (Ta1–H1 = 1.92(6) Å, N1–B1–H1 = 101(3)°). The second and most significant difference between **3** and **4** is the linear phenylimido moiety of **4**, which is the fragment expected to result from the silyl group migration off the NPN-ligand amide group and onto a dinitrogen-derived nitride ligand. After the migration, the boron hydride and the phenyl group bound to former NPN ligand amide N3 are then arranged in a manner that allows for elimination of benzene, a requirement for formation of **3** from **4**. The elimination of the boron hydride with the phenyl substituent of N3 as benzene can be detected by ^1H and ^{13}C NMR spectroscopy—both benzene and **3** can be identified in $[D_8]THF$ solutions of **4** after a few days. This benzene elimination would leave N3 as a terminal nitride ligand. One

final question arises: does this nitride (N3) attack the other Ta atom (Ta2), displacing the bridging N1-BC₈H₁₄ moiety to a new position as the terminal and linear imidoborane seen in **3**, or does it simply acquire the BC₈H₁₄ group from the bridging nitride N1 in **4** to give **3**? The labeling study described above indicates that the former occurs, and that the B1–N1 bond remains intact throughout these transformations. Compared to the ¹¹B NMR spectrum of **3**, the ¹¹B spectrum of ¹⁵N₂-**3** shows a poorly resolved splitting attributed to ¹⁵N–¹¹B coupling. The considerable strength of the B–N bond^[9] makes this rearrangement more likely than migration of the borabicyclononyl fragment. Therefore N1 and N2 in **3** are dinitrogen-derived atoms.

A proposed mechanism for the transformation of **2** into **3** is shown in Scheme 1. Considering the overall reaction as the initial formation of **1** from N_{2(g)} and tantalum(IV) hydride precursor [(NPN)Ta]₂(μ-H)₄, this system achieves the six-electron reduction of the N₂ unit in a stepwise fashion, with a number of isolatable intermediates and detectable byproducts. As discussed previously, the first four electrons required for activation of N₂ to N₂⁴⁻ derive from elimination of two bridging hydride ligands as H₂ and from a Ta^{IV}–Ta^{IV} bond (which is itself derived by H₂ elimination from the Ta^V starting material [(NPN)TaMe₃] following hydrogenation).^[4] This is the reaction between the precursor and N₂ to generate **1**. We suggest that reductive elimination of H₂ from **2** provides the last two electrons for the overall six-electron reduction of the N₂ unit to two N³⁻ nitride units. Remarkably, the six electrons required to cleave the N₂ unit were all obtained by reduction of hydride ligands to H₂ gas.



Scheme 1.

In conclusion, a new reaction for coordinated dinitrogen has been explored, in which a B–H bond adds across a Ta–N bond to give a complex with a functionalized N₂ ligand and a new terminal hydride ligand. The spontaneous transformations of this complex result from H₂ elimination and N–N bond cleavage, which lead to dinitrogen-derived nitride ligands. While such processes are unique reactivity patterns in dinitrogen chemistry, the irreversible ligand degradation that occurs limits the usefulness of this reaction. Nevertheless, experiments to extend this chemistry using modified ancillary NPN ligands and different primary and secondary alkylboranes are underway.

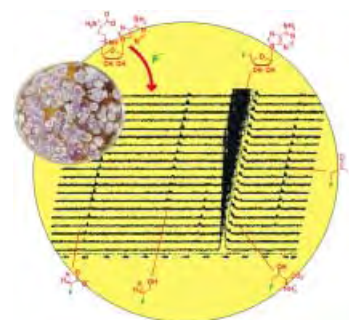
Complete experimental details are available in the Supporting Information.

Received: July 9, 2002 [Z19695]

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- a) The solid-state molecular structure obtained for **2** features two discrete molecules, one of each possible enantiomeric form. These two molecules are isostructural and we report parameters for one of them throughout this paper. b) Information regarding collection, solution, and refinement of this data is summarized in the Supporting Information. CCDC-188057 (**2**), CCDC-188056 (**3**), CCDC-188058 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
- The terminal hydride was successfully modeled using XHYDEX at a Ta–H separation of 1.6 Å. For XHYDEX, see A. G. Orpen, *J. Chem. Soc. Dalton Trans.* **1980**, 2509.
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COVER PICTURE

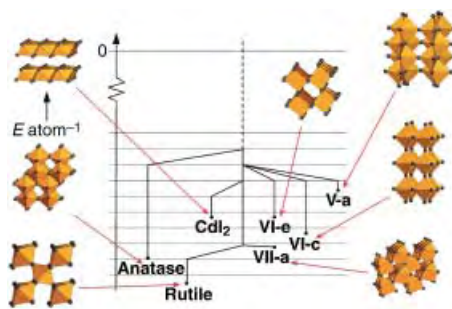
The cover picture shows a series of ^{19}F NMR spectra taken every hour during the monitoring of a time-course experiment after addition of 5'-fluoro-5'-deoxyadenosine (5'-FDA) to a cell-free extract of *Streptomyces cattleya*. This bacterium has the unusual capacity to biosynthesise organofluorine compounds from inorganic fluoride. The ^{19}F NMR spectra illustrate that 5'-FDA is a true intermediate in the biosynthesis of fluoroacetate and 4-fluorothreonine. Other intermediates such as fluoroacetaldehyde are also observed for the first time. In a separate experiment, inorganic fluoride was converted into fluoroacetate, thus indicating that all of the enzymes involved in the fluoroacetate biosynthesis pathway are active in the cell-free extract. These experiments report the first cell-free biotransformations of inorganic fluoride into fluoroacetate, the most ubiquitous organic fluorine natural product, and pave the way for a biotechnological approach to organofluorine synthesis. Full details are described by O'Hagan and co-workers on p. 3913 ff.



REVIEW

Contents

Hunter gatherers and not creators is how synthetic chemists could be described following a concept for the development of the (currently not yet feasible) goal-oriented synthesis of new solid-state compounds. The first step consists of the identification of realistic synthesis goals, which is achieved by the exploration of the energy landscape of the chemical system of interest using global optimization methods. Less developed are approaches for the second step, the rational design of feasible synthesis routes. Here, the crucial issues are the use of synthesis routes with extremely low activation and the control of nucleation processes. The picture shows the results of the theoretical exploration of the energy landscape of MgF_2 (structure candidates of low energy and the barrier structure depicted as a tree graph.)



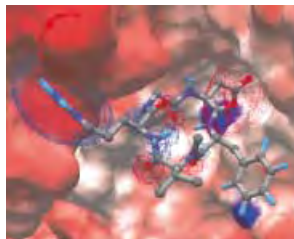
M. Jansen * 3746–3766

A Concept for Synthesis Planning in
Solid-State Chemistry

Keywords: solid-state chemistry • solid-state reactions • structure prediction • synthesis planning

Angew. Chem. 2002, 114, 3896–3917

A milestone in integrin research was the determination of the structure of the extracellular domain of $\alpha_v\beta_3$ integrin both in the free and complexed forms (an integrin complex with a cyclic RGD peptide is shown). Calculations on the interactions of the transmembrane α and β helices, NMR studies of the intracellular domain, and electron microscopic investigations provide a new insight into the mode of action of the integrin as well as a plausible model for signal transduction through the cell membrane.



K.-E. Gottschalk,
H. Kessler* 3767–3774

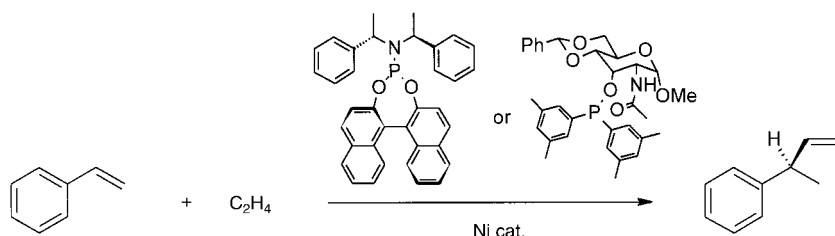
The Structures of Integrins and Integrin–Ligand Complexes: Implications for Drug Design and Signal Transduction

Keywords: membrane proteins • molecular modeling • protein structures • signal transduction • structure–activity relationships

Angew. Chem. **2002**, *114*, 3919–3927

HIGHLIGHTS

At last the possibility of tailored catalyst design: Advances in the asymmetric hydrovinylation of olefins had not been made for a long time despite much effort, such that the interest in the reaction had dwindled. Recently, however, Leitner's and RajanBabu's research groups developed highly efficient, modular catalytic systems for this reaction (see scheme); thus, the prerequisite for further developments of this elegant reaction have finally been fulfilled.



L. J. Goossen* 3775–3778

Asymmetric Hydrovinylation: New Perspectives through Use of Modular Ligand Systems

Keywords: alkenes • asymmetric catalysis • dimerization • hydrovinylation • nickel

Angew. Chem. **2002**, *114*, 3929–3932

VIPs

The following communications are “Very Important Papers” in the opinion of two referees. They will be published shortly (those marked with a diamond will be published in the next issue). Short summaries of these articles can be found on the *Angewandte Chemie* homepage at the address <http://www.angewandte.org>

A Synthesis Route to Enantiomerically Pure Jasmonoids

M. Ernst, G. Helmchen* ◆

Pd^{II}-Catalyzed Cyclization of Alkynes with Aldehydes, Ketones, or Nitriles Initiated by the Acetoxypalladation of Alkynes

L. Zhao, X. Lu*

Experimental Observation and Confirmation of Icosahedral W@Au₁₂ and Mo@Au₁₂ Molecules

X. Li, B. Kiran, J. Li, H.-J. Zhai, L.-S. Wang*

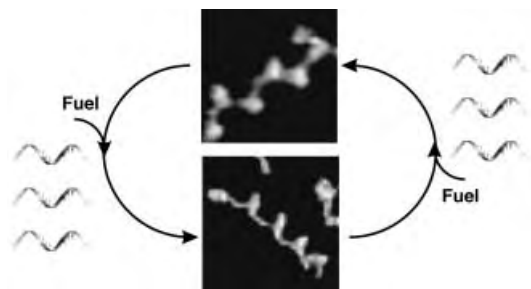
Isoprenoid Biosynthesis through the Methylerythritol Phosphate Pathway: The (*E*)-4-Hydroxy-3-methylbut-2-enyl Diphosphate Synthase (GcpE) is a [4Fe–4S] Protein

M. Seemann, B. Tse Sum Bui, M. Wolff, D. Tritsch, N. Campos, A. Boronat, A. Marquet, M. Rohmer*

Tuning the Regioselectivity in the Palladium(II)-Catalyzed Isomerization of Alkylidenecyclopropyl Ketones: A Dramatic Salt Effect

S. Ma*, J. Zhang

Conformational changes of tailored DNA motifs, induced by chemical or physical means, can lead to nanomechanical motion, such as rotational movement, linear shrinking, and extension, and opening and closing of tweezer-shaped devices (see schematic illustration). The development of nanomotors based on nucleic acids might open up ways to fabricate molecular machines which are programmable to autonomously perform logical or mechanical tasks.



Angew. Chem. **2002**, *114*, 3933–3937

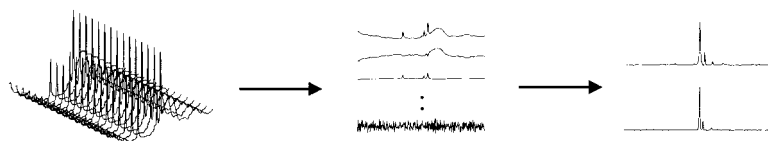
C. M. Niemeyer,* M. Adler . 3779–3783

Nanomechanical Devices Based on DNA

Keywords: DNA • molecular devices • nanostructures • supramolecular chemistry

COMMUNICATIONS

The pure-component spectra of $[\text{HRh}(\text{CO})_4]$ and $[\text{DRh}(\text{CO})_4]$ were obtained by investigating solutions of $[\text{Rh}_4(\text{CO})_{12}]$ in *n*-hexane upon exposure to varying partial pressures of H_2/CO and D_2/CO . The in situ high-pressure FTIR spectra were measured and subjected to band-target entropy minimization (BTEM), an advanced signal processing technique (shown schematically).



Angew. Chem. **2002**, *114*, 3940–3943

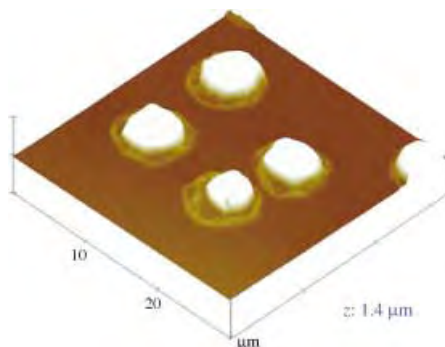
C. Li, E. Widjaja, W. Chew,
M. Garland* 3785–3789

Rhodium Tetracarbonyl Hydride:
The Elusive Metal Carbonyl Hydride

Keywords: carbonyl complexes • deuterium • hydrides • IR spectroscopy • rhodium

Water-soluble species can be deposited into preformed, multilayered polyelectrolyte capsules, templated onto melamine formaldehyde particles, with high integrity. Efficient encapsulation of albumin within capsules formed from a poly(styrene sulfonate)/poly(allylamine hydrochloride) composite was achieved at pH values below the isoelectric point of the protein through spontaneous deposition (see picture).

Angew. Chem. **2002**, *114*, 3943–3947



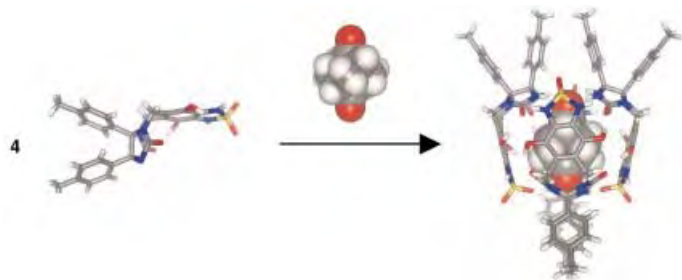
C. Gao,* E. Donath, H. Möhwald,
J. Shen 3789–3793

Spontaneous Deposition of Water-Soluble
Substances into Microcapsules:
Phenomenon, Mechanism, and
Application

Keywords: capsules • colloids • layered compounds • polyelectrolytes • self-deposition



A tightly packed cavity that contains a guest molecule, 2,6-adamantanedione, is formed by a capsular hydrogen-bonded assembly (see figure). The crystal structure reveals an intricate network of hydrogen bonds, which specifically orients the ketone guest in the capsule cavity. The solid-state data complement the behavior of the assembly in the solution phase and provide a rationale for the guest-binding selectivity of the capsule.



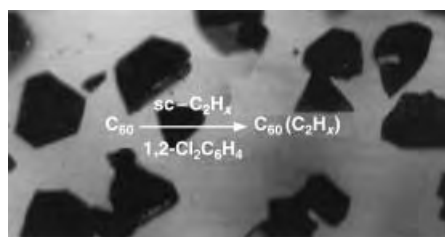
Angew. Chem. **2002**, *114*, 3947–3950

D. W. Johnson, F. Hof, P. M. Iovine,
C. Nuckolls, J. Rebek, Jr. * .. 3793–3796

Solid-State and Solution Studies of a
Tetrameric Capsule and Its Guests

Keywords: host-guest systems • hydrogen
bonds • molecular recognition • self-
assembly • supramolecular chemistry

The intercalation of ethane and ethene into the octahedral interstitial sites of the C_{60} lattice can be achieved by antisolvent precipitation, using supercritical C_2H_4 and C_2H_6 . This method of crystallization (see picture), which has yielded unprecedented intercalation compounds with hydrocarbons once thought too large to form such species, should be applicable to other gases, solvents, and fullerenes.



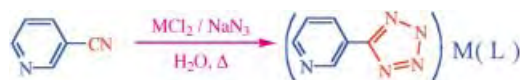
Angew. Chem. **2002**, *114*, 3950–3953

A. O'Neil, C. Wilson,* J. M. Webster,
F. J. Allison, J. A. K. Howard,
M. Poliakoff* 3796–3799

The Supercritical Fluid Antisolvent
Synthesis of $C_{60}(C_2H_x)$ ($x = 4$ or 6): The
Crystal Structures of Two Materials
Which Were Thought Unlikely to Exist

Keywords: crystal growth • fullerenes •
hydrocarbons • intercalations •
supercritical fluids

The pyridyltetrazolate ligand formed in situ from NaN_3 and 3-cyanopyridine in the presence of $ZnCl_2$ or $CdCl_2$ in water affords acentric (**1**) or chiral (**2**) coordination polymers, respectively. The corresponding reaction of $ZnCl_2$ with 4-cyanopyridine gives acentric **3** (not shown). Compounds **1–3** are second harmonic generation active.



(**1**: $M = Zn$, $L = OH$, $T = 160^\circ C$; **2**: $M = Cd$, $L = N_3$, $T = 120^\circ C$)

Angew. Chem. **2002**, *114*, 3954–3957

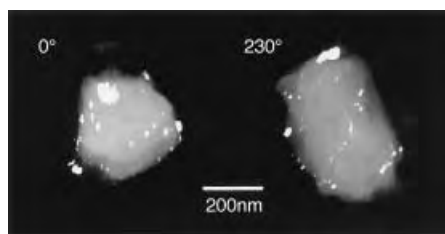
R.-G. Xiong,* X. Xue, H. Zhao,
X.-Z. You, B. F. Abrahams,*
Z. Xue 3800–3803

Novel, Acentric Metal–Organic
Coordination Polymers from
Hydrothermal Reactions Involving In Situ
Ligand Synthesis

Keywords: cadmium • coordination
polymers • hydrothermal synthesis •
N ligands • nonlinear optics • zinc



Images of supported nanoparticle catalysts have been recorded by scanning transmission electron microscopy (STEM), with a combination of high-angle annular dark-field (HAADF) imaging and back-scattered electron (BSE) imaging, which both utilize Rutherford-scattered electrons. The incoherent scattering process ensures that images are ideal for electron tomography and the reconstruction of 3D nanoparticle distributions (such as palladium on carbon, see picture).



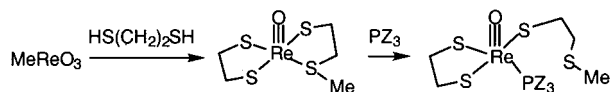
Angew. Chem. **2002**, *114*, 3958–3961

P. A. Midgley,* M. Weyland,
J. M. Thomas,* P. L. Gai,
E. D. Boyes 3804–3807

Probing the Spatial Distribution and
Morphology of Supported Nanoparticles
Using Rutherford-Scattered Electron
Imaging

Keywords: back-scattering • electron
microscopy • electron tomography •
heterogeneous catalysis • nanoparticles

Methylation of a thiolate group, which has only been observed in vitamin B₁₂ and its mimics, has been accomplished with [MeReO₃] and [MeReO(edt)PPh₃] (edt = 1,2-ethanedithiolato; see scheme). The proposed mechanism involves the formation of [MeRe^{VII}O(edt)₂] through two stepwise condensation reactions; nucleophilic attack of a thiolate ligand on the methyl group leads to the product.



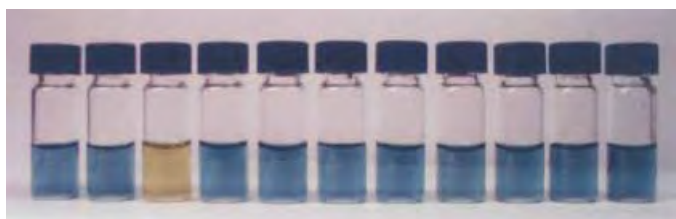
Angew. Chem. **2002**, *114*, 3961–3963

X. Shan, A. Ellern,
J. H. Espenson* 3807–3809

Methyl Transfer from Rhenium to
Coordinated Thiolate Groups

Keywords: kinetics • methyl transfer •
phosphane ligands • rhenium • S ligands

A color change occurs when phosphate anions are added to an aqueous solution of H-bpmp (2,6-bis(bis(2-pyridylmethyl)aminomethyl)-4-methylphenol), zinc perchlorate, and pyrocatechol violet in a 1:2:1 molar ratio. The photograph shows the color of the mixture in the presence of no anions (far left), phosphate ions (yellow solution), and various other inorganic anions.



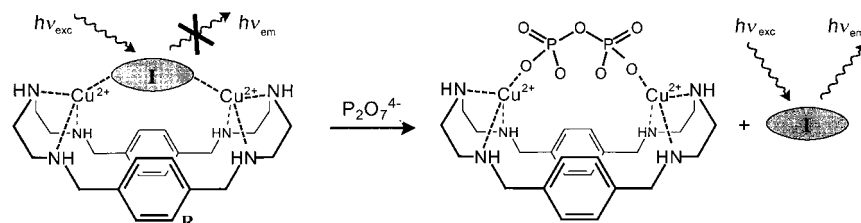
Angew. Chem. **2002**, *114*, 3963–3965

M. S. Han, D. H. Kim* 3809–3811

Naked-Eye Detection of Phosphate Ions
in Water at Physiological pH:
A Remarkably Selective and Easy-To-
Assemble Colorimetric Phosphate-
Sensing Probe

Keywords: anions • calorimetry •
chromophores • phosphate • sensors

Displacement of the previously bound, and quenched, fluorescent indicator (I) by coordination of the pyrophosphate ion to the two Cu^{II} centers of the receptor R results in the generation of the natural fluorescence of the indicator, and thus signals pyrophosphate recognition (see scheme). Discrimination from interfering anions (HPO₄²⁻, SO₄²⁻, NO₃⁻, Cl⁻, NCO⁻, N₃⁻, acetate, benzoate) can be achieved by tuning the indicator affinity towards the receptor.



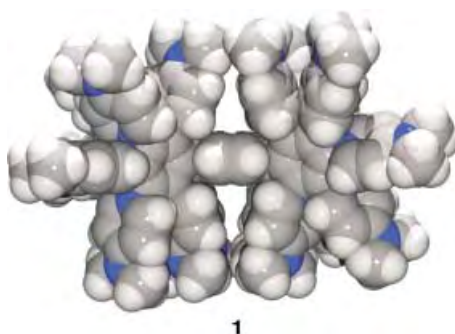
Angew. Chem. **2002**, *114*, 3965–3968

L. Fabbrizzi,* N. Marcotte, F. Stomeo,
A. Taglietti 3811–3814

Pyrophosphate Detection in Water by
Fluorescence Competition Assays:
Inducing Selectivity through the Choice of
the Indicator

Keywords: fluorescent probes •
molecular recognition • N ligands •
pyrophosphate • sensors

Cavities, indentations, and pockets aplenty! By means of self-activated silyl-assisted polyonion substitution (SASAPOS), *meso*-tetrakis(pentafluorophenyl)porphyrin can be nearly quantitatively converted into the twentyfold positively charged polycation **1**, within which 20 counterions are housed. The most drastic steric and electronic transformation of a porphyrin derivative to date has thus been achieved easily and efficiently.



Angew. Chem. **2002**, *114*, 3969–3971

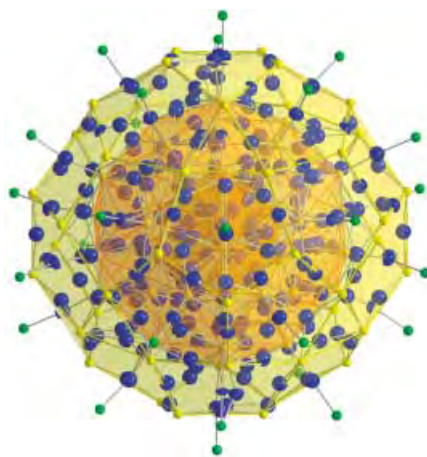
R. Weiss,* F. Pühlhofer, N. Jux,
K. Merz 3815–3817

SASAPOS, not Sisyphe: Highly Efficient
20-Step One-Pot Synthesis of a Discrete
Organic–Inorganic Ion Cluster with a
Porphyrin Core

Keywords: cluster compounds • electron
transfer • electrostatic interactions •
polycations • porphyrinoids



An almost spherical cluster with a diameter of about 2.5 nm is formed by Ag atoms (blue), S²⁻ ligands (yellow), and P atoms (green) of PnPr₃ ligands in [Ag₁₈₈S₉₄(PnPr₃)₃₀] (see picture). The phosphane ligands from the spherical Ag₂S cluster core point out like the spines of a hedgehog. The sulfur substructure is constructed from three almost spherical shells.



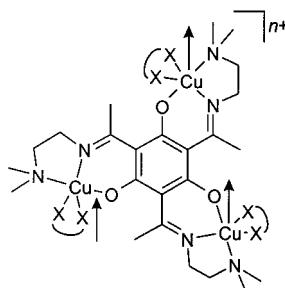
X.-J. Wang, T. Langetepe, C. Persau,
B.-S. Kang, G. M. Sheldrick,
D. Fenske * 3818–3822

Syntheses and Crystal Structures of the
New Ag–S Clusters
[Ag₇₀S₁₆(SPh)₃₄(PhCO₂)₄(triphos)₄] and
[Ag₁₈₈S₉₄(PR₃)₃₀]

Keywords: cluster compounds • silver •
structure elucidation • sulfur • X-ray
diffraction

Angew. Chem. **2002**, *114*, 3972–3977

Trinuclear copper complexes have been obtained by using a 1,3,5-trihydroxybenzene ligand modified by attachment of pendant arms at the 2, 4, and 6 positions (see picture; X = bipyridine, 2-formylphenolate). The *m*-phenylene linkage results in ferromagnetic interactions through spin polarization in these complexes.



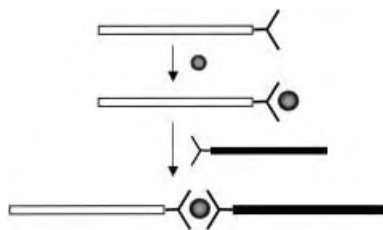
T. Glaser,* M. Gerenkamp,
R. Fröhlich 3823–3825

Targeted Synthesis of Ferromagnetically
Coupled Complexes with Modified 1,3,5-
Trihydroxybenzene Ligands

Keywords: copper • ferromagnetic
interactions • magnetic properties •
N ligands • O ligands

Angew. Chem. **2002**, *114*, 3984–3986

Metallo-supramolecular AB block copolymers are the first examples of macromolecular engineering. A new concept for the formation of block copolymers by a supramolecular approach is presented. For this purpose the authors utilized an asymmetrical bis(terpyridine)–ruthenium complex as the supramolecular linkage between the two blocks (see figure).



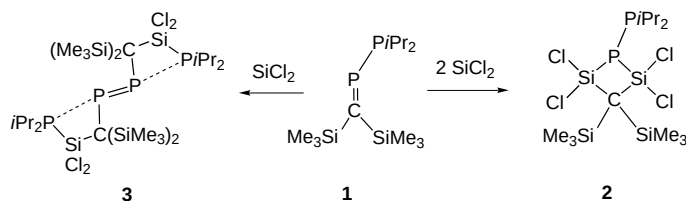
B. G. G. Lohmeijer,
U. S. Schubert * 3825–3829

Supramolecular Engineering with
Macromolecules: An Alternative
Concept for Block Copolymers

Keywords: metal complexes • polymers •
supramolecular chemistry • terpyridine
ligands

Angew. Chem. **2002**, *114*, 3980–3984

Silicon implants for double bonds: An unusual tetrasilylmethane derivative, the 2-phospha-1,3-disiletane **2** is formed through the spontaneous consecutive addition of two equivalents of SiCl₂ to the phosphalkene **1**. Simultaneously the diphosphene **3** is also formed, which contains a central P=P bond and silylphosphane groups.



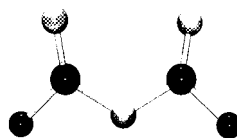
W.-W. du Mont,* T. Gust, E. Seppälä,
C. Wismach, P. G. Jones, L. Ernst,
J. Grunenberg,
H. C. Marsmann 3829–3832

Unusual P=C Bond Cleavage by Double
Dichlorosilylene Transfer from
Trichlorosilyltrimethylgermane to
P-Phosphanil Phosphalkenes

Keywords: cycloaddition • insertion •
phosphaalkenes • phosphenes • silylenes

Angew. Chem. **2002**, *114*, 3977–3979

The missing link in the family of compounds $\text{FC(O)}\text{O}_x\text{C(O)F}$ ($x = 0, 1, 2, 3$), the anhydride of fluoroformic acid (see picture), has been isolated in pure form and characterized. FC(O)OC(O)F is stable at room temperature for several days in a glass cell with a well conditioned surface.



H. Pernice, H. Willner,* K. Bierbrauer,
M. Burgos Paci,
G. A. Argüello* 3832–3834

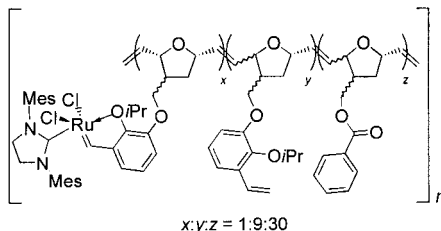
Fluoroformic Acid Anhydride,
 FC(O)OC(O)F

Keywords: ab initio calculations •
anhydrides • fluorine • NMR
spectroscopy • radical reactions

Angew. Chem. **2002**, *114*, 3987–3989



Sequential ring-opening-metathesis polymerization and cross-metathesis reactions allow a one-pot synthesis of the illustrated ruthenium catalyst. This conceptually novel polymer-bound catalyst shows excellent metathesis activity and recyclability.



S. J. Connon, A. M. Dunne,
S. Blechert* 3835–3838

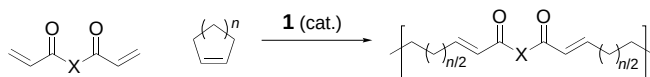
A Self-Generating, Highly Active, and
Recyclable Olefin-Metathesis Catalyst

Keywords: alkenes • homogeneous
catalysis • metathesis • polymers •
ruthenium

Angew. Chem. **2002**, *114*, 3989–3993



A variety of highly A,B-alternating copolymers are formed from diacrylates and cycloalkenes in the presence of $[\text{Cl}_2(\text{PCy}_3)(\text{H}_2\text{IMes})\text{Ru}=\text{CHPh}]$ (**1**). The high conversion and the high selectivity come from the thermodynamically favored formation of a C–C double bond between these monomers.



T.-L. Choi, I. M. Rutenberg,
R. H. Grubbs* 3839–3841

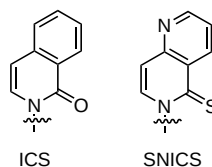
Synthesis of A,B-Alternating Copolymers
by Ring-Opening-Insertion-Metathesis
Polymerization

Keywords: copolymerization • cross-
coupling • metathesis • ring-opening
polymerization • ruthenium

Angew. Chem. **2002**, *114*, 3995–3997



More efficient and selective synthesis as well as more efficient extension by a DNA polymerase is achieved for unnatural base pairs upon heteroatom substitution. This has been demonstrated with modification of ICS (structure shown): Replacement of C6 with nitrogen and thio substitution at C10 provides the base SNICS, which forms stable self-pairs and can therefore be used for efficient unnatural base pair replication.



C. Yu, A. A. Henry, F. E. Romesberg,*
P. G. Schultz* 3841–3844

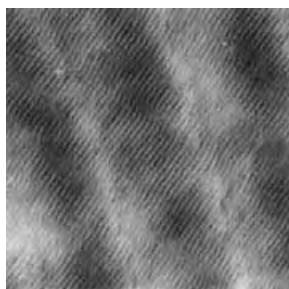
Polymerase Recognition of Unnatural
Base Pairs

Keywords: base pairs • DNA
recognition • hydrophobic effect •
nucleotides • substituent effects

Angew. Chem. **2002**, *114*, 3997–4000



Unusual lamellar mesostructures of metal oxides are obtained with silicone surfactants as templates. The authors present evidence for the unrestricted chain configuration of silicone surfactants being responsible for the formation of lamellae. The addition of a copolymer can create a hexagonal mesophase in the layered walls, thus leading to a hierarchically ordered mesophase (see TEM image).



A.-W. Xu,* Y.-P. Cai, H.-X. Zhang,
L.-Z. Zhang, J. C. Yu 3844–3848

Hierarchically Ordered Silica Mesophases
Using Mixed Surfactant Systems as
Templates

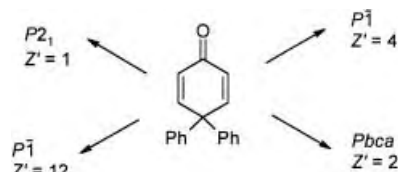
Keywords: lamellar structures •
mesophases • silicon • surfactants

Angew. Chem. **2002**, *114*, 4000–4004



Small yet subtle conformational changes

resulting from the correlated rotation of the geminal phenyl rings in the title compound lead to different crystal packing arrangements and thus different X-ray crystal structures (the four space groups are given in the picture). This provides the simultaneous occurrence of conformational polymorphism, conformational isomorphism, and concomitant polymorphism for the same molecule.



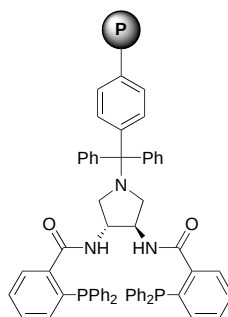
V. S. S. Kumar, A. Addlagatta, A. Nangia,* W. T. Robinson,* C. K. Broder, R. Mondal, I. R. Evans, J. A. K. Howard,* F. H. Allen * 3848–3851

4,4-Diphenyl-2,5-cyclohexadienone: Four Polymorphs and Nineteen Crystallographically Independent Molecular Conformations

Keywords: conformation analysis • hydrogen bonds • polymorphism • structure elucidation • supramolecular chemistry

Angew. Chem. 2002, 114, 4004–4007

Easy recovery and reutilization of the catalyst in consecutive reactions: These are the advantages offered by a new class of polymer-bound Trost-type ligands (see Figure; is a polystyrene-based resin or JandaJEL). A complex is formed with $[(\eta^3\text{-C}_3\text{H}_5)\text{PdCl}]_2$ that catalyzes asymmetric allylic substitutions with excellent activity and enantioselectivity (up to 99% ee).



C. E. Song,* J. W. Yang, E. J. Roh, S.-g. Lee, J. H. Ahn, H. Han * 3852–3854

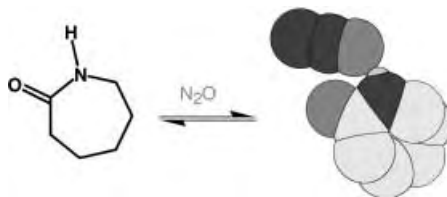
Heterogeneous Pd-Catalyzed Asymmetric Allylic Substitution Using Resin-Supported Trost-Type Bisphosphane Ligands

Keywords: asymmetric catalysis • heterogeneous catalysis • palladium • P ligands • polymers

Angew. Chem. 2002, 114, 4008–4010

Is hydrogen bonding between N_2O and amides and peptides possible?

Secondary *cis* amides and N_2O were found to interact in chloroform through hydrogen bonds and electrostatic interactions. In the absence of competing water molecules, such interactions may take place in hydrophobic enzyme pockets and in biological fluids, and may be responsible for a physiological activity of this gas.



G. V. Zyryanov, E. M. Hampe, D. M. Rudkevich * 3854–3857

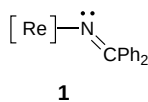
Noncovalent Chemistry of Nitrous Oxide: Interactions with Secondary *cis* Amides in Solution

Keywords: amides • hydrogen bonds • molecular recognition • nitrogen oxides • noncovalent interactions

Angew. Chem. 2002, 114, 4010–4013



An enhanced reactivity towards isocyanates was found with compound **1** ($[\text{Re}] = [\text{Re}(\text{CO})_3(\text{bpy})]$) when compared with *N*-silylimines. A crystal structure determination established that **1** is a transition-metal *N*-metalloimine.



$d(\text{Re}-\text{N}) = 2.113(4) \text{ \AA}$
 $\text{Re}-\text{C}-\text{N} = 133.9(4)^\circ$

E. Hevia, J. Pérez,* V. Riera, D. Miguel 3858–3860

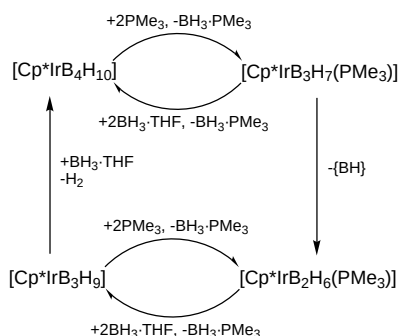
Insertion and Cycloaddition Reactivity of a Transition-Metal *N*-Mettalloimine

Keywords: cycloaddition • imines • insertion • isocyanates • rhenium

Angew. Chem. 2002, 114, 4014–4016

Reaction cycles of clusters:

$[\text{Cp}^*\text{IrB}_3\text{H}_9]$ and $[\text{Cp}^*\text{IrB}_4\text{H}_{10}]$ react with PMe_3 to give cleavage products that undergo addition of borane to reconstruct the parent clusters. Overall, a new reaction cycle is formed, comprising two reversible and two irreversible steps, which involve the formation of new phosphane-substituted iridaboranes (see scheme).



R. Macías,* T. P. Fehlner, A. M. Beatty 3860–3862

An Iridaborane Reaction Cycle Driven by PMe_3 and $\text{BH}_3 \cdot \text{THF}$: Synthesis and Characterization of $[\text{Cp}^*\text{IrB}_3\text{H}_7(\text{PMe}_3)]$ and $[\text{Cp}^*\text{IrB}_2\text{H}_6(\text{PMe}_3)]$

Keywords: boranes • cluster compounds • reaction cycles • transition metals

Angew. Chem. 2002, 114, 4016–4018

More pronounced twisting and divergence of the strands is seen for peptides containing type I' turn nucleated β -hairpins. Superposition of the structure of the synthetic octapeptide Boc-Leu-Phe-Val-Aib-D-Ala-Leu-Phe-Val-OMe (black) with that of a peptide with the same strand residues but a type II' turn nucleated β -hairpin (gray) illustrates the flattened nature of the latter. Aib = aminoisobutyric, Boc = *tert*-butoxycarbonyl.



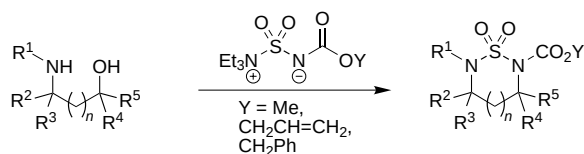
Angew. Chem. **2002**, *114*, 4019–4021

S. Aravinda, N. Shamala,* R. Rajkishore, H. N. Gopi, P. Balaram * 3863–3865

A Crystalline β -Hairpin Peptide Nucleated by a Type I' Aib-D-Ala β -Turn: Evidence for Cross-Strand Aromatic Interactions

Keywords: amino acids • hydrogen bonds • peptides • protein folding • protein structures

A practical and high-yielding method for the efficient, one-step synthesis of diverse classes of *N,N'*-differentiated sulfamides has been developed from a wide range of amino alcohols and simple amines using Burgess-type reagents (see scheme). This method enables the possible differentiation of both sides of any cyclic sulfamide product.



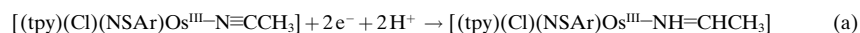
Angew. Chem. **2002**, *114*, 4022–4026

K. C. Nicolaou,* D. A. Longbottom, S. A. Snyder, A. Z. Nalbanadian, X. Huang 3866–3870

A New Method for the Synthesis of Nonsymmetrical Sulfamides Using Burgess-Type Reagents

Keywords: amines • Burgess reagents • cyclization • sulfamides • synthetic methods

 **The reversible two-electron reduction** of an acetonitrile ligand to the corresponding imine has been demonstrated for the first time with the title compound. Electrochemical reduction generates the Os^{III} -imino product [Eq. (a)], which can be isolated as the PF_6^- salt and used in further reactions for the reduction of organic carbonyl compounds. Ar = C_6H_5 , 4- MeC_6H_4 , 3,5- $\text{Me}_2\text{C}_6\text{H}_3$.



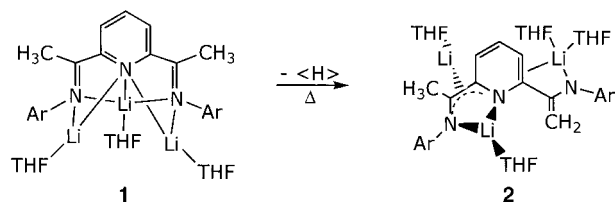
Angew. Chem. **2002**, *114*, 4026–4029

M. H. V. Huynh,* R. T. Baker, D. E. Morris, P. S. White, T. J. Meyer * 3870–3873

$[\text{Os}^{\text{III}}(\text{tpy})(\text{Cl})(\text{NCCH}_3)(\text{NSAr})]$: Reversible Reduction of Acetonitrile by Os^{III} -Sulfilimido Complexes

Keywords: acetonitrile • imines • N ligands • osmium • reduction

Three electrons can be accepted into the antibonding orbitals of the α,α' -{2,6-(*i*Pr) $_2$ PhN=C(Me)} $_2$ (C $_5$ H $_3$ N) ligand, so that reduction with [Li(naphthalenide)] yields the trianionic diamagnetic complex **2**. Treatment with Li metal, a stronger reducing agent, gives a mixture of **2** and paramagnetic complex **1**, which is thermally unstable and is converted into **2** on heating in toluene (see scheme).



Angew. Chem. **2002**, *114*, 4029–4032

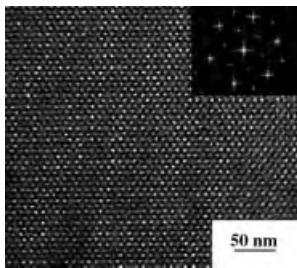
D. Enright, S. Gambarotta,* G. P. A. Yap, P. H. M. Budzelaar * 3873–3876

The Ability of the α,α' -Diiminopyridine Ligand System to Accept Negative Charge: Isolation of Paramagnetic and Diamagnetic Trianions

Keywords: density functional calculations • imino compounds • lithium • paramagnetism • radical ions



A triblock copolymer template and an organo-siloxane or organic additive facilitated the first synthesis of large-pore (up to 9.5 nm) three-dimensional bicontinuous mesoporous silica with *Ia3d*-type symmetry at room temperature in acidic medium. The picture is a transmission electron micrograph showing the pores along [111] and the corresponding diffractogram (inset).



Angew. Chem. **2002**, *114*, 4032–4034

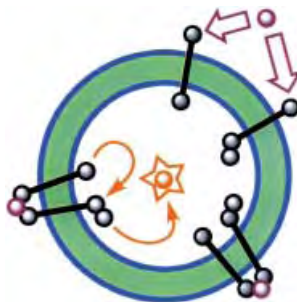
X. Liu, B. Tian, C. Yu, F. Gao, S. Xie, B. Tu, R. Che, L.-M. Peng, D. Zhao * 3876–3878

Room-Temperature Synthesis in Acidic Media of Large-Pore Three-Dimensional Bicontinuous Mesoporous Silica with *Ia3d* Symmetry

Keywords: mesoporous materials • silica • template synthesis • zeolite analogues



Talking through walls: A synthetic system has been developed for transducing a signal across a vesicular bilayer membrane. The external messenger (purple) does not cross the membrane itself, but instigates the release of a secondary messenger (red) on the interior of the vesicle.



Angew. Chem. **2002**, *114*, 4034–4037

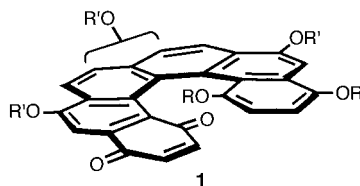
P. Barton, C. A. Hunter,* T. J. Potter, S. J. Webb, N. H. Williams * . 3878–3881

Transmembrane Signalling

Keywords: liposomes • membranes • signal transduction • supramolecular chemistry • vesicles



Oriented by an electric field (but not otherwise), a lyotropic nematic phase of helical discotic **1** in dodecane exhibits second-harmonic generation, the intensity of which is affected by the helicity of the irradiating circularly polarized light. The change reverses sign when the polarity of the orienting electric field reverses.



Angew. Chem. **2002**, *114*, 4038–4040

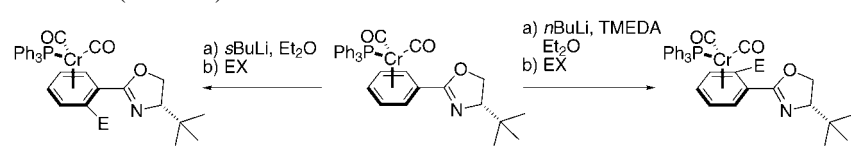
T. Verbiest,* S. Sioncke, A. Persoons, L. Vyklický, T. J. Katz 3882–3884

Electric-Field-Modulated Circular-Difference Effects in Second-Harmonic Generation from a Chiral Liquid Crystal

Keywords: chirality • circular dichroism • helical structures • liquid crystals • nonlinear optics



Incorporation of a triphenylphosphane ligand is the key to the direct lithiation of (η^6 -2-phenyloxazoline)chromium(0) complexes. As diastereoselection can be modulated by the presence or absence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA), both diastereomers of 1,2-disubstituted η^6 -arene chromium(0) oxazoline complexes, which possess planar chiral moieties of opposite absolute configuration, can be prepared in useful chemical yields and high diastereoselectivities (10–50:1).



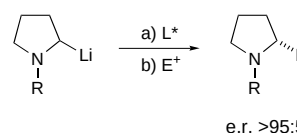
Angew. Chem. **2002**, *114*, 4040–4043

L. E. Overman,* C. E. Owen, G. G. Zipp 3884–3887

Diastereoselective Lithiation of (η^6 -Arene)dicarbonyltriphenylphosphane Chromium(0) Oxazoline Complexes—Direct Preparation of Enantiopure Complexes Having Planar Chiral Fragments of Either Configuration

Keywords: arene complexes • chromium • lithiation • P ligands

Not restricted to allylic or benzylic derivatives: The dynamic resolution of chiral organolithium species in the presence of a chiral ligand, L^* , followed by addition of an electrophile, E^+ (see scheme), has been shown to occur with excellent enantioselectivity at ambient temperature by using nonactivated 2-lithiopyrrolidines.



Angew. Chem. **2002**, *114*, 4043–4045

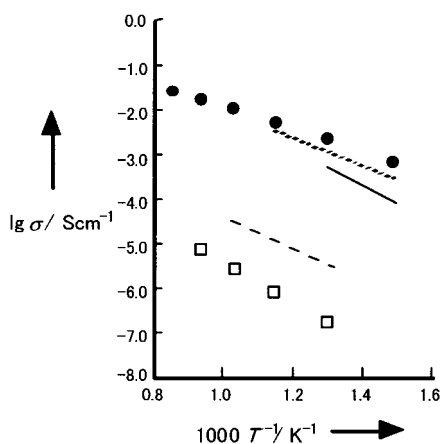
I. Coldham,* S. Dufour, T. F. N. Haxell, S. Howard, G. P. Vennall 3887–3889

Enantioselective Synthesis of Substituted Pyrrolidines by Dynamic Resolution

Keywords: amines • carbanions • dynamic resolution • enantioselectivity • lithiation

Calcium doping levels of up to 20 % can be achieved for the $\text{La}_{1-x}\text{Ca}_x\text{OCl}_{1-x}$ solid solution series. At the highest doping levels ($x = 0.2$; see graph (●)), the conductivity of the solid solution is three orders of magnitude greater than that of undoped LaOCl (□). The potential for the design of new functional materials stems from their high thermal stability, relative density, and hardness, in addition to their insolubility in water.

Angew. Chem. **2002**, *114*, 4046–4048



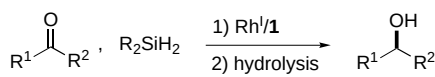
N. Imanaka,* K. Okamoto,
G.-y. Adachi 3890–3892

Water-Insoluble Lanthanum
Oxychloride-Based Solid Electrolytes
with Ultra-High Chloride Ion
Conductivity

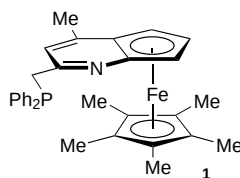
Keywords: conducting materials •
electrochemistry • solid electrolytes •
solid-state structures • X-ray diffraction



Comparable to or even better than the best enantioselectivities that can be obtained through asymmetric hydrogenation of dialkyl ketones are the *ee* values obtained in the catalytic asymmetric hydrosilylation of such ketones with the catalyst system **Rh/1** (see scheme). In terms of both scope and stereoselectivity, this method compares favorably with previously described catalysts for this process as the **Rh/1** system also furnishes consistently excellent *ee* values and yields with aryl alkyl ketones.



$\text{R}^1 = \text{alkyl}; \text{R}^2 = \text{aryl or alkyl}$



B. Tao, G. C. Fu* 3892–3894

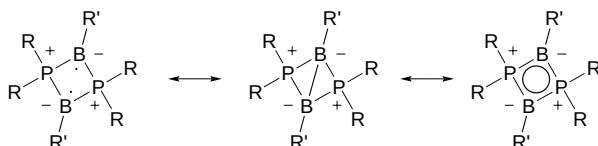
Application of a New Family of P,N
Ligands to the Highly Enantioselective
Hydrosilylation of Aryl Alkyl and Dialkyl
Ketones

Keywords: asymmetric catalysis •
hydrosilylation • P,N ligands •
reduction • rhodium

Angew. Chem. **2002**, *114*, 4048–4050



Substantial control over frontier orbital splittings in 1,3-diphospha-2,4-diboretanes can be achieved by variation of phosphorus substituents R, thereby enhancing diradical character (see scheme; e.g. $\text{R} = \text{SiMe}_3$, $\text{R}' = t\text{Bu}$).



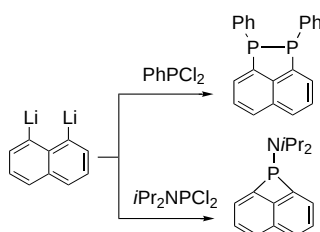
Angew. Chem. **2002**, *114*, 4050–4052

M. Seierstad, C. R. Kinsinger,
C. J. Cramer* 3894–3896

Design Optimization of 1,3-Diphospha-
2,4-diboretane Diradicals

Keywords: density functional
calculations • electronic structure •
phosphorus heterocycles • radicals •
singlet–triplet splitting

Strained rings and metal insertions: The product of the reaction between 1,8-dilithionaphthalene and RPCl_2 differs depending on the R group on the phosphorus atom. PhPCl_2 gave $(\text{PhP})_2$ -*peri*-bridged naphthalene, while $i\text{Pr}_2\text{NPCl}_2$ gave the $i\text{Pr}_2$ -bridged compound (see scheme). The reactivity of the new compounds with transition-metal complexes is also discussed.



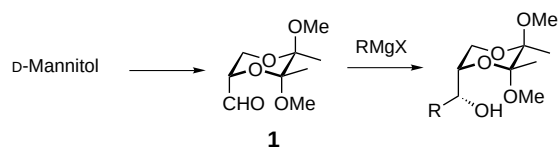
Angew. Chem. **2002**, *114*, 4052–4054

T. Mizuta,* T. Nakazono,
K. Miyoshi* 3897–3898

Naphtho[1,8-*b,c*]phosphete and 1,2-
Diphosphaacenaphthene from the
Reaction of 1,8-Dilithionaphthalene with
 RPCl_2

Keywords: heterocycles • metallacycles •
P ligands • small ring systems • tungsten

Available on a large scale in both enantiomeric forms, the butanediactal-protected aldehyde **1** is a stable glyceraldehyde derivative. The potential of **1** as a new chiral building block is illustrated by the highly stereoselective addition of Grignard reagents (see scheme).



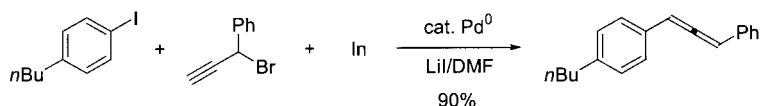
Angew. Chem. **2002**, *114*, 4054–4057

P. Michel, S. V. Ley* 3898–3901

Butane-2,3-diacetals of Glyceraldehyde:
A Stable Alternative to Glyceraldehyde
Acetonide

Keywords: aldehydes • diacetals •
diastereoselectivity • glyceraldehyde

Versatile, convenient, mild: Allenylindium intermediates generated from the reaction of indium with propargyl bromides were employed as effective coupling partners in Pd-catalyzed cross-coupling reactions with a variety of electrophiles to produce allenes, polyallenes, and unsymmetrical bis(allenes) in excellent yields with complete regioselectivity and chemoselectivity (see scheme for one example).



Angew. Chem. **2002**, *114*, 4057–4059

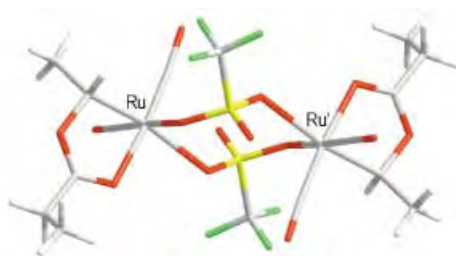
K. Lee, D. Seomoon,
P. H. Lee* 3901–3903

Highly Efficient Catalytic Synthesis of
Substituted Allenes Using Indium

Keywords: allenes • cross-coupling •
indium • palladium



The reaction of an ethene-coordinated Ru^{II} complex with carboxylic acids is catalytic and produces equimolar amounts of ethane and 1,1'-diesters. The intermediate of the catalytic cycle is the alkyl complex [RuL_n{CHCH₃(OC(O)C₂H₅)}-(CO)₂]⁽¹⁻ⁿ⁾⁺ (L = RCOO⁻, CF₃SO₃⁻), which was isolated in the dinuclear form.



Angew. Chem. **2002**, *114*, 4061–4063

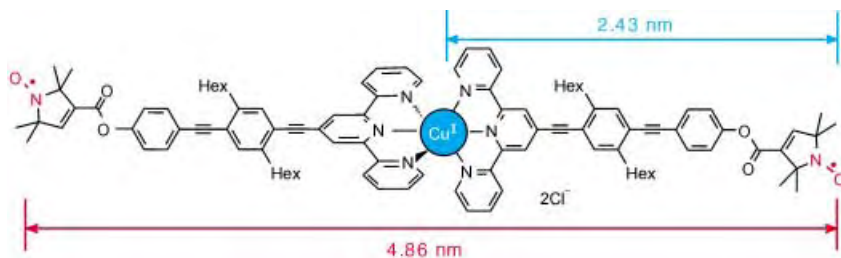
T. Funaioli,* F. Marchetti,
G. Fachinetti* 3905–3907

Ethane and Ethylidene Dicarboxylates
from the Ruthenium(II)-Catalyzed
“Disproportionative Addition” of
Carboxylic Acids to Ethene

Keywords: alkenes • carboxylic acids •
disproportionation • nucleophilic
addition • ruthenium



Self-assembled supramolecular complexes that contain paramagnetic transition metal ions, such as that illustrated below, can be structurally characterized by the precise measurement of the separation between metal centers and spin labels. The technique, which employs double electron electron resonance (DEER), should also be applicable to metalloproteins.



Angew. Chem. **2002**, *114*, 4063–4066

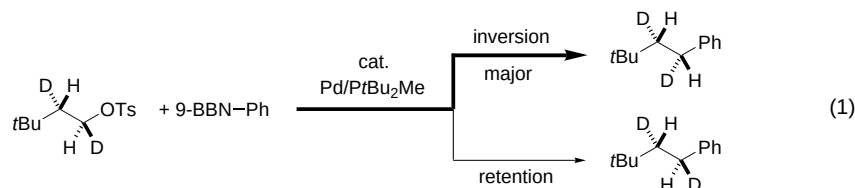
E. Narr, A. Godt,
G. Jeschke* 3907–3910

Selective Measurements of a Nitroxide –
Nitroxide Separation of 5 nm and a
Nitroxide – Copper Separation of 2.5 nm
in a Terpyridine-Based Copper(II)
Complex by Pulse EPR Spectroscopy

Keywords: copper • EPR spectroscopy •
metalloproteins • structure elucidation •
supramolecular chemistry



A striking dependence of reactivity on phosphane structure was observed in the first Suzuki-type cross-coupling process that is effective for functionalized alkyl tosylates. In this reaction, in which solely commercially available reagents are used, PrBu_2Me is the ligand of choice. Through the use of deuterium-labeled compounds, it has been established that the coupling proceeds with predominant inversion of configuration at the carbon atom [Eq. (1), 9-BBN = 9-borabicyclo[3.3.1]nonane].



Angew. Chem. **2002**, *114*, 4066–4068

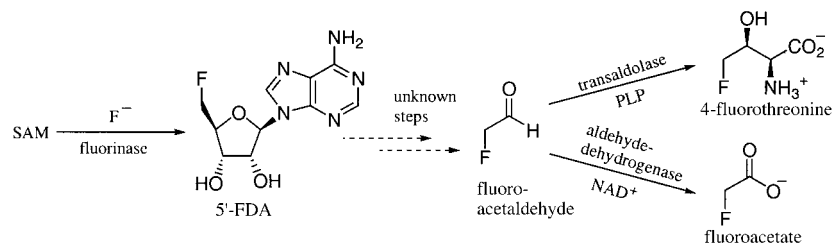
M. R. Netherton, G. C. Fu* . 3910–3912

Suzuki Cross-Couplings of Alkyl
Tosylates that Possess β Hydrogen Atoms:
Synthetic and Mechanistic Studies

Keywords: alkyl tosylates • C–C
coupling • ligand effects • palladium •
Suzuki reaction



The biosynthesis of organofluorine compounds, for example, fluoroacetate, was demonstrated from (*S*)-adenosyl-L-methionine (SAM) and fluoride ions in a cell-free extract of *Streptomyces cattleya*. Incubation of 5'-fluoro-5'-deoxyadenosine (5'-FDA), the first organofluorine product formed in the fluoroacetate pathway, with the cell-free extract resulted in the transient accumulation of fluoroacetaldehyde, thus confirming its role as an intermediate in the synthesis of fluorometabolites (see scheme).



Angew. Chem. **2002**, *114*, 4069–4071

C. Schaffrath, S. L. Cobb,
D. O'Hagan* 3913–3915

Cell-Free Biosynthesis of Fluoroacetate
and 4-Fluorothreonine in *Streptomyces*
cattleya

Keywords: biosynthesis •
biotransformations • enzymes • fluorine



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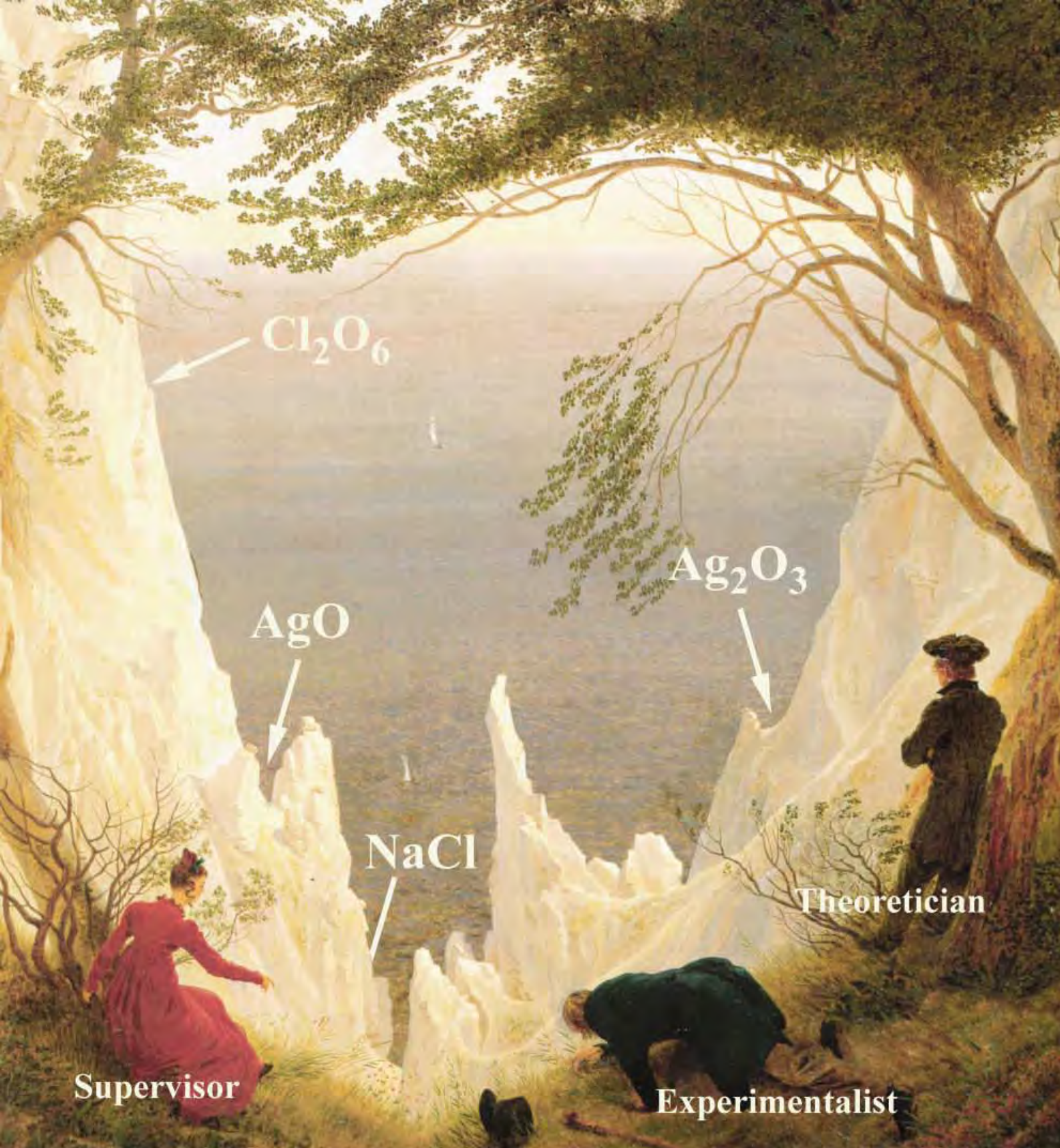
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CORRIGENDUM

In the Communication by **J.-M. Lehn and co-workers** in Issue 15, **2002**, pp. 2760–2764, references [4] and [5] were accidentally combined in the print version. The references should read:

- [4] See, for instance,: a) C. Piguet, G. Bernardinelli, B. Bocquet, A. Quattropiani, A. F. Williams, *J. Am. Chem. Soc.* **1992**, *114*, 7440; b) A. Marquis-Rigault, A. Dupont-Gervais, P. N. W. Baxter, A. Van Dorsselaer, J.-M. Lehn, *Inorg. Chem.* **1996**, *35*, 2307; c) A. Marquis-Rigault, A. Dupont-Gervais, A. Van Dorsselaer, J.-M. Lehn, *Chem. Eur. J.* **1996**, *2*, 1395; d) M. D. Levin, P. J. Stang, *J. Am. Chem. Soc.* **2000**, *122*, 7428.
- [5] a) M. T. Youinou, N. Rahmouni, J. Fischer, J. A. Osborn, *Angew. Chem.* **1992**, *104*, 771; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 733; b) P. N. W. Baxter, J.-M. Lehn, B. O. Kneisel, D. Fenske, *Chem. Commun.* **1997**, 2231; c) G. S. Hanan, D. Volkmer, U. S. Schubert, J.-M. Lehn, G. Baum, D. Fenske, *Angew. Chem.* **1997**, *109*, 1929; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1842; d) D. M. Bassani, J.-M. Lehn, K. Fromm, D. Fenske, *Angew. Chem.* **1998**, *110*, 2534; *Angew. Chem. Int. Ed.* **1998**, *37*, 2364.

The editorial office apologizes for this mistake.



Caspar David Friedrich [about 1818]

An early, allegoric representation of the energy landscape of chemical systems, and of people exploring it.

ANGEWANDTE
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A Concept for Synthesis Planning in Solid-State Chemistry

Martin Jansen*

Dedicated to Professor Rudolf Hoppe on the occasion of his 80th birthday

There is a widely-held belief that the preparation of new solid-state compounds based on rational design is not possible. Herein, we present a concept that points the way towards a rational design of syntheses in solid-state chemistry. The foundation of our approach is the representation of the whole material world, that is, the known and not-yet-known compounds, on an energy landscape, which gives information about the free energies of these compounds. From this it follows that all chemical compounds capable of existence are present on this landscape. Thus the chemical synthesis always corresponds to the discovery of compounds, not their creation. Consequently, the first step in planning a synthesis can and must be to identify a synthesizable compound. Up to now, materials capable of existence are discovered in the course of an experimental exploration of the energy landscape; however, an a priori identification of a synthesis goal requires an exploration using theoretical methods.

In contrast to those computational approaches currently employed for structure determination for fixed composition and already known unit cells, our aims clash with such restrictions and full global optimizations have to be performed on the landscape. Although for reasons of computational feasibility the accuracy of the energy calculations is not yet as high as one would wish, our approach proves to be surprisingly robust. One always finds the already known compounds of a given chemical system, and, in addition, further plausible structure candidates are discovered. The second step of a rational planning of syntheses is the design of feasible synthesis routes. Modeling such routes requires highly accurate computations for realistic thermodynamic conditions, however this is usually beyond our current capabilities. Thus, we have not seriously pursued such a deductive approach; instead we have attempted, to reproduce the “computational annealing” employed during our structure predic-

tions in the experiment. Educts, generated by vapor deposition methods, that are dispersed on an atomic level are found to react with surprisingly low activation energies to give highly crystallized products. However, even this technique does not yet provide the possibility to selectively synthesize a specific solid compound. For this final step, modeling and experimental control of nucleation processes will be the key ingredient. Only when viewed superficially, our goal of a “rational design” of solid-state syntheses and the “high-throughput” syntheses are in contradiction. But an exhaustive exploration of the unimaginably large combinatorial diversity of chemistry remains beyond our capabilities, even with an exceedingly high throughput. The future of solid-state synthesis will be found in a union of these two conceptual approaches.

Keywords: solid-state chemistry • synthesis planning • solid-state reactions • structure prediction

1. Introduction

The alchemist's saying “solve et coagula” describes in a nearly paradigmatic way the basic goals of modern chemistry, which provide it with genuine and distinct characteristics in a time of increasing overlap among the various disciplines of natural science. This special feature is the sometimes seemingly playful disintegration and recombination of matter in

千里之行 始于足下

—— 老子 第64章^[1]

ever new combinations and their characterization, that is, the synergetic interplay of synthesis and analysis. For example, a current focus of (solid-state) chemistry is the construction of ordered structures just above the atomic length scale.^[2, 3] Clearly, such solids structured on a nanoscopic or mesoscopic scale fill a true gap in sizes between the atomic and macroscopic, and they are of a not-to-be-underestimated importance because of their very special chemical and physical properties caused by various size and boundary effects.^[4]

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However, the new nomenclature should not fool us into thinking that either the problems encountered or the ideas proposed for their solutions are truly new. In particular, one needs to counter the impression that the synthesis of traditional (atomically structured) solid compounds has been mastered. In fact, the lack of control and selectivity encountered in attempts to construct materials structured on the nanometer-level (chemical interactions as the order principle, bottom-up approach^[5]) is a well-known phenomenon in classical solid-state synthesis. It is still impossible to synthesize an up-to-now unknown solid compound with a prescribed composition, structure, or even properties, intentionally and in a reproducible generalizable fashion. This fact, which has been referred to many times already since the beginnings of solid-state chemistry,^[6, 7] has led to the widely accepted, and often somewhat resigned, attitude that experimental solid-state chemistry is not amenable to detailed design and thus is intrinsically of an explorative nature.^[8–12] Obviously, the state of matter, in which the chemical reaction takes place, plays a decisive role. The contrast to molecular syntheses,^[13] in particular in organic chemistry, which are predominantly performed in liquid or gaseous solutions, could not be more extreme. In molecular chemistry it has for a long time been possible, to design molecules capable of existence and then prepare them. And even more importantly, an extensive toolbox of chemical reactions is available to prepare the intended molecule by following a sequence of predictable and often highly selective synthesis steps.^[14]

A comparison of the different boundary conditions (and their consequences) in solid-state and molecular synthesis, lets us view the nearly antagonistic situation regarding the relevant features of these two sub-fields of synthetic chemistry.^[15, 16] Ignoring some minor details, the difference in success can be reduced to one fundamental issue, the difficulty in solid-state chemistry to bring the reaction partners sufficiently close together, that is, close on an atomic level, over macroscopic distances. In traditional solid-state reactions, this macroscopic diffusive transport usually requires a high thermal activation, which ruins any hope for subtle control of the reaction, and in addition often closes off the routes to thermally labile and metastable solids. Because of this mainly thermodynamic control of the reaction processes, the possibilities for a rational design of a synthesis towards a prescribed compound appear to be severely limited. Never-

theless the scientific imperative remains, to continue developing and improving preparative solid-state chemistry until a goal-oriented rational approach becomes feasible. Only then will it be possible to reach the, also economically crucial, efficiency in the development of new solid compounds that constitutes the first step in materials research.

Thus, about ten years ago, we began to develop an approach for the rational synthesis in solid-state chemistry.^[15–20] Such a concept has to consist of at least two steps:

- 1) Prediction of compounds capable of existence,^[21] and their structures,
- 2) Development of a synthesis route towards these compounds.

In this Review the current state of the enterprise is presented.^[24] From the point of view of efficiency, the so-called “combinatorial”, or better: “high-throughput”, methods^[25] constitute a possible alternative to our method based on rational design. Thus, at the end of this article a comparison of these rather opposite approaches is attempted.

2. Heuristic Aspects of Design in Solid-State Chemistry

The fascinating, yet sometimes confusing, multitude of structures, valence states, and properties of solid matter have early on nudged, if not pushed, the workers in the field to assess and classify this plethora of experimental data. Always one has chosen the inductive approach, so successful throughout chemistry, where generalizable connections and rules are derived from individual observations. At the beginning, the focus was on structural aspects. Not even twenty years after the discovery of X-ray diffraction on crystals and the first successful structure determinations, V. M. Goldschmidt recognized the composition, the ratios of the radii of the constituting particles, and the polarization (type of chemical bonds) as the three most crucial factors determining the observed structure.^[26] During this early period, W. Biltz conceived his “Raumchemie der festen Stoffe” (spatial increment chemistry of solids), too.^[27] Later, F. Laves added the principles of maximal space filling and highest possible symmetry.^[28, 29] Side to side with these classical criteria one has to place L. Pauling’s crystal-chemical rules,^[30] which are the origin of the bond-length bond-strength relations.^[31–34]



Martin Jansen, born in 1944 on Pellworm, Schleswig-Holstein, studied chemistry at the Justus-Liebig-Universität Giessen, where he gained his doctorate in 1973 under the supervision of Professor Rudolf Hoppe. After his habilitation in 1978, he accepted a professorial chair for Inorganic Chemistry at the university Hannover. In 1987 he moved to the Rheinische Friedrich Wilhelms Universität in Bonn. Since 1998, he has been a member of the scientific council of the Max-Planck Society and a director at the Max-Planck Institute for solid-state research in Stuttgart. His main research lies in the field of preparative solid-state chemistry, crystal chemistry, materials research, and the structure – property relationship of solids. Among others, he has been awarded the Gottfried Wilhelm Leibniz prize, the Otto Bayer prize, and the Alfred Stock Gedächtnis prize for his work. He is a member of the Editorial Board of Angewandte Chemie.

These approaches only take local interactions into account, clearly a defect considering the importance of long-range interactions in crystalline solids. For ionic crystals, R. Hoppe's MAPLE^[35–37] and concepts such as CHARDI,^[38] derived from MAPLE, which are based on the Coulomb contribution to the (lattice) energy and the partial, that is, referring to a particular crystallographic site, Madelung energies, address this problem by providing data for correlating different crystal structures and structure elements. Quite generally, the often noticeable multi-facetedness of crystal structures requires an analysis from as many diverse points of view as possible.

In addition to the methods mentioned, the calculation of minimal- and equipotential surfaces^[39] yields many insights, just as the recognition of hierarchical structural connections^[40] and the description of structure elements as virtual displacements, such as shear motions^[41, 42] and twinning operations.^[43] Inherent to all these approaches is the classification according to symmetry properties. Quite often, crystal system, crystal class, or even the space group of a compound are mentioned in one breath with its formula. Here, the generation of group–subgroup relations has proven to be a particularly efficient tool in the analysis of structural relations.^[44] Beyond their applicability to classifications, symmetry considerations are of fundamental importance, for example, for the understanding of phase transitions and solid-state properties.^[45]

The two most common ways to describe newly discovered crystal structures are based on the analysis of the anion substructure complemented by the cations occupying the various holes in the anion packing, and/or the description of the coordination polyhedra and their connectivity. Both approaches are also employed for the purpose of systematic classification. Concerning the analysis of atom packings, it has turned out to be a surprisingly successful alternative to read the structures starting with the arrangements of the cations, instead.^[46–49] The polyhedra and their topological connectivity and spatial arrangements have become the foundation of, for example, a comprehensive structure systematics of the silicates and related classes of compounds following F. Liebau,^[50] or A. Simon's concept of condensed clusters.^[51]

In the case of intermetallic phases, the valence electron concentration^[52, 53] takes on a similarly controlling role as the formula for ionic or covalent compounds. In particular for this class of compounds structure field diagrams serve a valuable role when trying to structure the experimental data.^[54–58] Surprisingly widely applicable consistent structure systematics can be developed on the basis of the Zintl–Klemm concept^[59–61] and following the ideas developed by Hume-Rothery and co-workers;^[62] in contrast the Laves phases are classified only following geometric considerations.^[28, 29]

This strongly abbreviated review of the crystal chemical repertoire predominantly serves for the description and classification of the otherwise overwhelming plethora of experimental information.^[63] Beyond this primary task, these tools offer qualitative ways to tentatively judge the plausibility and correctness of newly found crystal structures. Turning this line of reasoning around, these concepts can also be used as a guide for the imagination when conceiving of chemically reasonable but not-yet-observed atomic arrangements. In particular, one can strongly restrict the nearly

infinite multitude of imaginable structures just by considering the formula, the type of chemical bond, and the effective sizes of the building units (usually atoms or ions). Already the number of possible motives of mutual coordination of the different atomic species, which can be formulated in a compact way by the Niggli notation,^[69] can be greatly reduced using the above assumptions.^[70, 71] Taking furthermore the connection between the chemical formula and the multiplicity of the Wyckoff-sites into account, one can significantly reduce the number of possible space-group types.^[71–74] In particular, structures of simply constituted solids sometimes appear to follow from these assumptions alone.^[75, 76] Similarly, systematic permutations of the occupation of the holes in close anion packings while taking the space-group symmetries into account generate both the known structures and also plausible but so far unknown variants.^[77, 78]

However, one quickly reaches insurmountable limits when employing only these recipes that are purely based on geometric and topological structural properties, unless general heuristic rules based on experience or metaphysical expectations, such as “striving for the highest symmetry”^[28] or “employing a minimal number of structure elements” (Gott ist ein Gerechter! (God is a just one!))^[79], are used as additional criteria.

Yet the goals of solid-state chemistry are not limited to the realization of certain well-defined crystal structures. Primarily, the issue is the synthesis of new compounds and their characterization, also with an eye on possible applications, that is, the trinity of mutually interconnected aspects: structure, bonding, and property. The conscious tuning of material properties,^[9, 16, 80] which goes beyond the sheer optimization of an already well-known material, is without doubt the final goal, currently, however, barely more than a dream.

Of course, those approaches that have the greatest hope for success, are where the causal connection between microscopic basis and desired macroscopic physical property is known in detail. Such a situation pertains for ionic conduction, as long as the mechanism can be described as a random walk in a concentration gradient.^[81] For example, the discoverers of the fast ionic conductor NASICON make the claim to have developed this material in a consciously planned fashion.^[82] However, in general the successful route to a new material has been based on a mixture of analogies, intuition, and empirical knowledge. Examples of this latter approach abound, these include, the many instances of successful syntheses of compounds with unusual valence states, such as paramagnetic Ag^{3+} ^[83] or high oxidation states of transition metals.^[84–91] Similarly, one could mention the adjustment of band gaps in semiconductors,^[92, 93] the optimization of ferro-electric compounds,^[94, 95] superconductors,^[96, 97] or GMR-materials (GMR = giant magneto-resistance)^[98, 99] belonging to the extended structure family of perovskites. Often, the “models” behind those results constitute just extra- or interpolations of known compounds, and/or the more accidental improvement of some property is only afterwards explained in terms of structure and chemical bonding. Nevertheless, these indisputable successes have encouraged the appearance of optimistic essays^[100] with titles such as “Predictive Character of Solid-State Chemistry”.^[101, 102]

On its own, the rational development of goals for solid-state synthesis, the subject of our discussion so far, is not sufficient. A second hurdle is the development of feasible synthetic routes leading to the desired compound.^[13] Although quantitative verifiable models for chemical reactions among solids^[103–108] are usually only available for model systems, the results of such investigations have long been taken into consideration in preparative solid-state chemistry, at least on a qualitative level. The most influential guiding mottoes have been “increase of mobility in the solid state” and “achieving as good as possible a mixture of the educts”. Pioneers in this field are G. Tammann,^[109] A. Hedvall,^[6] and R. Fricke;^[110] their ideas are still being felt today, and employing specially prepared (“activated”) starting compounds belongs to the elementary tools of every experimental solid-state chemist.

A large number of methods are being employed today to provide such highly activated educts, both by mixing the components as intimately as possible and by creating a very high defect concentration.^[6, 10, 110, 111] Among the most important ones are co-precipitation, thermal decomposition of precursors (for example, of nitrates, carbonates, oxalates and carboxalates^[112–114]), freeze drying,^[115] mechano-chemical procedures,^[116] sol–gel methods,^[117–119] or polymer routes.^[120, 121] The activation required for the solid-state synthesis can be reduced most effectively by using chemical transport reactions,^[122–125] melting reactions,^[126–130] solvothermal syntheses,^[131] or topotactic reactions (intercalation, de-intercalation).^[132–137] This progress in the development of preparative techniques has continued unabated until the present, clearly proving that the creativity of chemists has not yet reached its limits.^[138–140] For completeness, one should also mention the efforts to increase the range of temperatures and pressures accessible to solid-state syntheses.^[141–145] Besides modifying the reactivity of the materials, this extension also changes the equilibrium structures one can reach and enlarges the accessible part of the thermodynamic phase space spanned by the thermodynamic variables.

Even this highly abbreviated sketch of the conceptual foundations of classical preparative solid-state chemistry gives an idea of the fruitfulness of these basic concepts, as one also realizes by considering the seemingly inexhaustible productivity of this branch of chemistry. Nevertheless, all these successes cannot hide fundamental deficiencies on the conceptual level. Perhaps the most grave ones are the lack of coherence and consistency of the models employed, and their often unclear or insufficient physical basis. While the strengths of the current models can be found in the systematic classification and subsequent validation and/or explanation of experimental data, they only exhibit a very limited predictive power. Up to now, they have not been sufficient to significantly decrease the inherent unpredictability of syntheses in the solid state.

3. Multi-Minima Energy Landscapes as Representations of Material Systems

For an n -component material system in thermodynamic equilibrium, chemical thermodynamics produces a unique

relation between the state of the system and the prevailing thermodynamic conditions, the values of the state variables p , T , $x_1, \dots, x_{n-1}$ (x_i : molar fractions). Here, the thermodynamic state of the system is completely described by the knowledge of the co-existing phases, their mole fractions, and their compositions. This information can be encoded in a compact and elegant way in the guise of phase diagrams. If one were to assume that solid-state synthesis is fully controlled thermodynamically, a rational prior determination of realizable synthetic goals would necessitate the computation of the phase diagram for the chemical system under investigation.

Long-term efforts to determine phase diagrams as completely as possible because of their great importance in solid-state and materials science have been underway for many years, with quite impressive results. Thus, in the context of the CALPHAD-project,^[146] algorithms and computer programs have been developed that allow us to employ caloric data of a system drawn from a variety of sources to optimize and supplement experimentally determined phase diagrams. In addition, attempts are made to derive the basic structure of the phase diagram of multi-component systems from information about the few-component boundary systems. Going beyond these extra- and interpolations, a few largely ab initio based computations have been performed^[147–149] of, among others, excess enthalpies^[150] or phase separations, for example, through spinodal mechanisms.^[151] With respect to rational synthesis design, the predictive value of these or the other methods mentioned above is rather limited, since we are interested in the determination of new compounds, which of course cannot be part of known phase diagrams. Within the context of the CALPHAD approach, only experimentally known data can be employed, and in general one cannot recognize and eliminate a fatal defect such as a missing thermodynamically stable phase. A second restriction is of a fundamental nature. When pursuing the goal of predicting all compounds capable of existence, and thus also capable of being synthesized, in principle, a restriction to thermodynamically stable compounds is unacceptable. In fact, the overwhelming part of the accessible solid matter is found to be in a metastable, only kinetically stable state. And this applies even more strongly to the combinations of compounds that are employed in technological applications.

If one's goal is the determination of all compounds capable of existence, including those that are only kinetically stable, one has to leave the usual depiction of a chemical systems at equilibrium in the form of phase diagrams behind, and analyze the full function of the free energy F for all locally equilibrated states in the system. This idea can be visualized using a one-component system (Figure 1). For every state of matter, F can be plotted as a function of p and T . The intersections of these surfaces characterize the thermodynamic conditions for co-existence of the different states. For given p and T conditions, the state with the lowest value of the free energy is the thermodynamically stable one. The corresponding sections of the free-energy surfaces are projected onto the (p, T) -plane in the usual representation of phase diagrams. In general, one expects that in the liquid and gaseous states of matter, usually only one phase is going to be

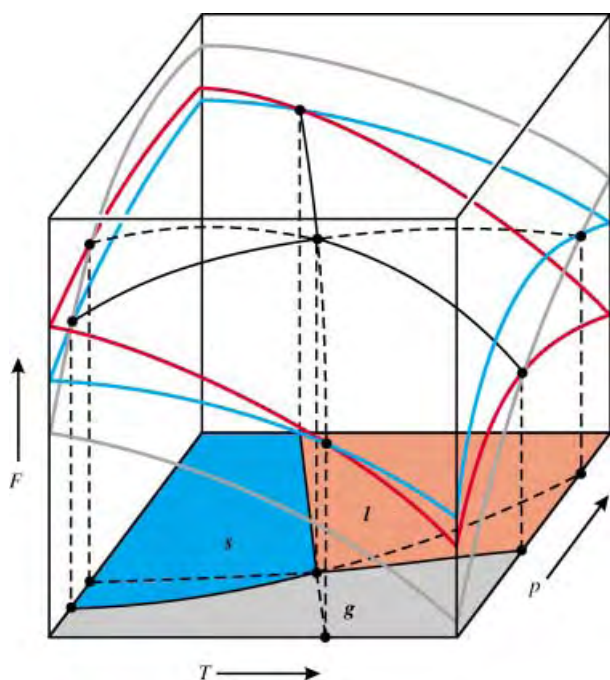


Figure 1. Phase diagram for a single-component system (schematic). The free energies for the solid, liquid, and gaseous state, respectively are shown, and their projections onto the surface spanned by the state variables p and T .

present, while in the solid-state polymorphism can occur, that is, several modifications might be formed. The corresponding surfaces of the free energy can, but need not cross. In contrast, there always exist intersections with the surfaces belonging to the liquid and gaseous state, defining respectively, the vapor-pressure and melting-pressure curves of the corresponding solid modification.^[152] However, with respect to their realizability it does not matter, whether we are dealing with thermodynamically stable or metastable compounds.^[153]

The claim that by fixing a full set of state variables (here: p and T) the state of matter and at the same time the thermodynamic state functions are uniquely determined, only refers to a system in thermodynamic equilibrium and is a purely phenomenological and descriptive statement. Usually, the state of the system (type, number, and composition of the phases present in equilibrium) is determined experimentally. When trying to include non-equilibrium-states, the uniqueness of the relation between thermodynamic state and state variables is lost, and the phase content of a system can vary for the same values of the state variables, depending on the experimental path taken.

A crucial difference to equilibrium systems is that now the macroscopic thermodynamic state must be treated as potentially variable in time, that is, time needs to be taken into account as an additional “coordinate”.^[154] The resulting complex interplay of the variables may be visualized using a thought experiment. For this we consider all states that can be realized for an arbitrary (n -component) system at $T = 0$ K and fixed atom positions (i.e. with time frozen, $\Delta t = 0$ s). For all combinations of compositions and spatial arrangements of atoms (configurations)^[19, 155, 156] one can then assign, formally, a value of the free energy, which, for $\Delta t = 0$ s exactly

corresponds to the potential energy of the particular configuration. Using these hypothetical assumptions, one can formally construct a connected hypersurface of the free energy. In the classical picture one can distinguish unstable, metastable, and stable regions. If one now lifts the restriction $\Delta t = 0$ s while keeping $T = 0$ K, this allows the system to slide from the unstable points into the nearest local minimum. Adding the zero-point vibrations, and choosing Δt large compared with the inverse frequencies of the vibrations around the minima, one needs to average over the regions in configuration space corresponding to the vibrational amplitudes, and one can only speak of the value of the free energy referring to this set of atomic configurations. Although some relaxation processes resulting from quantum tunneling will occur, transport by diffusion is not possible under these thermodynamic conditions ($T = 0$ K).

Moving to finite temperatures, the atomic positions are going to change continually, accompanied by a minimization of the free energy of the system, until finally thermodynamic equilibrium has been reached. During this process, many metastable intermediate states with various life times will be passed through. Which among these intermediary “compounds” or structures can be considered as “capable of existence” is a matter of judgment. A minimal requirement is surely that the metastable states must be detectable within the resolution of the available measurement probes.^[16, 19, 157] Thus, one would treat a molecule as capable of existence in molecular chemistry, if it survives for at least one vibrational period. In the case of solids one usually deals with time periods ranging from human experience to geological times.^[158] This is a result, less to the time resolution, which is essentially independent of the state of matter for spectroscopic probes, but reflects the transformation and reaction speeds of solid matter, which are on the order of seconds even for non-diffusive processes.

It follows from our considerations that at finite temperatures only subregions of the “virtual hypersurface” of the free energy, generated in the thought experiment, are going to be populated. These usually correspond to minimum regions in configuration space, which represent regions of locally equilibrated configurations with finite (in the case of the global minimum essentially infinite) life times.^[19] A chemical interpretation of these regions is not always trivial. In a simple case, a minimum can be associated with a well-defined crystalline compound without higher-dimensional defects. For fixed activities of the components and constant pressure, which takes on the character of an external variable for metastable compounds, the “width” of the minimum is then given by the vibrational amplitudes of the constituent atoms about their equilibrium positions and the concentration of point defects. The degree to which the resulting states are populated, is determined by the temperature. The value of the free energy (the macroscopic observable) follows from the summation over the corresponding densities of states.

Other examples from the multitude of possible constellations are metastable mixtures, for example, of annealed MgO and α -Al₂O₃, the polytypes of SiC,^[159, 160] which are close neighbors in configuration space but separated by high barriers, or a ferroelastic compound, such as As₂O₅,^[161, 162]

near the phase transition into the paraelastic high-temperature form (vanishing barrier).

When documenting metastable and stable solid states in form of phase diagrams, one can only reach those regions on the “virtual hypersurface” of the free energy described above, which can be assigned a value of the macroscopic parameter F under realistic conditions, that is, where a locally equilibrated region (around a minimum) in configuration space can be identified. Which piece of such a region associated, for example, with a minimum should be taken into account, depends on the prescribed temperature.

The above description may be visualized in Figure 2 again using a one-component system. Here, the surfaces of the free energy of three (solid) polymorphs are depicted as a function of pressure and temperature. The point ($p = 0$ Pa, $T = 0$ K) is assigned to the hypothetical surface of the free energy schematically described above. Clearly the transitions among the three modifications considered take place by shifting the atoms in position space. For finite pressures and temperatures the corresponding macroscopic thermodynamic state function (here: F) is computed by averaging over the populated microstates belonging to a locally equilibrated (minimum) region, and their temperature and pressure dependence can be represented in the usual fashion (Figure 2, right). If one restricts the considerations to ideally crystalline, chemically similar modifications, for example, S_8 , S_{10} , and S_{12} (three allotropes of sulfur),^[163] the vibrations of the atoms about their equilibrium positions is the most important aspect to be included. Since this contribution is nearly the same for each polymorph, taking it into account will only lead to minor modifications of the shape of the corresponding free-energy landscape. Thus, for temperatures far below the melting point, it is not at all unrealistic, to picture known (or still-unknown) compounds capable of existence as being represented on landscapes that essentially reflect the shape of the potential-energy surface over the corresponding configuration spaces. The move, required in principle, to the free-energy landscape leads, because of the averaging process mentioned above, to a more discrete energy landscape, where the locally equilibrated

(minimum) regions represent the stable or metastable chemical compounds capable of existence.

The one-component system discussed above can be a single-element compound or a multi-element compound with fixed component activities, that is, fixed composition. Chemical reactions assume an exchange of material. An exemplary phase diagram allowing such an exchange, a two-component system, is shown in Figure 3. The free energy (F function) is now a function of three thermodynamic variables, and its dependence on these can be depicted graphically only in form of cuts through thermodynamic space. For equilibrium, the phase content for given thermodynamic conditions can be

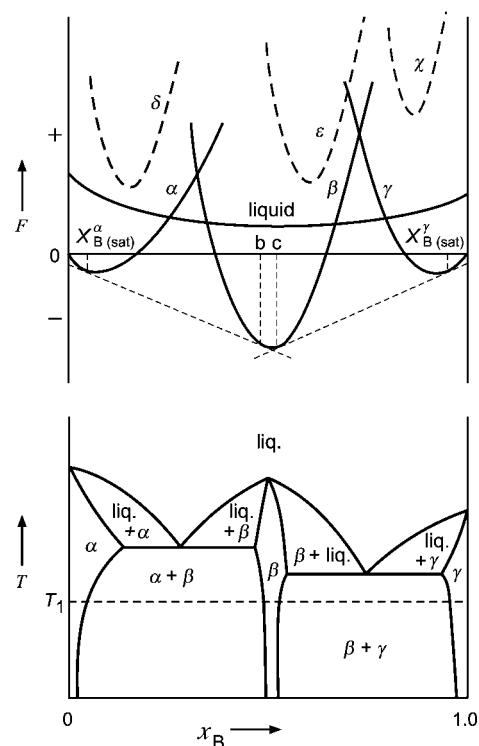


Figure 3. Phase diagram for a two-component system at constant pressure (bottom) and the free energy functions including metastable states (top), schematic representation for fixed pressure and temperature T_1 .

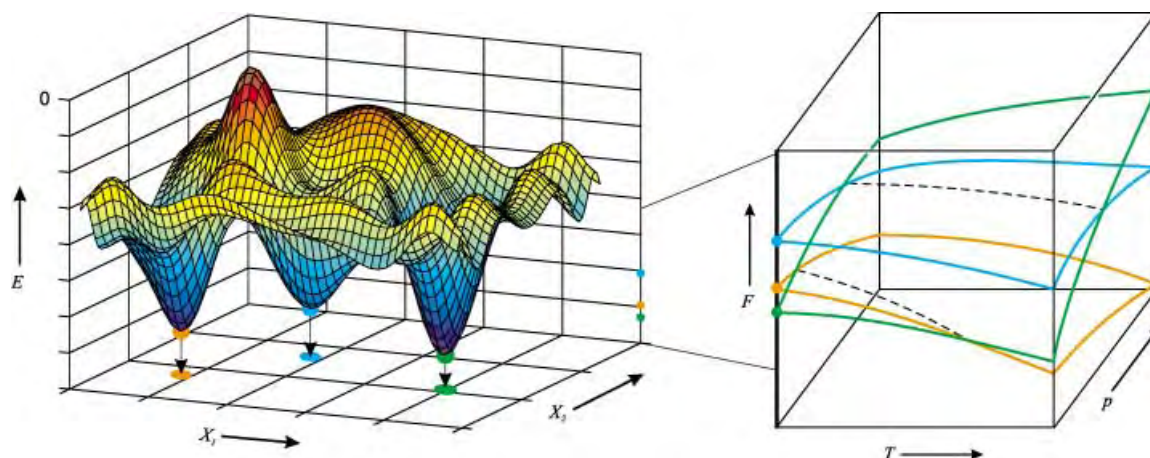


Figure 2. Schematic representation of a cut through a configuration space for a single-component system with fictive coordinates X_1 and X_2 (left) and the correlation with the usual representation of the free energy as function of pressure and temperature for three solid (metastable and stable) modifications (right).

derived from the equality of the chemical potentials of all co-existing phases. In an elegant and easily visualized fashion this can be done by constructing the common tangents to the F function in the representation $F_{p,T}(x_i)$. Such methods cannot be used, of course, to determine metastable phases that can co-exist with each other, since in general they exhibit different chemical potentials. The connecting element among all compounds capable of existence is again the configuration space. These compounds can all be found on the energy landscape, from which free energies can be computed for distinct locally equilibrated (minimum) regions.

A certain charm of these admittedly qualitative and partly abstract considerations, still far away from the compromises and approximations that will be necessary when moving to real implementations, is found in their universal validity. Even keeping in mind all the foreseeable difficulties (see next Section) involved with the development of a methodological route to the synthesis planning in solid-state chemistry, which today still appear insurmountable, this general approach, that is, to visualize the material world as being represented on energy landscapes, opens the window to important insights:

- All compounds capable of existence are already present on such energy landscapes (a picture that exhibits strong analogies to Plato's theory of forms). Thus the synthetic chemist is always the discoverer, not the creator of new materials,^[15, 16] and this holds without exception for all fields of synthetic chemistry.
- General precondition for a compound to be capable of existence is that it can be associated with a locally equilibrated region, for example, a local minimum, in its configuration space. The sign and amount of the free enthalpy of formation, and with this the question of thermodynamic stability, are not decisive as far as the feasibility of synthesizing a compound is concerned.
- These general considerations appear to open the door leading to a deductive approach to chemistry.

The approach presented removes a number of preconceptions widely held in the past and to some extent still held. The over-emphasis on the aspect of thermodynamic stability when discussing the existence of hypothetical compounds has definitely impeded the development of preparative chemistry, and, in particular, of solid-state chemistry. Claims such as “MgCl cannot be synthesized since it would be thermodynamically unstable against a disproportionation into MgCl_2 and Mg”, or an analogous justification of the lack of success up to now to synthesize CuF, are even part of the canonical teachings in chemistry.^[164] How deeply rooted such a point of view is becomes obvious when reading the, in principle, very inspiring monograph by W. E. Dasent “Nonexistent Compounds”,^[165] where in a number of instances the thermodynamic stability is presented as the only criterion for the feasibility of synthesizing a hypothetical compound. We feel that compounds such as MgCl or CuF can definitely be synthesized, and consider it to be much more fruitful to work on realizing such compounds than to justify their supposed nonexistence.

The energy landscape discussed is the foundation of the whole material world, and its investigation unites all of

natural science. Of course, this very satisfying conclusion does not exclude the fact, that, for pragmatic reasons, answering different classes of questions, and in particular the analysis of various specific sub-systems, will require the use of quite different techniques and methods. But at least fruitless polarizations and artificial distinctions, such as between natural and unnatural materials^[166] or static and dynamic solid-state chemistry,^[167] should lose their purpose.

4. Rational Planning and Performing of Solid-State Syntheses

4.1. Prefatory Remarks

Starting from the realization that the full set of both already known and up-to-now unknown chemical compounds capable of existence in some chemical system are represented on an energy landscape, one recognizes that “doing chemistry” just corresponds to exploring this landscape. Traditionally, this exploration is done by chemical synthesis, where each synthesized compound marks a locally equilibrated region of configuration space, for which one can determine, for example, a value of the free energy. This exploration by experiment can proceed by relying to a varying degree on “conceptional” input and purely explorative testing of a set of reaction parameters, depending on the class of chemical systems and the “maturity” of the field investigated.

A particularly noticeable current development is the gain of importance of an alternative option, the theoretical treatment of chemical issues. The great improvements both regarding the computational power available and the efficiency of the algorithms employed allow an ever increasing accuracy in the computations and the analysis of increasingly larger (number of atoms) systems.^[168] However, in most instances these tools are currently applied to a prescribed compound or element,^[169–175] and not used for the exploration of a chemical system as a whole with an eye on the identification of possible goals for syntheses. While for the case of experimental exploration the synthesis route is a necessary by-product of reaching a desired compound, finding an experimentally feasible synthesis route after theoretically identifying a promising not-yet-synthesized compound (for example as a local minimum on the energy landscape) constitutes a second, independent step. Thus, this chapter dealing with “rational solid-state synthesis” has been split into two parts, where the identification of compounds and the development of appropriate synthesis routes are discussed separately.

4.2. Exploration of Energy Landscapes of Chemical Systems by Using Theoretical Methods

As easy as it has been to state the task in general terms, so difficult it is to reach a practical solution. This applies in particular to the ambitious general goal: to compute a distribution of the expectation values of the free energy for the chemical system under consideration over regions on the microscopic landscape, for all p , T , x_i values. This aim requires,

in principle, quantum-mechanical energy calculations, and the derivation of the macroscopic state functions from these results based on the rules of statistical mechanics. Currently, it is well-recognized that a completely rigorous treatment of systems of realistic sizes is not yet possible. Among the necessary simplifications, the restriction to ideal crystalline solids and their properties at $T=0$ K are probably the least problematic within the context of this discussion. Using this assumption, one can compute the energy E_0 as the sum of the energy of cohesion U of the participating atoms at their (equilibrium) positions on the lattice and the energy of the zero-point vibrations^[45] [Eq. (1)].

$$E_0 = U + \frac{1}{2} \sum_{i=1}^{3N} h\nu \quad (1)$$

The amount of cohesive energy depends on the constituent particles, of course.^[176] In the case of quantum-mechanical calculations, these particles are all the atomic nuclei and electrons, while, for example, for noble-gas crystals it makes sense to treat whole atoms as the elementary building block.^[17] For ionic crystals, one can refer to ions or neutral atoms, where the cohesive energy would correspond to the lattice energy (consisting of long-range Coulomb plus short-range repulsive terms) for the ions, or the enthalpy of formation ΔU , from the neutral atoms, respectively.

The number of calculations that need to be performed depends on the number of components in the system under consideration and the steps in the thermodynamic variables p , T , and x_i . Similarly, the computational effort, for example, for an individual energy calculation is determined by the maximal number of atoms allowed and the (effective) charge of the nuclei or ion cores. Since the development of a set of tools for the planning of solid-state syntheses which can be of practical use, needs to take systems with three, four, and more components into account, one realizes right away that the number of computations necessary for a sensible scanning density of the space of thermodynamic parameters grows exceedingly large very quickly. Thus, a rigorous quantum-mechanical treatment, however desirable, is beyond our capabilities even when employing the usual approximations. These facts clearly show the limits of our capabilities, and decisively influence the approach chosen by us for the exploration of the energy landscape of solids.

Our concept has been discussed in great detail elsewhere; thus here we only give the most pertinent aspects.^[16–20, 177–184] Going beyond the restrictions of $T=0$ K, we neglect the zero-point vibrations, and consider the life times of the metastable states only in a rather qualitative fashion. This simplification results in a configuration space spanned by $3N$ position coordinates for a N -atom system.^[19] Of course, when using simplified potential-energy functions instead of quantum mechanical ones, the resulting energy landscape can only be a rough representation of the true (free) energy function. Quite generally, one needs to check carefully, whether employing such approximations might not put the desired goal in jeopardy. We are not necessarily interested in the absolute value of the energy of a hypothetical compound but whether it can be associated with a local potential-energy minimum (at low temperatures). Thus, the assumption of an

ideal crystalline solid and the neglect of zero-point vibrations are clearly acceptable simplifications. Similarly, the temperature dependence of the energy of cohesion that is associated with the thermal expansion, should leave the general structure of the (free) energy landscape unchanged when going to finite but low temperatures.

Indubitably, neglecting entropy is more problematic in our approach that focuses on local minima of the potential energy, since in this fashion entropy-stabilized^[185] compounds cannot be taken into account. However, if one restricts oneself to crystalline solids, this lack is not quite as critical, since the entropy term ($T\Delta S$) typically only contributes about 10% to the standard free-energy of formation. Thus, the number of local minima of the free energy, which are destroyed or newly created when taking entropy into consideration, should be limited. Of course, this justification only applies to low temperatures.

After constructing this multi-minima energy landscape employing the simplifications and approximations described above, it is now explored using global optimization methods.^[186] Here, periodic boundary conditions are applied, and the starting configurations are generated by randomly placing atoms belonging to the system under consideration into a simulation cell. The potential energy, which, for the noble-gas compounds^[17, 187] and ionic crystals,^[177] is usually computed using two-body potentials with Lennard-Jones and Coulomb terms, serves as the cost function of the global optimization. The weighted random walk (Monte Carlo method) in configuration space during the global optimization proceeds mainly by stepwise changes of both atomic positions and the shape and size of the simulation cell, and by transfer of charges between atoms or ions. In addition, we also exchange atoms, and, in principle, can add and remove atoms from the system. The route in configuration space mapped out by these changes that are accepted or rejected based on certain acceptance criteria,^[188] ends in some local minimum. A representative view of the energy landscape can be gained from the accumulation of the results of many such optimization runs.

Here, too, we want to discuss the limits of our approach, as implied by our choice of boundary conditions and method:

- The choice of periodic boundary conditions leads to crystalline structures; amorphous or quasi-crystalline solids are not included. One should note, however, that neither the symmetry of the translational lattice nor the basis vectors are fixed. They are freely varied during the exploration runs. Fixing only one of these aspects would strongly restrict the configuration space and make it impossible from the outset to determine all the structures imaginable.
- There exists an upper limit regarding the number of atoms in the simulation cell; this limit is essentially determined by the computational power available. A structure that exists or is at least capable of existence, but contains more atoms in the smallest unit cell than given by this limit cannot be found. The probability of the occurrence of such an event can be estimated based on the distribution of the number of formula units in already known crystal structures.^[189]
- An issue open to concern in our current implementation is surely the use of simple two-body potentials when calcu-

lating the energy, that is, the cost function for the global optimization. This approach is forced upon us by the very high number of energy calculations required. To really reach a significant fraction of all the minima on the energy landscape, thousands of “simulated annealing” runs are necessary, with each implying millions of energy evaluations. If one were to use more accurate methods for the energy calculation, one would only be able to explore very small regions of configuration space. But in this way, we would clearly miss our goal of predicting as many compounds as possible that are capable of existence in a chemical system. Of course, one would be able to reach a higher accuracy concerning, for example, the lattice constants, by employing empirical interaction potentials between the atoms or ions that have been optimized based on known structures.^[190] However, in this case one can easily, unwittingly restrict the general applicability of the energy function, since, all regions of the landscape must be explored with comparable weight.^[177, 180, 191] As a result of the simplifications in the potentials employed, the lattice constants of the structure candidates do not agree exactly with the experimentally determined ones. Similarly, structure distortions (spontaneous ferroic polarizations, Peierls-instabilities) resulting from electronic effects or phonon instabilities cannot be identified. However, we do not regard these latter restrictions as very worrisome, since we are primarily interested in identifying compounds and structures capable of existence, and not in these structural details.

To deal with this currently not resolved contradiction between the goal of employing an energy function as unbiased as possible that is suitable for global optimization and the desire to produce structures with accurate parameters, we use a two-step approach. In the first phase, we globally explore the configuration space using simple general potentials, while in the second step we perform local optimizations on an *ab initio* level for the seemingly most relevant minima (usually lying very low in energy).^[16, 19, 183] At this stage of the calculations one can, in principle, investigate the structure candidates with respect to, for example, structural instabilities caused by electronic effects.

The degree to which the approximations and simplifications discussed influence the results of the global optimizations is difficult to estimate. A first impression of the robustness of the approximation can be gained by checking, within what range, parameters in the interaction potential can be varied without producing qualitative changes in the energy landscape under consideration.^[177] A much more significant benchmark is whether, when performing an “unbiased” global optimization of the chemical system, one observes the structures already known from experiment. A final judgment about the, in principle, conclusiveness of our concept and the capabilities of our current implementation can only be made, once an unknown compound is first predicted, subsequently synthesized, and finally shown to exhibit the predicted structure. A very encouraging step in this direction has been the analysis of the landscape of sodium and chlorine. Here, a new structure type for ionic AB compounds has been found, where cations (A) and anions (B) coordinate each other in a very regular arrangement with coordination number five.^[15, 16, 177]

Only much later an order variant of this structure type has been experimentally observed in form of Li_4SeO_5 .^[192, 193] And additional structure candidates that are quite unusual for monohalogenide compounds have been identified during the global optimization, such as the NiAs- and the Wurtzite-type, that have been realized in the systems LaI ^[194] and LiI ,^[195] respectively.

In practice, the system under consideration is intensively explored using global optimization methods such that statistically robust claims can be made. For the structure candidates found, an analysis with respect to their symmetry is performed, within defined tolerances, the corresponding space group is determined, and the structure is transformed to a conventional crystallographic setting.^[196, 197]

But the exploration of the energy landscape of a chemical system produces far more information than just a list of local minima. Using appropriate algorithms,^[178, 198–202] one can analyze the barrier structure, from which neighborhoods of structure candidates in configuration space can be recognized, and first indications of the kinetic stability (height of the lowest saddle point) of the corresponding modification can be obtained.^[178, 182, 184, 200, 201, 203] Since the configuration is very high-dimensional even when restricted to a fixed composition, it is very difficult to visualize and present these insights into the structure of the corresponding energy landscape. Among the various methods available to compress the information we have chosen the representation by means of a tree graph,^[182, 184, 204] which yields a fast overview over the lowest-lying minima and their connections.

As representatives of the many systems that have been investigated to date, we want to discuss here Na_3N ^[183, 205] and MgF_2 .^[179, 182, 184] Both systems were analyzed without variation in the composition. For MgF_2 (Figure 4), the energetically

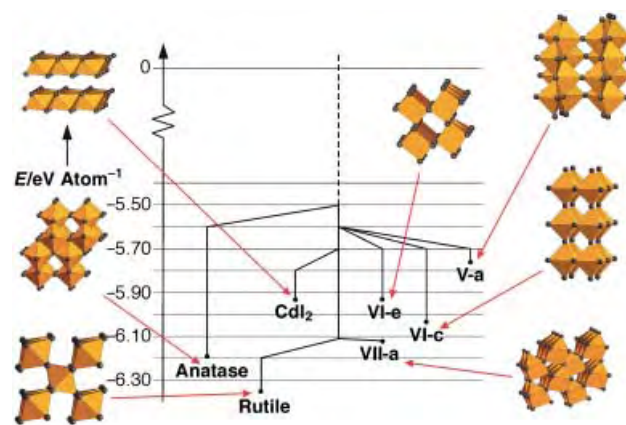


Figure 4. Results of a theoretical exploration of the energy landscape of MgF_2 .^[182, 184] Structure candidates with low energy are shown, together with the barrier structure in form of a tree graph.

most favorable structure found corresponds to the rutile-type, in agreement with the experiment. Remarkably, the second-lowest minimum found shows the anatase-structure, with a realistic barrier height between this and the rutile-type structure—a result that is very plausible bearing in mind that this is one of the well-known modifications of TiO_2 . Thus it would appear to be quite promising to attempt to synthesize

MgF₂ in this structure type. Similarly, the other structure candidates observed obey the standard criteria for crystallochemical plausibility without any problems.

At the time when our theoretical investigations of Na₃N were performed, this compound had not yet been synthesized. It is quite remarkable, how it was possible to generate convincing structure candidates with our method (Figure 5).

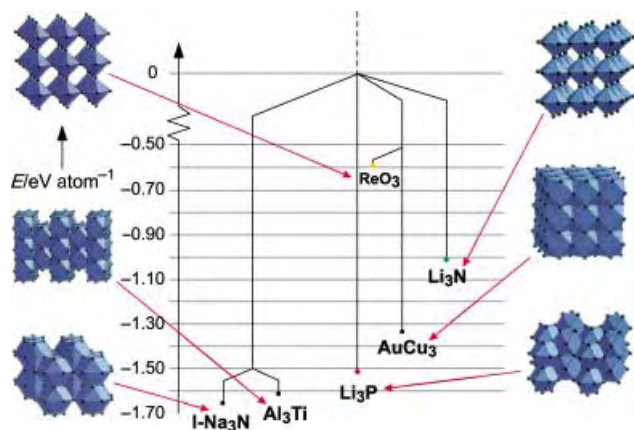


Figure 5. Structure candidates for Na₃N^[183, 205] determined by global optimization, together with the barrier structure depicted as a tree graph.

Even scientists well-versed in structural chemistry might have some trouble designing these model structures, in spite of the relatively high simplicity of the composition. For some of these structure types for Na₃N local optimizations were performed with *ab initio* methods (Crystal 95;^[206] Figure 6). In this process, the set of low-lying minima is preserved, but the absolute values of the cohesive energies per atom can change quite significantly.

Taken as a whole, our approach has proved to be surprisingly powerful, even in the boundary region to covalently bonded solids,^[16] and in the application to structures that contain complex building units.^[181]

It is natural that there are going to be various connections between our concept and both earlier and current work in the

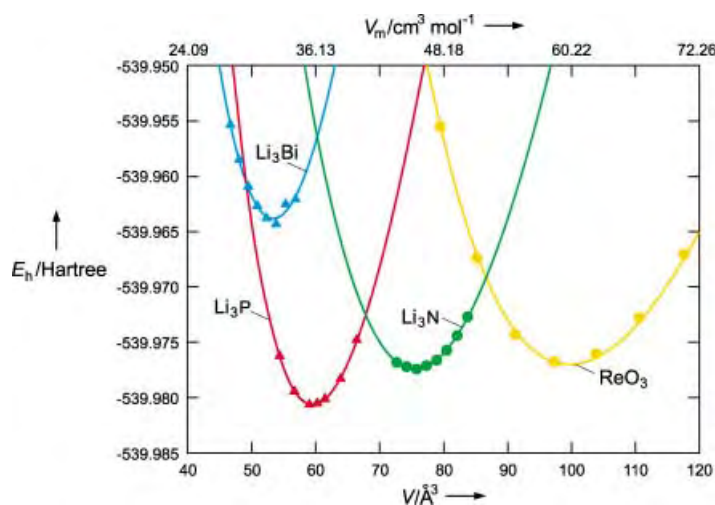


Figure 6. Results of the refinement optimization of selected structure candidates for Na₃N at Hartree–Fock level as a function of volume.^[238]

field of solid-state theory. In particular the interest in computing cohesive energies goes back to the beginnings of theoretical solid-state physics.^[207, 208] In addition to the computed binding energies further quantities such as lattice-constants values were often compared with experimental. In this fashion the quality of the calculations and, in particular, the empirical potentials employed could be evaluated. Furthermore, the motivation behind much work in proposing structures of solids has come from the field of X-ray crystallography of solids, where models of the structure under investigation were checked in a “trial-and-error” fashion, regarding their ability to reproduce the measured X-ray intensities.

With the increased availability of powerful computers, the call for an as unbiased as possible prediction of the structures of solids became more prominent.^[209] For the first successful modeling of crystal structures sometimes unphysical cost functions were employed,^[210] which in subsequent years were replaced by the cohesive energy as the only relevant quantity. In particular, researchers belonging to or being connected to Harwell in Great Britain prepared the ground for these developments. Among other work, they performed many structure determinations, where they usually employed empirically derived (effective) potentials.^[211] These, and subsequent semi-empirical quantum-mechanical approaches,^[212] allowed a rather impressively accurate calculation of various quantities, such as lattice constants, thermal expansion, or dielectric properties.^[213] Among the favorite materials investigated were oxides,^[214] halogenides,^[215] and zeolites.^[216] All these investigations have in common that they explore a greatly restricted energy landscape, that is, the size of the allowed configuration space is much reduced by fixing certain boundary conditions. As a consequence, often only relatively few structure candidates are present, perhaps even only one structure, usually of an already synthesized compound. One of the most common applications has been the determination of the crystal structure of a new compound, where the crystal system and the lattice constants have already been determined from a powder diffractogram and are prescribed during the optimization phase.^[216]

Although our approach^[16] exhibits some similarities to some of the earlier work, it is fundamentally different with regard to the basic concepts and the implementation. From the outset, our primary intention has been the identification of rewarding and realistic synthesis goals, constituting the first step in the rational planning of solid-state syntheses. The goal has always been the determination of all compounds (of not-yet-known composition), which are capable of existence in a chemical system. Taking this as the basic guideline, we reach the necessary conditions for a successful implementation: We need to perform global explorations on an unrestricted energy landscape, where, while using periodic boundary conditions, one must not fix symmetry or shape and size of the unit cell. Recently, work has appeared, which is based on the same motivation, although the implementation is different. In these studies, G. Férey and co-workers have presented a computational procedure for the automated generation of framework-structures from complex building units,^[217] where the resulting structures are also meant to serve as goals for synthetic efforts.

4.3. Musings About the Rational Development of Synthetic Routes

Within the context of the concept of energy landscapes as the representations of material systems, a chemical synthesis corresponds to the transition from a set of initial configurations, located somewhere in a locally equilibrated (minimum) region of configuration space, to an analogous set of final (minimum) configurations, where both are characterized by their corresponding values of the free energy. Since such a process requires some activation and some processing time, the simplifications discussed in Section 4.1 ($T = 0\text{ K}$, $\Delta t = 0\text{ s}$) are clearly not appropriate. Thus, the modeling of a synthesis route towards an as-yet-unknown solid compound has to take place taking all external and internal influences into account, and be based on the correct physical microscopic mechanisms. Up to now, it is not possible to fulfill these requirements.

As a reasonable first step, one can try to classify the reactions that are suitable for the generation of solid compounds according to various phenomenological aspects. In Table 1, such a classification scheme is given, which appears to encompass all types of solid-state syntheses currently

Table 1. Classification of solid-state syntheses.^[a]

A) Closed systems (compositions of the sums of the educts and products are identical)	
Without additives	
$A(s) + B(s) = AB(s)$	
$A(s) + B(l) = AB(s)$	
^[b]	
With activating additives	
$A(s) + B(s) + \text{solvent} = AB(s) + \text{solvent}$	
$A(s) + B(s) + \text{transport agent} = AB(s) + \text{transport agent}$	
B) Open system (formation of gaseous by-products)	
Molecular precursors (s,l,g) $\rightarrow AB(s) + \text{by-products}$	
Polymer precursors (s,l) $\rightarrow AB(s) + \text{by-products}$	

[a] As examples only binary compounds are listed, ones with more components can be included in an analogous fashion. [b] For all combinations of states of the system.

known. At this point, we would like to refer to the completely different situation encountered in molecular chemistry, where, at least in simple cases, one can follow reactions among individual molecules along one-dimensional reaction coordinates or, in more general situations, on still visualizable potential surfaces.

For some of the reaction types listed, methods for their quantitative description have already been developed. This applies in particular to the probably most intensively studied classical solid-state reactions, that is, the ones proceeding by interdiffusion. In this instance, one can perform quite reliable calculations for given thermodynamic conditions, based on the thermodynamic data of educts and products and the diffusion coefficients for the main participants in the transport processes.^[103, 104, 106–108, 122, 123, 125] This applies not only to the reaction rates, but also to the morphological changes of the interfaces between educts and products.^[218, 219]

Figure 7 shows a schematic representation of an example, the formation of a spinel (MgAl_2O_4) from the binary components in the phase diagram. The cut shown is reached by fixing p and T , while at the same time focusing on two minima in configuration space of the components Mg, Al, and

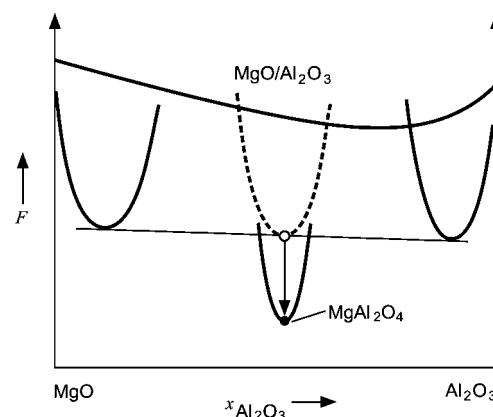


Figure 7. Synthesis of MgAl_2O_4 by interdiffusion of the binary components.

O. For the same composition, and the same amount of material, one minimum corresponds to a metastable mixture of educts $\text{MgO}/\text{Al}_2\text{O}_3$, the other to the spinel MgAl_2O_4 , which probably corresponds to the global minimum. Upon thermal activation, the product is formed by interdiffusion. As a rule, the high thermal activation necessary for this reaction type, leads to the establishment of the thermodynamic equilibrium. This situation also holds for reactions between metals or intermetallic phases, which can, in principle, be performed in an analogous fashion (by interdiffusion). In most cases, one actually chooses the route by the melt for this class of substances, from which the thermodynamically stable phase crystallizes. It appears that such reaction paths (Figure 8) should in principle be capable of being modeled.

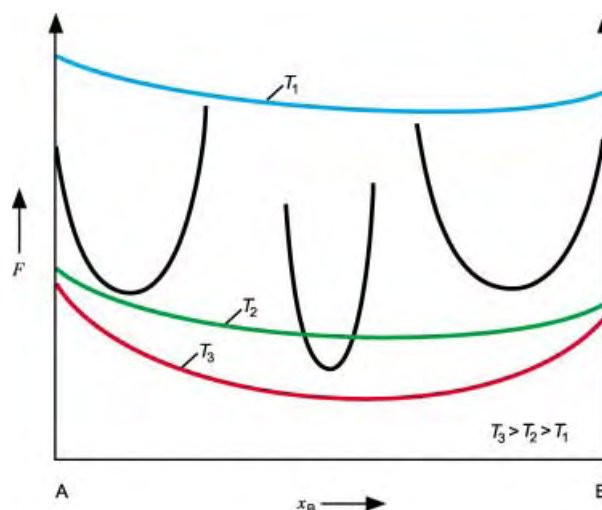


Figure 8. Schematic depiction of the synthesis of an intermetallic phase from the melt. Initial state (mixture of A and B) at T_1 (blue line shows the free energy of the melt), heating to a temperature above the melting point (T_3 , red line), and cooling to a temperature below the melting point of the product phase AB (T_2 , green line).

However, there exist numerous examples of solid-state syntheses by interdiffusion that proceed via non-equilibrium states. This process is always possible, once the mobility of one type of atoms exceeds those of the other components by several orders of magnitude. This group of reactions is commonly summarized under the heading of “topochemical reactions”.^[132, 134] Among these one counts the (reversible) incorporation of hydrogen in metallic glasses,^[220] ion exchange in zeolites, and intercalations in graphite^[133] or clay materials.^[221, 222] Over the years, this concept has led to the development of a broad field of synthetic chemistry.^[136, 223] In attempting to maintain elements or parts of the structure while only allowing specific regio-selective changes, the basic principles of this approach are close to those that hold sway in molecular chemistry. If one is willing to accept the structural framework as essentially unchangeable, one really can, within the limits this assumption imposes, perform purposeful goal-oriented syntheses. In this context, first interesting steps towards the development of theoretical models have been taken, where the preferred locations within the framework for certain reactions have been predicted based on the quantification of the chemical hardness or softness of the constituents.^[224, 225]

A very effective method to reduce the thermal activation required for a solid-state synthesis, and, at the same time, gain a higher degree of control about the reaction process, is the increase in mobility of the reactants by transferring them into a mobile gaseous or liquid phase (Table 1, A). Here, one has to recall one of the oldest techniques in chemistry, the dissolution of the educts in appropriate solvents, followed by the precipitation of the products. Another related approach is the chemical transport in the gas phase, which, after first having been described phenomenologically, has been systematically analyzed by H. Schäfer and has been made amenable to a quantitative description.^[13, 122] The developments to date now allow, even for complex chemical systems, a rational choice of transport media, the computation of the direction of transport and of the optimal temperatures for source and sink, and finally an estimate of the transport rates.^[226–228] However, if one wants to apply chemical transport not simply in an experimental fashion, one needs to know both the composition in the gas phase, which is often a very critical aspect, and the enthalpies and entropies of formation of all participating species at the temperature of the experiment. One should note that compared to the conditions in a classical solid-state reaction, the input of thermal energy is reduced. One of the strengths of this synthesis method is the possibility to synthesize solids, which are only stable at low temperatures (subsolidus-region). As another (often desired) consequence of the high mobility, the processes during chemical transport are close to equilibrium, and they can be used analyzing equilibrium phase diagrams.^[229]

There is an increasing tendency in preparative solid-state chemistry to employ compounds as educts (“precursors”), which produce the components of the desired compound in a highly reactive form by thermal degradation.^[119, 121] In the special case of single-source precursors, the constituent elements of the final compound are already in the right proportion dispersed on an atomic level, but still bonded

chemically.^[121, 230] In this instance, the product results from a thermal degradation of all the “volatile” constituents. In particularly fortuitous cases, the initial state of the system is as well defined as the final product. However, the many different heterogeneous, amorphous, and partly crystalline intermediary stages are very difficult to intercept and analyze. Thus, these synthesis methods defy a quantitative description to a large extent.

When designing a solid-state synthesis, as is true for every chemical synthesis, it is important to ensure that the thermodynamic precondition for all spontaneous processes holds, that is, that the free energy of the closed system decreases during each of the steps along the synthesis route. Of course, this issue is not a critical one as long as the final product corresponds to the global minimum of the system under consideration. If the desired compound is metastable, one either needs to employ starting compounds that are rich in excess energy and/or the reaction paths must be designed in such a way that by-products of a very low free enthalpy of formation are evolved. Another option consists in adding energy to the system from the outside, for example by electro- or photochemical methods. The minimal kinetic requirement for a reaction is the availability of a sufficiently efficient material transport. It has already been mentioned several times that as mild (thermal) conditions as possible should be used to achieve a certain degree of control over the reaction. This catalogue of tasks and issues involved in the planning of a synthesis route is usually addressed by today’s solid-state chemist for each problem individually in a mostly intuitive and empirical fashion. This approach is understandable, since all attempts to proceed in a more systematic rational way, which might, for example, include an active steering of the reaction process towards a pre-defined compound, would require a complete knowledge of the intermediate compounds and the barrier structure of the corresponding energy landscape for realistic thermodynamic conditions. Furthermore, a quantitative treatment of the transport processes during the reaction, as discussed above for interdiffusion and chemical transport, is at best feasible for model systems under the assumption that the necessary thermodynamic and kinetic data are available. Although one can reach some degree of insight for such isolated instances, a practical and generally applicable design of synthesis routes in solid-state chemistry is not yet within our reach.

5. High Mobility, Short Transport Distances: Reactions in the Solid-State with Minimal Thermal Activation

As discussed in Section 4.3, the second step necessary for a rational planning of syntheses, that is, the general unbiased development of a reaction path for the synthesis of a predicted compound that is capable of existence, cannot yet be taken with the theoretical methods available today. Thus we have not pursued such deductive approaches any further for the time being. Instead we have attempted to reproduce as closely as possible the “computational annealing” employed during structure prediction in the actual experiment. At the same

time we are trying to avoid the complications which are associated with an only macroscopic mixing of the educts and the subsequent need for a high thermal activation of the material transport. Since one cannot influence the elementary processes contributing to diffusion in solids, that is the local jumps of atoms, to a meaningful degree, we have concluded that one should instead attempt to reduce the distances across which the material has to be moved to a minimum, preferably to atomic distances. This goal can be achieved by generating a mixture of educts that contains the constituting elements randomly distributed on an atomic level.^[231, 232] If in addition the starting state exhibits the same composition as the desired crystalline product, one would not expect any large concentration gradients to develop in the course of the reaction that would require increased thermal activation for equilibration by an extended material transport.

The thermodynamic consequences, as in the Born–Haber cycle, of the use of educts that are distributed in an atomically disperse fashion, instead of macroscopic mixtures of the constituting components in their states under standard conditions, are an increase of the reaction energies by an amount that approximately corresponds to the atomization energies of the components. A comparison of the usual tabulated standard enthalpies of formation with such “atomical enthalpies of formation” can be quite instructive, since the latter show the intrinsic thermodynamic stabilities of chemical compounds, independent of the variations in the cohesive energies of the starting materials.^[233] Of course, this way of implementing a synthesis route for the realization of metastable solids meets a well-defined limit: If during the reaction no additional energy is added from the outside, only such metastable compounds will be accessible, which have a positive free enthalpy of formation that is smaller than the sum of the free energies of atomization of the components.

To implement this general approach experimentally, we have developed a vapor deposition method, where the desired components are first vaporized separately to form a gas of atoms in an ultra-high vacuum (UHV) chamber (Figure 9).^[231] These gas particles are then deposited simultaneously in a statistical distribution on a substrate. The evaporation sources are resistance-heated effusion cells and an electron-beam vaporizer together with a microwave plasma source for the dissociation/activation of the gases employed. One can mount a maximum number of five sources under an angle of 22° or 45° normal to the substrate. The substrate resides on a sample carrier, the temperature of which can be adjusted between 77 and 600 K. The sample carrier is part of a moveable transfer system, which is connected to the preparation chamber by a vacuum hatch. In this way, a transfer of the samples from the preparation chamber to, for example, a diffractometer or an exchange of samples through a glove box is possible while preserving both the cooling and the vacuum. In addition to the adjustment of the various sources the atmosphere in the chamber during the deposition is monitored using a mass spectrometer. The machine possesses a system of cryo-pumps, which creates a basic pressure of $< 1 \times 10^{-8}$ mbar, and allows pressures during processing in the range of $3\text{--}6 \times 10^{-5}$ mbar. Furthermore, it is possible to fill the evaporation sources with air- and humidity-sensitive substances through a transfer box.

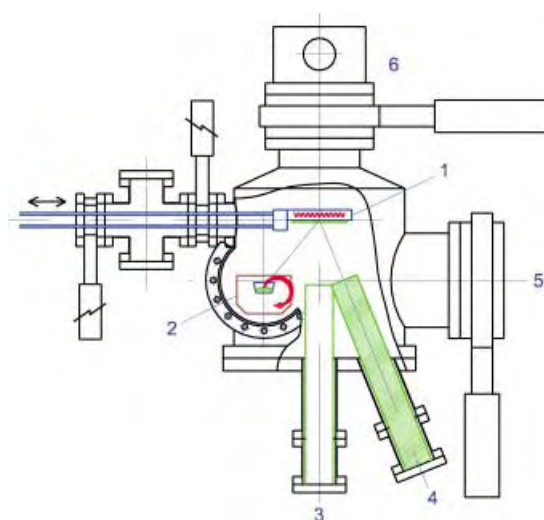


Figure 9. UHV-set up for the synthesis of solids from atomically disperse educt mixtures (preparation chamber including hatch to the movable transfer system). 1) Sample holder with sapphire substrate, integrated heating, and feed for LN₂, 2) electron-beam vaporizer, 3) effusion cell, 4) MW-plasma source, 5) gate valve to the cryo-pumps, 6) transferbox with gate valve.

We have checked the applicability of the basic concept and the functioning of the set-up in a number of case studies. From among these investigations, the results for the systems Ag/N/O, Ag/O, and Na/N are presented. In the first case, silver was deposited simultaneously with nitrogen and oxygen on a sapphire substrate cooled to 77 K.^[231] The educt mixture at this temperature is X-ray amorphous (Figure 10). On slowly

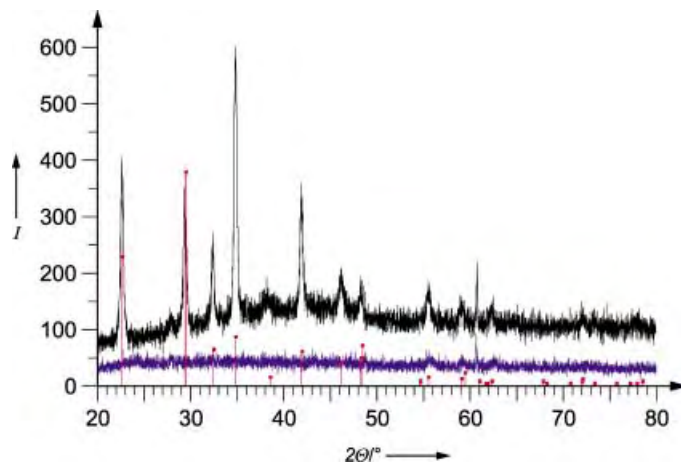


Figure 10. X-ray powder diffraction patterns of the educt mixture consisting of Ag, N, and O at 77 K (blue curve) and the reaction products after heating to room temperature (black), together with computed intensities for HT-AgNO₃ (red).

heating the sample to room temperature, reaction and crystallization occur. The diffractogram observed is, considering the temperatures employed, surprisingly well structured, and can clearly be assigned to the high-temperature phase of AgNO₃. If silver and oxygen are deposited in an analogous fashion on a sapphire substrate at room temperature, immediately a reaction to AgO occurs.^[231] However, in this instance the intensities of the Bragg reflections are

strongly affected by the preferred orientations of the crystallites. Similarly, in the case of sodium and nitrogen the components were transferred to the gas phase and simultaneously deposited in a random distribution on a cooled (77 K) substrate (sapphire).^[232] After heating to room temperature, the diffraction pattern shown in Figure 11 was collected. This result demonstrates that the route outlined above has enabled us to synthesize the compound Na_3N for the first time, a material that had been searched for over a long time and had even been claimed to be “not-capable-of-existence”. Its structure can clearly be assigned to the anti- ReO_3 type.

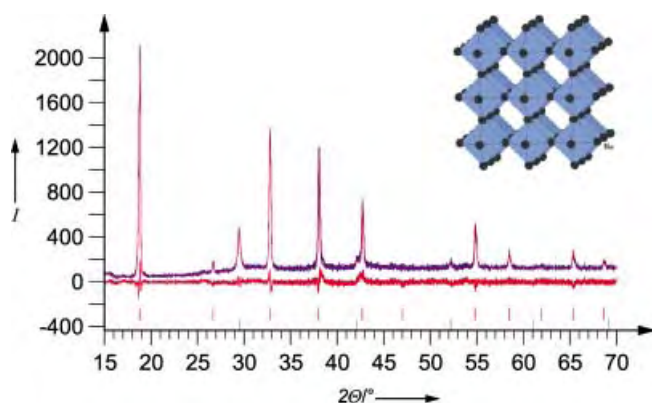


Figure 11. Powder diffraction pattern for Na_3N (Rietveld refinement) and structure candidate (anti- ReO_3 type).^[232]

These observations are quite unusual in several ways. In the context of the analysis presented here, one should surely highlight the unparalleled low thermal activation needed to transform the solid mixture of educts by a solid-state reaction into highly crystallized monophase products. Another remarkable fact is the straightforwardness, which is manifest in the synthesis of, for example, AgNO_3 from the elements, compared with the traditional synthesis of AgNO_3 (synthesis of ammonia, Ostwald-method for the production of nitric acid, dissolution of silver in nitric acid, crystallization). In particular the examples of AgO and Na_3N demonstrate the potential of the method for the synthesis of thermally extremely labile metastable compounds. Up to now, AgO has only been accessible by precipitation from aqueous solution^[234, 235] or by electrocrystallization.^[236] Of note is that Na_3N decomposes already at 360 K, and thus is unlikely to be accessible by conventional solid-state synthesis.

A crucial element for the ease with which the solid-state reactions described were able to proceed even below room temperature is definitely the extremely homogeneous and smooth distribution of the reactants in the initial mixture. The transport distances have been reduced to atomic length scales, and thus the notorious difficulties of a long-range transport of material in the solid can be circumvented. As a consequence, one can now perform chemical reactions in the solid phase under thermal conditions that are similarly mild as those usually employed in solution chemistry.

This novel set-up for solid-state syntheses appears to be universally applicable. Its particular advantages are reflected in the opportunity to experimentally reach especially high-lying and/or particularly flat minima of the energy landscapes

of chemical systems. This is an important partial success in our efforts to develop a rational and efficient solid-state synthesis. However, this approach still misses the mark in one decisive issue, the ability to generate a definite compound with a given structure in a completely intentional and controlled fashion.

Once one analyzes the results of the case studies described above, it becomes clear that the selection of the product phases actually produced from among the multitude of the possible ones is controlled by the speed of nucleation. Thus, following Ostwald's or Vollmer's rule, at high supersaturation first the modifications with the lowest density crystallize,^[237] that is, those for which with the smallest number of atoms the critical crystal size has been reached. In this way, one can easily understand, that a synthesis at low temperatures yields the high temperature phase of AgNO_3 , at first sight a paradoxical result. Similarly, for the case of Na_3N , for which theoretical investigations had predicted the most promising structure candidates,^[205] we did not find one of the modifications with the highest energies of cohesion. Instead, Na_3N was found in the anti- ReO_3 -type (see Figure 6^[238]), the modification with the lowest density. Thus, these observations place the focus on the initial step in the generation of crystalline phases, the formation of a crystal nucleus, when searching for the most important element in the control of a solid-state synthesis of a desired product.

In the widest sense one has to place the route we have taken to generate educt mixtures that are atomically disperse among the traditional PVD (physical vapor deposition) methods.^[239] Insights gained from these and the modern MBE (molecular beam epitaxy) methods^[240] have been crucial in the design and construction of our UHV-evaporation set-up. In general, PVD is mostly employed to evaporate chemical compounds and to deposit these as more or less thin films on a substrate.^[241] Interestingly enough, one had already noticed at the beginning of PVD-applications that the material deposited often was present in metastable modifications, in agreement with Vollmer's rule.^[242] The formation of metastable LiI in the Wurtzite type during PVD of LiI also serves as an example within this context.^[195]

In the examples discussed so far, the chemical nature of the evaporated and re-deposited materials remains unchanged. Chemical reactions of the substrate appeared during the development of MBE for the generation of semiconductors with well-defined structures. The constituting elements were deposited epitactically, monolayer after monolayer and converted into the desired semiconductor.^[243, 244] The synthetic relevance finally stepped into the foreground in the context of the creation of thin films of superconducting chevre phases from the elements.^[245, 246] To achieve this result, UHV-chambers were constructed, in which the constituent metals were evaporated, either in a H_2S atmosphere or together with elementary sulfur, and made to react on a heated substrate ($\sim 800^\circ\text{C}$). In similarly constructed evaporation chambers, D. C. Johnson et al. have deposited layers of metallic and non-metallic elements, and then induced a reaction.^[247–250] In a series of impressive studies they could show, how in this fashion novel, partly modulated layer structures could be built up,^[251, 252] where they paid special attention to the issue of nucleation and growth.^[253, 254] However, one should note that

the thickness of their layers approached macroscopic dimensions. This feature might explain, why the reaction temperatures necessary for their experiments were still in the range of 200–700 °C. In any case this difference to our approach cannot be related to the properties of the elements involved, in particular their diffusion coefficients, since these are, for metal ions, typically larger in chalcogenides and pnictides than in oxides.

6. Rational Synthesis Planning or High-Throughput Exploration?

The traditional experimental approach to the exploration of energy landscapes of chemical systems has in recent years been enriched by the addition of an attractive option. The modification consists mainly of the fact that solid-state syntheses are being performed in an automated and parallelized fashion, which results in a much higher throughput.^[25, 255] The set of compounds produced in this fashion is often denoted a “library”, a term that has been recently and justifiably challenged.^[256] The compounds synthesized in parallel can be tested for various structural, bonding, or materials properties of interest, by using appropriate probes. Since an “automated” generation of many different initial mixtures and their traditional reactions (only in parallel and thus more efficient) do not really justify the attribute “combinatorial”; at least in the field of solid-state synthesis, we prefer the alternative name “high-throughput method”. This approach has only been used for a few years, but it has already had substantial successes, in particular regarding the optimization of materials properties of already known compound families. Especially impressive applications have been results in the field of inorganic phosphorescent materials,^[257] ceramic superconductors,^[258] and heterogeneous catalysts.^[259, 260] There can be no doubt that a systematic use of high-throughput methods will raise the efficiency of solid-state and materials research. This is a welcome development, no matter whether the original motivation has been of an economic or academic nature. However, one must warn against an uncritical application of these methods. One can very easily overlook compounds capable of existence, while having a false sense of security because one has chosen a very fine resolution in composition space. Already the directing force of nucleus formation and selection will favor certain phases under given reaction conditions and suppress others. In addition, the synthesis of a specific solid compound usually requires individually optimized synthesis parameters (going beyond the composition of the initial mixture). Additional problems can result from using small sample sizes which can result in a non-negligible amount of interface and surface effects. Furthermore, some of the properties cannot be screened easily in parallel, necessitating a rather large screening effort.^[261] Finally, if one really wants to know which material is responsible for a certain effect, each sample has to be analyzed in detail (in the case of a new phase, one needs to determine its structure); in particular, its homogeneity has to be verified.

How does this increase in efficiency of exploring the energy landscape of chemical systems with experimental methods face up to the task of identifying all the compounds capable of existence? To answer this question, let us perform some crude estimates regarding the minimum number of syntheses required for such a task. Taking the number of reactive elements with sufficiently long-lived atomic nuclei to be 86, we find the number of chemical systems that need to be investigated (see Figure 12) to be the unimaginably high

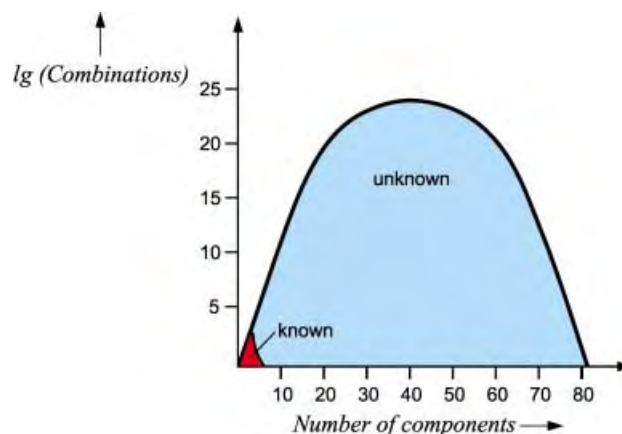


Figure 12. Dependence of the number of possible systems on the number of components; red: systems investigated up to now.

number of 2^{86} .^[262] From among these, today only the unary and nearly all binary ones have been investigated, a state of affairs that is not to be confused with “completely explored”. Of course, the total number of experiments to be performed depends on the resolution in parameter space one employs. But the number of compounds to be synthesized during a restriction-free exploration of our material world easily reaches $10^{80} - 10^{90}$ (Table 2). These gigantic numbers, comparable to the estimated number of atoms in the universe, do not lose anything of their power, if one were to exclude “obviously unproductive” element combinations. This would at most reduce the number of compounds by ten to perhaps twenty orders of magnitude.

Let us take as a specific example the high-temperature superconductor $\text{YBa}_2\text{Cu}_3\text{O}_{7-x}$, and investigate, how many samples need to be synthesized and tested, to definitely include this compound in the output of a high-throughput method. Even with the highly restrictive information that we are dealing with a quaternary oxide, where oxygen is to be offered in unlimited amounts, one would need to prepare about 10^{12} samples. Using a (today still very optimistic) throughput-rate of 10^5 samples per day, a systematic and unbiased, one might even say “mechanical”, search through the parameter space would take about 27 000 years.

The numerical examples given above demonstrate the overwhelming chemical variability that grows out of the comparatively small number of available elements. We feel that this is an essential characteristic of chemistry in general. At present, we have gained access only to a minute fraction of the possible chemical compounds, nearly infinitely less than the proverbial “tip of the iceberg”. This explains in a natural

Table 2. Considerations concerning the number of experiments needed to explore chemical systems by a high-throughput synthesis.

- Number of systems overall:^[a]

$$\sum_{n=0}^{86} \binom{86}{n} = 2^{86}$$

- Number of systems with n elements:^[a]

$$\binom{86}{n} = \frac{86!}{n!(86-n)!}$$

- Number of possible compositions of all elements:
–without variation of experimental conditions^[b]

$$\sum_{n=0}^{86} \binom{86}{n} I^n = (I+1)^{86}$$

–Including experimental conditions^[b,c]

$$(I+1)^{86} \cdot n_p \cdot n_T \cdot n_R \cdot n_A$$

- As comparison: total number of atoms in the universe: $\approx 10^{80}$

Case study: $\text{YBa}_2\text{Cu}_3\text{O}_{7-x}$

$n = 3$ ^[d], $I = 10$, $n_p = 10$, $n_T = 10$, $n_R = 10$, $n_A = 10$

N_{Exp} : Number of high-throughput experiments that need to be performed.

$N_{\text{Exp}} = \binom{86}{3} \cdot 10^3 \cdot 10 \cdot 10 \cdot 10 \cdot 10 \approx 10^{12}$ experiments

[a] Assumption: 86 elements available. [b] Assumption: Every element A in a system contributes i_A ($i_A = 1, \dots, I$) atoms to a formula unit. Number of compositions for n components: I^n . [c] Assumptions: n_p pressures, n_T temperatures, n_R reaction pathways, n_A machines available for high-throughput exploration. [d] Oxygen adjusts to the composition and the experimental conditions

way, why newly discovered compounds and unconventional structures are often experienced as “accidental” or “surprising”, which in reality means nothing else but that they cannot (yet) be placed into the general context of chemical compounds and structures based on our current level of understanding.

Thus, the answer to the question posed in the heading of this section is quite clear: Trying to rely only on high-throughput methods is clearly not the most efficient way to explore chemical systems. One needs to find reasonable criteria to restrict the parameter space under investigation. This can either occur on the basis of intuition and experience, or with the help of theoretical methods. For example, one might want to use our concept of the exploration of the landscape of chemical systems by global optimization to identify very promising regions in configuration and parameter space, or, subsequently, to check, whether one has overlooked important regions, for example, deep minima, within the space explored using high-throughput methods.

7. Outlook

We have presented a concept for the development of a rational planning of syntheses in solid-state chemistry. The foundation of our approach is the fact that the material world is represented on an energy landscape, which leads to a unified and consistent picture that allows us to include, in principle, all aspects of planning a rational synthesis route. At the current state of development, only parts of this approach have been implemented. Thus, in some ways, it still carries a visionary feeling. However, we do not consider our approach a utopian one, and we feel that each of the separate steps presented can be realized. And even though we are still far

away from a routine application of our concepts, wrestling with them yields many insights into conventional explorative solid-state chemistry. The competition between traditional methods and syntheses involving rational design will, in the end, be decided based on their usefulness in practice. But in both cases, this measure will reflect the efficiency in exploring the energy landscape, as seen in the number and novelty of new solid compounds compared to the effort required. Considering the productivity and output of current solid-state chemistry, it is obvious that rational synthesis planning will face a steep climb. However, we are convinced that with the passing of time, the scales will tip in its favor.

Indubitably, the path ahead is still quite long. The most likely goal to be reached in the nearer future appears to be the theoretical exploration of the energy landscape of chemical systems, that is, the prediction of compounds capable of existence. Currently, the most critical issue is the computation of the energy of a given configuration during the global optimization. This is not yet feasible with the desired accuracy and in an acceptable time for the relative large systems investigated. The weak point of the current implementation is the necessity to use simple empirical potentials, which tends to push the system towards a certain type of bonding. Even though this can often be estimated with good accuracy for many element combinations, such an approximation negates the stated purpose of an unbiased exploration of the configuration space. The most straightforward solution would be to employ *ab initio* quantum-mechanical energy calculations instead. Although there has been much progress in this respect,^[174, 263–266] the algorithms developed are still too slow. Their application does not yet allow a global exploration of configuration space of realistic systems within an acceptable length of time. In this respect, our hopes rest with further methodological advances and the not-yet-abating increase in computational power. Possible intermediary solutions might be the use of “learning” empirical potentials or a Pareto-optimization^[267] using as cost function a linear combination of energies computed according to different methods (corresponding, for example, to the three most important types of chemical bonding). However, it is doubtful, whether the ratio of computational effort to quality of the results might not be even more unfavorable than the one encountered when employing simplified Hartree–Fock or density-functional approaches. Nevertheless, we feel that our current two-step procedure, the global optimization with a very general two-body potential followed by a local refinement optimization with *ab initio* methods, is at the moment the most efficient solution to the problem. Of course, the danger of overlooking interesting structure candidates cannot be completely excluded. This aspect might gain in relevance once one tries to determine compounds capable of existence that possess only a very low kinetic stability.

The second step, the rational design of a feasible synthesis route, is not yet possible for most instances. The reason for this can be found to a large extent in the requirement that the modeling needs to take place under realistic p/T conditions and for systems with realistic sizes, which does not allow us to use several of our standard approximations. Furthermore, larger regions on extended configuration spaces need to be

analyzed, which include both the possible educts and the final product.^[268, 269] Thus, one still has to rely on procedures that are essentially of an exploratory nature. But here, too, significant improvements are possible as we could show with our approach to solid-state synthesis with minimal thermal activation.^[231, 232] In particular these mild reaction conditions open the door towards the synthesis of thermally labile (metastable) solids. If designed as a high-throughput method, this synthesis technique should be capable of being developed into an efficient explorative solid-state-synthesis method.

The progress made to date cannot hide the fact that up to now there does not yet exist an approach to the rational goal-oriented design of a synthetic route to a (predicted) novel solid. As our own results confirm, the route to such a methodology proceeds through a theoretical description and experimental control of formation of crystal nuclei.^[270–272] Going beyond the macroscopic, classical phenomenological description, first attempts to model nucleus formation on an atomic level have already been presented.^[273–275] Compared to these first steps, the tools available for an experimental control of this process are disappointingly rudimentary. Depending on the external conditions, spontaneous formation of crystal nuclei leads either to the crystallization of the thermodynamically stable phase or, according to Ostwald's rule, first to a modification with low density usually followed by (eventually a cascade of) phase transformations to the phase corresponding to the global minimum.

It is clear that both these routes will only lead to a small fraction of the (predicted) compounds capable of existence. One can influence the formation of nuclei by varying temperature, pressure, and supersaturation. However, with respect to the desired selectivity these are rather blunt instruments. Providing a seed in the most general interpretation can serve as a universal tool for the control of crystallization. In addition to adding a crystal seed of the desired compound—which assumes that such seeds are already available (see below)—using heterogeneous nucleation appears to be most useful. Particularly promising should be epitactic growth on a substrate, the lattice parameters and symmetry of which agree with those of a plane of the desired substance. Such a substrate could be used either as the macroscopic base for the initial mixture of educts during the atomically disperse vapor deposition, or as a very finely ground additive. But a fundamental advance would entail an effective control and steering of the homogeneous nucleation. Solving this problem requires us to set the external parameters (p , T , supersaturation) such that the critical size for nucleation is reached first for those nuclei belonging to the desired product. If one demands a rational approach in this respect, one will have to perform the corresponding modeling of nucleation for the desired compound as a function of the external parameters while including interface and matrix effects. These, and other conceivable approaches, which are based on a systematic building of the nucleus atom by atom with physical or chemical means, are quite reasonable, of course, but are today still far from being realizable.

When dealing with the many issues discussed in this Review, certain conclusions and ramifications are naturally impressed upon us, the discussion of which, however, would

exceed the limited range of the topic we have been trying to address. According to our ideas, all chemical compounds capable of existence (with a certain lifetime) are already present on the energy landscape, and are just waiting to be discovered. If one considers the fundamental importance of solid matter in the form of traditional and novel materials for the welfare of mankind, should one not then propose to start a systematic world-wide coordinated effort with the goal of tabulating all the compounds capable of existence? Reminding oneself of Lao-Tse's teachings,^[1] the size of such an enterprise should not scare us. It would be comparable to the development of the botanical and zoological classification in classical biology or, even more, the exemplary "Human Genome Project", which has succeeded in fully deciphering the human genetic information.

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The Structures of Integrins and Integrin – Ligand Complexes: Implications for Drug Design and Signal Transduction

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Integrins are pivotal proteins in cell–cell adhesion, signaling and apoptosis. These properties render them attractive targets for drugs, especially those involved in cancer treatment. Recently, the structures of the extracellular domains of one of the integrin subtypes was solved with X-ray crystallography in the free form as well as bound to a ligand. These structures in combination with NMR spectroscopic data, electron microscopy images, and molecular modeling provide deeper insight into the mechanism of integrin-mediated signal transduction. The structures make structure-based rational drug design possible and are certainly hallmarks in integrin research.

communication which are connected to many regulatory phenomena. They can interact with the extracellular matrix as well as with proteins of the same cell, for example, the urokinase receptor uPAR. Furthermore they are involved in many common diseases. One major reason for the interest of researchers in pharmaceutical companies and academia alike is the fact that certain classes of integrins are overexpressed in tumor cells, rendering them attractive antitumor targets.^[3, 4] Herein we describe how structural information on integrins can shift drug design attempts from ligand-based rational design to protein-based rational design, and on how different techniques, namely biochemical investigations, X-ray diffraction, and NMR spectroscopy in combination with electron microscopy and molecular modeling provide new insight into signal transduction by integrins.

1. Introduction

In the postgenomic era it has become a common approach for drug development to specifically block the function of certain previously identified key proteins in signal pathways. Membrane-spanning receptors such as G protein-coupled receptors (GPCR), ion channels or integrins constitute the majority of drug targets. The biggest dilemma in rational drug design for these kinds of targets is the lack of sufficient high-resolution structural information of the involved proteins. A number of recent structural studies on integrins shed new light on the background of ligand binding and signal transduction of this highly important class of proteins.

Integrins are involved in a large number of fundamental cellular processes such as cell-matrix adhesion, differentiation, proliferation, apoptosis (natural cell death), and stress response.^[1] They couple intracellular signals with extracellular responses and vice versa. Integrins consist of two noncovalently bound subunits, an α and a β subunit. Different subunit combinations confer different specificities for extracellular ligands.

A large number of pathways have been connected with integrin function.^[2] Integrins are pivotal proteins in cell–cell

2. Structure of the Extracellular Domains of $\alpha_v\beta_3$ Integrins

Integrins are heterodimeric receptors that are composed of large extracellular domains, one transmembrane (TM) helix, and small intracellular domains per subunit.^[5] Recently, the structure of the extracellular domains of $\alpha_v\beta_3$ has been solved in a pioneering work by Xiong et al.^[6] In accordance with earlier electron-microscopy (EM) work,^[7] it has been shown that integrins consist of an ovoid head and two linear stalk regions. In contrast to the EM studies, these tails are severely bent at defined regions (Figure 1, left). This flexibility might be a crystallization artifact or related to integrin function. As the head groups of integrins have been identified as the major ligand-binding regions, their structure is of primary interest for drug design (Figure 1, right).

The head domain of the α subunit consists of a seven-bladed β propeller; each blade is formed by a four-stranded antiparallel β sheet (Figure 2, top). The β A domain of the β subunit assumes a Rossmann fold, which is also found in G β domains and α A domains of integrins. Helices surround a central six-stranded β sheet (Figure 2, middle). The central interfacial residue appears to be the Arg261 of the β subunit, which inserts into the β propeller of the α subunit and stabilizes the complex by cation– π interactions (Figure 2, bottom).

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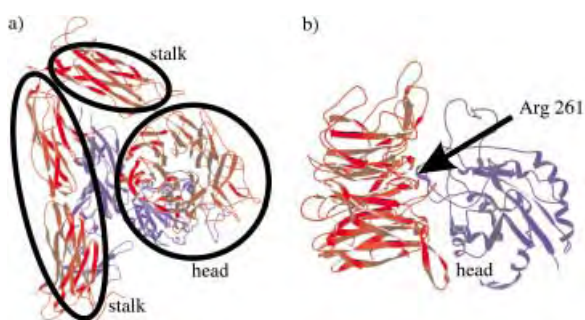


Figure 1. Crystal structure of the extracellular domains of integrin $\alpha_v\beta_3$. a) The α subunit is shown in red, the β subunit in blue. A kink in the stalk regions can be observed, which is not in accordance with EM images. b) Head groups: In accordance with EM images, the head group of $\alpha_v\beta_3$ has an ovoid form. A tight interface is formed, with (β)-Arg261 inserting into the β propeller of the α subunit.

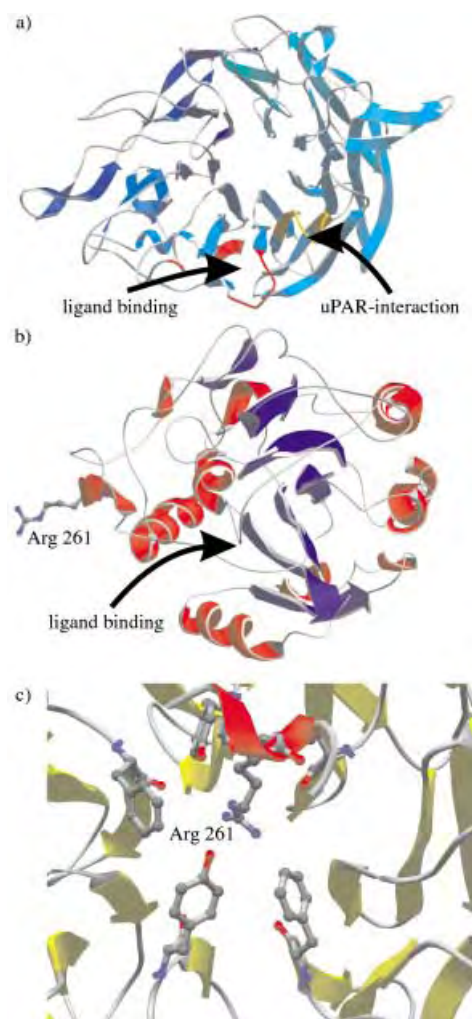


Figure 2. The interface of the head groups. a) The β propeller of the α subunit. The N-terminal domain of the α subunit forms a seven-bladed β propeller. The loops that are affected by ligand binding or by interactions with the urokinase receptor uPAR (in the case of $\alpha_3\beta_2$) are colored red and orange, respectively. b) The βA domain of the β subunit. Arg261 inserts into the β propeller of the α subunit. Ligand binding occurs close to Arg261. c) Cation- π interactions between Arg261 of β_3 (red) and surrounding aromatic residues of α_v (yellow) stabilize the head-group interactions. Cation- π interactions are ideally suited to fine tune protein-protein interfaces: Slight changes in the position of the involved residues can render these interactions repulsive, inducing large conformational changes.

3. Structure of the Integrin-Ligand Complex

According to an X-ray structure analysis of the integrin ligand complex,^[9] the overall structure does not change very much after binding of c(-RGDf[NMe]V-)^[8] as ligand. This might be caused by crystal contacts, which inhibit large movements. The root-mean-square deviation between the head groups of the free and complexed form is smaller than 1 Å. The α subunit does not change; the main changes are at the β subunit close to the ligand-binding site. A previously unoccupied MIDAS region (MIDAS = metal-ion-dependent adhesion site) now becomes occupied, and a loop nearby shifts towards the α subunit, allowing interactions of the ligand with both subunits. The aspartic acid residue of the RGD ligand binds to the metal ion in the MIDAS region. The only residue of the ligand that is in contact with the α subunit is the arginine, which binds to a region of negative charge in α_v .

An unusual feature of the ligand-binding site is that essentially no hydrophobic interactions can be observed (Figure 3, top). Only D-Phe of c(-RGDf[NMe]V-) is involved in some hydrophobic interactions. The central glycine residue lies directly on the integrin surface and might also add to the stability of the complex. Any substitution of the glycine unit (e.g., by Ala or D-Ala) destroys $\alpha_v\beta_3$ -binding activity.^[10] The main interactions are between the positively charged arginine and negatively charged side chains in the α subunit and between the anionic aspartic acid and the metal cation in the MIDAS region of the β subunit. Further stabilization occurs through hydrogen bonds between the NH group of Gly-Asp amide bond and the carbonyl oxygen atom of (β)-R216 as well as between the Asp side chain and the NH group of (β)-N215 (Figure 3, bottom). This confirms earlier observations

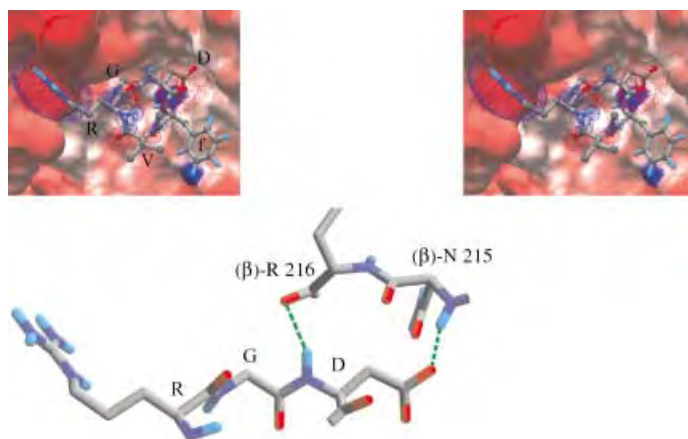


Figure 3. Structure of the crystalline complex. Top: Stereoview. Interactions of c(-RGDf[NMe]V-) with $\alpha_v\beta_3$. The ligand appears to interact mainly through electrostatic forces. R and D form a charged clamp that attaches to regions with opposite charges in the protein: Asp interacts with a metal cation in the β subunit, Arg with two Asp of the α subunit. Gly forms close contact with the proteins surface, D-Phe is involved in hydrophobic interactions. Neither the N-methyl moiety nor the side chain of (NMe)V form any contact with the protein. Bottom: The interaction is further stabilized by hydrogen bonds involving the backbone of the protein and the ligand. The NH of Asp forms a hydrogen bond with the oxygen atom of the carboxy group of (β)-Arg261, whereas the Asp side chain not only complexes the metal ion in the MIDAS region, but furthermore forms a hydrogen bond with (β)-N215. MIDAS = metal-ion-dependent adhesion site

on retro-inverso peptides, which demonstrated the participation of the ligand backbone in binding.^[11]

The cleft in which the ligand resides is rather shallow, and large parts of the ligand make virtually no contact with the protein. It seems as if the Asp and Arg residues of the RGD ligand act as an electrostatic clamp, attaching to charged regions of the protein; usually ligands tend to attach to hydrophobic pockets with large interfaces determined by van der Waals interactions.

4. Docking Studies on Free $\alpha_v\beta_3$ Integrin

Prior to the publication of the X-ray crystal structure of the integrin complex, docking studies starting from the crystal structure of the free $\alpha_v\beta_3$ integrin tried to predict the conformational changes accompanying the ligand-binding event.^[12] The docking studies were based on the following considerations: in extensive ligand-based rational design studies (the so-called “spatial screening”) selectivity between different α as well as β subtypes of integrins was achieved.^[13] Although initially the focus was on discriminating between $\alpha_v\beta_3$ and $\alpha_{IIb}\beta_3$, later studies also achieved specificity for $\alpha_v\beta_3$, $\alpha_v\beta_5$, and $\alpha_v\beta_6$.^[14] It was further possible to distinguish between the non-RGD-binding integrins $\alpha_4\beta_1$ and $\alpha_4\beta_7$.^[15] This implies that the ligands interact with both subunits.

It was postulated earlier that Ca^{2+} bound to the MIDAS region of the α_A domain of the integrin subunit β_3 interacts with the aspartic acid residue of RGD peptides and the receptor.^[5, 16, 17] Surprisingly, in the crystal structure of free $\alpha_v\beta_3$ the MIDAS region of α_A is not populated by a metal ion, as opposed to the neighboring adMIDAS region. Further studies showed that the N-terminal β propeller of the α subunits are also involved in the binding process of ligands and that the arginine residue of RGD binds in this region.^[18, 19] Although the distance between the arginine and aspartic acid residues in cyclic RGD peptides is about 13 Å,^[9] the shortest distance between the Ca^{2+} bound to the adMIDAS region and the β propeller of the α_v subunit is in the order of 17 Å. Superposition of the β_A domain of β_3 and of the I domain of integrin α_2 reveals a high structural similarity between these two structures (Figure 4).^[12] Analysis of the structures of the free I domain of α_2 and the I domain in complex with collagen shows that the binding of the ligand results in a movement of the Ca^{2+} ion and the MIDAS region of the I domain.^[20] Assuming a similar structural change in β_3 as a working hypothesis enabled similar structural changes in β_3 to be modeled and an RGD mimetic to be docked to the modeled receptor conformation prior to the publication of the structure of the receptor complex with a cyclic RGD peptide.

5. Comparison of the Results of Docking Studies with Those of an X-ray Crystal Structure Analysis of Ligand-Bound Integrin

A comparison between the predicted and the experimentally observed protein and ligand conformation underlines the power of docking studies with human intervention. The trend



Figure 4. Superposition of the I domain of the collagen-associated integrin subunit α_2 (grey) with the β_A domain of the integrin subunit β_3 (green). The respective metal ions are depicted as spheres; the grey sphere represents the metal ion bound to the MIDAS region of α_2 , the green sphere the ion bound to the adMIDAS region of β_3 . The root-mean-square deviation of the backbone of the superimposed residues is 1.6 Å despite the large difference in metal position.

in the loop change has been predicted correctly, though the model overestimated the structural change (Figure 5, left). The ligand-binding metal ion is nearly at the correct position. As the main interaction of the aspartic acid of the ligand with the integrin takes place through this metal ion, the correct

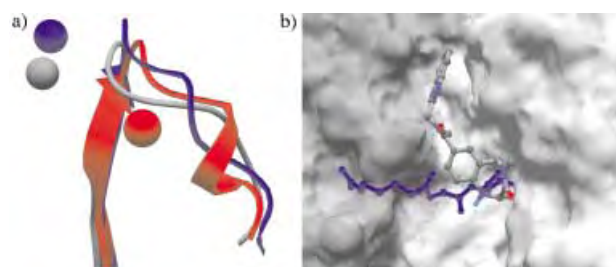


Figure 5. Structural comparison between experimentally determined and calculated structures. a) Comparison of the loop structure and metal position between the free (red) conformation of $\alpha_v\beta_3$, the ligand-bound (blue) conformation, and the modeled (grey) conformation. The main trend in loop change was predicted correctly, although the model overestimates the structural changes. The positions of the metal ions in the modeled form and the ligand-bound form are very similar. b) Comparison of the RGD orientation of the ligand in the crystal and the orientation of the docked ligand. Whereas the carboxy group is positioned nearly identically, the arginine moiety points to a different direction than the arginine mimetic of the docked ligand. This might be either caused by errors in the docking procedure or by the different nature of the ligand.

positioning of this ion leads to a correct orientation of the acid moiety of the docked peptidomimetic. The arginine mimetic in the bound ligand adopts a different orientation than the Arg in the crystal (Figure 5, right). This might either be a result of the different nature of the ligand or of errors in the docking procedure. Interestingly, the errors in the loop conformation of the modeled integrin structure do not lead to an incorrect orientation of the acid moiety, as only the position of the metal ion seems to be important. This corroborates the above-mentioned assumption that in the

case of RGD peptides the ligand protein interactions are determined by electrostatic interactions.

The differences in the ligand orientation resulting from both studies stress that an experimentally determined structure of the complex with a ligand is essential for rational drug design, especially if conformational changes upon ligand binding are expected to occur. Purely computational studies on the other hand can model trends in conformational changes correctly and can identify ligand-binding regions even in these modeled structures. But the results from these studies have to be regarded as a first approximation.

6. From Ligand-Based Design to Protein-Based Rational Drug Design

Extensive screening studies with cyclic RGD peptides without the knowledge of the protein structure have led to the development of superactive and selective RGD-based cyclic peptides.^[21, 22] With the structure of the ligand-bound integrin now available, these results can be interpreted in structural terms, especially as many of the synthesized peptides have been characterized by NMR spectroscopy.

The backbone conformation of the ligand in the crystals of the ligand–integrin complex^[9] and in solution determined by NMR spectroscopy in water^[23] are very similar (Figure 6, top); particularly the crucial distances between the C_{α} atoms

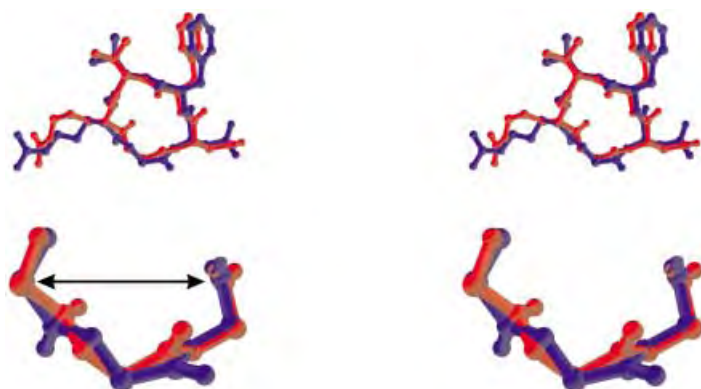


Figure 6. Stereoview of the conformation of c(-RGDf[NMe]V-) bound to the protein (red) and in the free state in aqueous solution (blue). The conformations are identical within the experimental error of the two structures. Especially the crucial C_{α} distance does not alter upon binding.

of the Arg and Asp residues are identical (Figure 6, bottom).^[24, 25] As the X-ray structure is only refined at 3.1-Å resolution, a detailed discussion of the differences in the two structures would not be meaningful. This demonstrates the power of NMR spectroscopy in the determination of the structures of conformationally restricted cyclic peptides in solution^[26] without the danger of crystal artifacts. It furthermore stresses the validity of the ligand-based design strategy: one goal is the creation of a rigid scaffold that does not change the conformation upon binding to the receptor. A rigid scaffold has two key advantages: the ligand always adopts the correct conformation, thus there is no equilibrium between different conformations, which would slow down the ligand

binding, and the entropic cost is minimized.^[26] If bound water is displaced, as may well be the case in a predominantly charged ligand-binding site, binding of ligand might actually be enhanced by an entropy gain.

Screening of different side chains at the Val and D-Phe positions of c(-RGDf[NMe]V-) revealed that in the case of $\alpha_3\beta_3$, Val can be replaced by many moieties of variable size.^[10] In the crystal, Val does not make any contact with the protein. Substitution of D-Phe by D-Trp increases the binding affinity, whereas D-Pro disables binding.^[10] Superposing the NMR-derived structures of the respective RGD peptides with the X-ray crystal structure now reveals that D-Trp enlarges the hydrophobic interaction, whereas *cyclo*-RGDpV cannot bind to the protein in a similar way without causing collisions between the D-Pro side chain and the integrin (Figure 7, top).

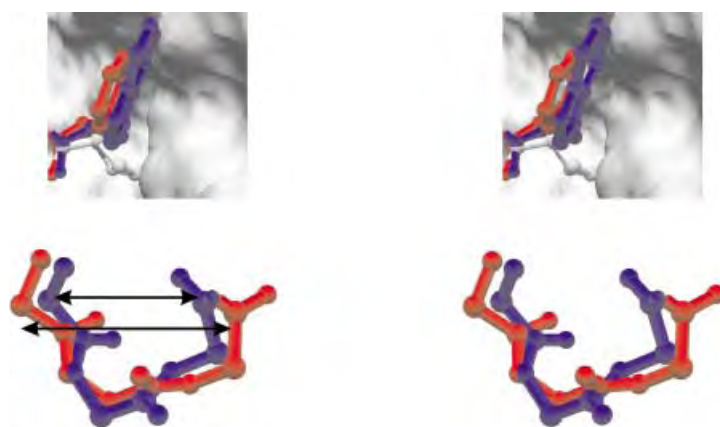


Figure 7. Effect of substitution on binding (stereoview). Top: Substitution of D-Phe (red) with D-Trp (blue) increases binding, but substitution of D-Phe with D-Pro (white) eliminates binding. This can now be easily explained in structural terms: whereas D-Trp increases the hydrophobic interaction, D-Pro overlaps with the protein (grey surface). Bottom: Effect of Methylation; in the nonmethylated form (blue) the C_{α} distance is shorter than in the methylated form (red).

N-Methylation of Val increases the binding affinity approximately fourfold. A comparison of the conformation of c(-RGDfV-)^[27] and c(-RGDf[NMe]V-) shows that the conformation is altered; the distance between the C_{α} atoms of Arg and Asp is shorter in the *N*-methylated than in the nonmethylated ligand (Figure 7, bottom).

7. Specificity of Interaction

As the only residue that is in contact with the α subunit is Arg, subunit specificity between different α subunits can only be achieved by different orientations of this side chain relative to the aspartic acid residue, by variations of the arginine moiety, or by secondary effects, for example, structural changes in the β subunit induced by different α subunits. Ligand-design studies have shown an involvement of Arg in subunit specificity. On the one hand, it was demonstrated that replacing Arg by Lys leads to a loss in binding to $\alpha_3\beta_3$, but not to $\alpha_{IIb}\beta_3$. On the other hand, the guanidinium group of the arginine residue can be substituted with aminopyridine and

other Arg mimetics without loss of binding to $\alpha_v\beta_3$, whereas the same substitution is not tolerated with $\alpha_{IIb}\beta_3$ ^[14]. These data led to the basic assumption that Arg is bound side-on in $\alpha_v\beta_3$, but end-on in $\alpha_{IIb}\beta_3$. Indeed, the X-ray crystal structure reveals the validity of this assumption: Asp218 shows a side-on interaction with Arg; further stabilization occurs through Asp150 (Figure 8a).

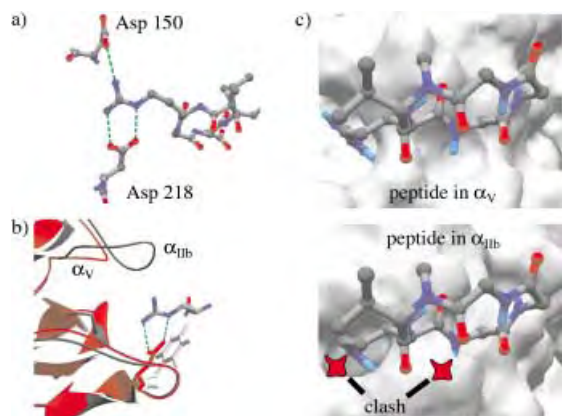


Figure 8. Comparison between $\alpha_v\beta_3$ and $\alpha_{IIb}\beta_3$. a) Binding of Arg: the Arg of the c(-RGDf[NMe]V-) is stabilized mainly by a side-on interaction of Asp218 of the α -subunit, in combination with an end-on interaction with Asp150 of the α subunit. b) A homology model of α_{IIb} superimposed on α_v reveals, that (α_v)-Asp218 is not conserved among the integrins. The corresponding residue is a Phe in α_{IIb} , rendering a side-on stabilization impossible. The residue which corresponds to Asp150 is a Glu, enabling an end-on interaction. The respective loop is also not conserved in the two integrins: in α_{IIb} (grey) the loop is longer, blocking the binding pocket. c) Whereas in α_v the peptide can insert the Arg into a negatively charged pocket of the protein (top), this pocket is much smaller for α_{IIb} (bottom), inducing an overlap between Arg and the protein. Further clashes between Gly and α_{IIb} increase the specificity of this ligand for α_v .

Sequence alignment shows that Phe231 of α_{IIb} corresponds to Asp218 of α_v . α_{IIb} -Phe231 cannot stabilize the Arg of the RGD ligand by side-on binding (Figure 8b). The residue that corresponds α_v -Asp150 is α_{IIb} -Glu157, which might serve as an end-on binding partner for Lys. An homology model of α_{IIb} (unpublished results) superimposed on α_v reveals that the α_v -specific RGD ligand is not suited to bind α_{IIb} in the same orientation as in α_v . The loop at the C terminus of α_v – Asp150 or α_{IIb} – Glu157 is not conserved between the two integrin subtypes. The longer loop of α_{IIb} closes the pocket in which c(-RGDf[NMe]V-) binds to α_v . Further steric clashes occur between G in RGD and the surface of α_{IIb} (Figure 8C). The X-ray crystal structure can thus not only rationalize different binding affinities of RGD-based ligands to $\alpha_v\beta_3$, but it can also help to understand different subtype specificities.

8. Models of Signal Transduction

Electron-microscopy (EM) images have led to the conclusion that the structural changes observed in ligand binding are not the final answer to questions regarding signal transduction. It has been shown in a number of studies that major structural rearrangements occur after the ligand-binding event^[5, 28–32] which are not seen in the crystal structures of

the extracellular domains. Depending on the nature of the experiments, two models of signal transduction have been developed and further refined (Figure 9).^[28, 31] Both models

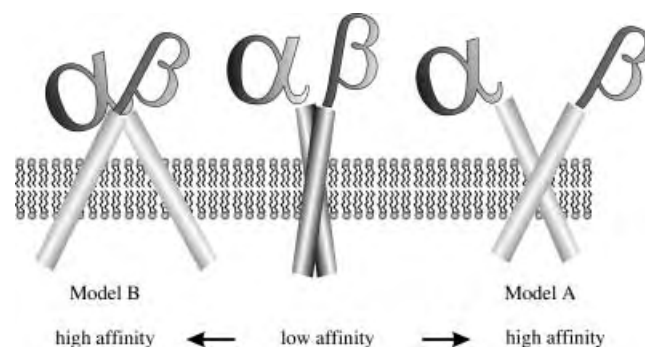


Figure 9. Two models for signal transduction by integrins. Whereas in Model A (right) the TM parts of the integrin subunits stay associated, in Model B (left) the hinge region is closer to the extracellular head group and the TM region is separated.

show that a scissorlike movement takes place, but they differ in the location of the hinge region. Whereas in the one model (model A) the hinge region is located in the membrane, the other model (model B) postulates a hinge region close to the head groups of the integrin. In model A the head groups dissociate after ligand binding, whereas in model B they remain associated. Recently model B has been refined and information has been incorporated from the X-ray crystal structure and further NMR spectroscopic studies of the stalk domains. Now a combination of a scissorlike opening of the kinked integrin structure has been proposed (Figure 10).^[33] This model would explain

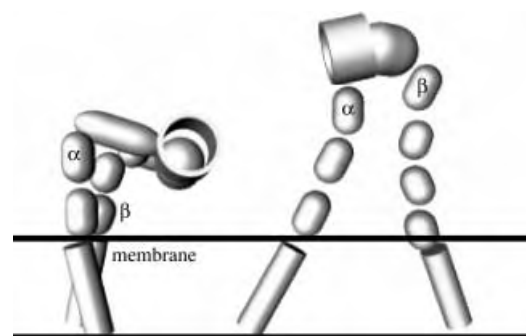


Figure 10. Switchblade-like opening of integrins. This model of signal transduction has been derived by a combination of an analysis of the X-ray crystal structure, EM pictures, and NMR spectroscopic experiments of the stalk region of integrins. It is also in agreement with sedimentation experiments.

sedimentation experiments, which demonstrate an enlargement of the hydrodynamic radius of the integrin after ligand binding. These sedimentation data are also in accordance with the model with dissociating head groups. The available EM data are contradictory and do not allow a clear distinction between the two models. There is evidence for both models.^[7, 28, 34–37]

Whereas model A was derived from whole integrins, model B used a construct in which the activation step consisted of the cleavage of one of the TM domains from the integrin. Although it is known that cleavage of the TM domains does activate the integrin, the removal of the structural restraints provided by the membrane might possibly affect the validity of the model. It has been shown by previous EM investigations that cleavage of the TM domains does not lead to a dissociation of the head groups,^[38] whereas addition of ligand does.^[7, 28] On the other hand, there are many investigations in which dissociation of the head groups has not been described.^[34]

Biochemical studies demonstrated recently that the activation process is not a two-step, but rather a multistep process, which most probably consists of three states.^[39, 40] This is corroborated by extensive computational studies of the TM domains of a large number of different integrin subtypes.^[41] Two conformations (a high- and a low-affinity conformation) of the TM regions have been identified based on the calculations in combination with experimental data. The high-affinity conformation of integrins is similar to the structure of glycophorin A,^[42] a homodimeric glycoprotein.

A calculated pathway between these two conformations revealed the existence of a third state and a rather complex movement of the helices during the transition. The activating movement is a rotation of the helix of the α subunit; the dissociation is accompanied by a back rotation of the α subunit to approximately the initial rotation angle, by an increase in the tilt angle between the helices and by a rotation of the β subunit. How these TM movements are translated to movements of the head groups is not clear. It has been postulated that this newly introduced intermediate is an activated state, which corresponds to the crystal structure without the TM and intracellular domains.^[41] The crystal structure should represent an activated form for a variety of reasons:

- 1) The TM and intracellular domains are missing, which has been shown to render the integrin active.^[5]
- 2) The substitution of Ca^{2+} by Mg^{2+} ions, which also activates the integrin, does not change the structure.^[5, 16, 43]
- 3) The structural changes after ligand binding are minor; nevertheless the head groups are still associated.

These observations corroborate the conclusion drawn from the computational studies that activation does not dissociate the head groups, but rather alters their relative orientation. Although the computational studies are in agreement with a scissorlike movement of the two subunits, the conformational change of the TM domains might also induce a rearrangement of disulfide bridges in the stalk region, which would be in accordance with the switchbladellike opening model.

A possible mechanism of dissociation of the head groups after ligand binding involves the central residue at the α/β interface, the Arg261 of the β subunit.^[6] Two loops that alter their conformation upon ligand binding are close to (β)-Arg261. (β)-Arg261 inserts into the β propeller of the α subunit. It is surrounded by aromatic residues of the β propeller domain of α_v (Figure 2). Thus, cation- π interactions should contribute to the stabilization of the α/β interface.^[6] A slight change in the position of (β)-Arg261

induced by allosteric rearrangement caused by ligand binding can lead to repulsive cation- π interactions.^[44] This might initiate the dissociation of the head groups. The dissociation event may either not take place if the ligands are cyclic RGD peptides, or it might be inhibited by the crystallization or soaking conditions. It is not yet clear where the RGD peptide binds after dissociation of the head groups. One possible mechanism would be that Arg of the RGD peptide replaces (β)-Arg261 and binds to the β -propeller domain, thus inhibiting a reassociation of the head groups.

9. Clustering

Transduction of signals into the cell after ligand binding is accompanied by clustering of integrins. This effect is partially regulated by interactions of integrins with other membrane-spanning proteins such as calveolin, the urokinase receptor (uPAR = CD87), and others.^[45–48] Whether integrins interact directly in the clustering process or are only connected through their ligands or through other proteins to the cell surface is unknown. Recently, a short peptide sequence in the β -propeller domain of the α_3 subunit has been identified which inhibits $\alpha_3\beta_2$ -uPAR interactions (Figure 2).^[45] The corresponding loop is occluded by the β subunit in the crystal structure. To be involved in integrin-uPAR interaction, dissociation of the head groups has to occur to expose the loop, provided that the $\alpha_3\beta_2$ integrin adopts a similar structure as $\alpha_v\beta_3$ (Figure 11). These experiments in connection with the structural data available strongly corroborate the notion that the integrin head groups have to dissociate for clustering to occur. Crosslinks with other membrane-spanning receptors such as the human growth factor has also been observed.^[49, 50]

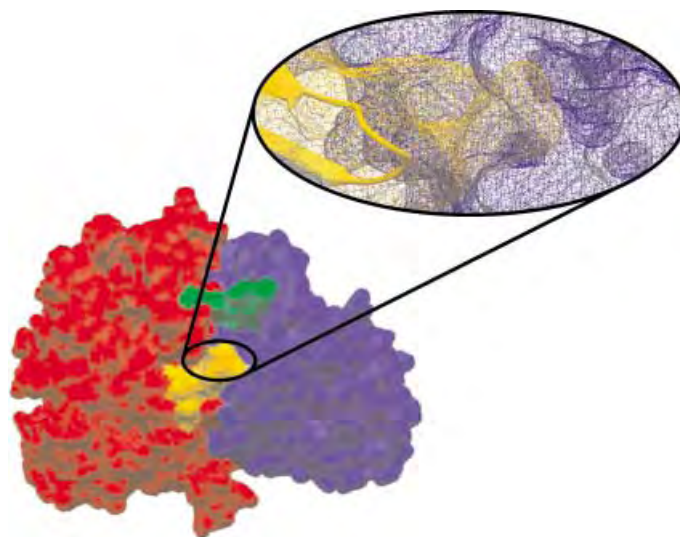


Figure 11. Interaction of integrins with uPAR. A loop located in the β propeller domain of α_3 has been identified to interact with uPAR. The β propeller domain of the α subunit is shown in red, with the surface of the bound ligand shown in green. The surface of the β subunit is shown in blue. The corresponding loop that interacts with uPAR (orange) is close to the ligand (green) and partially occluded by the β -subunit (blue surface and inset). To interact with uPAR, the head groups of the respective integrin have to dissociate.

Even direct interactions between integrins can in principle occur at all domains. One model for these direct interactions is that one domain of the dissociated head groups of one integrin dimer make place for the respective counterpart of another integrin dimer. But the studies on $\alpha_2\beta_3$ -uPAR interactions rather imply that the head groups serve as interaction regions for other membrane-associated receptors, which in turn induce clustering of integrins. EM images imply a possible mechanism in which the stalk regions of integrins may interact in the absence of other proteins.^[37]

10. Emerging Themes in Signal Transduction

Closer investigation of the signal transduction mechanism of integrins and the interplay of G proteins and G-coupled proteins reveal conceptual similarities, which might indicate a common general mechanism for signal transduction events (Figure 12). In both cases an inactive conformation exists,

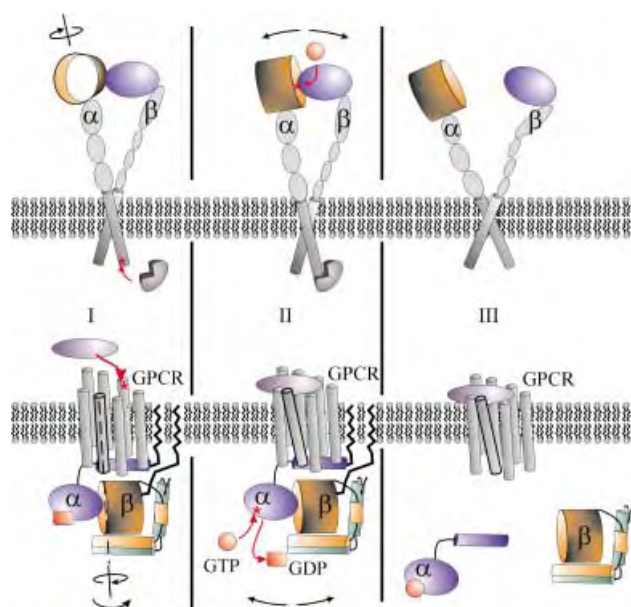


Figure 12. Conceptual similarity of signal transduction with integrins and G-coupled receptors. In both cases a ligand induces a reorientation of the TM helices (panel I). This conformational change is transduced to another ligand binding domain at the other side of the membrane, allowing binding or exchange of ligand (panel II). Binding of the second ligand induces separation of two domains close to the binding site (panel III). This separation can be the starting point for further signal cascades.

which is activated by intra- or extracellular signals. In the case of integrins, this activation appears to be a rotation of one of the subunits, as concluded from computational studies.^[41] In G-coupled proteins, the activation step also includes the structural reorientation of helices (Figure 12, I).^[51–57]

The conformational change is followed in the case of integrins by the binding of extracellular ligands,^[5] in the case of G-coupled receptors it leads to replacement of GDP with GTP (Figure 12, II).

Binding of ligands or replacement of GDP with GTP induces further structural changes, which in both cases involve

the dissociation of proteins or protein domains: In integrin signal transduction, the head groups dissociate,^[28] whereas in G proteins, the α subunits dissociate from the $\beta\gamma$ complex (Figure 12, III).^[58] In this case, the conceptual similarity is reflected by a striking structural similarity: the interfaces of the interaction domains resemble each other very much.^[6, 59, 60] Cation– π interactions stabilize the interface for $\alpha_v\beta_3$, but not for G proteins. For G proteins, a network of salt bridges leads to strong interactions. Cation– π interactions are very well-suited to regulate the affinity of two domains for each other: small structural changes can render the attractive force repulsive, thus leading to dissociation of the respective domains. Dissociation of the domains is the starting point for a cascade of further events. For integrins, the final step in signal transduction is comprised of interaction with other receptors and cluster formation.^[50] The common theme which emerges is a mechanism that comprises three states (inactive, activated, dissociated), possibly followed by clustering.

11. Conclusion and Outlook

The recent studies of integrin $\alpha_v\beta_3$ and other integrins have led to a new understanding of ligand binding to integrins and of signal transduction by integrins. Nevertheless, many questions regarding further structural changes after ligand binding and dynamical processes, for example, interactions with further proteins and cluster formation remain unanswered. The structures of integrin $\alpha_v\beta_3$ in the free form as well as in complex with a cyclic RGD ligand are certainly hallmarks in integrin research. They will stimulate research both by medicinal chemists as well as by biophysicists and biochemists. The aim of the different research will be to develop highly potent integrin antagonists by rational protein-structure-based design and to improve the understanding of signal transduction and cell adhesion mediated by integrins.

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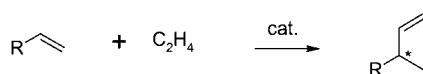
Asymmetric Hydrovinylation: New Perspectives through Use of Modular Ligand Systems**

Lukas J. Gooßen*

Asymmetric Hydrovinylation of Olefins

Reaction steps in which readily accessible synthetic building blocks are regio- and enantioselectively incorporated into complex molecular frameworks without producing side products are essential for the development of modern atom-economical syntheses.^[1] Prominent examples that fulfil these requirements are asymmetric hydrogenation, hydroformylation, and Diels–Alder reactions. In contrast, the hydrovinylation of olefins has received much less attention over the last few years, although the synthetic potential of this reaction is comparable.^[2]

In 1953 Ziegler et al. observed that the buildup of polyethylene on alkylaluminum compounds is suppressed when traces of nickel are present in the reaction mixture, which results in the formation of 1-butene (“nickel effect”).^[3] Wilke et al. reported in 1963 the selective dimerization of propylene using nickel–phosphane catalysts and found that the product distribution is strongly dependent on the phosphane ligand employed.^[4] When analogous reactions of mixtures of two different olefins (e.g. ethylene and norbornene) were carried out in the presence of certain nickel–phosphane catalysts, highly selective heterocodimerization was achieved, in this case to give 2-*exo*-vinylnorbornane.^[5] This represented the birth of a new reaction, which has come to be known as hydrovinylation: formally, a hydrogen atom and a vinyl group are added to an olefin (Scheme 1).

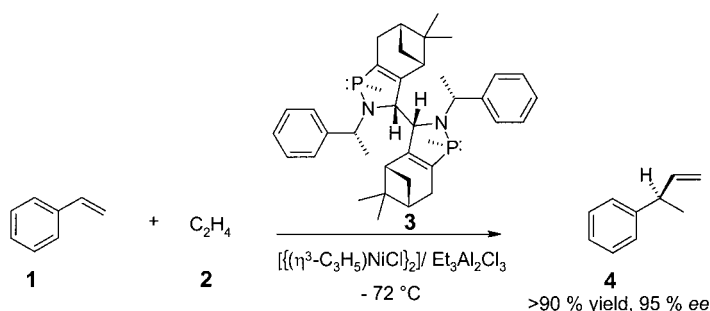


Scheme 1. Hydrovinylation of olefins.

The use of chiral phosphanes to achieve asymmetric hydrovinylation was first mentioned in 1967,^[2d] and a few years later Bogdanović and Wilke observed asymmetric inductions of up to 70 % *ee* for the coupling of 1,3-octadiene

and ethylene in the presence of (–)-dimenthylisopropylphosphane.^[6]

The highpoint of these initial developments came in 1988 when Wilke et al. isolated the dimeric azaphosphole **3** from a rather complex reaction of a pinene derivative and a chiral amine. The azaphosphole **3** turned out to be an excellent ligand for asymmetric hydrovinylation.^[7] For the codimerization of styrene **1** and ethylene **2** to give (*R*)-3-phenyl-1-butene (**4**) an enantiomeric excess above 95 % was observed—a record that has not been surpassed yet (Scheme 2).



Scheme 2. Asymmetric hydrovinylation of styrene.

A systematic tuning of the properties of ligand **3** was limited because of its complex structure. Therefore, in the following years a lot of effort was put into the development of alternative ligand systems that could be obtained more easily. Different approaches were investigated, for example palladium complexes with P-chiral ligands that gave good *ee* values but low yields, and nickel complexes bearing 2-diphenylphosphanyl-2'-alkoxy-1,1'-binaphthyl (“MOP”) ligands that gave high yields but low asymmetric induction.^[8, 9] Significant breakthroughs in this area were not forthcoming and thus interest in hydrovinylation dwindled.

Recently, Leitner et al. and RajanBabu et al. independently published new catalysts that are comparable in terms of activity and enantioselectivity to the system developed by Wilke.^[10, 11] The major advance made lies in the modular strategy that allows the development of new ligands with a diverse range of variable building blocks. Thus the necessary prerequisites were in place to permit the design of catalysts for hydrovinylation on a rational basis, which has led to a reawakening of this area of research.

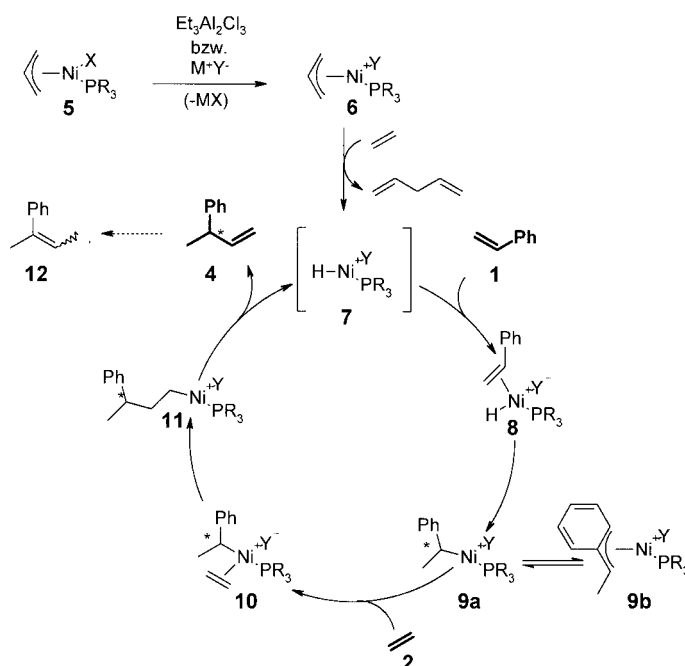
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Problems Associated with Developing New Catalyst Systems

A look at the catalytic cycle explains why it is inherently difficult to design new catalysts for the hydrovinylation of olefins (Scheme 3).^[2b] First, the active catalyst, which is most



Scheme 3. Catalytic cycle for Ni-catalyzed hydrovinylation.^[2b]

likely a phosphane-stabilized nickel-hydride species, has to be generated in situ from a readily available nickel precursor. Usually $[(\text{Ni}(\text{allyl})\text{Cl})_2]$ is treated with a phosphane to give the monomeric complex **5**. In the next step the strongly coordinating chloride ion is replaced by a weakly coordinating anion. In the original process this exchange was achieved by using highly flammable alkylaluminum halides that are difficult to handle. In addition, the high Lewis acidity of these compounds limited the application of the process. New techniques for the activation of the given precatalyst involve a much more facile anion exchange with metal salts such as $\text{Na}^+\text{BPh}_4^-$. By using different metal salts, a number of counter anions can be incorporated into the catalytic system thus providing additional possibilities to tune the catalytical properties.

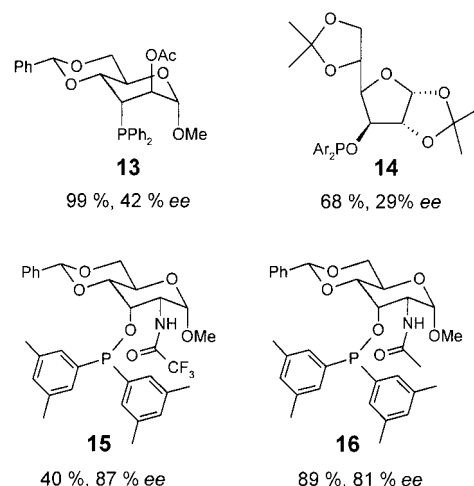
Cleavage of the allyl substituent leads to the actual catalyst, the highly active and coordinationally unsaturated nickel-hydride species **7**, which is most likely stabilized during the whole catalytic process by additional ligands. This nickel-hydride species **7** should selectively coordinate to only one of the two olefins present, so that only this olefin inserts into the Ni-H bond. Vinylarenes are electronically favored, especially since the resulting benzylic complex **9** can be further stabilized through η^3 -coordination of the olefin. The asymmetric induction through the chiral phosphane ligands occurs at this stage.^[2d] In the subsequent step, a molecule of the second olefin (usually ethylene (**2**)) coordinates to the metal center, whereas the competing reaction with another molecule of the vinylarene should be suppressed. The second

insertion must happen only once, otherwise oligomers will be formed rather than the desired dimers. Therefore the last step in the catalytic cycle, the cleavage of the target molecule **4** and the regeneration of the catalytically active nickel-hydride species **7** by β -hydride elimination, must be significantly favored. This is usually achieved by the use of sterically demanding ligands.

One additional requirement for a good hydrovinylation catalyst is its low activity for isomerization, since moving the double bond in the product **4** would result in the formation of less valuable and optically inactive olefins **12**. Owing to the large number of possible side reactions small changes to the catalyst often have an unpredictable influence on the outcome of the reaction, a fact that makes improvements of the catalysts even more difficult.

Approaches to New Ligand Systems

In their search for a suitable lead structure for a new generation of ligand systems RajanBabu et al. decided after numerous preliminary investigations to focus on chiral diaryl-monophosphinites (Scheme 4).^[10] These compounds can be synthesized readily from diarylchlorophosphane and one of the numerous enantiopure alcohols that are commercially available.^[13]



Scheme 4. Phosphane and phosphinite ligands for the hydrovinylation of styrene with ethylene.

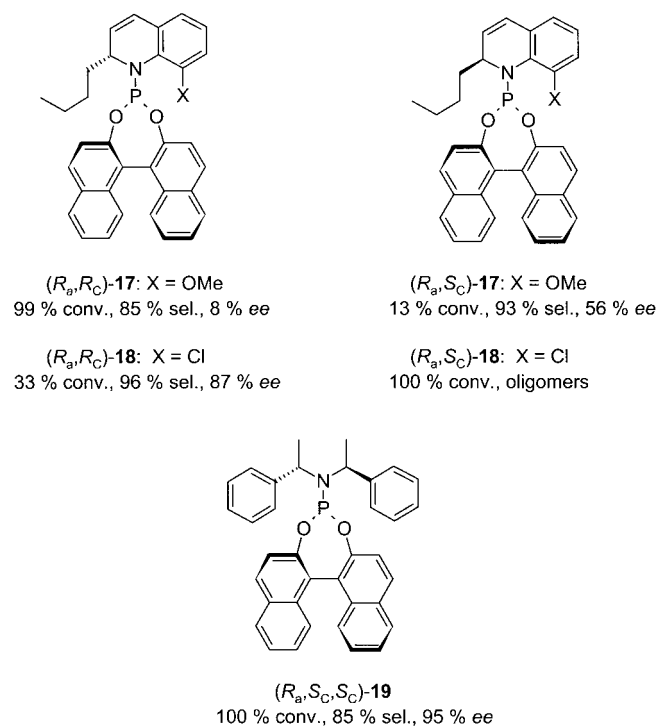
Good chemoselectivities in favor of the heterocodimerization were observed with these ligands in the reaction of styrene with ethylene according to Scheme 2. The best results were obtained by using monophosphinites derived from sugars especially 2-acetamido-2-deoxyglycopyranoside derivatives.

The modular construction of the ligands **13–16** allows a multitude of variations through the use of different sugars, through derivatization by introducing different functional groups at the sugar moiety, and through the use of different aryl substituents at the phosphorous atom. The enormous impact of these fine tunings is clearly apparent from a comparison of the results obtained by using **15** and **16**: The

replacement of only one group on the ligand resulted in a doubling of the yield.

Interestingly, the counterion used has a big influence on the activity and selectivity of the catalyst. The best results were obtained with tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate ("BARF") or SbF_6^- , whereas BF_4^- and CF_3SO_3^- (OTf^- , triflate)-derived complexes were significantly less reactive. This is surprising since Wilke et al. had observed in their correlation of data from catalysis experiments with those from conductivity measurements^[12] that higher activities of the catalyst were obtained for weakly coordinating rather than noncoordinating counterions.

A comparable degree of modularity to that shown by the systems developed by RajanBabu et al. is displayed by the phosphoramidites introduced by Leitner et al. (Scheme 5).^[11] A large number of these compounds is readily accessible from chiral alcohols and amines on reaction with PCl_3 .^[13] Owing to the excellent asymmetric induction together with lower costs for the syntheses, phosphoramidites^[14] and phosphites,^[15] for example for asymmetric hydrogenation, have recently become viable alternatives to well-established ligands such as BINAP.



Scheme 5. Phosphoramidites for the hydrovinylation of styrene with ethylene.

For the Ni-catalyzed hydrovinylation of styrene with ethylene the phosphoramidites again turned out to be excellent ligands. Particularly good results were obtained with (R_a, S_c, S_c) -**19** (Scheme 5): almost 95 % ee and 85 % selectivity for the desired heterocodimer. As side products only 4 % isomerized product and 8 % oligomers were detected.

Both, axial chirality within the diol fragment as well as the center of chirality in the amine are important for the asymmetric induction of the ligand. This is clearly apparent

from the strong dependency of the yields obtained on the diastereomer of the ligand used. For the "mismatched" isomers the optical as well as the chemical yield is significantly decreased. For (R_a, R_c) -**18** 93 % selectivity and 84 % ee were observed, whereas the diastereomeric ligand (R_a, S_c) -**18** led only to oligomerization due to the disfavored geometry of the ligands.

Likewise for these systems the counterions have a strong influence on the catalytic properties. The best results were obtained by using NaBARF as the activating agent. If $\text{Na}[\text{Al}(\text{OC}(\text{CF}_3)_2\text{Ph})_4]$ is used instead of NaBARF a higher chemoselectivity can be achieved, whilst the enantiomeric excess drops to 89.7 %. Weakly coordinating counterions such as BF_4^- or NTf_2^- led to much poorer results.

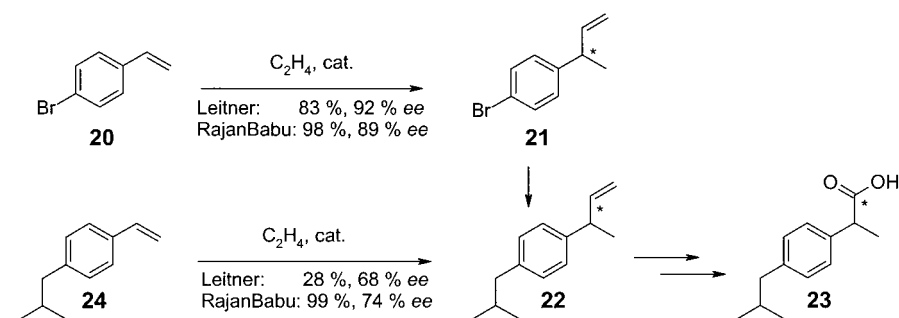
The activities of these new catalysts are intriguingly high. Leitner et al. used (R_a, S_c, S_c) -**19** with a catalyst-to-substrate ratio of 1:13 000 and observed 69 % conversion at 0 °C within 30 min. This corresponds to a turnover frequency of approximately 18 000 h^{-1} . At lower temperatures this number drops to 8000 h^{-1} but higher chemo- and enantioselectivities can be achieved.

Applications of the Reaction

A potential application for hydrovinylation is the asymmetric synthesis of pharmacologically important phenylpropionic acids such as Ibuprofen or Naproxen.^[16] In this context, other approaches using asymmetric hydroformylation, hydrocyanation, or hydrocarbonylation have already been tested; however, for a variety of reasons these proved to be no better than well established processes.^[17] For hydroformylation the drawbacks are low turnover numbers as well as the tendency for racemization of the resulting aldehydes. Alternative approaches using the asymmetric hydrovinylation of styrene derivatives might have major advantages.^[7, 12] Although the oxidative cleavage of the vinyl groups necessitates an additional synthetic step, the products obtained after the asymmetric steps are configurationally stable.

RajanBabu and Leitner and their respective co-workers demonstrated the potential of their new systems by way of synthesizing ibuprofen starting from *p*-bromo- or *p*-isobutylstyrene (Scheme 6).^[10, 11] Hydrovinylation of *p*-bromostyrene was achieved with very good yields and enantioselectivities in both cases. For the phosphoramidite (R_a, S_c, S_c) -**19** a substrate-to-catalyst ratio larger than 2500 was used, and an enantiomeric excess of 92 % was achieved. For the monophosphonite **16** (with a higher catalyst loading) a yield of 98 % and an enantiomeric excess of 89 % was achieved.

To complete the synthesis of ibuprofen the vinyl group of the hydrovinylation product has to be oxidized to the corresponding carboxylic acid, and the bromo substituent replaced by an isobutyl group. The shorter route to ibuprofen starting from *p*-isobutylstyrene proved to be less favorable since poorer results were obtained in the hydrovinylation of this more electron-rich substrate: RajanBabu's system gave the desired product in 99 % yield but with only 74 % ee, whereas Leitner's system gave the product in only 28 % yield with 68 % ee.



Scheme 6. Asymmetric synthesis of Ibuprofen.

Despite the significant advances, it is clear that there is still a lot of potential for further improvement. The optimization of the new systems is still in its infancy; however, given the modularity of the new ligands it is envisaged that even more efficient members of these new classes of ligands will be identified in the near future.

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Nanomechanical Devices Based on DNA**

Christof M. Niemeyer* and Michael Adler

Biomolecular compounds, such as proteins and nucleic acids, which are evolutionary optimized, with respect to specificity of binding to their target structure as well as to functionality, for distinct biochemical transformation and translocation, are currently explored as building blocks in the “bottom-up” self-assembly of nanometer-scale functional devices.^[1] So far, applications include the organization of metal and semiconductor nanoclusters,^[2] numerous bioanalytical techniques,^[1] as well as biomolecular electronics^[3] and nanomechanical devices. While the development of the latter was, in past years, mainly focused on motor proteins, such as actin, kinesin, and myosin,^[4] nowadays an increasing number of reports are being devoted to the construction of nanomechanical devices from DNA. This biomolecule plays an outstanding role in the development of artificial biomolecular hybrid elements, since the specificity of simple A-T and G-C base pairing as well as its robust physicochemical nature allows for the fabrication of nanostructured molecular scaffolding and surface architecture,^[5] and to selectively position proteins,^[6] inorganic colloidal components,^[2] carbohydrates,^[7] organometallics,^[8] and reactive chemical compounds^[9] on the nanometer length scale.

Another interesting property of the DNA double helix is its intrinsic susceptibility to external stimuli mediated by small molecules or ions, which opens up ways to fabricate nanomechanical devices. For example, the contour length and the flexibility of a DNA molecule can be effectively altered by use of intercalators, such as acridinium or ethidium bromide derivatives, which bind in between the stacked nucleobases of the double helix and thereby significantly increase the DNA contour length.^[10] Seeman and co-workers made use of this phenomenon: They reported on the induced change in torque of a circular DNA molecule containing a partially mobile branched DNA junction on intercalation of ethidium bromide as a potential supercoiling motion for nanomechanical elements.^[11]

More recently, the Seeman group established an elegant means to utilize electrostatic interaction of Co^{3+} ions for switching a DNA device comprised of two rigid DNA double-crossover motifs. The latter were covalently linked to each other by a short $\text{d}(\text{CG})_{10}$ proto-Z sequence which is capable of changing its conformation from a right-handed B- to a left-handed Z-DNA double helix (Figure 1 A).^[12] The conforma-

tional change leads to a spatial separation of two fluorescent labels, attached to each of the two double-crossover moieties, which can be measured by fluorescence resonance energy transfer (FRET).

In a different approach, the increase in concentration of Mg^{2+} ions was used to trigger a supercoiling of two DNA strands within supramolecular aggregates comprised of biotinylated DNA and streptavidin (STV).^[13] The twisting of the DNA strands leads to a decrease in the distance between adjacent STV particles (Figure 1 B). Potential applications of such structural changes might include the fabrication of ion-dependent molecular switches within nanomaterials, for example, to control nanoparticle spacing and to regulate the accessibility of the DNA to enzymes.

Whilst the above examples concern the more or less gradual conformational switching of molecular devices by small molecule effectors,^[14] a different strategy relies on DNA motifs whose conformation is sharply switched by intermolecular hybridization with complementary nucleic acids. The developments of “molecular beacons” can be considered as a simple example of such a process, thus allowing the utilization of hybridization-induced changes in DNA conformation for the macroscopic detection of intermolecular binding.^[15] DNA beacons are single-stranded DNA (ssDNA) molecules which, as a result of their nucleotide sequence, form an intramolecular hairpin-loop structure (Figure 2 A). Both ends are chemically modified with a fluorophore F and a dye Q, the latter of which effectively quenches the fluorescence of F by its spatial proximity. Upon hybridization with nucleic acid targets containing a sequence stretch complementary to the loop region of the beacon, Q is spatially removed from F, which leads to a strong enhancement in fluorescence. Since its first description, this simple yet powerful principle has been applied to numerous applications ranging from homogeneous hybridization analysis, to real-time polymerase chain reaction (PCR) and detection of single nucleotide polymorphism.^[16]

Recently, a new class of molecular beacons has been introduced, in which the organic quencher dye Q was replaced by a gold metal cluster (Figure 2 C).^[17] This hybrid construct was synthesized from a 3'-amino-5'-thiol-modified ssDNA oligomer by subsequent coupling with an amino-reactive fluorophore and with commercially available 1.4-nm gold clusters containing a single maleimido group in their ligand shell. The performance of the hybrid molecular beacon was optimized by determining the quenching efficiency (QE), that is, the difference in fluorescence between the open duplex and the intramolecularly closed beacon, for several dyes. The best QE value of about 99.5% was obtained for rhodamine 6G, which indicates that the fluorescence signal of the beacon increases about 200-fold upon hybridization with the complementary target. Consequently, the gold-oligomer-dye hybrids were applied to the detection of single mismatches in DNA. Competitive hybridization assays revealed that the ability to

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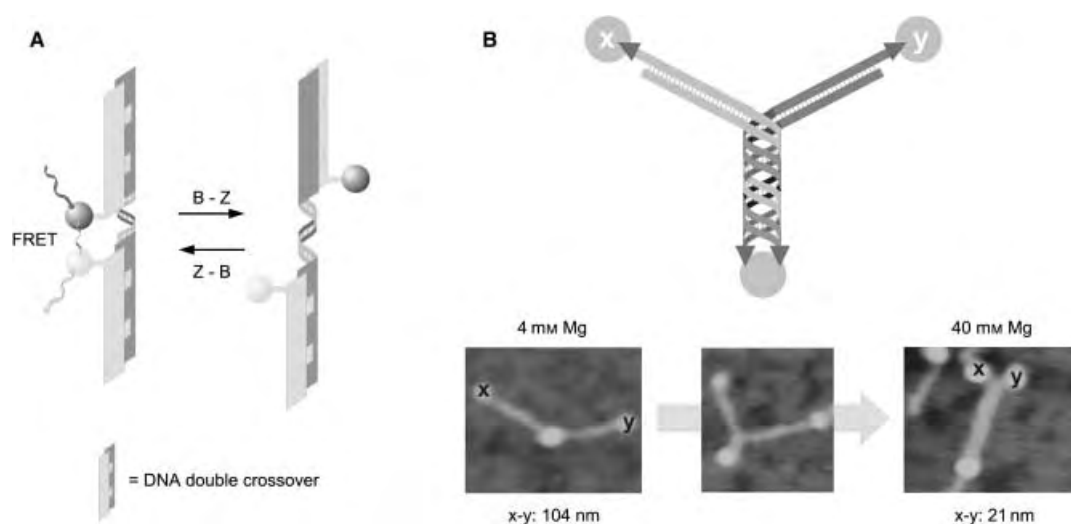


Figure 1. Electrostatic switching of DNA devices. A) A nanomechanical device consisting of two rigid double-crossover structures connected by a double-helical DNA fragment. The presence of $[\text{CoCl}_3(\text{NH}_3)_6]$ triggered the conformational change of the double helix from a right-handed B to a left-handed Z helix, thus separating two adjacent fluorophores coupled to each of the double-crossover moieties. The rotational movement was detected by the interruption of the FRET signal occurring between the two fluorophores in the B-DNA conformation and was reversed by eliminating the $[\text{CoCl}_3(\text{NH}_3)_6]$ from the solution. B) Aggregates consisting of STV and bis-biotinylated DNA change their conformation in the presence of Mg^{2+} ions. AFM images of aggregates comprised of three STV and two DNA molecules are shown. The Mg^{2+} -induced supercoiling of the DNA strands leads to alterations in the STV–STV distance between “x” and “y” from 104 to 21 nm.

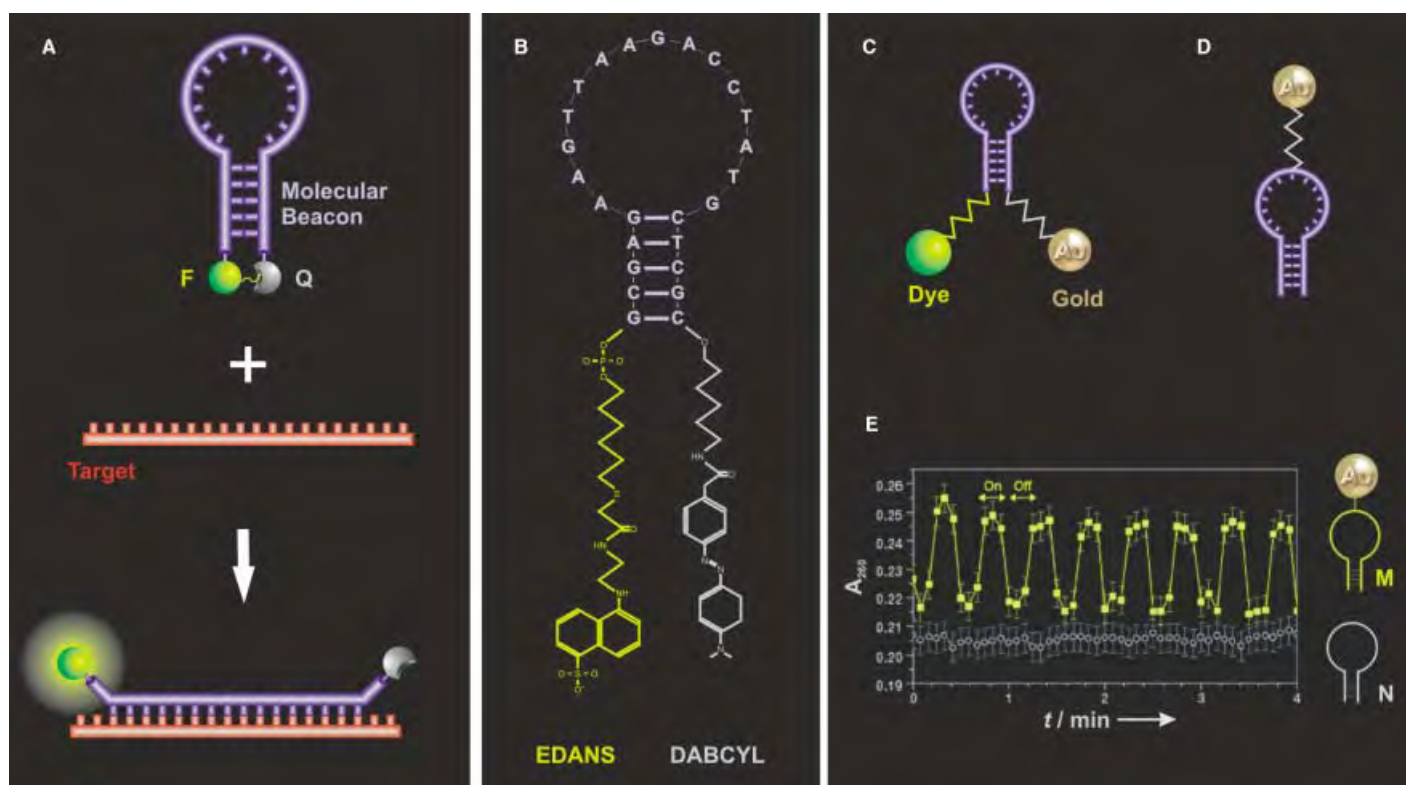


Figure 2. Nanomechanical motion of nucleic acid motifs with a hairpin structure. A) Conventional molecular beacons.^[15] B) Example of fluorescent dyes attached to a DNA hairpin molecule. C) Molecular beacon containing a 1.4-nm gold nanocrystal as a quencher.^[17] D) Electronic switching of DNA hybridization.^[18] The hairpin molecule M is self-complementary at the ends for seven bases, with a primary amine in the loop to which a 1.4-nm gold nanocrystal is covalently linked. E) The absorbance of a solution of M at 260 nm is plotted as a function of time in which the radio-frequency magnetic field is switched on and off. The increase in absorbance reflects the denaturation of the DNA double helix. For control purposes, a solution of hairpin molecule N, which lacks the gold nanocrystal, was analyzed under similar conditions. Adapted with kind permission from ref. [18].

detect single base mutations is about eightfold greater than with conventional molecular beacons while the sensitivity of detection is enhanced up to 100-fold.^[17] Nonetheless, limita-

tions in the applicability of such hybrid constructs in routine diagnostics are currently a consequence of the limited physicochemical stability of the metal clusters, their ligand

shell, and the chemical linkage between the clusters and the DNA.

Gold nanoparticle/DNA molecular beacon conjugates have recently been exploited for the remote electronic control of DNA hybridization (Figure 2D).^[18] By inductively coupling a radio-frequency magnetic field (RFMF) with a frequency of 1 GHz to the 1.4-nm metal nanocrystal, which functions as an antenna in the DNA constructs, the local temperature of the bound DNA is increased, thereby inducing denaturation while leaving surrounding molecules relatively unaffected. The switching is fully reversible (Figure 2E). Although inductive heating has already been applied to macroscopic samples, as well as in the treatment of cancer cells with magnetic-field-induced excitation of biocompatible superparamagnetic nanoparticles,^[19] the use of gold nanocrystal/DNA conjugates should allow extension of this concept. For example, complex operations, such as gene regulation, biomolecular assembly, and enzymatic activity, of distinct portions of nucleic acids or proteins might be controlled, while the rest of the molecule and neighboring species would remain unaffected. Moreover, because the addressing is not optical, this technology would even be applicable in highly scattering media.

Conformational changes induced by intermolecular hybridization of complementary DNA molecules were also translated into a nanomechanical response by using an array of eight microfabricated cantilevers.^[20] Each individual cantilever contained a different capture oligonucleotide, and the hybridization with target oligomers led to differences in surface stress between cantilevers functionalized with complementary or noncomplementary DNA oligomers. Hybridization experiments revealed that a single-base mismatch between two 12-mer oligonucleotides were clearly detectable. Recently, such cantilever-based nanomechanical sensor devices were applied in the detection of cancer antigens^[21] and single nucleotide polymorphisms.^[22] Moreover, systematic DNA hybridization experiments revealed that the origin of the motion of the cantilever lies in the interplay between changes in configurational entropy and intermolecular energetics induced by specific biomolecular interactions.^[23]

Intermolecular DNA hybridization also plays a key role in the concept of “fueling” DNA nanomechanical devices by strand-exchange reactions. A first example of this type was reported by Yurke et al.^[24] They constructed a molecular tweezer from three oligonucleotides, one of which is doubly labeled with a 3'-TAMRA (carboxytetramethylrhodamine) and a 5'-TET (tetrachlorofluorescein) fluorogenic group (strand T_a in Figure 3A). Strands T_b and T_c are partially complementary to strand T_a and form two rigid double helices and a four-base-hinge single-stranded region within the intermolecular tweezer complex. In this conformation, termed as the machine's “rest state”, the remaining two unhybridized 24-base portions of 42-mer strands T_b and T_c dangle floppily from the ends of the tweezer. In the rest state, the two fluorophores of strand T_a are spatially separated and no intermolecular resonant energy transfer from TET to TAMRA, and thus, no quenching of TET fluorescence occurs. The tweezer is operated by the addition of fueling strands F_c and F_o (Figure 3A). Closing strand F_c is comprised of three

regions, two of which are 24-mers fully complementary to the dangling ends of strands T_b and T_c , and the third region is an 8-mer overhang at which interaction with opening strand F_o begins. Addition of F_c pulls the ends of the tweezer together by intermolecular hybridization (Figure 3A), which leads to a decrease of the TET fluorescence by a factor of six. The tweezer is re-opened by addition of F_o , which is fully complementary to F_c . Starting with intermolecular hybridization of F_o and F_c at the 8-mer overhang stretch, F_c is displaced from the tweezer by branch-migration and leads to the formation of the F_cF_o duplex as a “waste” product. The opening/closing process is fully reversible, and the switching time for the machine is less than 20 s with second-order rate constants for opening and closing being approximately equal. Interestingly, thermodynamic calculations suggest a closing force of the tweezer of about 15 pN, which is at the upper end of the range of measured forces exerted by single-group kinesin and myosin motors.^[24]

The above scheme has recently been modified by Li and Tan.^[25] They constructed a 17-mer DNA nanomotor which can adopt an intramolecular tetraplex (TE) conformation through the formation of two layers of intramolecular G-quartets (Figure 3B). In this shrunken state, the fluorophore F and the quencher Q are in spatial proximity, and consequently the nanomotor is in its dark state. Hybridization with complementary fueling oligomer F_a results in the nanomotor extending into a duplex (DU) conformation, thereby separating the two ends from each other, and thus, the fluorescence intensity increases approximately fourfold. The nanomotor shrinks back to the TE when strand F_a is displaced by hybridization with complementary strand F_b , thereby producing a waste DNA duplex F_aF_b . Addition of F_a starts a new extending/shrinking cycle. Cycling of the nanomotor in homogeneous solution revealed that the process is almost fully reversible. Moreover, nanomotors were immobilized at a surface and the fully reversible cycling of the extending/shrinking motion suggested that such devices might be useful for pulling together and pushing apart two nanoelements in a future nanosystem. Theoretical calculations allowed the estimation of the shrinking force ($F_{sh} = 2.2$ pN) and the extending force ($F_{ex} = 20.7$ pN), which are in the same order of magnitude or about tenfold greater, respectively, than those of kinesin and myosin protein nanomotors.

Seeman and co-workers have recently described a highly sophisticated DNA nanomechanical device^[26] which demonstrates that ssDNA fragments can be used to control and fuel a DNA device cycle by inducing the interconversion between two topological motifs—paranemic crossover (PX) DNA and its topoisomer (JX₂) DNA (Figure 3C). The two crossover motifs can be converted into each other by removal of internal strands with the aid of biotinylated fueling strands, which allow their elimination with streptavidin-coated magnetic beads. The cycling of the PX/JX₂ device was demonstrated by gel electrophoresis as well as by atomic force microscopy. The latter was conducted by modifying the PX/JX₂ device with a regular array of topographic markers in the form of half-hexagon motifs formed by DNA double helices (Figure 3D). Switching of the DNA device from the PX to the JX₂ state

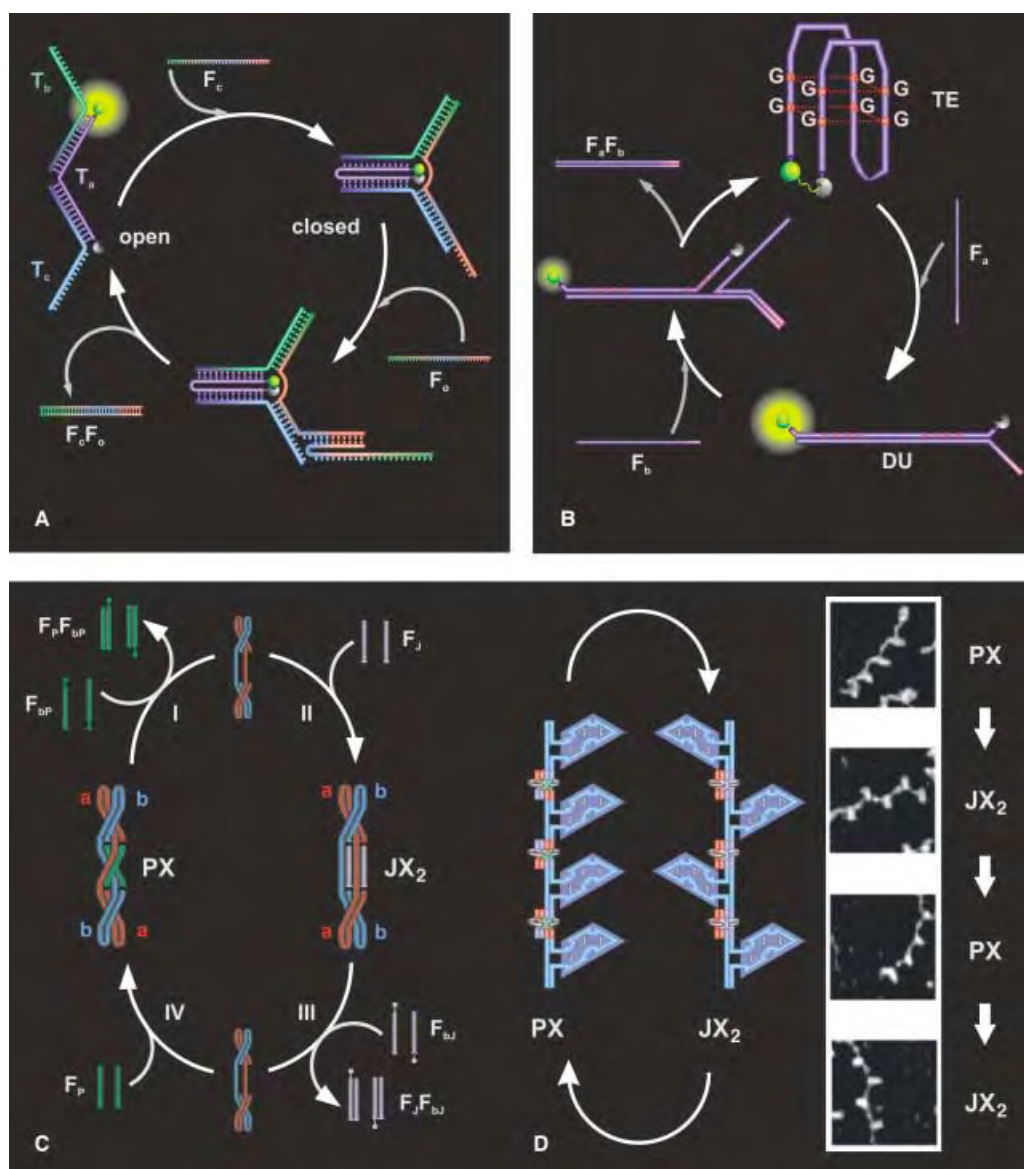


Figure 3. Control of nanomechanical motion of DNA motifs by “fueling” with single-stranded DNA molecules. A) The molecular tweezer structure comprised of three oligonucleotides T_a , T_b , and T_c is opened and closed by the addition of fueling oligonucleotides, which close the tweezer (F_c) and re-open it (F_o) by strand exchange.^[24] B) Schematic drawing of the DNA nanomotor cycled between the intramolecular TE and intermolecular DU conformation by means of fueling oligomers F_a and F_b .^[25] C) Schematic drawing of the PX/JX₂ device.^[26] The PX motif consists of two helical domains formed by four strands that flank a central dyad axis. The JX₂ motif lacks two crossovers in the middle. Two strands are drawn in red and two in blue, and the letters a and b show that strands at the bottom of the JX₂ motif are rotated 180° relative to the PX motif. The device is operated by the addition of biotinylated fuel strands F_{bp} (green) which remove complementary strands F_p from the PX motif in process I. The unstructured intermediate is converted into the JX₂ motif by the addition of the purple set of strands F_j in process II. The JX₂ molecule is converted into the unstructured intermediate by the addition of biotinylated pale purple fuel strands F_{bj} in process III. The two intermediates are identical. The cycle is completed by the addition of the green set of strands F_p in process IV, thus restoring the PX device. D) Experimental evidence for the operation of the PX/JX₂ device. A one-dimensional array of half hexagons is joined by PX/JX₂ motifs. The half-hexagons, each of which consists of three edge-sharing DNA triangles, are used as topographic markers that are traceable by AFM, as shown in the right panel. The images represent four steps of the operation of the device, originating from PX state (top) to JX₂ to PX, and back to JX₂ state (bottom). The PX linear arrays are clearly in the *cis* arrangement while the JX₂ linear arrays are in the *trans* arrangement. All images show an area of 200 × 200 nm. Adapted with kind permission from ref. [26].

leads to conversion of the arrangement of the half-hexagons from a *cis* to a *trans* configuration.

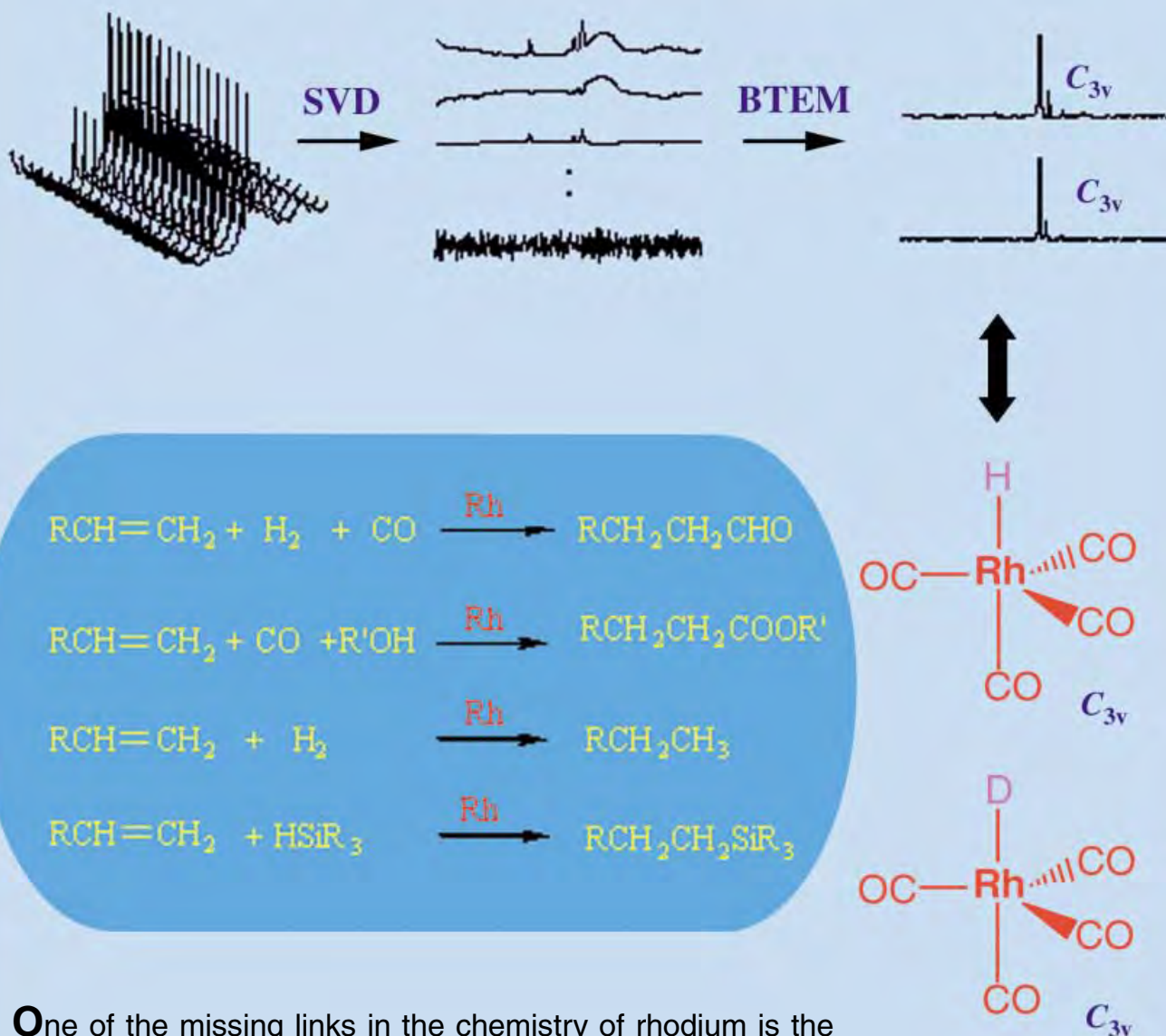
These examples indicate how various kinds of nanomechanical motion of DNA motifs can be realized, and range from an opening/closing of a DNA tweezer, to a crawling shrinking/extention linear movement and a relatively simple rotation around a central DNA axis. It seems likely that the next steps will concern the implementation of these

mechanical actions to the construction of hybrid devices which contain functional moieties, such as ribozyme motifs, proteins, colloids, or low-molecular-weight components, tethered to the mechanical entity. Such devices might be applied to investigate the interaction of chemically active components attached to the ends of a tweezer or to alternatively hide and reveal target groups attached to the DNA. DNA strands that act as fuel might also be used as information carriers to

coordinate components of a complex machine or to carry signals between machines.^[24] In regard to the latter, it should be noted that Benenson et al. have recently demonstrated a programmable computing machine made of biomolecular components, namely, DNA and DNA-manipulating enzymes, which is capable of autonomously solving computational problems.^[27] One may anticipate plenty of exciting new developments in this young field of research.

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Rhodium Tetracarbonyl Hydride



One of the missing links in the chemistry of rhodium is the spectroscopic identification of the simple, unmodified rhodium carbonyl hydride $[\text{HRh}(\text{CO})_4]$. Pure-component spectra of this compound and its deuterium analogue, $[\text{DRh}(\text{CO})_4]$, were obtained by investigating solutions of $[\text{Rh}_4(\text{CO})_{12}]$ in *n*-hexane upon exposure to varying partial pressures of H_2/CO and D_2/CO . The in situ high-pressure FTIR spectra were measured and subjected to band-target entropy minimization (BTEM), an advanced signal-processing technique (SVD = single-value decomposition). For more information see the following pages.

Rhodium Tetracarbonyl Hydride: The Elusive Metal Carbonyl Hydride**

Chuanzhao Li, Effendi Widjaja, Wee Chew, and Marc Garland*

Rhodium exhibits considerable activity in a wide range of heterogeneously and homogeneously catalyzed reactions.^[1] Accordingly, many large-scale industrial plants, such as those for the synthesis of acetic acid and hydroformylation, have a total inventory of only a few kilograms of rhodium; hydroformylation is one of the five most important homogeneously catalyzed processes worldwide and responsible for about 10⁷ t of organic products per year.^[2] The activity of rhodium is certainly one of the primary reasons for the enormous number of rhodium complexes developed to date. This activity and industrial utility, together with the rarity of rhodium, are the main reasons for its position as the most expensive precious metal. Undoubtedly, the most well-known rhodium organometallic complexes are the Wilkinson complexes [RhCl(PPh₃)₃] and [HRh(CO)(PPh₃)₃],^[3] which are extensively used in many homogeneously catalyzed reactions, in particular the hydroformylation of alkenes in the presence of molecular hydrogen and carbon monoxide to give aldehydes. One of the primary missing links in the industrial chemistry of rhodium is the identification of the simple, unmodified rhodium carbonyl hydride [HRh(CO)₄]. Here we report the spectroscopic identification, thermodynamics, and deuterium substitution of this compound.

In spite of the considerable synthetic effort invested in rhodium organometallic chemistry and the significant historical role played by metal carbonyl chemistry in the chemical process industry, the known chemistry of unmodified rhodium carbonyl complexes is very limited. Notable developments include the synthesis of the clusters [Rh₄(CO)₁₂]^[4] and [Rh₆(CO)₁₆]^[5] by Chini and co-workers, and the observation of [Rh₂(CO)₈] under considerable CO partial pressures.^[6] Ozin and Hanlan were able to spectroscopically identify [RhCO], [Rh(CO)₂], [Rh(CO)₃], and [Rh(CO)₄]; however, these were in low-temperature argon matrices.^[7] The geometry of the latter species is a distorted tetrahedron, and the infrared spectra accordingly contain two terminal carbonyl vibrations at 2012 and 2019 cm⁻¹. In terms of simply substituted rhodium carbonyl compounds, only the mononuclear acyl complex [RCORh(CO)₄] has been reproducibly observed.^[8] Some 17 acyl complexes having aliphatic substituents for R have been characterized under hydroformylation conditions.^[9]

In terms of rhodium carbonyl chemistry and homogeneous catalysis, the key species is the mononuclear hydride [HRh(CO)₄]. It represents the starting point for the catalytic hydrogenation of alkenes to alkanes and aldehydes to alcohols,^[10] the catalytic hydroformylation of alkenes to aldehydes,^[11] the hydrocarbonylation of alkenes with alcohols to form esters,^[12] the hydrosilylation of alkenes,^[13] and many other reactions. Metal hydrides hold a special place in organometallic chemistry,^[14] and they play a key role in homogeneous catalysis.^[15] From a mechanistic perspective, the coordination of unsaturated ligands and subsequent insertion into the metal–hydride bond is the starting point for a wide variety of important and complex transformations.

Given its importance, numerous attempts to synthesize [HRh(CO)₄] have been documented. Hieber and Lagally described the isolation of a yellow solid, assigned the tentative formula [HRh(CO)₄], at cryogenic temperatures upon reduction of rhodium chloride with molecular hydrogen.^[16] Chini and Martinengo made numerous unsuccessful attempts to protonate [HRh(CO)₄]⁻.^[17] Finally, Vidal and Walker reported the treatment of [Rh₄(CO)₁₂] with 1300 bar of hydrogen and carbon monoxide and the in situ observation of an infrared spectrum with bands at 2008 (w), 2039 (vs), and 2070 (m) cm⁻¹, which they assigned to [HRh(CO)₄], although four bands should be observed in the mid-infrared region.^[18] It is important to note that the primary laboratories or groups involved with in situ spectroscopic studies of rhodium carbonyl chemistry and catalysis, namely Whyman at ICI, Pino and Bor in Zürich, and Markó at Veszprém,^[19] never reported a successful attempt.

Recently, we introduced band-target entropy minimization (BTEM),^[20] an advanced and model-free deconvolution technique based on a Shannon entropy criterion.^[21] Tests of this novel algorithm with real in situ catalytic spectroscopic data have indicated that it is typically possible to account for more than 99% of the experimental spectroscopic data. Even more striking is the ability to retrieve extremely weak spectra of pure components, for example, corresponding to species with less than 0.07% of the integral intensity of the entire spectroscopic data set. With this tool, we have reinvestigated the [Rh₄(CO)₁₂]/H₂/CO system in an aliphatic hydrocarbon solvent.

Experiments were conducted in *n*-hexane in a high-pressure batch reactor system with in situ FT-IR capability. The experiments typically lasted 24 h, and the spectra were taken at 5–10 min intervals in the range between 1000 and 2500 cm⁻¹. Details of the equipment and typical experimental procedures used as well as methods of purification and safety issues can be found elsewhere.^[22] The experimental design typically involved 300 mL of solvent and other conditions in the following ranges: *T* = 285–303 K, *P*_{H₂} = 1.0–5.0 MPa (or *P*_{D₂} = 0.5–2.0 MPa), *P*_{CO} = 1.0–5.0 MPa, initial concentration of [Rh₄(CO)₁₂] = 58–315 mg, and *P*_T = 2.0–8.0 MPa. Each experiment was conducted in the semi-batch mode, whereby multiple perturbations in the variables hexane, H₂ or D₂, CO, and [Rh₄(CO)₁₂] could be achieved in any 24-h run. Upon each perturbation of the reactive system, very small changes could be observed in the mid-infrared spectra during the subsequent few minutes. In total, 475 spectra were taken for

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reactions involving only molecular hydrogen, and about 200 spectra were recorded with molecular deuterium alone or with deuterium and hydrogen.

A singular value decomposition was performed on the data sets. Figure 1 shows some of the right singular vectors from

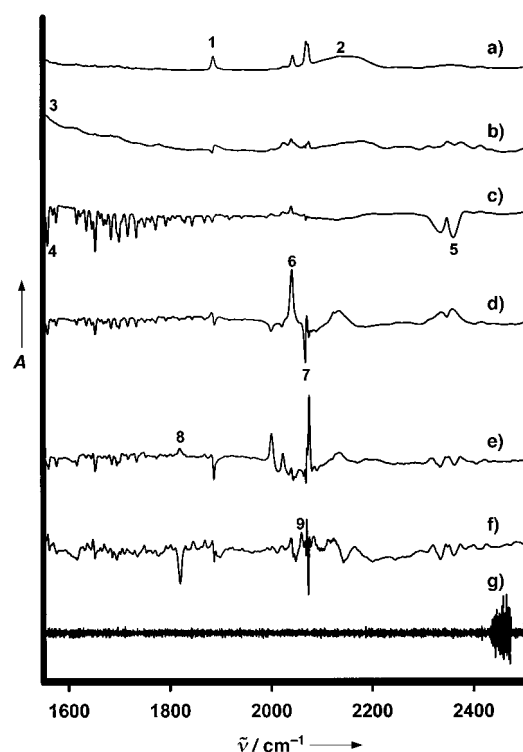


Figure 1. Several right singular vectors from the singular value decomposition: a) 1st vector, b) 4th vector, c) 5th vector, d) 6th vector, e) 13th vector, f) 17th vector, g) 475th vector.

the semi-batch experiments involving only molecular hydrogen. The numbers in Figure 1 indicate prominent spectral features in the vectors which were subsequently targeted in the BTEM algorithm. Details of the mathematical constructs and implementation of BTEM can be found in the literature.^[20a,b] The first few vectors represent the primary contributions to signal variance, while the subsequent vectors have increasing contributions from white noise.

Figure 2 presents the reconstructed pure-component spectra of the “major” species present. These spectra were obtained by targeting the features 2 (CO), 3 (hexane), 4 (vapor-phase moisture), and 5 (vapor-phase carbon dioxide) indicated in Figure 1. Figure 3 shows the reconstructed pure-component spectra of the “minor” components, that is, the rhodium organometallic species. These spectra were obtained by targeting the features 1 ($[\text{Rh}_4(\sigma\text{-CO})_9(\mu\text{-CO})_3]$, maxima at 1885.8, 2043.8, 2070.2, 2073.8 cm^{-1}), 9 ($[\text{Rh}_2(\sigma\text{-CO})_6(\mu\text{-CO})_2]$, maxima at 1845.6, 1861.6, 2060.2, 2084.2 cm^{-1}), 7 ($[\text{Rh}_4(\sigma\text{-CO})_{12}]$, maxima at 2068.0, 2076.0 cm^{-1}),^[20b] and 8 ($[\text{Rh}_6(\text{CO})_{16}]$, maxima at 1819.2, 2075.4 cm^{-1}). The concentration of $[\text{Rh}_6(\text{CO})_{16}]$ was typically on the order of ppm or less, and its presence could be detected by unaided visual inspection only in a few experimental spectra.

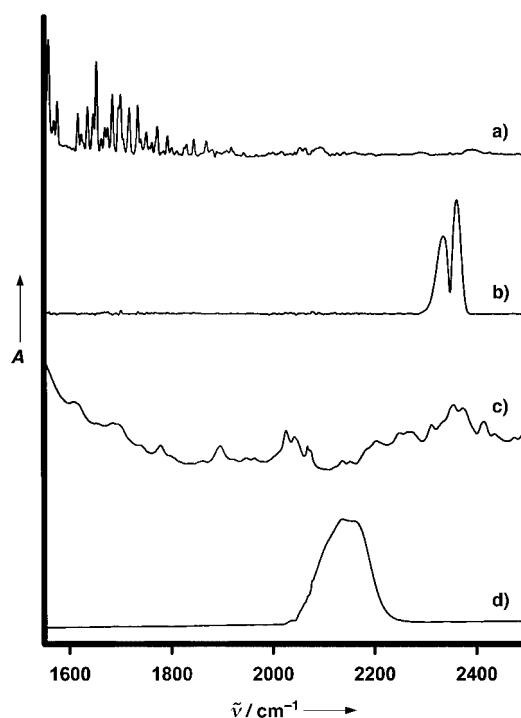


Figure 2. The reconstructed pure-component spectra of the major components: a) vapor-phase moisture, b) vapor-phase CO_2 , c) *n*-hexane, d) dissolved CO.

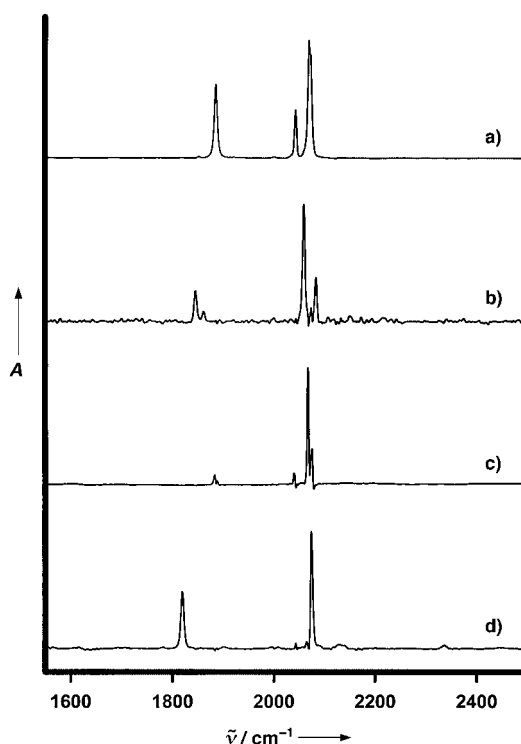


Figure 3. The reconstructed pure-component spectra of the minor organometallic components: a) $[\text{Rh}_4(\sigma\text{-CO})_9(\mu\text{-CO})_3]$, b) $[\text{Rh}_2(\sigma\text{-CO})_6(\mu\text{-CO})_2]$, c) $[\text{Rh}_4(\sigma\text{-CO})_{12}]$, d) $[\text{Rh}_6(\text{CO})_{16}]$.

Most importantly, BTEM was able to reconstruct two new and previously unknown mid-infrared pure-component spectra. One spectrum arose exclusively in the experiments with molecular hydrogen (spectral feature 6 in Figure 1) and the

other arose exclusively in the experiments with molecular deuterium. These pure-component spectra correspond to only about 0.15 % of the signals in the respective data sets. In the interest of completeness, it must be mentioned that BTEM also was able to reconstruct only one additional spectrum belonging to $[\text{Fe}(\text{CO})_5]$ with bands at 1964.8 (w), 2001.0 (vs), 2023.6 (m) cm^{-1} . The presence of $[\text{Fe}(\text{CO})_5]$ could be detected in some but not all experiments. It is an omnipresent trace impurity in commercial CO stored in stainless steel cylinders.

Figure 4 reports the entire mid-infrared region from 1550 to 2500 cm^{-1} , where either M–H or M–CO vibrations are

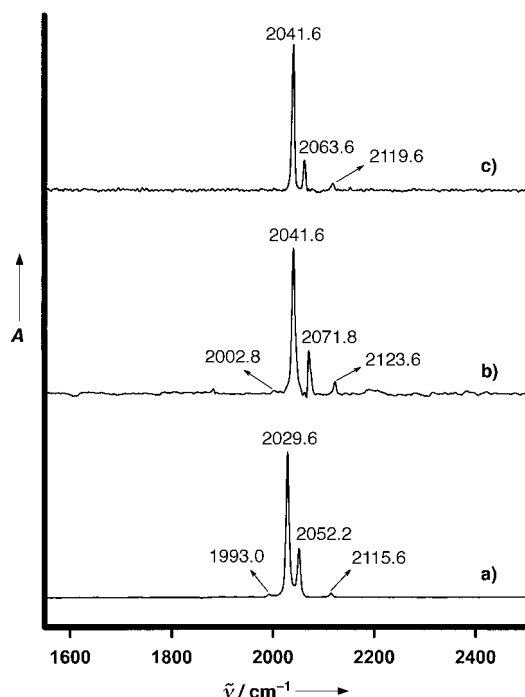


Figure 4. The reconstructed pure-component spectra of the organometallic carbonyl hydrides: a) $[\text{HCo}(\text{CO})_4]$, b) $[\text{HRh}(\text{CO})_4]$, c) $[\text{DRh}(\text{CO})_4]$.

expected to occur. Shown are a spectrum of $[\text{HCo}(\text{CO})_4]$ obtained in our laboratory as well as the new spectra recorded upon the use of molecular hydrogen and deuterium. $[\text{HCo}(\text{CO})_4]$ is known to have a trigonal-bipyramidal geometry with the hydrogen ligand in an axial position.^[23] Accordingly, the symmetry of the molecule corresponds to the point group C_{3v} .^[24] Three metal–carbonyl vibrations are expected and indeed observed at 2029.6 (vs), 2052.2 (m), and 2115.6 (w) cm^{-1} and the metal–hydrogen vibration appears at 1993.0 (w) cm^{-1} . In comparison, the literature values (with relative intensities) in *n*-heptane are 2029.8 (10), 2052.3 (3.2), 2116.1 (0.2), and 1993.0 (0.2) cm^{-1} .^[25] The new spectrum observed under molecular hydrogen alone also has four vibrations in the mid-infrared range, and these occur in the same pattern, namely, a band of minor intensity at 2002.8 (w) cm^{-1} and three more intense bands at 2041.6 (vs), 2071.8 (m), and 2123.6 (w) cm^{-1} . The new spectrum observed under molecular deuterium has only three vibrations in the mid-infrared region at 2041.6 (vs), 2063.6 (m), and 2119.6 (w) cm^{-1} .

The new spectra clearly correspond to $[\text{HRh}(\text{CO})_4]$ and $[\text{DRh}(\text{CO})_4]$. These molecules have the expected trigonal-

bipyramidal geometries with the protium or deuterium ligand in an axial position (Scheme 1). The vibrations at the very high wavenumbers 2123.6 and 2119.6 cm^{-1} correspond to the totally symmetric mode and are conclusive evidence that the molecules have very high symmetry and are mononuclear.^[26]



Scheme 1. Schematic representation of the trigonal-bipyramidal structures of $[\text{HRh}(\text{CO})_4]$ and $[\text{DRh}(\text{CO})_4]$.

Furthermore, the shift in metal–carbonyl vibrations and the loss of the metal–hydrogen vibration upon substitution with deuterium is highly analogous to the case of cobalt tetracarbonyl hydride. Edgell and co-workers reported band at 2043, 2062, 2121, and 1934 cm^{-1} for $[\text{HCo}(\text{CO})_4]$ and at 2043, 2058, 2120, and 1396 cm^{-1} for $[\text{DCo}(\text{CO})_4]$.^[27] The vibration at 2041.6 cm^{-1} for $[\text{HRh}(\text{CO})_4]$ / $[\text{DRh}(\text{CO})_4]$ belongs to the *e* mode and is insensitive to substitution, whereas the other two carbonyl vibrations belong to the *a*₁ mode and are moderately sensitive to substitution with deuterium. The D–Rh vibration could not be directly observed since the spectral window 1350–1500 cm^{-1} is opaque due to strong solvent absorption.

The equilibrium thermodynamics were also measured. The concentrations of all reactants were considered in mole fraction units, and the equilibrium was modeled as either a two-parameter expression in enthalpy and entropy of reaction or as a three-parameter expression in enthalpy, entropy, and volume of reaction. The equilibrium constant K_{eq} is given by Equation (1).

$$K_{\text{eq}} = [\text{HRh}(\text{CO})_4]^4 / [\text{Rh}_4(\text{CO})_{12}]^1 [\text{CO}]^4 [\text{H}_2]^2 \quad (1)$$

Since the overall reaction can be written as $[\text{Rh}_4(\mu\text{-CO})_3(\sigma\text{-CO})_9] + 2\text{H}_2 + 4\text{CO} \leftrightarrow 4[\text{HRh}(\sigma\text{-CO})_4]$, at least 19 bonds are broken and formed: six Rh–Rh bonds broken, three $\mu\text{-CO}$ bonds converted into three $\sigma\text{-CO}$ bonds, two H–H bonds broken, four new Rh–H bonds formed, and four new Rh–CO bonds formed. The two-parameter model provided the thermodynamic parameters $\Delta_r H = -69.7 \pm 19.8 \text{ kJ mol}^{-1}$ and $\Delta_r S = -0.38 \pm 0.07 \text{ kJ mol}^{-1} \text{ K}^{-1}$. The exothermic nature of the reaction is consistent with the known thermochemistry of rhodium, namely, the low heat of formation of Rh–Rh and bridging Rh–CO bonds and the high heat of formation of Rh–H and Rh–CO bonds. Accordingly, higher conversions into $[\text{HRh}(\text{CO})_4]$ are achieved at lower temperatures. Also the negative entropy of reaction is consistent with the reaction of seven molecules to give only four molecules as products. The three-parameter model provided the thermodynamic parameters $\Delta_r H = -82.4 \pm 16.2 \text{ kJ mol}^{-1}$, $\Delta_r S = -0.44 \pm 0.06 \text{ kJ mol}^{-1} \text{ K}^{-1}$, and $\Delta_r V = -1131 \pm 313 \text{ mL mol}^{-1}$. The negative sign for the volume of reaction is consistent with the loss of the unusually large partial molar volumes of dissolved molecular hydrogen and carbon monoxide of about 60 mL mol^{-1} upon reaction.^[28] However, a value on the order of -250 mL mol^{-1} rather than $-1100 \text{ mL mol}^{-1}$ is expected.^[29]

These results indicate the severe limitation of the atypically small total pressure interval of ca. 5 MPa used in this study versus pressure intervals of ca. 100 MPa used in traditional reaction volume studies.^[30]

The intrinsic reaction kinetics were too rapid to be captured with the present experimental setup. Indeed, characteristic times for gas–liquid mass transfer as well as liquid-phase mixing were on the order of a few minutes. Therefore, transport-controlled rather than intrinsic kinetics were observed.

Nevertheless, an informed assumption about the mechanism(s) can be proposed. After each perturbation, hydrogen activation on $[\text{Rh}_2(\text{CO})_8]$ (or equilibrated and unsaturated $[\text{Rh}_2(\text{CO})_7]$) probably occurs very rapidly. After depletion of the dinuclear carbonyl species, the fragmentation of $[\text{Rh}_4(\text{CO})_{12}]$ (or possibly the equilibrated, open polyhedron structure $[\text{Rh}_4(\text{CO})_{14}]$)^[31] is likely to be the rate-limiting step. Hence, the kinetics can be anticipated to involved contributions from a number of parallel pathways.

Finally, the BTEM analysis of data from previous and ongoing hydroformylation studies was performed. In these catalytic studies involving $[\text{Rh}_4(\text{CO})_{14}]$ as catalyst precursor in *n*-hexane with less reactive alkene substrates (i.e., cyclooctene and α -methylstyrene) it was possible to recover again the pure-component spectrum of $[\text{HRh}(\text{CO})_4]$. The assignment of the fundamental vibrations at 2002.8 (w), 2041.6 (vs), 2071.8 (m) and 2123.6 (w) cm^{-1} is entirely reproducible. In some of these reconstructions, the rhodium–hydrogen vibration at 2002.8 cm^{-1} is better resolved or more pronounced.

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Spontaneous Deposition of Water-Soluble Substances into Microcapsules: Phenomenon, Mechanism, and Application**

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Novel hollow microcapsules with sizes ranging from 60 nm to 10 μm have recently been produced by the layer-by-layer (LBL) assembly of oppositely charged polyelectrolytes onto colloidal templates, followed by removal of the template cores.^[1] Great progress has been made towards optimizing the fabrication conditions for capsules templated onto melamine formaldehyde (MF) particles, with an integrity of 90% having

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been achieved.^[2] The physicochemical properties of the capsule wall can be customized by introducing functional components such as nanoparticles, biomacromolecules, lipids, photosensitive dyes, inorganic crystals, and multivalent ions. Polyelectrolyte capsules with versatile properties have been fabricated and characterized with respect to their surface morphology, film thickness, elasticity, stability, pH sensitivity, capacitance, conductance and photosensitivity.^[3]

Many efforts have been devoted to altering the properties of the interior of the capsule, in particular through the nanoscale encapsulation of polymers, drugs, minerals, dyes, proteins, enzymes, and genes. By modifying the solubility of a compound by solvent or pH variation, the hollow polyelectrolyte capsules have been filled with lipid micelles, and low-molecular-weight dyes such as 6-carboxyfluorescein (6-CF) and rhodamine 6G (Rd6G).^[4] Macromolecules, such as poly(styrene sulfonate) (PSS), have also been incorporated into the capsules either by the extraction of multivalent ions, which constitute the inner layers of the capsule, with oppositely charged polymers that are then released into the capsule interior, or by in situ polymerization of monomers inside the capsules by a “ship-in-bottle” synthesis.^[5] By changing the permeability of the capsule wall at different pH values, biomacromolecules such as dextran can be temporarily loaded inside the capsules.^[6]

However, precipitation or polymerization inevitably occurs both in the capsule interior and in the bulk simultaneously, leading to difficulties with purification and low encapsulation efficiency. Since the loading amount is limited by the bulk concentration, a large degree of encapsulation, especially for water-soluble substances, is impossible. The harsh conditions may also destroy the microstructure and the integrity of the capsules. On loading PSS into the capsules, a size increase resulting from the osmotic pressure has been observed,^[7] whilst a temperature increase may cause either capsule shrinkage or swelling depending on the composition of the capsule.^[8]

Herein we describe a novel encapsulation method based on a recently discovered property of the capsules: the spontaneous deposition of water-soluble substances under ordinary conditions (room temperature, pH 7.0, in pure water). The self-accumulation of water-soluble substances such as rhodamine, poly(allylamine hydrochloride) (PAH), and dextran leads to a higher concentration of such species in the interior of the capsule, rather than in the bulk; the encapsulation proceeds easily. Clarification that the mechanism was distinct from those methods described above was achieved when water-soluble biomolecules, such as albumin and peroxidase, were successfully deposited into the interior of the capsule. Under the optimal fabrication conditions for capsules templated on MF particles, (PSS/PAH)₅ capsules (negatively charged PSS is the first layer and positively charged PAH is the last layer, with five double layers in total) were successfully produced with higher than 90% integrity (Figure 1 a), and negatively charged 6-CF was used to label the capsules. After being aged at room temperature for one month, however, more intense fluorescence was observed from the capsule interior rather than from the bulk (Figure 1 b) when a suspension of the capsules was mixed with a solution of Rd6G

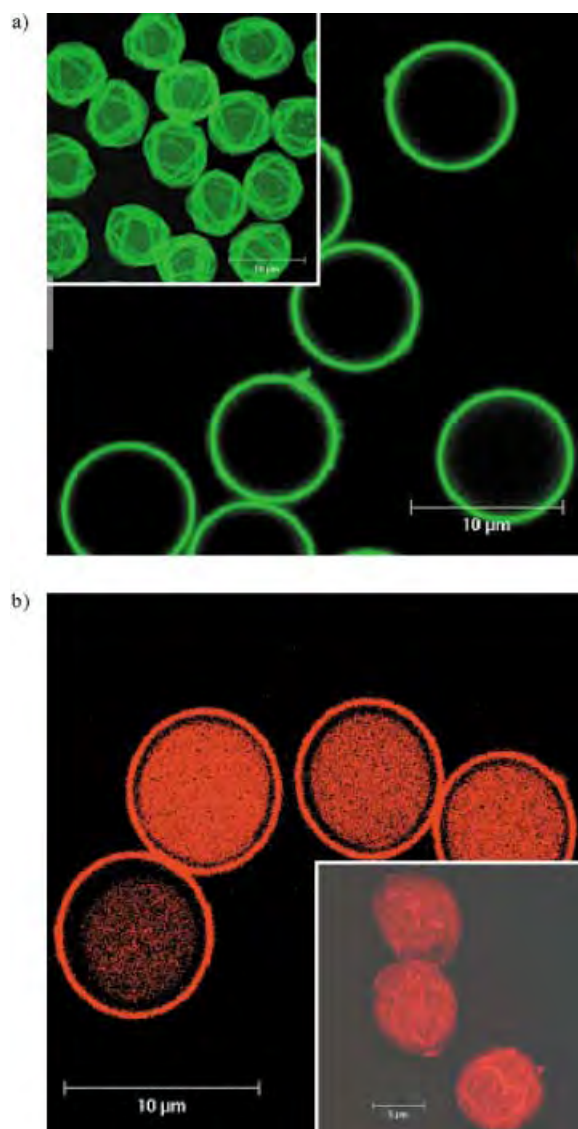


Figure 1. Confocal laser scanning microscopy (CLSM) images of control polyelectrolyte capsules composed of (PSS/PAH)₅ with a diameter of 8.7 μm both in (a) and out of solution (inset). After the capsules were incubated in Rd6G (2 mg mL⁻¹) solution, spontaneous deposition occurred (b). The out-of-solution morphology revealed further that the capsules were filled with rhodamine (b, inset).

under normal conditions. This phenomenon is spontaneous and has a lifetime of seconds, depending on aging and molecular weight. The ball-like morphology of the capsules when observed out of solution (Figure 1b, inset) further confirmed the self-accumulation of rhodamine. This compares with the control experiment (Figure 1a, inset) where the typical folds and creases for normal capsules can be discerned.

Figure 2 shows that tetramethylrhodamine isothiocyanate-labeled PAH (TRITC-PAH) and TRITC-dextran could also self-deposit into the interior of capsules composed of either (PSS/PAH)₅ or (PSS/PDADMAC)₅ (PDADMAC = polydiallyldimethylammonium chloride), yielding a higher concentration than in the bulk material. Further studies revealed that this spontaneous deposition was observed as a general phenomenon for polyelectrolyte capsules templated on MF particles, rather than being an occasional result, regardless of

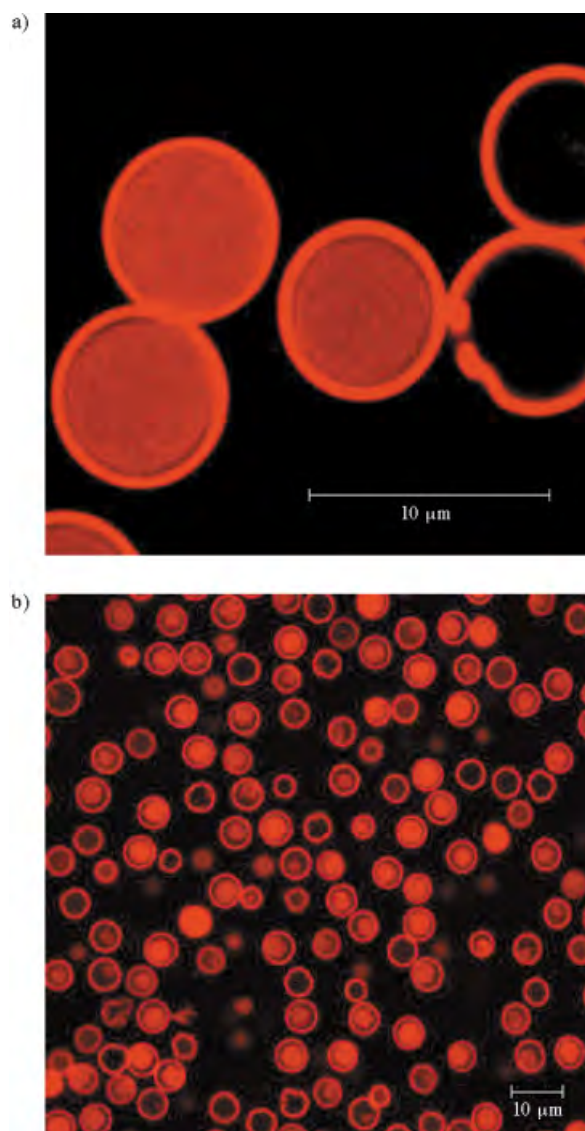


Figure 2. CLSM images illustrating that spontaneous deposition of water-soluble substances occurs within capsules templated on MF particles, regardless of the capsule size, diameter, and wall composition. a) TRITC-PAH self deposited into (PSS/PAH)₅ capsules with a diameter of 8.7 μm. b) TRITC-dextran ($M_w = 65$ kD) spontaneously incorporated into (PSS/PDADMAC)₅ capsules with a diameter of 5.5 μm.

the capsule size, layer thickness, and wall composition. Many water-soluble substances could be spontaneously encapsulated, but positively charged species displayed a more prominent tendency for self-deposition. In contrast, no self-deposition was observed for capsules derived from other templates such as CdCO₃, fluorescein diacetate, or red blood cells with the same nominal capsule composition, regardless of the charge of the water-soluble substances being encapsulated.

These results revealed the surprising fact that a substance can spontaneously diffuse from a low-concentration region to a high-concentration region of the capsule suspension system, without any means of assistance. There must, therefore, exist a force that drives the water-soluble substances from low- to high-concentration regions. A reasonable explanation for this phenomenon must be attributed exclusively to the special structure of the polyelectrolyte capsules templated on the MF

particles. We postulate that the additional driving force emanates from the charged species already existing within the interior of the intact capsules. This would most likely constitute a complex formed from PSS, the negatively charged inner wall material, and the degradation product of MF, the positively charged core template (Figure 3). Upon subjecting

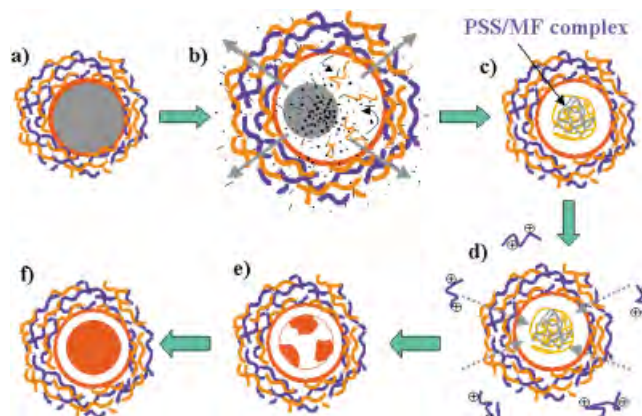


Figure 3. Schematic illustration of the spontaneous deposition mechanism, based on the formation of the PSS/MF complex during the core decomposition process.

the polyelectrolyte-coated MF particle (a) to lower pH conditions (0.1M HCl) the core material, a slightly cross-linked MF resin, is degraded into small particles that penetrate through the capsule wall simultaneously, while the capsule increases its size because of the osmotic difference (b). While this process occurs, the first layer (PSS) is partially dissociated from the wall and released into the interior because of the removal of the supported MF core. Hence, a complex is formed by the negatively charged PSS and some of the positively charged MF degradation product, which is too large to penetrate through the intact capsule wall (c). The PSS/MF complex is negatively charged, as has been proved by zeta-potential measurements (see below). The existence of the PSS/MF complex provides an additional driving force that induces water-soluble substances, especially positively charged species, to penetrate through the capsule wall and deposit around the complex (d, e), thus promoting self-deposition (f). It should be noted that the deposited substance must be in an aggregated or complexed form, rather than in its free state, so that the concentration of the substance within the interior of the capsule is always lower than in the bulk.

To verify this postulation, a model complex of PSS/MF was prepared from PSS and the MF-core degradation product. The zeta potential of this complex is -30.4 ± 0.9 mV, demonstrating that it is negatively charged. Confocal laser scanning microscopy (CLSM) proves that the positively charged rhodamine or TRITC-dextran (zeta potential 10.8 ± 1.0 mV) is selectively adsorbed onto the negatively charged PSS/MF complex, while no adsorption is found when negatively charged 6-CF is employed. The particle size of the PSS/MF complex observed under CLSM ranges from several hundred nanometers to several micrometers. This is large enough so that the complex cannot penetrate through the intact capsule

wall, whereas it can be released from the broken capsule interior through the large holes shown in Figures 2a and 2b. Spontaneous deposition was not observed for capsules with apparently broken shells under any conditions. This again proves that the existence of the complex is necessary and indispensable for the spontaneous deposition effect.

It has previously been shown by single-particle light scattering (SPLS) measurements that as much as 4% of the total mass of the capsule is formed from residual core material. Energy transfer studies, performed using a rhodamine labeled core and a fluorescein isothiocyanate (FITC) labeled wall, have further confirmed the existence of core residues within the interior of the capsule.^[2] A possible explanation that self-deposition only occurs in aged capsules is that the PSS/MF complex may contain an excess of the MF component. The smaller MF particles would only gradually be released from the complex and diffuse to the bulk solution, leaving net charges in the PSS/MF complex.

The fluorescence recovery after photobleaching (FRAP) technique has been employed to demonstrate that water-soluble substances are deposited in an aggregated or complexed form (Figure 4); FITC-dextran ($M_w = 77$ kD) was used as a detecting probe. Two capsules were selected: capsule 1 exhibited spontaneous deposition, whereas capsule 2 did not. After photobleaching the spots shown in Figure 4a, the interior of capsule 2 became dark, which proved that the fluorescein was completely destroyed. In contrast, only the bleached spot in capsule 1 became dark, which suggests that there had been no mass exchange within the interior. The fluorescence recovery profiles (Figure 4b) clearly demonstrate that no recovery occurs for capsule 1, whereas recovery is apparent for capsule 2, which indicates that mass exchange had occurred. These results prove that deposited materials should be in an aggregated or complexed form, and that capsule 2 has large holes in its walls.

Spontaneous deposition provides a route for the encapsulation of many water-soluble substances, especially biomolecules such as proteins, enzymes, and genes. At pH 7.0 albumin is negatively charged (Figure 5a; the zeta potential of FITC-albumin is -15.4 ± 3.6 mV) and, therefore, spontaneous deposition of FITC-albumin was not observed. After decreasing the pH value to 2.5, below the isoelectric point of albumin (4.2), the charge of FITC-albumin was reversed (zeta potential $+44.6 \pm 1.1$ mV), and was then found to sponta-

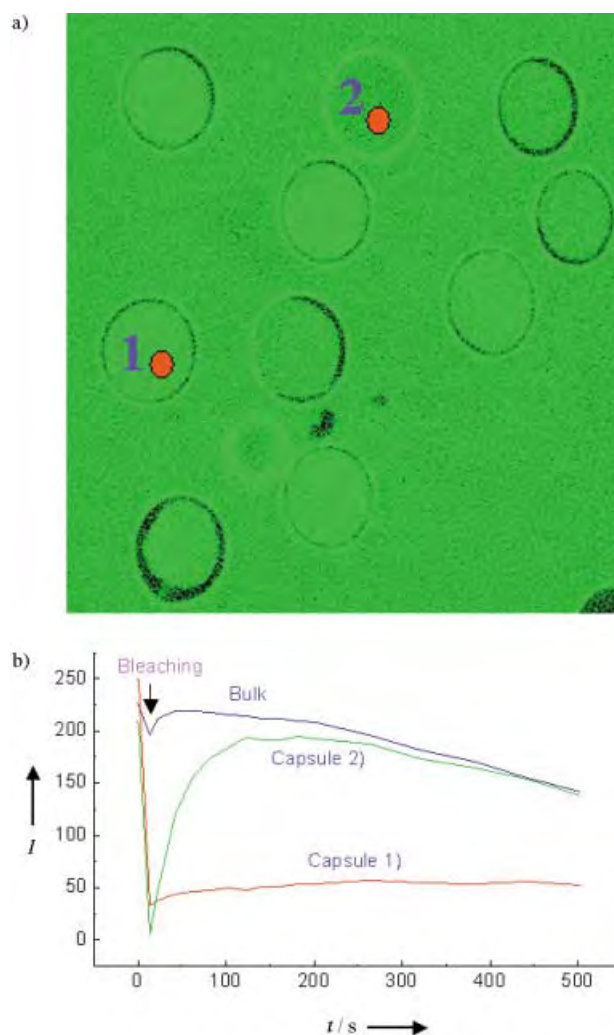


Figure 4. Fluorescence recovery after photobleaching (FRAP) analysis demonstrates that water-soluble substances only self-deposit in an aggregated or complexed form, rather than in their free state. FITC-dextran ($M_w = 77$ kD) was employed as a detecting probe. Two capsules were bleached simultaneously at the marked spots in (a). Capsule 1 exhibits the spontaneous deposition effect, while capsule 2 does not. After bleaching, the fluorescence intensity profiles (b) were obtained.

neously accumulate within the interior of the capsule (Figure 5b). The scanning force microscopy (SFM) image, obtained in tapping mode and out of solution, clearly displays

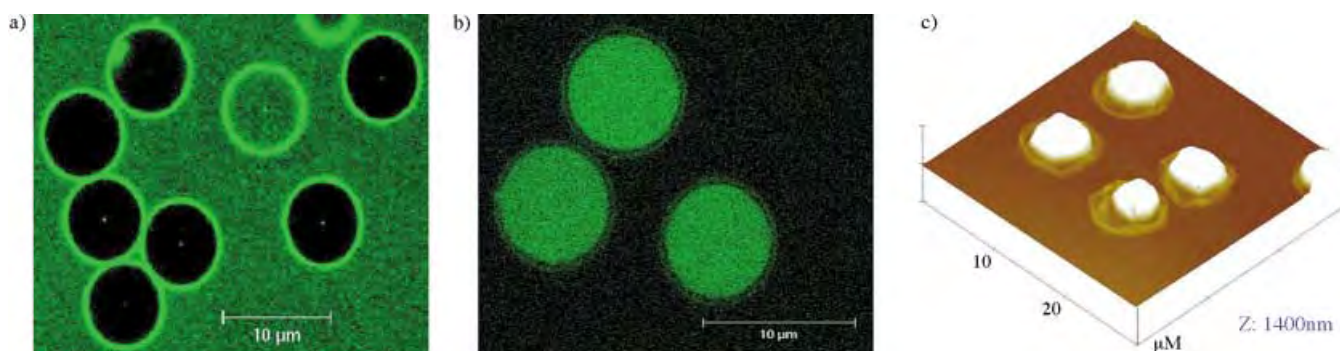


Figure 5. Spontaneous encapsulation of albumin utilizing the self-deposition effect. a) At pH 7.0 albumin is negatively charged hence no encapsulation occurs. b) After decreasing the pH value to 2.5 the charge was reversed and, hence, albumin was spontaneously encapsulated. c) Out-of-solution scanning force microscopy (SFM) clearly displays the large quantity of deposited albumin.

that a large accumulation of albumin had taken place (Figure 5c). Peroxidase and vitamin B2 have also been successfully encapsulated by employing this method.

It has been shown that many water-soluble substances such as rhodamine, PAH, and dextran can spontaneously accumulate in the interior of the aged polyelectrolyte capsules templated on MF particles, forming filled capsules under ordinary conditions. The driving force for this phenomenon is attributed to the existence of a negatively charged complex (PSS/MF) within the capsule interior. The deposited material is in an aggregated or complexed form, rather than existing in its free state, which constrains the system so that the real concentration of the deposited substance within the interior of the capsule remains lower than in the bulk. By utilizing this effect, biomolecules such as albumin have been successfully encapsulated in large quantity by simple alteration of the pH value. In conclusion, we have shown herein that spontaneous and quantitative encapsulation of a drug can occur by deposition within the interior of a macromolecule, which specifically binds to it and initiates its precipitation. This process might in turn be useful in controlling the sustained release of water-soluble agents.

Experimental Section

The sources of the chemicals employed in this study were as follows: PSS ($M_w = 70$ kD), PAH ($M_w = 15$ kD), and PDADMAC ($M_w = 200$ – 350 kD, 20% w/w in water, Aldrich; FITC-albumin (12:1 FITC:albumin molar ratio), FITC-Dextran ($M_w = 77$ kD), TRITC-dextran ($M_w = 65$ kD) and Rd6G, Sigma; MF particles, Microparticles GmbH, Berlin, Germany. All chemicals were used as received. TRITC-PAH was prepared by the literature route.^[9] The water used in all experiments was prepared in a three-stage Millipore Milli-Q Plus 185 purification system and had a resistivity higher than 18.2 MΩ cm.

Membrane filtration was employed to consecutively adsorb PSS and PAH onto MF particles.^[10] The adsorption of polyelectrolyte (1 mg mL^{-1}) was conducted in 0.5 M NaCl solution for 5 min followed by three washings in H_2O . After the desired number of oppositely charged layers had been adsorbed, the coated particles were added to 0.1 M HCl solution, in order to decompose the MF cores. The decomposition products and any excess HCl were then removed in H_2O by filtration with gentle agitation until pH neutrality was established. The model PSS/MF complex was prepared by dropping the core decomposition solution into a stirred 0.25 mg mL^{-1} PSS solution, followed by sufficient washing and filtration to remove the excess PSS or MF decomposition products.

Equal amounts of capsule suspension (aged for at least one month) and Rd6G, TRITC-PAH, TRITC-dextran, FITC-dextran, or FITC-albumin solution (2 mg mL^{-1}) were mixed together and stored for several minutes at room temperature to obtain the filled capsules. The solutions were then directly observed using CLSM.

CLSM images were taken with a Leica TCS NT inverted confocal system (Leica, Germany) equipped with a $100\times$ oil immersion objective. The images of capsules in aqueous solution were acquired immediately, whereas images of species out of solution were taken after any residual water had evaporated. The marked spots in FITC-dextran filled capsules were bleached for 1 sec at maximum laser output at 488 nm. The recovery images were recorded and the relative fluorescence intensity was calculated automatically by using Leica TCS NT software.

SFM images were recorded in air at room temperature (20–25 °C) using a Nanoscope III Multimode SFM (Digital Instrument Inc., Santa Barbara, CA). The samples were prepared by applying a drop of the capsule solution onto freshly cleaved mica.

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Solid-State and Solution Studies of a Tetrameric Capsule and Its Guests**

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Synthetic capsules, assembled and even self-assembled from their many components, are host structures available in variety. Whether held together with hydrogen bonds or metal–ligand interactions, their reversible encapsulation of guests provides a modern vehicle for physical organic chemistry. Molecular recognition, stabilization of reactive

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intermediates,^[1–3] and control of reactivity^[4–9] and of the assembly process itself are amenable to study within capsules.^[10–13] Like many of their biological counterparts,^[14] these assemblies do not form in the absence of suitable guests.^[15,16] Accordingly, there are intermolecular forces (in addition to mechanical ones) holding the guest within the host. Shape complementarity and the proper filling of space^[17] play roles, but the attractions of host and guest, at least in neutral capsules, lack detail. We report here on some of these interactions through crystallographic and complementary solution-phase studies of an assembly consisting of four host subunits and a nucleating guest (Figure 1a). The studies reveal a remarkable hydrogen-bonding motif: Each carbonyl oxygen atom of the diketone guest accepts hydrogen bonds from four identical N–H donors of the host.

The curvature and chemical surfaces of monomer **1** encode information that permits 24 hydrogen bonds to form when a tetrameric capsule assembles around a guest. The specific interactions between the guest molecule 2,6-adamantane-dione (**3**) and host (**1**)₄ that ultimately drive capsule assembly were elucidated by X-ray diffraction analysis.^[18] The four subunits of **3**⊂(**1**)₄ are held in a head-to-tail arrangement of

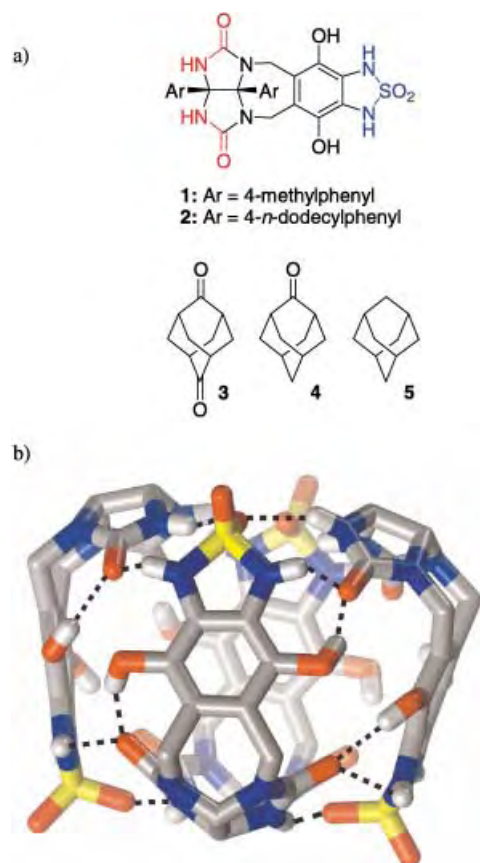


Figure 1. Summary of the monomers, guests, and capsules described herein: a) molecular structures of the monomers (**1** and **2**) and guests (**3**–**5**) used in this study. The glycoluril hydrogen bonding functionality is shown in red and the sulfamide group in blue; b) wireframe representation of the single-crystal X-ray structure of tetrameric capsule (**1**)₄. The guest, along with the glycoluril phenyl rings of the host and the hydrogen atoms not participating in hydrogen bonding have been omitted for clarity. Nitrogen atoms are shown in blue, oxygen atoms in red, sulfur atoms are depicted in yellow, and carbon atoms are shown in gray.

glycoluril (urea) and sulfamide functionalities (Figure 1b).^[19] Compared to an earlier generation of tetrameric capsules,^[13] this new capsule has an additional belt of eight phenolic hydrogen bonds around its equator that further stabilizes the assembly. The hydroxy groups on opposing sides of each monomer donate hydrogen bonds to different acceptors—one intermolecular and one intramolecular. The result is an alternating hydrogen-bonding motif that breaks the mirror symmetry of the monomer, leading to a chiral twist in the overall tetrameric capsule (Figure 1b). The tetramer crystallizes as a racemate with no symmetry, although the structure has very nearly *D*₂ symmetry.

The width of the capsule, measured between opposing aromatic walls, is approximately 10 Å in the solid state, and approximately 8 Å separates the two glycoluril/sulfamide hydrogen-bonding seams. Coupled with the curvature of the monomer, these dimensions provide a host cavity with an interior volume of 184 Å³.^[20] Cross-sectional views of the capsule depict the environment inside the cavity occupied by **3** (Figure 2). A perfect symmetry match for the cavity, guest **3** forms numerous CH–π interactions and van der Waals con-

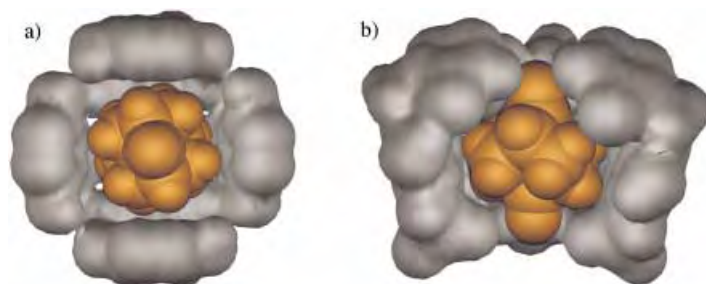


Figure 2. Space-filling views of **3**⊂(**1**)₄ from the single-crystal structure highlighting the orientation of the guest inside the host: a) cross-section of the structure of tetramer (**1**)₄ showing the close packing of the guest (**3**, brown space-filling spheres) inside the host (shown as a gray van der Waals surface); b) view showing the orientation of the guest (**3**) within the capsule. One of the four host monomers has been removed for clarity.

tacts with the electron-rich aromatic wall of the host. The guest is not disordered about any of the three pseudo-twofold axes of the capsule. Rather, its position within the host is well-defined and exposes the multiple intermolecular forces—including an intimate network of hydrogen bonds—that wedge the guest tightly into the capsule.

The long axis of the guest is oriented along the short axis of the host cavity. The orientation of the guest is determined by an unusual array of hydrogen bonds bridging the host and guest (Figure 3). The ketone oxygen atoms of the guest are fixed at each end of the cavity by polar interactions with the glycoluril/sulfamide hydrogen-bonding seam. The distances between each ketone oxygen atom of the guest and the four proximal urea nitrogen atoms, as well as the corresponding N–H···O angles all fall within the permissible ranges for hydrogen bonds in the solid state.^[21] This pattern represents an exceptional mode of hydrogen bonding: each ketone carbonyl group accepts hydrogen bonds from four identical donor atoms. These multiple attractive interactions between the guest and the host (a total of eight bifurcated hydrogen

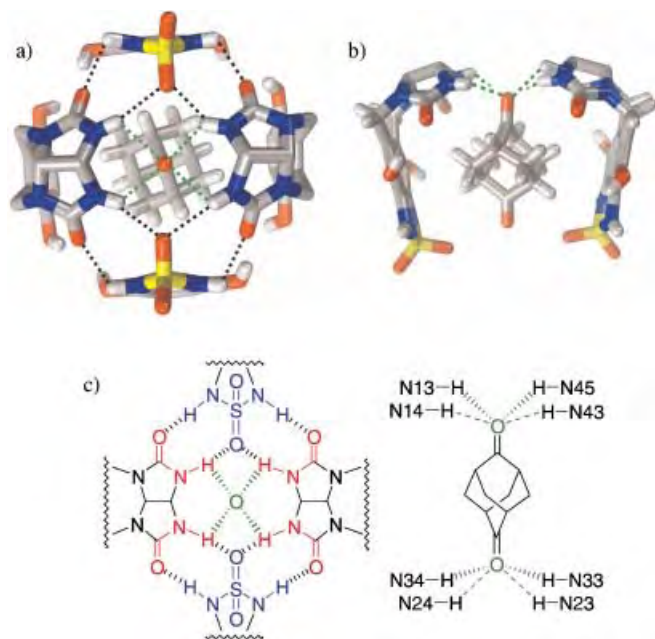


Figure 3. Detailed views of the hydrogen-bonding schemes between the guest and the tetrameric capsule shell: a) view down the axis of $(1)_4$ coincident with the oxygen–oxygen axis of **3**, which shows the hydrogen bonding between the urea groups and the guest ketone groups; b) side view of the same hydrogen-bonding interaction with two monomers of $(1)_4$ removed for clarity. The same color scheme as in Figure 1 has been used, and hydrogen bonds between the guest and host are shown as green dashed lines; c) left: a representation showing the hydrogen-bonding interactions between glycoluril functionalities (red), sulfamide groups (blue) and the ketone groups (green) of the guest, showing how the capsule is stitched together and the role the guest plays, right: the hydrogen-bonding interactions between the eight urea hydrogen atoms and the two ketone oxygen atoms. Selected hydrogen-bond lengths [Å] and N–H...O angles [°]: N13–O200 2.98, N14–O200 2.99, N43–O200 2.98, N45–O200 2.87, N23–O201 3.11, N24–H201 2.92, N33–O201 2.87, N34–O201 3.04; N13–O200 111, N14–O200 122, N43–O200 98, N45–O200 129, N23–O201 105, N24–H201 125, N33–O201 130, N34–O201 97.

bonds and at least four CH– π interactions) result in the guest filling approximately 72 % of the available space in the capsule cavity. This cavity packing coefficient was compared to several nanoscale capsules^[22–27] found in the Cambridge Structure Database (CSD). Our survey revealed that between 40 % and 65 % volume of the capsule cavities is typically filled by guests in the solid state; the structure of $3C(1)_4$ is unique in this regard.^[20]

When one equivalent of a suitable guest such as 2,6-adamantanedione (**3**), 2-adamantanone (**4**), or adamantane (**5**) is added to a CD_2Cl_2 solution of **2**, the ^1H NMR spectrum indicates the formation of a discrete assembly.^[13,28] Sharp, concentration-independent signals emerge, including singlets at approximately 10.6 ppm and 6.2 ppm, which correspond to the sulfamide N–H and glycoluril N–H protons, respectively (see Supporting Information). Upfield-shifted resonances appear for the bound guest; their 1:4 ratio relative to the host provides unambiguous evidence for the existence of a tetrameric assembly encapsulating one equivalent of guest in solution. Unlike the solid-state tetramer, the solution assembly exhibits overall D_{2d} symmetry, perhaps as a result of fast exchange between the two slightly twisted D_2 -symmetric enantiomers.

Do the host–guest contacts observed represent attractive interactions or do they exist only to minimize repulsions in the solid state? In solution, adamantane (**5**) is a sufficient guest to drive capsule assembly, presumably because of its ability to form CH– π interactions with the aromatic walls of the host, similar to those observed in the structure of $3C(1)_4$. ^1H NMR spectroscopic competition experiments show that 2-adamantanone (**4**) and 2,6-adamantanedione (**3**) are bound more favorably than adamantane by ≈ 0.7 kcal mol^{–1} and ≈ 1.8 kcal mol^{–1}, respectively. These differences can only be attributed to the stabilizing influence of hydrogen bonds between the guest carbonyl groups and the urea hydrogen atoms of the capsule. Although each individual hydrogen bond to the guest must be quite weak (ca. 0.2 kcal mol^{–1}), the solution and solid-state studies show that host–guest hydrogen bonding is not only an important driving force for capsule formation, but also dictates the guest binding selectivity.

As more complicated receptors capable of enclosing larger “empty” spaces are elaborated, the importance of solvent and other guests filling these spaces is appreciated. Other X-ray structures of multimeric hydrogen-bonded capsules are all the more spectacular given the larger number of components involved,^[29,30] with only one example reporting the presence and positions of the multiple solvent molecules occupying the capsule.^[31] Here, studying the lone guest within a constrained environment reveals two features: 1) the guest fills an inordinately large amount of space inside the capsule, and 2) the guest experiences a unique mode of hydrogen bonding for a carbonyl group. This novel binding motif^[32] may have implications in the activation of carbonyl compounds by multiple Lewis acids or in the binding of compounds in biological settings.

Experimental Section

General: The synthesis and characterization of all compounds, as well as a description of the procedure used to determine solution guest binding constants, are in the Supporting Information.

X-ray diffraction study of $3C(1)_4 \cdot 3CH_2Cl_2 \cdot 2C_5H_{12}$: A general crystallographic experimental is in the supporting information. CCDC-183906 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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The Supercritical Fluid Antisolvent Synthesis of $C_{60}(C_2H_x)$ ($x = 4$ or 6); The Crystal Structures of Two Materials Which Were Thought Unlikely to Exist**

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Synthetic routes to $C_{60}(\text{gas})$ intercalation compounds have reached the point where the intercalation of molecules larger than CO_2 has appeared impossible.^[1] We report the synthesis of the intercalation compounds of C_{60} with C_2H_4 and C_2H_6 , by using supercritical fluid (SCF) antisolvents to grow single crystals from C_{60} dissolved in 1,2-dichlorobenzene.

Interest in $C_{60}(\text{gas})$ intercalation compounds remains high. Their use as gas storage media has been suggested, with approximately 40 bar of intercalated gas able to be held at atmospheric pressure, with the possibility of controlled release.^[1,2] More recently, superconducting properties have been reported in these materials by hole and electron doping.^[3,4]

The lattice compressibility studies of Morosin and co-workers led to the discovery of the intercalating behavior of He and Ne into C_{60} .^[5] The field was expanded by Gadd et al., who introduced hot isostatic pressing (HIP, greater than 1.5 GPa and above 500°C) to open thermally the fullerene lattice and facilitate diffusion.^[1,2] In 1999, this work culminated in a review of all gas-intercalated species. There was no clear evidence for the intercalation of hydrocarbons larger than CH_4 because the forcing conditions of HIP appear to promote polymerization.^[1] It was concluded that true intercalation of hydrocarbons larger than CH_4 was unlikely.

In contrast, fullerene(solvent) intercalation compounds are known for a wide range of hydrocarbon solvents.^[6,7] These are related to the $C_{60}(\text{gas})$ materials, although they have several solvent molecules per C_{60} unit, with a complete rearrange-

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ment of the crystal lattice. They can be prepared by several routes; the evaporation of C_{60} solutions to dryness, conventional antisolvent precipitation, or vapor deposition.^[7]

C_2H_4 and C_2H_6 are too large and thermally unstable to be intercalated by HIP and both are poor solvents for C_{60} . Herein we show that C_2H_4 (critical temperature, $T_c = 9^\circ\text{C}$) and C_2H_6 ($T_c = 32.6^\circ\text{C}$) can be intercalated into C_{60} by greatly extending a route which has already been used successfully to form $C_{60}(\text{CO}_2)$, with supercritical CO_2 as the antisolvent.^[8]

The route involves a combination of traditional crystallization and supercritical antisolvent techniques (see Figure 1). Large crystals of $C_{60}(\text{C}_2\text{H}_4)$ and $C_{60}(\text{C}_2\text{H}_6)$ are produced despite using only very small quantities of C_{60} (typically 5 mg

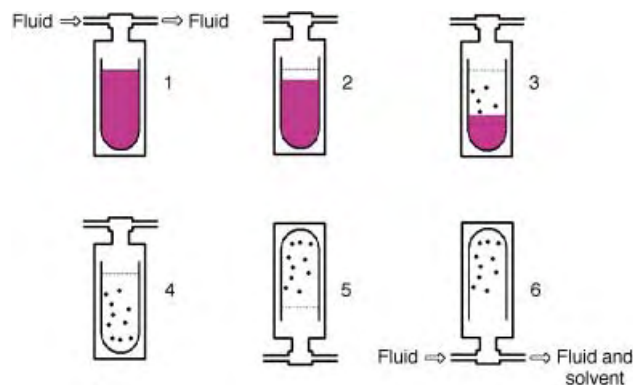


Figure 1. Schematic illustration of the supercritical technique for synthesizing $(\text{C}_2\text{H}_x)\text{-C}_{60}$ intercalation compounds. 1) A solution of C_{60} in 1,2- $\text{C}_6\text{H}_4\text{Cl}_2$ is placed in a glass tube inside a high-pressure view-cell; by placing the tube away from the direct path of incoming gas, the cell can be pressurized to 150 bar with the appropriate supercritical fluid at 35°C with minimal disturbance of the solution (C_2H_4 , $T_c = 9^\circ\text{C}$; C_2H_6 , $T_c = 32.6^\circ\text{C}$). 2) The cell is sealed and the fluid is allowed to diffuse into the solution. Gas is added periodically to maintain the pressure at 150 bar. 3) Crystallization takes place over a period of 3–5 days until the solution is completely colorless. 4) The view-cell is then turned upside down and flowing supercritical fluid is used to flush out the solvent and dry the crystals. 5 and 6) The dry crystals can then be recovered from the tube.

per experiment) and with relatively mild temperatures and pressures being applied (35°C , 150 bar). Smaller crystallites can also be prepared by supercritical antisolvent procedures similar to those used for $C_{60}(\text{CO}_2)$.^[8] The materials were analyzed by powder and single-crystal X-ray diffraction, which confirmed the formation of $C_{60}(\text{C}_2\text{H}_x)$ intercalated compounds that showed no noticeable change in gas content over six months. The single-crystal X-ray diffraction studies are, to the best of our knowledge, the first for any low-temperature phase of a $C_{60}(\text{gas})$ intercalation compound, the only similar studies relating to pure C_{60} .^[9]

The room-temperature X-ray powder pattern for $C_{60}(\text{C}_2\text{H}_4)$ (Figure 2) is similar to that of pure C_{60} apart from the emergence of a (200) peak, consistent with an fcc lattice with $a = 14.338(4) \text{ \AA}$ (compared with $a = 14.16(1) \text{ \AA}$ for pure C_{60}).^[9] Thus, C_2H_4 demonstrates the largest known lattice expansion of C_{60} without a change in the crystal lattice type (for example, $a = 14.243(3)$ and $14.247(2) \text{ \AA}$ for $C_{60}(\text{CO}_2)$ and $C_{60}(\text{Xe}_{0.316})$, respectively).^[8,10]

Single-crystal X-ray analysis at 290 K reveals a cubic F-centred lattice with $a = 14.28(3) \text{ \AA}$ and, on cooling, a phase

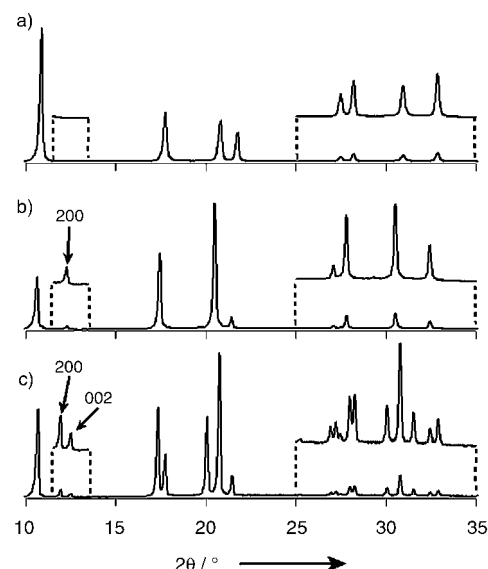


Figure 2. Powder X-ray diffraction patterns for C_{60} (a), $(\text{C}_2\text{H}_4)\text{-C}_{60}$ (b), and $(\text{C}_2\text{H}_6)\text{-C}_{60}$ (c) at room temperature.

change occurs leading to a primitive cubic lattice; this phase change is also observed for pure C_{60} . Differential scanning calorimetry (DSC) of $C_{60}(\text{C}_2\text{H}_4)$ suggests a transition temperature of 210.1 K, which is in good agreement with the change observed by X-ray diffraction (211(2) K); this is approximately 40 K lower than for pure C_{60} (249 K).^[11] 210 K is one of the lowest transition temperatures reported for $C_{60}(\text{gas})$ compounds (compared with 241, 235, and 240.2 K for compounds with CH_4 , CD_4 , and Ar, respectively).^[10,12] The 210 K transition is reversible and reproducible with no observable deterioration in crystal quality with repeated cycling.

Full structural refinements were carried out for data collected at 150, 90, and 30 K, with similar results for all three temperatures; all values are quoted for 150 K, further details are given below.^[13] The low-temperature structure of $C_{60}(\text{C}_2\text{H}_4)$, space group $Pa\bar{3}$, is very similar to that of pure C_{60} with the C_2H_4 molecules occupying octahedral interstitial sites, as has been observed in other gas intercalation compounds.^[10,12] Figures 3 and 4 show the molecular and packing structure. Neighboring C_{60} units have the same orientation as in pure C_{60} ^[9,14] such that, when viewed along the [110] direction, a bond fusing two hexagons of a neighboring unit is located above the center of a pentagonal face (C1–C5) which optimizes the alignment of an electron-rich region (the [6,6] bond) over an electron deficient one (the pentagonal face).^[14] These are the shortest intermolecular contacts between C_{60} molecules (3.252 and 3.338 Å). The bonds in the C_{60} molecule, which were refined freely, fall into two distinct groups, with shorter [6,6] bonds ranging from 1.386(3) to 1.391(3) Å and longer bonds fusing pentagons and hexagons ([6,5] bonds) ranging from 1.442(3) to 1.454(3) Å. We see no indication of disorder within the C_{60} unit but the intercalated C_2H_4 molecule does exhibit disorder and was modeled over three orientations at this site. As the hydrogen atoms could not be located, the discussion of the orientation of the C_2H_4 moiety with respect to the C_{60} unit is limited; the

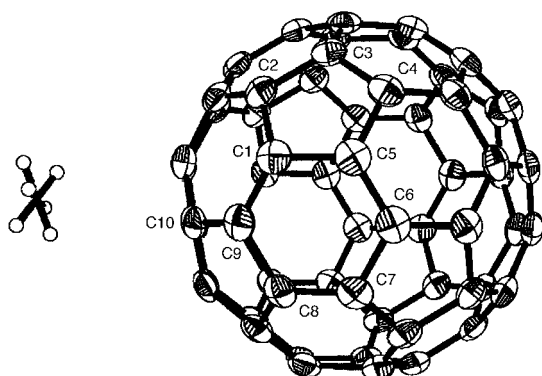


Figure 3. The molecular structure of $(\text{C}_2\text{H}_4)\text{-C}_{60}$, with the three orientations of ethene carbon displayed. Ellipsoids are drawn at the 50% probability level; ethene carbon atoms drawn as spheres of arbitrary radius.

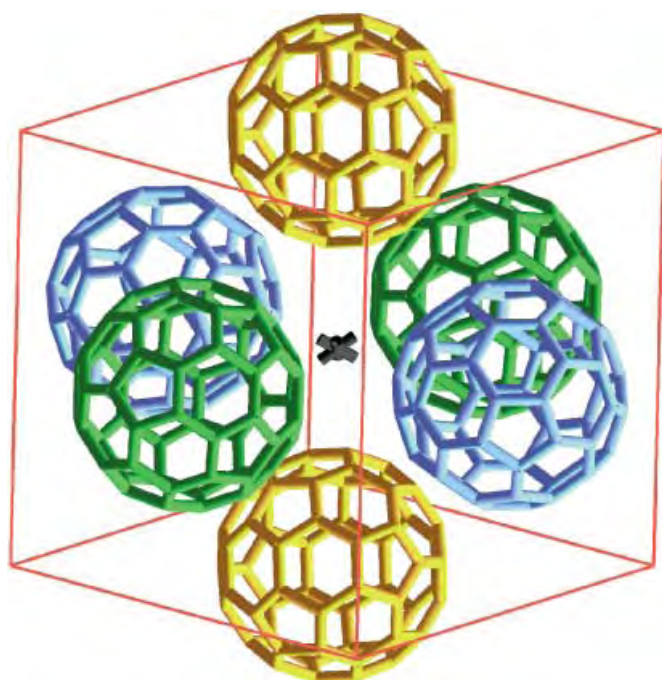


Figure 4. An illustration of the octahedral nature of the interstitial site occupied by the intercalated ethene molecule.

shortest $\text{C}\cdots\text{C}$ contact between the C_{60} and C_2H_4 units is 3.266 Å (to C10).

By contrast, $\text{C}_{60}(\text{C}_2\text{H}_6)$ differs from previous $\text{C}_{60}(\text{gas})_x$ ($x \geq 1$) intercalation compounds, as it has a body-centered tetragonal cell at room temperature; $a = 9.970(1)$, $c = 14.772(2)$ Å. This is the first reported instance of a new room-temperature phase occurring in such intercalation compounds. A phase transition occurs on cooling, but at a relatively high temperature (~ 268 (DSC) and 269(2) K (X-ray diffraction)).

As with $\text{C}_{60}(\text{CO}_2)$, the DSC results for $\text{C}_{60}(\text{C}_2\text{H}_6)$ suggest that a second transition occurs over a wide temperature range in addition to the sharp feature at about 268 K. Below 268 K, the crystals appear to have a primitive tetragonal lattice, similar to $\text{C}_{60}(\text{CO}_2)$, where $a \approx a_{\text{cubic}}/\sqrt{2}$.^[15] Repeated efforts to

solve and refine the structure in a number of tetragonal space groups were not successful as tetragonal symmetry constrains the mirror plane of C_{60} molecules to lie in the ab plane. As these problems could be caused by disorder, so data were collected at 30 K in an attempt to “freeze out” any motion of C_{60} . However, the same problems with the higher symmetry models occurred. This observation is similar to the neutron powder diffraction study of $\text{C}_{60}(\text{CO}_2)$ (5–293 K), where a reduction of the symmetry from tetragonal to monoclinic led to a satisfactory model.^[15] This same model with C_{60} in the monoclinic space group $P2_1/n$ was used as our starting point, which led to a far more satisfactory result with both C_{60} and

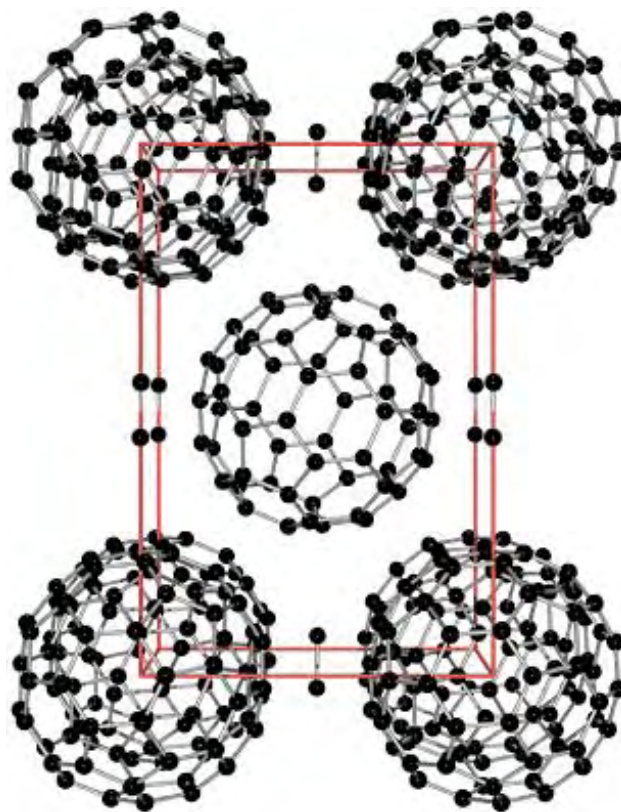


Figure 5. Packing diagram of $(\text{C}_2\text{H}_6)\text{-C}_{60}$ viewed along the $[100]$ direction, which shows the alignment of the ethane molecules with the c axis.

C_2H_6 units being well-ordered (Figure 5). While the agreement factors are still high, the model is chemically reasonable. Indeed, all models for $\text{C}_{60}(\text{C}_2\text{H}_6)$ are consistent regarding the alignment of the C_2H_6 molecules, which are located in the octahedral interstitial sites within the C_{60} lattice. The major difference between $\text{C}_{60}(\text{C}_2\text{H}_6)$ and $\text{C}_{60}(\text{CO}_2)$ is that the C_2H_6 molecules are almost exactly aligned with the c axis (Figure 5) while the CO_2 molecules lie at an angle of 21° to the bc plane and approximately 5° from the ac plane. This orientation is consistent with the expansion of the cell in the c -direction ($c = 14.829(2)$ Å, 150 K) when compared with pure C_{60} (14.061(5) Å).^[9]

In this paper, we have described a new route to previously inaccessible $\text{C}_{60}(\text{gas})$ intercalation compounds, which yields single crystals of sufficient quality for X-ray diffraction

studies. There are encouraging indications that our technique can be extended to larger hydrocarbons (for example, propene and propane). The same approach could also be applicable to other fullerenes. It has the distinct advantage over other routes to gas intercalation compounds in that it can be used with very small quantities of reagents, and all of the material is easily recovered at the end of the process. It is also likely that this technique could provide a simple method for crystallization of endohedral C_{60} compounds which have previously required large molecules as cocrystallites.^[16]

Experimental Section

Safety Warning: Experiments with supercritical fluids are performed at high pressure and should only be carried out with appropriate equipment. C_{60} (SES Research Inc, Houston, TX, 99.5%) was dissolved in 1,2-dichlorobenzene (Aldrich, 99.0%) to give a purple solution, which was filtered through a 0.45 μm filter prior to use.^[17–19] C_2H_4 and C_2H_6 were used as supplied (Air Products and Chemicals, Inc., 99.5%). A Gilson 303 HPLC pump with a chilled 10 SC pump head was used to generate pressure, controlled with a Jasco 880-81 back-pressure regulator. Powder X-ray diffraction patterns of all the new materials were taken at room temperature (Philips XPERT θ -2 θ diffractometer, $\text{Cu}_{K\alpha}$ radiation, $\lambda = 1.5405 \text{ \AA}$). Diffraction patterns were collected over a 2θ range of 5–60°, and indexed using the DICVOL91 program.^[20] DSC analysis was performed using a power-compensated Perkin Elmer DSC-7 under argon, with empty Al pans used as a reference prior to collection of the data. The material was initially cooled to –90°C and held at that temperature for 5 min before heating to 20°C at a rate of 10°C min^{–1}. The sample was then cooled to –90°C at a rate of 200°C min^{–1} and held at that temperature for 10 min prior to heating again from –90 to 20°C at a rate of 10°C min^{–1} to record the data.

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- [13] Single-crystal diffraction data were collected for $C_{60}(C_2H_4)$ at 150, 90, and 30 K and for $C_{60}(C_2H_6)$ at 150 and 30 K. In all cases, X-ray diffraction data were collected using graphite-monochromated $\text{Mo}_{K\alpha}$ radiation ($\lambda = 0.71073 \text{ \AA}$) on a Bruker CCD area-detector diffractometer. Integrated intensities, corrected for Lorentz and polarization effects, were obtained using SAINT v6.02a.^[21] For data collected at 150 and 90 K the crystals were cooled using an Oxford Cryosystems Cryostream N_2 -flow, and for the data collected at 30 K, an Oxford

Cryosystems HELIX open-flow He gas cryostat was used.^[22] The structure of $C_{60}(C_2H_4)$ was solved by direct methods (SHELXS97) and all refinements were made against F^2 using full-matrix least-squares (SHELXTL97).^[23,24] All ordered carbon atoms were refined with anisotropic atomic displacement parameters; hydrogen atoms were not located. The C_2H_4 moiety was modeled as a 0.333 occupied site after anisotropic refinement of the occupancy gave this value, with an estimated standard deviation of 0.002. Hence, three orientations of C_2H_4 are generated by symmetry (giving 1:1 $C_{60}:C_2H_4$). All $C_{60}(C_2H_4)$ crystals examined showed merohedral twinning. For $C_{60}(C_2H_6)$, the structural model from Gadd et al. was used as a starting point.^[15] A twin law was applied (–100, 010, 001) and the ratio of components was refined to 0.415(6) and 0.395(6) at 150 and 30 K, respectively. A different crystal was used for each set of data; all crystals (except for that of $C_{60}(C_2H_6)$ at 150 K, which was glued using araldite) were mounted in perfluoropolyether oil on dual-stage fibers and flash frozen. The 150 and 90 K data for $C_{60}(C_2H_4)$ were collected on a Bruker SMART1000 diffractometer, the 30 K data on a SMART 1 K diffractometer, and the 150 K data for $C_{60}(C_2H_6)$ on a Bruker APEX diffractometer. $C_{60}(C_2H_4)$: Black tablet-shaped crystal, size $0.22 \times 0.20 \times 0.11 \text{ mm}$, $M_r = 748.65$, cubic, space group $Pa\bar{3}$ (no. 205), $a = 14.1902(12) \text{ \AA}$, $V = 2857.4(7) \text{ \AA}^3$, $T = 150 \text{ K}$, $Z = 4$, $\rho_{\text{calcd}} = 1.740 \text{ g cm}^{-3}$, $\mu(\text{Mo}_{K\alpha}) = 0.10 \text{ mm}^{-1}$, 25297 reflections measured ($2\theta_{\text{max}} = 58^\circ$), 1340 unique ($R_{\text{int}} = 0.072$), $wR_2(F^2) = 0.103$ (all data), $R_1(F) = 0.046$ (916 data with $I > 2\sigma(I)$, 96 parameters). $C_{60}(C_2H_6)$: Black platelike crystal, size $0.15 \times 0.08 \times 0.02 \text{ mm}$, $M_r = 750.67$, monoclinic, space group $P2_1/n$ (no. 14, non-standard setting of $P2_1/c$), $a = 9.8467(12)$, $b = 9.8465(12)$, $c = 14.829(2) \text{ \AA}$, $\beta = 90.038(2)^\circ$, $V = 1437.8(3) \text{ \AA}^3$, $T = 150 \text{ K}$, $Z = 2$, $\rho_{\text{calcd}} = 1.734 \text{ g cm}^{-3}$, $\mu(\text{Mo}_{K\alpha}) = 0.10 \text{ mm}^{-1}$, 7375 reflections measured ($2\theta_{\text{max}} = 50^\circ$), 2523 unique ($R_{\text{int}} = 0.057$), $wR_2(F^2) = 0.338$ (all data), $R_1(F) = 0.133$ (2497 data with $I > 2\sigma(I)$, 281 parameters). CCDC-187490–187494 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit @ccdc.cam.ac.uk).

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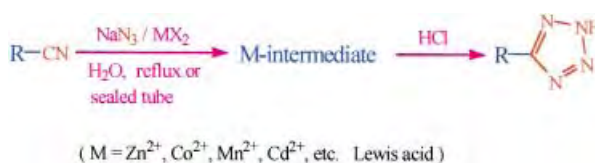
Novel, Acentric Metal–Organic Coordination Polymers from Hydrothermal Reactions Involving In Situ Ligand Synthesis**

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Many solid-state physical properties, such as pyroelectricity, piezoelectricity, ferroelectricity, second harmonic generation (SHG), and triboluminescence, are only found in noncentrosymmetric bulk materials.^[1] In spite of the practical importance of these properties in many technological applications, including telecommunications, optical storage, and information processing, the generation of acentric solids from achiral building blocks still depends upon “Edisonian” approaches. The rational construction of structurally ordered noncentrosymmetric and chiral metal–organic solids remains a great challenge. Recently, attempts to generate acentric metal–organic coordination polymers (MOCs) and organic solids by employing crystal engineering strategies have met with some success.^[2] However, crystal engineering has not developed to the stage where a desired structure or crystal symmetry can be ensured.^[3]

Although it is not always possible to exert synthetic control, a fascinating variety of acentric and novel MOCs have been obtained from hydrothermal reactions.^[4] These reactions are often quite complicated and may involve in situ hydrolysis, oxidation, and ligand synthesis. The products generated under hydrothermal conditions cannot normally be obtained by direct mixing of solutions of metal ions and ligands.^[4]

Recently, Sharpless et al. reported a safe, convenient, and environmentally friendly procedure for the synthesis of a variety of 5-substituted 1*H*-tetrazoles in water. The 1*H*-tetrazoles are prepared by addition of azide to nitriles in water with Zn salts as Lewis acid catalysts (Scheme 1).^[5] The role of Zn in this reaction is unclear, but it was suggested that the solid intermediate in the reaction of PhCN with ZnBr₂ and NaN₃ is (PhCN₄)₂Zn. The characterization of such an



Scheme 1. Synthesis of 1*H*-tetrazoles.

intermediate may provide important clues to the role of Zn in this reaction, and this in turn may allow synthetic chemists to further optimize this synthetic approach.

We recently combined metal salts with potentially bridging organic ligands under hydrothermal conditions to produce a range of new materials.^[4b–f,6] Our experience with such systems prompted us to conduct structural studies of the products or “intermediates” in the hydrothermal reaction of ZnCl₂ (or CdCl₂) with 3-cyanopyridine (or 4-cyanopyridine) and NaN₃ in water (Scheme 2). To our surprise, the intermediates trapped or synthesized at high temperature all crystallize in acentric space groups and display SHG responses in the solid state which are unprecedented in tetrazole–metal coordination chemistry, as far as we are aware.^[7] Here we report their solid-state structures and preliminary SHG properties.



Scheme 2. Synthesis of 1–3.

The reaction of NaN₃, 3-cyanopyridine, and ZnCl₂ or CdCl₂ in water yields [Zn(OH)(3-ptz)] (1) and [CdN₃(3-ptz)] (2), respectively, while the corresponding reaction of 4-cyanopyridine with ZnCl₂ gives [ZnCl(4-ptz)] (3). For each reaction the IR spectrum indicates the absence of the cyano group, which is consistent with a [2+3] cycloaddition between the cyano group and the azide anion. Crystal structure analyses of all products confirm the formation of 5-(3-pyridyl)tetrazolate (3-ptz) and 5-(4-pyridyl)tetrazolate (4-ptz), and show that the new ligand acts as a bridging ligand in each of the products 1–3.

Compound 1 contains hydroxide and the 3-ptz ligand. In this structure parallel –Zn–OH–Zn–OH– chains extend in the *c* direction, while triply connecting 3-ptz ligands link the chains together (Figure 1a).^[8] The result is a complex two-dimensional (2D) polymer with five-coordinate Zn atoms bound to two OH[–] and three 3-ptz ligands. Each ptz ligand coordinates through the 2,3 nitrogen atoms of the tetrazole and the pyridyl nitrogen atom. All donor atoms form reasonably strong bonds with the zinc atom (2.156(4) Å),

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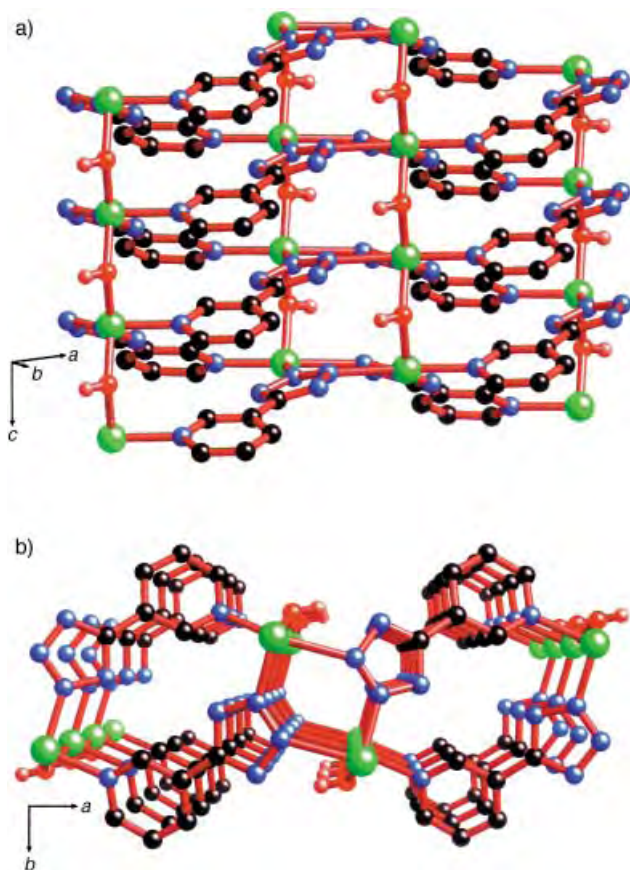


Figure 1. The 2D structure of **1**. a) A view almost normal to the axes of the twofold helices that extend in the *c* direction. b) A perspective view of the sheet structure from a direction parallel to the *c* axis.

except for the tetrazole nitrogen atom *trans* to the pyridyl group, which has a Zn–N distance of 2.464(4) Å. A unique structural feature present in each 2D sheet are helices that extend in the *c* direction. Zinc atoms of neighboring –Zn–OH–Zn– chains, bridged by the pyridyl and tetrazole units of a single 3-ptz ligand, form part of twofold –Zn–ptz–Zn–ptz–Zn– helices. Two such helices within a sheet are apparent in Figure 1a. Within a single sheet all helices have the same handedness, while neighboring sheets have helices of opposite handedness. Figure 1b shows the sheet almost parallel to the axes of the helices.

Compound **2** unexpectedly contains azide.^[8] The structure determination indicates a 3D polymer in which azide ligands adopt two distinct bridging modes in the structure. One unique 3-ptz ligand acts as a tetradentate unit. The complex structure is perhaps best understood by first considering zig-zag chains of cadmium atoms extending in the *c* direction (Figure 2a). The two unique types of azide ions alternate as bridging ligands along the chain. In addition, each ptz ligand is linked to three cadmium atoms within each chain through the 1,2 nitrogen atoms of the tetrazole and the pyridyl nitrogen atom. Figure 2b shows the chains viewed down the *c* axis. The bridging azide and 3-ptz ligands depicted in Figure 2a provide five of the six donor atoms attached to the cadmium centers.

Identical parallel zig-zag chains also extend in the *c* direction. In addition to the coordinate bonds shown in Figure 2a and 2b each 3-ptz ligand also forms another link

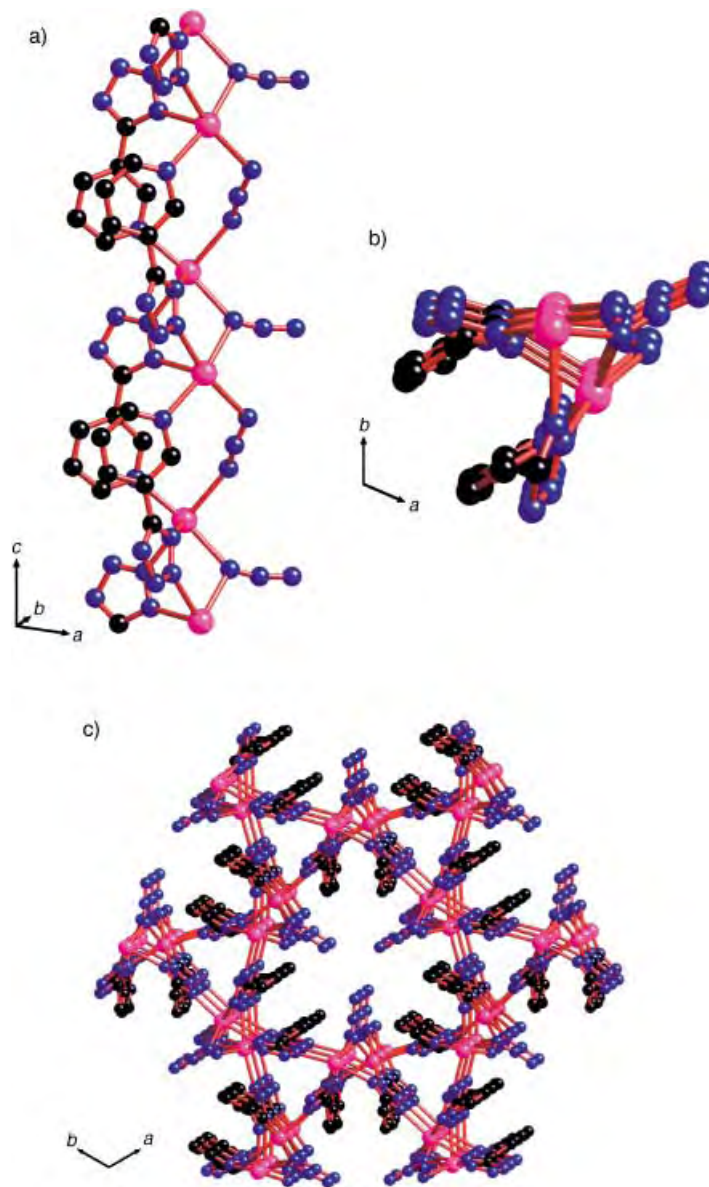


Figure 2. The 3D structure of **2**. a) Part of the zig-zag chain of Cd atoms bridged by azide ions and 3-ptz ligands. b) The zig-zag chains viewed down the *c* axis. c) The 3D structure of **2** viewed down the *c* axis. The interchain connections are almost normal to the *c* axis. Only one orientation for each disordered azide ion is shown.

from the tetrazole ring (the nitrogen atom in the 4-position) to a cadmium center on a neighboring chain and thus completes the octahedral environment of the metal atom. All Cd–N bond lengths fall in the range 2.320(5)–2.495(12) Å. From each chain, links from the ptz ligands extend to two neighboring chains. Two other neighboring chains provide nitrogen atoms that link to the metal centers. Thus, each chain is linked to four other chains by coordinate bonds that are almost perpendicular to the *c* axis.

Trios of connected chains form narrow channels of approximate trigonal cross section (Figure 2c). Each chain is part of two such trios. Also present are larger channels formed by connection of six chains. Azide ligands extend from three of these chains towards the center of these larger channels and partially fill the network voids. These voids represent 220 Å³

per unit cell, that is, 14.7% of the cell volume. The distance between cadmium atoms on opposite sides of the channel is equal to the cell dimension a of 13.8325(4) Å. The overall structure is chiral, with the crystal adopting the trigonal enantiomeric space group $P3_121$.

Compound **3** has the formula $[\text{ZnCl}(\text{4-ptz})]$ and a 3D network structure. Each 4-ptz ligand is bound to three Zn atoms, and each Zn atom is bound to three 4-ptz ligands. The tetrahedral coordination environment of each Zn atom is completed by a terminal chloride ion. All Zn–N distances are in the range between 2.026(4) and 2.037(3) Å. This complex coordination polymer is perhaps best understood in terms of $[\text{ZnCl}(\text{4-ptz})]$ strips that extend in the c direction. There are two unique four-coordinate Zn atoms and two unique 4-ptz ligands. In the strip shown in Figure 3a, one of the Zn atoms has its tetrahedral coordination environment completed by atoms within a strip. The other zinc atom relies upon coordination of a pyridyl group from a neighboring strip to complete its coordination sphere. Two identical parallel strips lying in a plane beneath the strip represented in Figure 3a provide the pyridyl groups that coordinate to the zinc atoms.

The apparently uncoordinated pyridyl groups represented in Figure 3a are in fact coordinated to Zn atoms of two identical parallel strips that lie above the plane of the strip shown. Thus, each strip is linked to four other strips in this infinite 3D network. Figure 3b shows the interstrip connections viewed parallel to the strips.

Inspection of Figure 3b reveals large channels with an approximately hexagonal cross section. These intraframework voids are occupied by a second identical network. The two networks are represented in Figure 3c.

Thermogravimetric analysis (TGA) of these crystalline complexes showed that **1–3** are stable up to about 270, 330, and 390°C, respectively, while beyond these temperatures, they all decompose and lose their crystallinity.

The adoption of acentric space groups by **1–3** prompted an investigation of their optical activity. Preliminary investigations show that **1–3** are SHG active, with a relative strength order of $\mathbf{3} > \mathbf{1} > \mathbf{2}$. The strong powder SHG response of **3** may be attributed to a good donor–acceptor system in which the pyridyl ring acts as acceptor and the tetrazole ring as donor. Such electronic asymmetry is essential for second-order optical nonlinearity.

In conclusion, apart from affording insights into the nature of the solids produced in the reactions by Sharpless et al., the work here provides strong encouragement that a wide variety of coordination polymers can be produced by hydrothermal generation of bridging ligands in the presence of appropriate metal ions. In particular the formation of ligands such as 3-ptz and 4-ptz that tend to place metal atoms in irregular arrangements but still allow the formation of infinite networks offers good prospects for generating acentric crystalline materials that may possess desirable physical properties such as SHG.

Experimental Section

Preparation of $\text{C}_6\text{H}_5\text{N}_5\text{OZn}$ (**1**): Hydrothermal treatment of ZnCl_2 (2.0 mmol), 3-cyanopyridine (2.0 mmol), NaN_3 (3.0 mmol), and water (3.0 mL) for 1 d at 160°C yielded crystalline colorless needles. The yield of **1** was about 75% based on 3-cyanopyridine. Elemental analysis (%) calcd

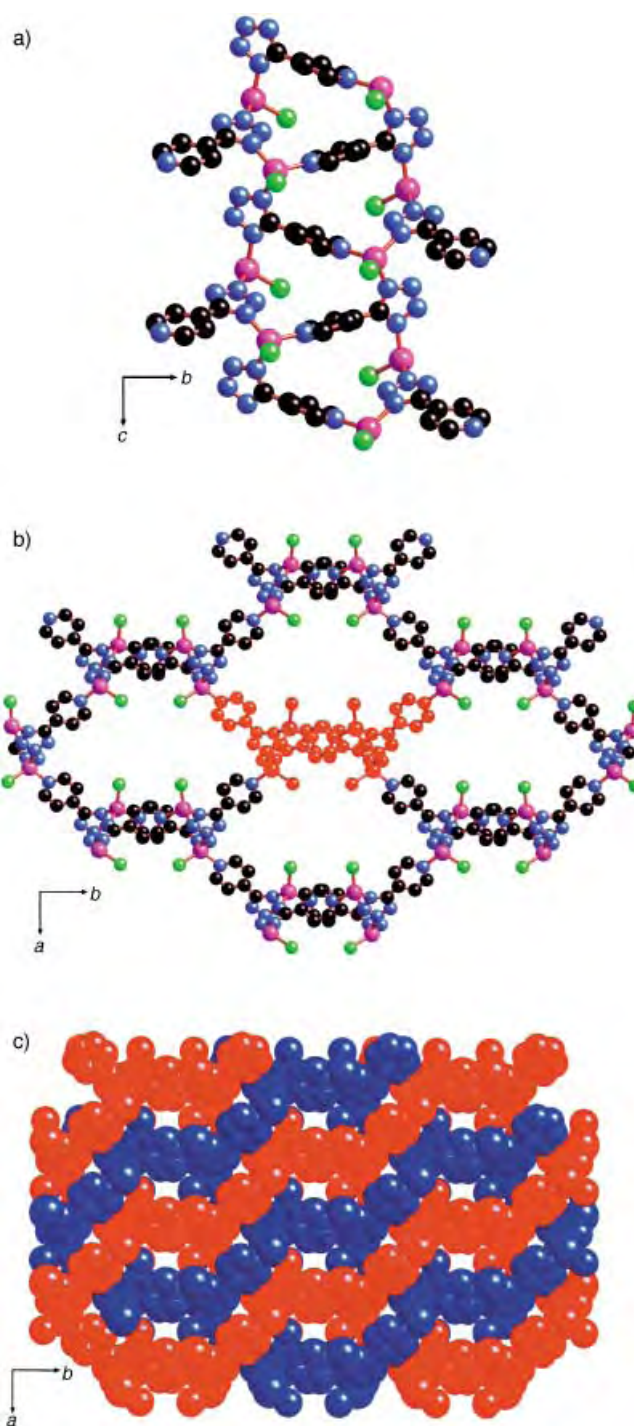


Figure 3. The 3D interpenetrating structure of **3**. a) $[\text{ZnCl}(\text{4-ptz})]$ strips extending in the c direction. b) A view down the c axis of **3** showing the connections between strips. The central strip is highlighted with red spheres. c) A space-filling model showing the interpenetration of the independent networks within the crystal.

for $\text{C}_6\text{H}_5\text{N}_5\text{OZn}$ (**1**): C 31.51, H 2.19, N 30.63; found C 31.72, H 2.26, N 30.92. IR (KBr): $\tilde{\nu}$ = 3398(vs), 3077(w), 1614(w), 1473(w), 1424(s), 1198(w), 1168(w), 1148(m), 1129(m), 1099(w), 1045(w), 1018(m), 952(w), 982(w), 818(m), 753(m), 717(m), 696(s), 650(w), 471(m) cm^{-1} .

Preparation of $\text{C}_6\text{H}_5\text{N}_5\text{Cd}$ (**2**): The procedure was identical to that of **1**, except that CdCl_2 was used instead of ZnCl_2 and the temperature was 120°C. Colorless crystalline needles of **2** were formed in 55% yield. Elemental analysis (%) calcd for $\text{C}_6\text{H}_5\text{N}_5\text{Cd}$ (**2**): C 23.95, H 1.33, N 37.26; found: C 23.82, H 1.42, N 37.52. IR (KBr): $\tilde{\nu}$ = 3406(brw), 3089(w), 2075(vs);

$\nu(\text{N}_3^-)$, 1612(w), 1585(w), 1457(w), 1428(m), 1363(m), 1291(w), 1202(w), 1165(m), 1128(w), 1022(m), 956(w), 931(w), 816(m), 762(m), 726(w), 696(m), 644(w), 450(w) cm^{-1} .

Preparation of $\text{C}_6\text{H}_4\text{N}_5\text{ClZn}$ (**3**): The procedure was identical to that of **1** except that 4-cyanopyridine was used instead of 3-cyanopyridine. Colorless crystalline blocks of **3** were formed with a 55% yield. Elemental analysis (%) calcd for $\text{C}_6\text{H}_4\text{N}_5\text{ClZn}$ (**3**): C 29.16, H 1.62, N 28.34; found: C 29.30, H 1.60, N 28.52. IR (KBr): $\tilde{\nu}$ = 3538(s), 3374(m), 3249(w), 3110(w), 3043(w), 2097(s), 1626(s), 1466(w), 1437(s), 1402(w), 1275(w), 1237(w), 1224(w), 1184(w), 1140(w), 1104(w), 1065(m), 1023(m), 847(m), 835(m), 759(w), 721(s), 564(w), 534(w), 472(w) cm^{-1} .

Measurement of SHG response: The second-order nonlinear optical intensity was approximately estimated by measuring a powder sample of 80–150 μm diameter in the form of a pellet (Kurtz powder test^[9]) relative to urea. A pulsed Q-switched Nd:YAG laser at a wavelength of 1064 nm was used to generate the SHG signal from the sample. The backscattered SHG light was collected by a spherical concave mirror and passed through a filter that transmits only 532 nm radiation. Thus the SHG response of **1–3** are about 0.4, 0.2, and 1.25 times that of urea, respectively.

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Probing the Spatial Distribution and Morphology of Supported Nanoparticles Using Rutherford-Scattered Electron Imaging**

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There is a growing need for ultrasensitive methods that can determine the size, elemental composition, precise location, spatial distribution, and detailed morphology of a wide variety of nanoparticles anchored on high-area supports. In the field of heterogeneous catalysis alone, and in the related area of fuel-cell technology, many different high-area (and generally low-atomic-number, Z) supports such as silica, alumina, and magnesia, as well as graphitic, amorphous, or adamantane carbons and thermally stable polymers, are employed. The active nanoparticles consist almost invariably of either pure, high- Z elements such as Pt, Pd, and Ru, or heterometallic species such as Pt–Pd, Pt–Fe, Pt–Cu, Pt–Ru, or Pt–Fe–Co, Pt–Cr–Co, and Pt–Co–Ga.^[1–7] In the field of constrained colloidal and metal clusters which exhibit electronic quantum size effects, typical nanoparticle materials are CdS, CdSe, and Cd₃P₂.^[1,8,9] There are, in addition, many other areas of nanotechnology and biology where it is important to obtain three-dimensional (3D) morphological information, as well as knowledge of the spatial distribution and composition of nanoparticles.

It has been shown previously that the size and distribution of minute particles of the kind described above are conveniently investigated using high-resolution scanning transmission electron microscopy (STEM) equipped with a high-angle annular dark-field (HAADF) detector.^[10–14] To a good approximation, electrons scattered at high angles (greater than 30 mrad) obey Rutherford's scattering law: that the scattering cross-section is proportional to Z^2 . Moreover, the scattered electron wave is predominantly incoherent in nature, so that images formed using a HAADF “Rutherford”

detector do not show the complicating contrast changes associated with coherent scattering, such as those which occur in bright-field (BF) images (formed from Bragg-scattered electrons). As a consequence, HAADF images can be interpreted directly and their intensity is a monotonic function of the sample thickness and atomic number, which is a prerequisite for the electron tomography experiments described below.

Back-scattered electrons (BSEs), which are those electrons scattered to angles greater than 90° (see Figure 1), also yield sharp images for nanoparticles that contain more than

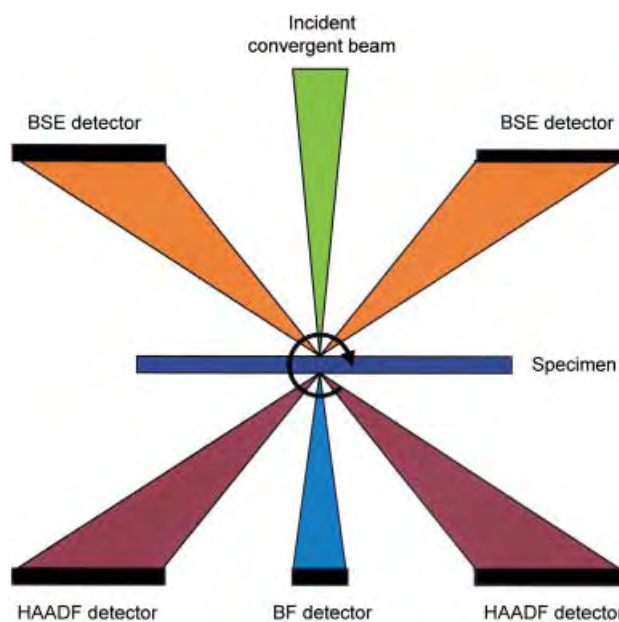


Figure 1. Schematic diagram illustrating the geometry of detectors used for STEM BF, STEM HAADF, and SEM BSE imaging.

100 atoms of high- Z materials distributed over low- Z supports, because they too obey Rutherford's scattering law. BSE scattering may be thought of as “reverse Rutherford scattering” although the exact form of the experimental BSE scattering is modified by the high (greater than 90°) scattering angle and by the bulk specimen environment.^[15–17] Figure 2 shows typical examples of Rutherford-scattered imaging of nanoparticles of a commercially important palladium-on-carbon catalyst recorded with a BSE detector in a field-emission scanning electron microscope (a), as well as a STEM HAADF image of the same sample (b), recorded in the same instrument. It is clear that high spatial resolution (of the order of 1 nm) is achievable by scanning electron microscopy (SEM), which was performed at 30 kV, and that similar images are obtained in either back-scattered (BSE) or forward-scattered (HAADF) mode. It is a simple matter to identify small particles in thin sections by energy dispersive X-ray (EDX) methods. With a bulk (electron-opaque) sample the sensitivity of the BSE method in the nanometer range, and of EDX on the submicron scale, increases at medium-to-low voltages (limited by instrumental parameters). The mixing of the SEM BSE signal, primarily for higher- Z particle imaging, with a component of secondary-electron imaging, for lower- Z support topography, together with the use of medium-to-low

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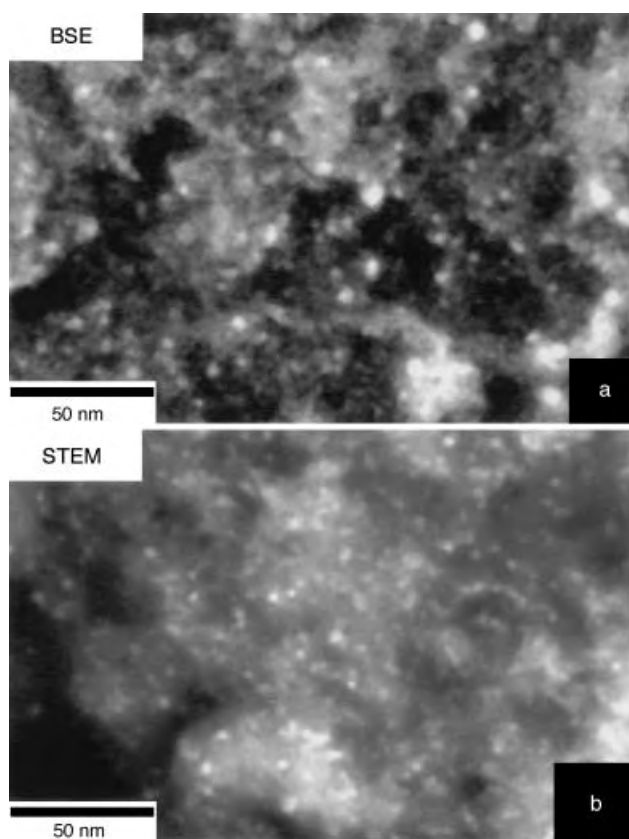


Figure 2. a) SEM BSE image and b) STEM HAADF image of Pd nanoparticles supported on a semicrystalline carbon support.

beam energies, may prove to be the optimum combination for SEM imaging.^[18]

Since the late 1960's,^[19,20] electron tomography has been used in the biological sciences to investigate the 3D structure of both highly symmetric objects (for example, viruses and macromolecules) as well as those lacking crystallographic (or other) order (for example, cells). However, it is only very recently that this approach has been applied successfully by de Jong, Koster, and co-workers^[21,22] to the study of physical systems, in particular zeolitic materials, using conventional BF (Bragg-scattering) transmission electron microscopy (TEM) imaging.

For electron tomography, a series of images must be recorded at successive tilt angles using a signal that satisfies the “projection requirement”, namely that the signal used to form the images must be a monotonic function of the projected thickness of the object under study.^[19,23] For a crystalline object, the diffraction contrast prevalent in a BF image generally rules out such images for tomographic use. Furthermore, if a coherent (or even partially coherent) beam is used, as is the case in most modern field-emission electron microscopes, the images of even non-crystalline objects may show Fresnel fringes, the intensities of which will also not satisfy the projection requirement.^[24]

High-angle-scattered electrons, recorded by STEM with a HAADF detector and SEM with a BSE detector, offer an essentially incoherent signal that does satisfy the projection requirement, even for crystalline objects. Firstly, such images are monotonically dependent on the atomic number of the

object and its thickness. The strong Z-dependence can be seen from Figure 2: the “heavy” (high-Z) nanoparticles stand out clearly from the semicrystalline carbon support. The clarity of the image is testimony to the superiority of the HAADF and BSE approach over either BF STEM or BF TEM for imaging these structures. Secondly, the large beam currents used in fixed-beam methods (e.g. conventional TEM) can very rapidly damage any material that is beam-sensitive; many catalyst systems fall into this category. However, in STEM and BSE SEM, a much smaller degree of beam exposure is involved. Although the current density within the convergent probe is high, its energy can be dissipated to the surrounding (non-illuminated) areas. In addition, it is possible to minimise ionisation damage by changing the operating voltage in the STEM to a high voltage (300 kV) which reduces the inelastic scattering cross-section.

We turn now to the results from the sample of the commercial 5 % Pd/C catalyst. Figure 3a shows a single raw image from a series of HAADF images taken using a Philips CM300 field-emission gun (FEG) (S)TEM apparatus at successive tilt angles from +60 to –54°. A modified high-tilt holder allows us to go beyond the manufacturer's limits.^[25] Figure 3b shows a selection of images of the same specimen where each image is now a projection of the reconstructed 3D structure (at the stipulated angles).^[26] The reconstruction was obtained by using an iterative back-projection approach;^[22,27–30] the concept of back-projection is shown schematically in Figure 4. The wealth of retrievable information pertaining to the nature of this supported catalyst from the electron-tomographic (Z-contrast) method is unprecedented. It is clear that the original image has a better spatial resolution than the reconstruction. This is primarily because the overall resolution is limited by the field depth. The object is about 600 nm in diameter and so, from previous work,^[27] we would expect a spatial resolution of about 6 nm in all directions, even though the resolution in a single original image is nominally about 1 nm. The loss of resolution, particularly in the direction parallel to the optic axis of the microscope, is brought about by the missing “wedge” of data resulting from the limited tilt range. Despite this loss of resolution, it is obvious that this is a powerful high-resolution technique for monitoring progressive changes in the 3D distribution and attributes of supported nanoparticles and their use as catalysts.

We have shown that the STEM method of probing materials can be complemented with field-emission SEM. The resolution achievable with these instruments is such that the ability to locate the position (and determine the composition) of nanoparticles anchored at the surface (or buried just beneath the surface) of supports, is very considerable (see Figure 2). A comparison of HAADF and BSE images of a commercial 5 % Pd/C system has shown that BSE imaging can be a simple and effective method in the study of surface-loaded nanocatalysts. BSE imaging does not require electron transparency through the support, in contrast to TEM or STEM analysis. This will allow access to larger (mm scale) support units, as will often be the case in many industrial applications, although by its nature it will primarily reveal distributions at the surface, and not deep within any support-

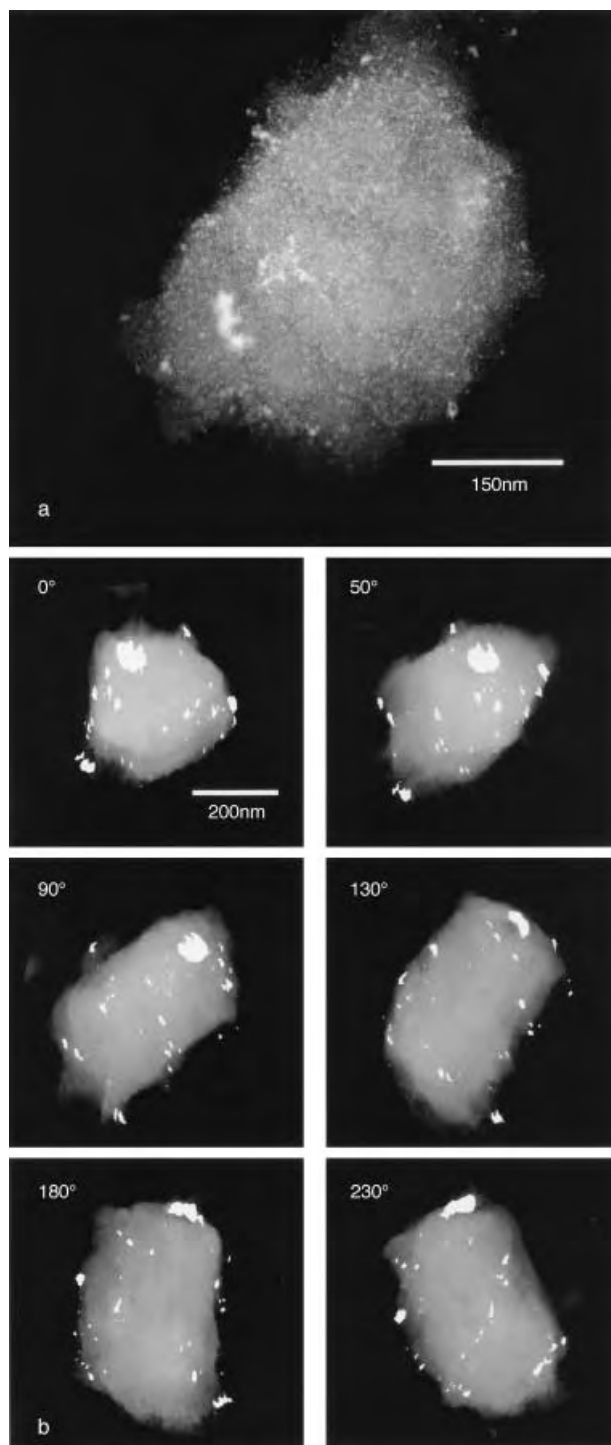


Figure 3. a) A STEM HAADF image acquired from the same Pd/C sample as shown in Figure 2. The large difference in atomic number between the nanoparticles and the support gives rise to high (and directly interpretable) contrast in the image. b) A selection of views taken from an animation of the 3D reconstruction of the object seen in (a). The angle refers to the rotation about a vertical axis.

ing medium. The challenges are to devise a high-tilt-angle stage ($\pm 60^\circ$) for the FEG SEM apparatus that is of similar quality to that in the FEG STEM system, and to improve the sensitivity of the BSE detection to discriminate narrower atomic number differences from the support in extended tomographic or topographic analyses. Fortunately, a whole

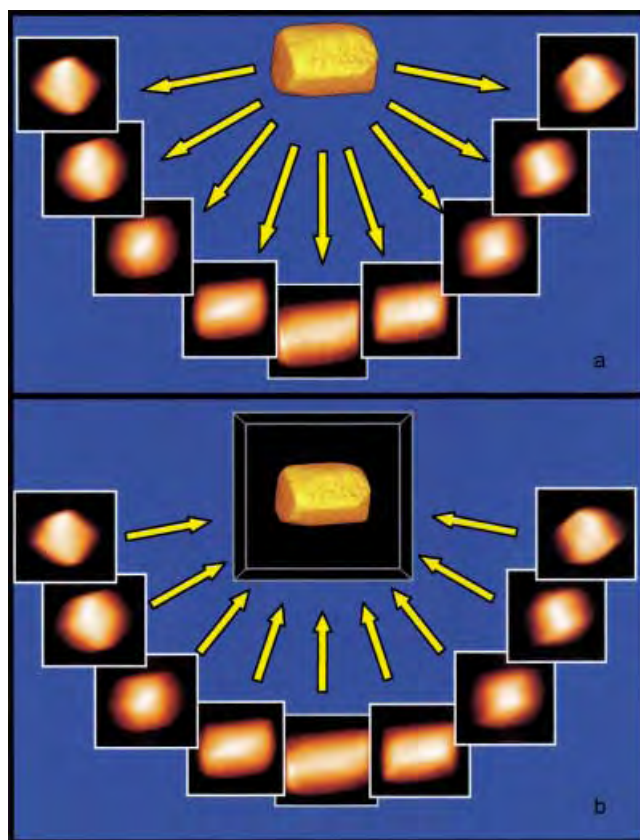


Figure 4. A schematic diagram illustrating a) the acquisition of a series of tilted projections and b) the reconstruction of the 3D object by back-projection (after A. J. Koster^[21]). The object is a magnetite nanocrystal from the "backbone" of a magnetotactic bacterium.^[31]

class of heterogeneous catalysts are composed of heavier metal particles either in or on a much lighter support. These are particularly suited for both BSE and HAADF imaging because of the similar underlying Rutherford high-angle scattering processes mentioned above. The current data display the considerable potential of the method for chemical and materials science and the possibility of applying the technique to bio-nanomaterials and labeled biomaterials; the latter typically comprising a particle consisting of heavy atoms within a matrix comprised mainly of light atoms.

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Methyl Transfer from Rhenium to Coordinated Thiolate Groups**

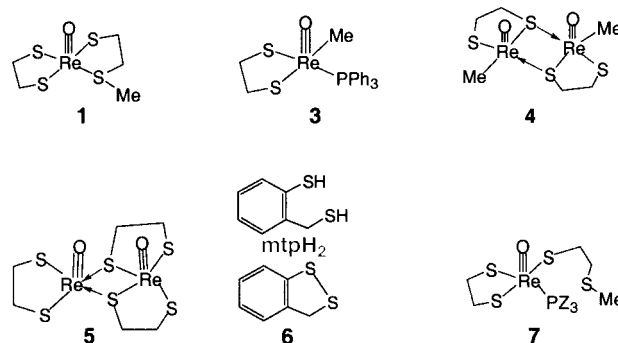
Xiaopeng Shan, Arkady Ellern, and James H. Espenson*

A prominent reaction of vitamin B₁₂ is the conversion of D,L-homocystein, HS(CH₂)₂CHNH₂CO₂H, to L-methionine, MeS(CH₂)₂CHNH₂CO₂H, with methylcobalamin and methylcobinamide.^[1–4] Methyl bis(dimethylglyoximate)cobalt(III)

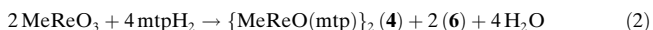
and related complexes also convert thiols to thioethers [Eq. (1)]:^[5]



There are, however, a lack of precedents in the literature for similar conversions that do not involve organocobalt complexes. In this work, new reactions of rhenium complexes have been examined, and sound evidence for the analogous conversion has now been obtained.



MeReO₃ (MTO, **2**)^[6] reacts with the readily-oxidized 2-(mercaptomethyl)thiophenol (mtpH₂), to yield a disulfide [Eq. (2)]:



With 1,2-ethanedithiol (edtH₂), however, a quite different result was obtained. As Re^{VII} was reduced to Re^V, one edtH₂ molecule was transformed to HS(CH₂)₂SMe, which remains coordinated to the rhenium(v) center through both sulfur atoms in a κ² fashion [Eq. (3)]:



Details of the synthesis and characterization of the dark-red complex **1** are given in the Experimental Section. A similar reaction starting with [MeReO(edt)(PPh₃)] (**3**)^[7] gave the same product in lower yield. Crystals of **1** suitable for X-ray diffraction could not be obtained. We have formulated the composition of **1** to be [ReO(κ²-edt)(κ²-edtMe)] based on elemental analysis and spectroscopic data. An alternative formulation as an organorhenium(VII) compound, [Me-ReO(edt)₂], could not be ruled out by these data. However, the evidence is in favor of structure **1** as the CH₃ resonance appears at δ = 1.90 ppm, which is further downfield than would be expected for a methyl group coordinated to a Re^{VII} center. Indeed, the proposed mechanism suggests that [MeReO(edt)₂] lies on the pathway to **1**.

Chemical methods were therefore used to obtain information about the molecular structure of **1**, particularly with respect to whether the Me–Re interaction present in the starting material is retained. The reaction of **1** with H₂O₂ in wet acetonitrile gave ReO₄[−] ions, which are easily recognized from the characteristic UV spectrum. The same product was obtained from **5**, another compound that lacks a Me–Re bond. In contrast, several compounds that do contain a Me–Re bond (**2**, **3**, and **4**) cleanly reacted with H₂O₂ to form

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[MeReO(κ^2 -O₂)(OH₂)], with a characteristic absorption maximum at 360 nm (ϵ = 1200). Thus, these results suggest that no Me–Re bond exists in **1**.^[8]

The reaction of compound **1** with phosphanes (PZ₃, in general) yields a new series of compounds, [ReO(κ^2 -edt)(κ^1 -edtMe)(PZ₃)] (**7**) in which the thioether arm has been displaced. One such compound, where PZ₃ = 1,3,5-triaza-phosphaadamantane (PTA),^[9] has been characterized crystallographically; the molecular structure is displayed in Figure 1. Phosphanes are generally much stronger Lewis bases than

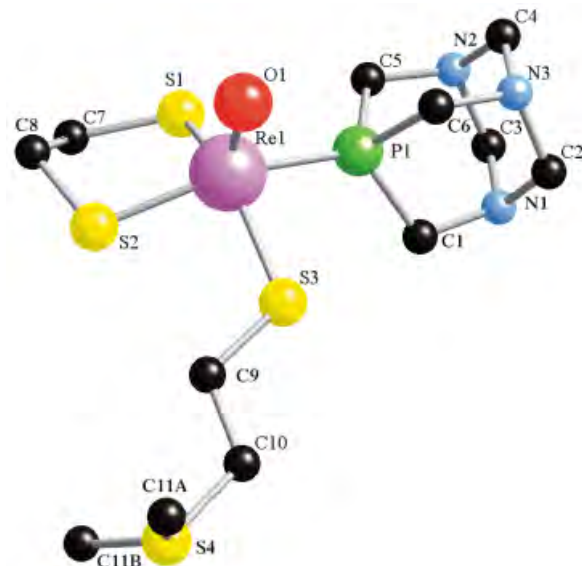
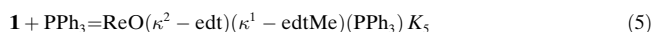


Figure 1. The molecular structure of [ReO(κ^2 -edt)(κ^1 -edtMe)(PTA)]. The methyl group at S₄ was disordered; the structure was refined at 50% occupancy of the two sites. Selected bond lengths [pm] and angles [°] are: Re–O 170.0(5), Re–S3 230.54(17), Re–P 242.25(18), S4–C10 181.0(9), S4–C11A 175.6(17), S4–C11B 184.0(4); O–Re–S3 110.68(19), O–Re–P 97.3(2), S2–Re–P 153.94(6), S1–Re–S3 133.58(7), C10–S4–C11A 102.7(7), C10–S4–C11B 104.3(17), C11A–S4–C11B 133.1(14). The structure was drawn with the CrystalMaker program.^[13]

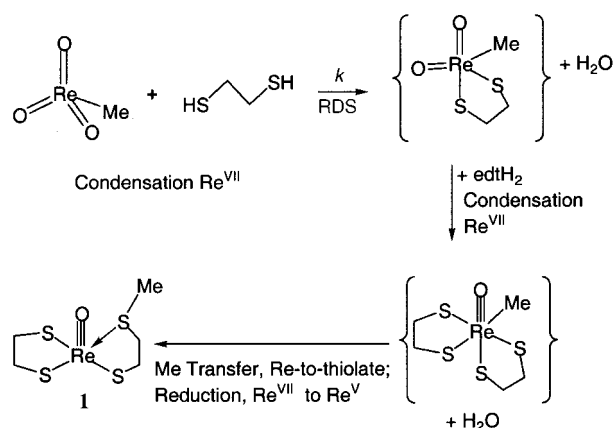
thioethers and will, to a great extent, displace RSR' groups. In keeping with this fact, the equilibrium constant for PPh₃ [K₄, Eq. (4)] is 6×10^5 (C₆H₆, 25 °C),^[10] whereas the equilibrium constant for Equation (5) (K₅) is 8.0 under the same conditions. The large difference in these values arises from the chelate effect, and illustrates its very substantial importance in this case.



The formation of **1**, as shown in reaction (3), follows the net 1:2 stoichiometry given. It is a sequential process that obeys the rate law [Eq. (6)]:

$$d[\mathbf{1}]/dt = k[\mathbf{2}][\text{edtH}_2] \quad (6)$$

with $k = 7.3 \times 10^{-2} \text{ L mol}^{-1} \text{ s}^{-1}$ (Me₂SO, 25 °C). Clearly the first condensation step is rate determining, as the methylation step occurs more rapidly and is not manifest in the kinetics. The sequential mechanism proposed is given in Scheme 1. The



Scheme 1. Proposed mechanism for the formation of **1** (RDS = rate-determining step).

final step appears to involve nucleophilic attack of the coordinated thiolate sulfur atom on the methyl group of the intermediate. Precedents for this mechanism, aside from those found in organocobalt systems, are rare. While the transfer of a phenyl group to the oxo group of an intermediate species ([TpRe(O)₂Ph]⁺, Tp = hydrotris(1-pyrazolyl)borate) represents a distantly related example,^[11] a more relevant case is the thermal decomposition of [MeReO(κ^2 -O₂)(OH₂)], which yields MeOOH and [HReO₄].^[12]

In summary, a novel transformation of the [MeRe(edt)] complex to give a [Re(thiolate–methylthioether)] complex (**1**) has been discovered and established. This transformation is without precedent, aside from the homocystein-to-methionine transformation found for vitamin B₁₂ and its mimics. Furthermore, the thioether group can be replaced by a phosphane; the derivative with PTA was characterized crystallographically. All of these reactions proceed to equilibrium, but owing to the chelate effect, the equilibrium constants are smaller by a factor of 10⁵ than the analogous values of *K* for the displacement of a nonchelated RSR' group.

Experimental Section

1: Dimethylsulfoxide (0.2 mmol) was added to **2** (0.5 mmol) in toluene (5 mL). 1,2-Ethanedithiol (0.5 mmol) was added to this mixture, whereupon the solution turned red. After 4 h, hexanes (10 mL) were layered on top of the solution, which yielded a deep-red solid (87% yield) which was purified by recrystallization from dichloromethane/hexanes. Elemental analysis (%) calcd for C₅H₁₁OReS₄: C 14.95, H 2.76, S 31.94; found: C 15.16, H 2.82, S 32.09; ¹H NMR (400 MHz, [D₆]benzene, 25 °C): δ = 3.55 (m, 1H; CH₂), 3.36 (m, 1H; CH), 2.70 (m, 1H; CH₂), 2.51 (m, 2H; CH₂), 2.11 (m, 1H; CH₂), 1.92 (m, 1H; CH₂), 1.90 (s, 3H; CH₃), 0.84 ppm (m, 1H; CH₂); ¹³C NMR (100 MHz, [D₆]benzene, 25 °C): δ = 45.6, 45.0, 43.5, 36.2, 22.3 ppm; UV/Vis (C₆H₆): λ_{max} (ϵ) = 510 (160), 389 nm (3400).

[ReO(κ^2 -edt)(κ^1 -edtMe)(PTA)]: A 1:1 reaction between **1** and PTA in toluene gave dark, shiny single crystals after recrystallization from toluene/hexanes. Elemental analysis (%) calcd for C₁₁H₂₃ON₃PReS₄: C 23.65, H 4.15, N 7.52, S 22.96, P 5.54; found: C 23.57, H 4.12, N 7.55, S 23.25, P 5.61; ¹H NMR (400 MHz, [D₆]benzene, 25 °C): δ = 4.34 (m, 1H; CH₂), 4.21 (m, 7H; CH₂), 3.86 (m, 6H; CH₂), 3.43 (m, 1H; CH₂), 3.34 (m, 1H; CH₂), 3.20 (m, 1H; CH₂), 2.97 (m, 1H; CH₂), 2.41 (m, 2H; CH₂), 1.98 ppm (s, 3H; CH₃); ¹³C NMR (100 MHz, [D₆]benzene, 25 °C): δ = 72.5 (d, *J*(C,P) = 7 Hz), 51.9 (d, *J*(C,P) = 16 Hz), 43.6 (d, *J*(C,P) = 8 Hz), 42.0(s), 37.2(s), 35.5 (d, *J*(C,P) = 9 Hz), 15.3 ppm (s); ³¹P NMR (162 MHz, [D₆]benzene, 25 °C): δ = −74.0 ppm; UV/Vis (C₆H₆): λ_{max} (ϵ) = 386 (1900), 318 (1600; sh),

262 nm (3800). CCDC-190226 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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Naked-Eye Detection of Phosphate Ions in Water at Physiological pH: A Remarkably Selective and Easy-To-Assemble Colorimetric Phosphate-Sensing Probe**

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Phosphate anions are one of most important constituents of living systems. Together with heterocyclic bases and sugars, phosphates make up the genes, the hereditary elements of living systems. In addition, phosphate ions and their derivatives play pivotal roles in signal transduction and energy storage in biological systems.^[1] Numerous sensors for anions, including phosphate ions, have been devised, but most of them use organic solvents as the detection medium because these sensors rely on hydrogen-bonding and electrostatic

interactions for the recognition of analytes.^[2] These interactions are, however, attenuated drastically in a highly polar medium such as water, because of the competing solvation effect.^[3] The detection of anions such as phosphate in water is, hence, a challenging task.^[4] We report herein a colorimetric sensor that can detect phosphate anions in an aqueous solution of neutral pH values. The sensor is easy to assemble and shows a high sensitivity and excellent selectivity for phosphate ions over other anions.

In assembling the sensor, we took advantage of metal–ligand interactions. Such interactions are so highly favorable that they occur even in polar media. Furthermore, the metal ion can present some geometrical preferences, thus imparting selective binding tendencies towards anions of a given shape.^[5] 2,6-Bis(bis(2-pyridylmethyl)aminomethyl)-4-methylphenol (H-bpmp) was reported to form a crystalline dinuclear complex with Co^{II} ,^[6] and Seo et al. reported that the phenylphosphonate anion binds to the dinuclear complex of Co^{III} with H-bpmp by bridging the two metal ions.^[7] These reports led us to explore the metal complex of H-bpmp as a receptor for phosphate ions. The dinuclear Zn^{II} complex of H-bpmp was readily obtained by dissolving H-bpmp and zinc perchlorate in water; the complex is colorless and has a good water solubility, which are features desirable for using the complex as a receptor for a water-soluble chemosensor. We chose pyrocatechol violet, a catechol-type pH-sensitive dye, as the chromogenic indicator for the sensor. Catechols are known to coordinate to the two metal ions in a phenoxo-bridged binuclear metal complex.^[8] Furthermore, it is known that the yellow color of pyrocatechol violet at neutral pH may change to blue when it binds to a metal ion.^[9] Therefore, the displacement of the receptor-bound pyrocatechol violet by a phosphate anion would be communicated visually as well as spectrophotometrically. The competition approach^[10] used for assembling the present sensor is schematically illustrated in Figure 1.

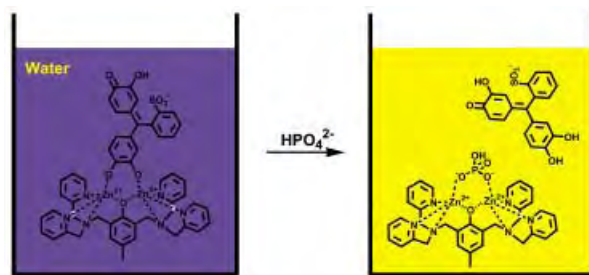


Figure 1. A schematic representation of the phosphate anion sensor.

The sensing ensemble was prepared by simply mixing H-bpmp,^[11] zinc perchlorate, and pyrocatechol violet^[12] in a 1:2:1 molar ratio in an aqueous solution of 10 mM HEPES buffer pH 7.0 (HEPES = 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid). Figure 2a shows the UV/Vis spectra obtained when the solution of $[\text{Zn}_2(\text{H-bpmp})]^{3+}$ was titrated into the aqueous buffer (pH 7.0) solution of the indicator (50 μM). The color change from yellow ($\lambda_{\text{max}} = 444 \text{ nm}$) to blue ($\lambda_{\text{max}} = 624 \text{ nm}$) observed upon the addition of $[\text{Zn}_2(\text{H-bpmp})]^{3+}$ is ascribed to the binding of pyrocatechol violet to the Zn^{II} ions

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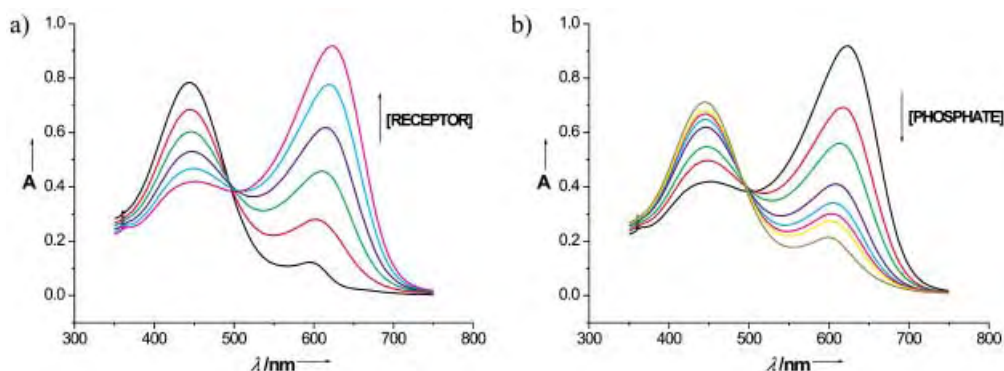


Figure 2. a) UV/Vis spectra obtained by additions of $[\text{Zn}_2(\text{H-bpmp})]^{3+}$ solution (final concentrations: 0, 10, 20, 30, 40, and 50 μM) to the pH 7.0 aqueous buffer (HEPES, 10 mM) containing pyrocatechol violet (50 μM); b) UV/Vis spectra obtained by additions of HPO_4^{2-} solution (final concentrations: 0, 25, 50, 100, 150, 200, 250, and 500 μM) to the pH 7.0 aqueous buffer (HEPES, 10 mM) containing $[\text{Zn}_2(\text{H-bpmp})(\text{pyrocatechol violet})]^+$ (50 μM).

in the receptor complex to form $[\text{Zn}_2(\text{H-bpmp})(\text{pyrocatechol violet})]^+$. As expected, the addition of phosphate anions to the aqueous solution of the ensemble resulted in a change of the color from blue to yellow, and caused changes in the UV/Vis absorption spectra: the peak at $\lambda_{\text{max}} = 624 \text{ nm}$ decreases while the peak at 444 nm increases (Figure 2b).^[13] The effect of the pH value of the medium on the phosphate ion sensing was studied, and we found that the UV/Vis absorbance changes described above occur in the pH range of 6.5–7.5, but most distinctively at pH 7.0.^[14] The thermodynamic parameters and kinetic constants for the bindings of the indicator as well as the analyte to the $[\text{Zn}_2(\text{H-bpmp})]^{3+}$ were determined^[14] by isothermal titration calorimetry (ITC).^[15] It can be seen from Table 1 that the phosphate anion binds the receptor over twofold more tightly than the indicator and the

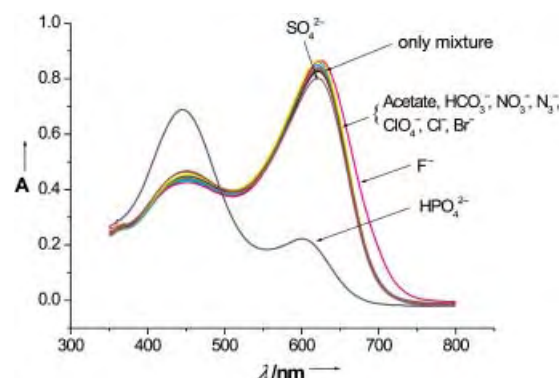


Figure 3. UV/Vis spectra of the $[\text{Zn}_2(\text{H-bpmp})]^{3+}$ –pyrocatechol violet mixture (50 μM in a pH 7.0 aqueous solution) in the presence of various anions (250 μM).

Table 1. Thermodynamic parameters and association constants (K_{ass}) for the binding of pyrocatechol violet or HPO_4^{2-} ions to $[\text{Zn}_2(\text{H-bpmp})]^{3+}$ in an aqueous solution of pH 7.0 (HEPES).

Data obtained from ITC experiment	Pyrocatechol violet	HPO_4^{2-}
ΔH° (kcal mol ⁻¹)	-11.83 ± 0.12	-7.55 ± 0.08
ΔG° (kcal mol ⁻¹)	-6.56	-7.01
ΔS° (e.u.)	-17.39	-1.79
K_{ass} (M ⁻¹)	$(5.3 \pm 0.2) \times 10^4$	$(11.2 \pm 0.8) \times 10^4$

binding is enthalpically driven, which suggests that there are strong coordinative interactions. The large unfavorable entropic contribution to the binding of the indicator compared to that of the phosphate anion suggests that ordering of water molecules at the complex interface in the binding may occur.

The present sensor exhibits excellent selectivity towards phosphate ions over other anions including sulfate and fluoride ions (Figure 3). This is remarkable because virtually no sensor reported to date can detect phosphate ions with such a high selectivity in an aqueous solution.^[16] Sensors that can detect analytes by the naked eye, without resorting to any spectrometer, is of particular interest because of its convenience. Only a few such sensors have, however, been reported.^[17] The use of the present ensemble for such a purpose is demonstrated in Figure 4: the color change from blue to yellow occurred only when phosphate ion was added to the

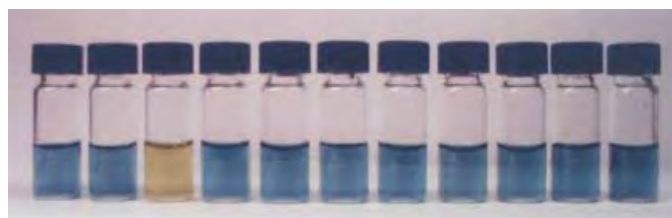


Figure 4. The color of the mixture (50 μM) in the absence and presence of anions (250 μM): from left to right; no anion, CH_3CO_2^- , HPO_4^{2-} , HCO_3^- , NO_3^- , N_3^- , ClO_4^- , SO_4^{2-} , F^- , Cl^- , and Br^- .

aqueous solution of the ensemble. Other anions failed to cause the color change.

In summary, we have assembled a novel colorimetric sensor for phosphate anions by simply mixing H-bpmp, which can be prepared readily in high yield, zinc perchlorate, and pyrocatechol violet, a commercially available dye, in water of a neutral pH value in a 1:2:1 molar ratio. The probe can detect phosphate ions in an aqueous solution of physiological pH, spectrophotometrically and visually, with unprecedented high selectivity towards phosphate anions over a variety of mono- and dianions. This sensor also allows a quantitative assay of the analyte in a neutral aqueous solution containing the ions that are commonly found in biological systems down to the concentration range of 10^{-5} M .^[14] We are currently exploring

the development of an inexpensive phosphate ion assay device useful for biological samples.

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Pyrophosphate Detection in Water by Fluorescence Competition Assays: Inducing Selectivity through the Choice of the Indicator**

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Fluorescent sensors have been designed for a variety of analytes during the last decade by following the classical “fluorophore-spacer-receptor” (FSR) approach in which a light-emitting fragment is covalently linked to a receptor subunit.^[1] More recently, a different approach has been introduced, the “chemosensing ensemble” (CE) paradigm, which relies on the use of an indicator (**I**) bound to a receptor (**R**) by means of noncovalent interactions.^[2] In this approach the highly colored or fluorescent probe **I** is displaced from **R** by the competing analyte (**S**), and this displacement produces a drastic change in the optical properties of released **I**. All the CE systems described until now were designed for anion sensing and most of them were based on hydrogen-bonding interactions. These interactions are relatively weak and in most cases do not compensate for the rather endothermic desolvation of **R** and **S**, which prevents the utilization of such receptors in pure water. We have recently reported the first example of a CE operating through metal–ligand interactions in which the receptor core is a dinuclear Cu^{II} macrobicyclic complex which is able to detect the carbonate ion in water through the revival of visible light emission of the displaced indicator.^[3] The availability of optical molecular sensors for anion detection is highly beneficial for the investigation of aqueous media in food science, cell physiology, and environmental chemistry.^[4]

Transition metal ions, for example, Cu^{II}, offer substantial advantages when designing CEs for anions. First of all, coordinatively unsaturated Cu^{II} complexes display strong binding tendencies towards anionic substrates because of the d⁹ electronic configuration of the metal center, which ensures high ligand field stabilization effects: as a consequence, anionic substrates can be bound and effectively recognized even in the strongly solvating medium water. Moreover, the Cu^{II} ion provides an operative control of the signal as it is able to completely quench the emission of a coordinated indicator, either of an electron-transfer or an energy-transfer nature, by means of very efficient intramolecular processes.^[5] We now demonstrate how the judicious choice of the indicator can turn macrocyclic complexes of Cu^{II} ions with well-known recognition tendencies towards anions into smart optical sensing devices, whose spectral and

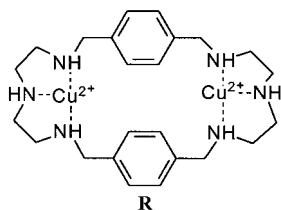
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selectivity features can be tuned as required, by simply changing the indicator.

Polyphosphate anions, which participate in several bioenergetic and metabolic processes,^[6] represent a relevant target in anion sensing, but very few examples of effective sensors have so far been reported.^[7] To the best of our knowledge, the only system able to detect pyrophosphate (PPi) in water at physiological pH values with an off/on fluorescent response was designed following the FSR approach and involved the binding of $\text{H}_2\text{P}_2\text{O}_7^{2-}$ ions by a hexaprotonated anthryloctamine receptor.^[8] However, the fluorescent emission after analyte recognition was only onefold higher than in the absence of analyte, and, most disappointingly, the emission and excitation wavelengths were lower than 400 nm, and thus not suitable for biological applications.^[9] Moreover, a receptor comprised of a guanidinium–pyrene conjugate was able to sense PPi through formation of an excimer in MeOH.^[10]

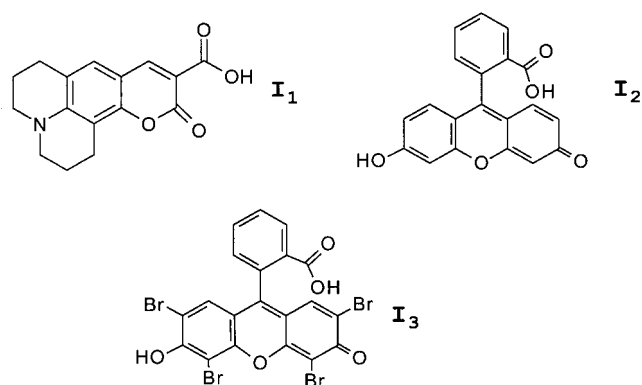
We have now chosen as a receptor the dicopper(II) complex of the bisdiene macrocycle 3,6,9,16,19,22-hexaazatricyclo[22.2.2.2(11.14)]triaconta-1(26),11(12),13,24,27, 29-hexaene (**L**). We expected that, in view of the coordinative unsaturation of the two metal centers and the correct $\text{Cu}^{\text{II}}\cdots\text{Cu}^{\text{II}}$ distance, the dinuclear complex of **L**, $[\text{Cu}_2^{\text{II}}(\text{L})]^{4+}$ (**R**), could be a reasonably good candidate for behaving as a fluorescent CE for PPi.^[11]



Then, we had to find a fluorescent indicator **I** to be coupled to the receptor **R**, whose ideal behavior requires full quenching of **I** when bound to **R** and an appropriate affinity constant (K_1) for the $\text{R} + \text{I} \rightleftharpoons \text{RI}$ equilibrium. In particular, if a substrate **S** displays an affinity constant K_S for **R** at a given pH value, while the interferent **S'** gives its own $K_{S'}$ value, the best situation for discrimination is expressed by the inequality $K_S \gg K_1 \gg K_{S'}$.

Under these conditions only the envisaged substrate **S**, and not the interferent **S'**, will be able to displace **I** from **R**, with subsequent revival of indicator fluorescence. In the present case, indicators were chosen on the basis of their spectral features (excitation and emission wavelength higher than 400 nm, high quantum yield) and their capability to interact with the dimetallic receptor: in particular, the indicator should be anionic and should present two donor atoms capable of bridging the two Cu^{II} centers of the receptor. From these perspectives the anion dyes coumarine 343 (**I**₁), fluorescein (**I**₂), and eosine y (**I**₃) containing the carboxylate and phenolate functional groups were chosen.

A complete quenching of the emission was observed on titrating a solution of the indicator (10^{-6}M) buffered at pH 7 (HEPES 0.05 M) with a standard solution of receptor **R**. In all cases, curve fitting of the titration profiles was consistent with



formation of a 1:1 adduct, whose apparent association equilibrium constants (K_1) are reported in Table 1.^[12]

Table 1. K_1 values for the equilibrium: $\text{R} + \text{I} \rightleftharpoons [\text{RI}]$ at pH 7.

Indicator	Coumarine 343 (I ₁)	Fluorescein (I ₂)	Eosine y (I ₃)
$\log K_1$	4.5 ± 0.1	5.9 ± 0.1	7.2 ± 0.1

Then, competition assays using CEs of **R/I**₁, **R/I**₂, and **R/I**₃ were carried out with several inorganic anions whereby a solution of the chosen **R/I** couple in the spectrofluorimetric cuvette was titrated with a standard solution of the envisaged anion (Figure 1).

The **R/I**₁ CE (Figure 1 a) is not able to discriminate between phosphates (PPi + orthophosphate (Pi)), but could be used to sense the overall amount of phosphates present in solution through the generation of a substantial enhancement in the probe emission. More interestingly, titrations on the **R/I**₂ CE (Figure 1 b) showed that only PPi is able to displace the fluorescent probe, and is evident (with a naked-eye-detectable tenfold enhancement of fluorescence) in the 2–20 μM concentration range, even in the presence of any other anions. Competition assays with PPi on the **R/I**₂ CE were repeated in the presence of 20 μM nitrate, sulphate, chloride, cyanate, azide, acetate, benzoate, and Pi to confirm the discriminating effects; in all cases, no interference was observed and perfectly superimposable titration profiles were obtained.

Moreover, when using the **R/I**₃ couple as the CE, the competition assays displayed discriminating behavior (Figure 1 c), with a tenfold fluorescence enhancement even at low concentrations, and allowed detection of PPi at micromolar concentrations. Low detection limits and high sensitivity are related to the K_1 value: in particular, the higher the K_1 value is, the lower the amount of receptor needed to bind the indicator and to quench its emission almost quantitatively (> 80 %), and the lower the concentration of substrate required to displace the equilibrium $[\text{Cu}_2^{\text{II}}(\text{L})(\text{I})] + \text{S} \rightleftharpoons [\text{Cu}_2^{\text{II}}(\text{L})(\text{S})] + \text{I}$ to the right. Calibration curves for PPi have been obtained by carrying out a series of reproducible competition assays.

Competition assays of the type described can also be used for determining the association constants for the receptor and the anions. In fact, K_S values for all the investigated substrates^[14] at pH 7 can be calculated knowing the relative K_1 value.^[15] The fitting of the titration profiles with a non-

linear least-squares procedure using a model which involves the two competitive equilibria gave the $\log K_s$ values reported in Table 2: the satisfactory agreement of the K_s values obtained for the same anion when using different indicators demonstrates the validity of the approach. The much higher affinity of PPI compared to Pi towards the dimetallic receptor can be ascribed to the capability of the diphosphate ion to coordinate the two Cu^{II} centers by using two oxygen atoms from the two phosphonate groups. On the other hand, Pi is forced to bridge the $\text{Cu}^{\text{II}}\cdots\text{Cu}^{\text{II}}$ distance with two oxygen atoms of the same phosphonate group, a strained situation

	Fluoresceine (I₂)	Eosine y (I₃)	Coumarine 343 (I₁)
PPi	7.2 ± 0.2	7.2 ± 0.2	> 6.5
Pi	4.4 ± 0.2	4.0 ± 0.2	4.2 ± 0.1
NCO ⁻	4.7 ± 0.2	4.6 ± 0.2	–
N ₃ ⁻	4.0 ± 0.2	–	–
Cl ⁻ , NO ₃ ⁻ , SO ₄ ²⁻ , N ₃ ⁻ , acetate, benzoate	< 3	< 3	< 3

In conclusion, the CE approach presents some significant benefits over the FSR paradigm: first, it does not involve any tedious synthetic step for covalently linking together the luminophore and the receptor. Moreover, a further element of selectivity is introduced in addition to that related to the analyte–receptor interaction. This selectivity term is associated with the choice of the indicator, whose affinity towards the receptor determines which analytes can be detected and which cannot. A final point is concerned with the signal transduction mechanism: covalent linking of the fluorophore and receptor in FSR systems does not necessarily imply switching on/off the fluorescence when recognition occurs. In fact, a signal can be generated if the analyte itself is photophysically active and quenches the fluorophore,^[16] or it interrupts a pre-existing quenching mechanism specifically designed into the system.^[8] Things are much simpler in the metal-containing CE described here, in which efficient quenching of the fluorophore is directly provided by Cu^{II} ions and is suspended when the indicator is released to the solution, with a full revival of the fluorescence detectable by the naked eye. We are currently using the CE approach with transition-metal-containing receptors for the fluorescent detection of biologically relevant substrates which possess an anionic functionality, for example, amino acids.

L was prepared as described elsewhere.^[17] All other chemicals were purchased from Aldrich/Fluka and used without any further purification. The complex **R** was prepared by dissolving Cu(NO₃)₂·3H₂O (1.52 g, 6.28 mmol) in MeOH and adding this to a solution of **L** (1.29 g, 3.14 mmol) in MeOH. The mixture was heated to reflux, and after 30 min the complex [Cu^{II}(**L**)](NO₃)₄ (**R**) was collected as a bright blue microcrystalline precipitate by filtration. Yield: 80%. Elemental analysis calcd for C₂₄H₃₈N₆Cu₂(NO₃)₄: C 36.69, H 4.87, N 17.68; found: C 36.42, H 4.56, N 17.68.

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solution was chosen to quench at least 80 % of the emission of the free indicator: 2.5×10^{-4} M for **I**₁, 1.6×10^{-5} M for **I**₂, and 2.4×10^{-6} M for **I**₃. The CE solution was titrated with standard solutions of anions. All spectrofluorimetric titration curves were fitted with the HYPERQUAD program.^[18]

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SASAPOS, not Sisyphe: Highly Efficient 20-Step One-Pot Synthesis of a Discrete Organic-Inorganic Ion Cluster with a Porphyrin Core

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As a result of their central role in coordination chemistry, porphyrins have been functionalized in many ways, mostly by the combination of synthetic building blocks, and to a lesser extent by electrophilic (S_E) or radical (S_R) substitution.^[1] Modifications by nucleophilic substitution (S_N) are limited to the replacement of fluorine atoms at the *para* positions of *meso*-tetrakis(pentafluorophenyl)porphyrin **1** with R_2N -, RS -, and RO -groups.^[2]

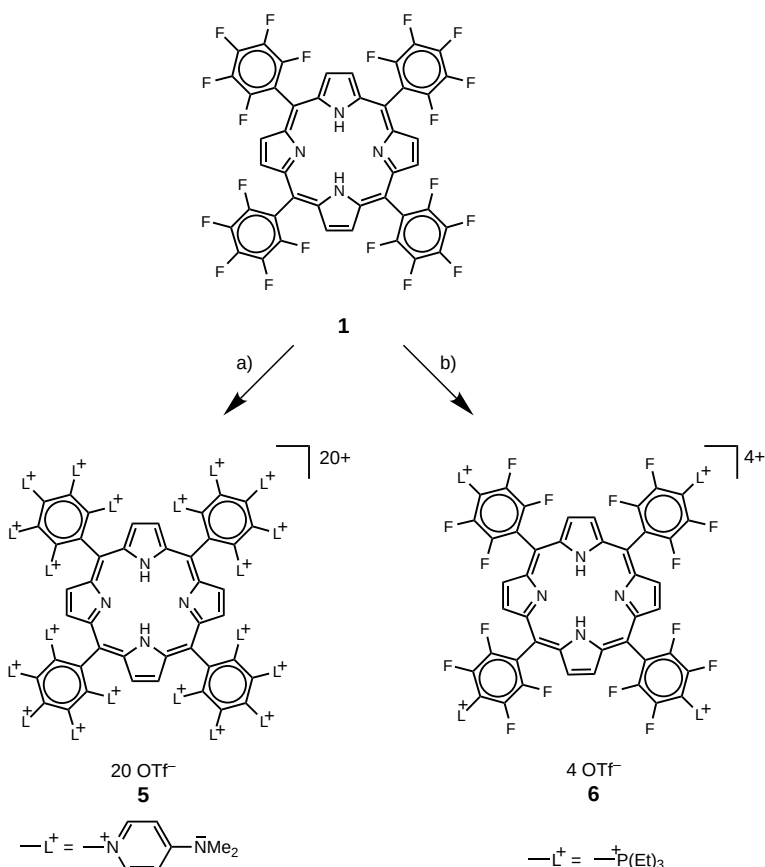
More recently, the introduction of cationic substituents has become an area of interest, because cationic porphyrins have been shown to be biologically active.^[3] In this context, up to four phosphonio^[4] or 4-pyridinio^[5] substituents have been introduced to peripheral positions of porphyrin derivatives by quaternization reactions. An electrochemical route that involves the oxidative addition of phosphonio-^[6] and 1-pyridinio substituents^[7] in the β or *meso* positions of porphyrin derivatives has recently also been successful for the first time. To date, there have been no reports of the direct introduction of cationic substituents into porphyrin derivatives by nucleophilic aromatic substitution ($S_N(Ar)$). We have now accomplished this through the development of Me_3SiOTf -assisted, selfactivated polyonio substitution of polyhalogenated (preferably fluorinated) substrates.^[8] We refer to this highly efficient method by the acronym SASAPOS (self-activated silyl-assisted polyonio substitution), in which the first attribute refers to the increasingly electrostatically facilitated addition steps, and the second to the energy-releasing elimination steps of the addition/elimination cascade.

We were thus able to synthesize the first peronio-substituted benzene derivative by the reaction of hexafluorobenzene with 4-dimethylaminopyridine (DMAP; **2**) and trimethylsilyl triflate (**3**) in a SASAPOS cascade to form the hexatriflate.^[8a] The concurrent energy-releasing formation of Me_3SiF causes this $S_N(Ar)$ reaction sequence to be strongly exothermic overall, resulting in a characteristic lack

of intermediate products. Once we found that pentafluorobenzene reacts in a similar fashion,^[8a] we undertook the conversion of more complex pentafluorophenyl-substituted compounds. We have had an initial success by using **1** as a model compound.

Compound **1** was treated with **2** or triethylphosphane (**4**) in the presence of an equal amount of **3** in boiling chlorobenzene. Regardless of the initial quantity of the reagents used, exclusively icosakis- **5** or tetrakis- **6** precipitated out of the organic solvent as analytically pure, dark violet salts. The yields were nearly quantitative when stoichiometric amounts of the reactants were used (Scheme 1).

Compounds such as **6** were recently synthesized for the first time by a relatively complex total synthesis.^[4] The structure of



Scheme 1. SASAPOS-cascades on **1**: a) + 20 DMAP, + 20 Me_3SiOTf ; - 20 Me_3SiF ; PhCl, Δ , 4 days, 99 %; b) + 4 PEt_3 , + 4 Me_3SiOTf ; - 4 Me_3SiF ; PhCl, Δ , 2 days, 97 %.

6 can be unequivocally determined from its analytical and spectroscopic data (see Experimental Section). The introduction of the phosphonio substituents at the 4-positions is as we expected.^[2] A further SASAPOS cascade (beginning with the 3,5-positions of the phenyl rings) is apparently sterically hindered. Such a steric block of thermodynamically favorable $S_N(Ar)$ reaction sequences did not occur when we tried the reaction with disk-shaped and strongly nucleophilic **2**.

We obtained porphyrin derivative **5**, with 20 cationic substituents, in high purity and were thus able to perform a crystallographic analysis. Unfortunately, four of the triflate ions were only detected as diffuse electron densities.^[9] The

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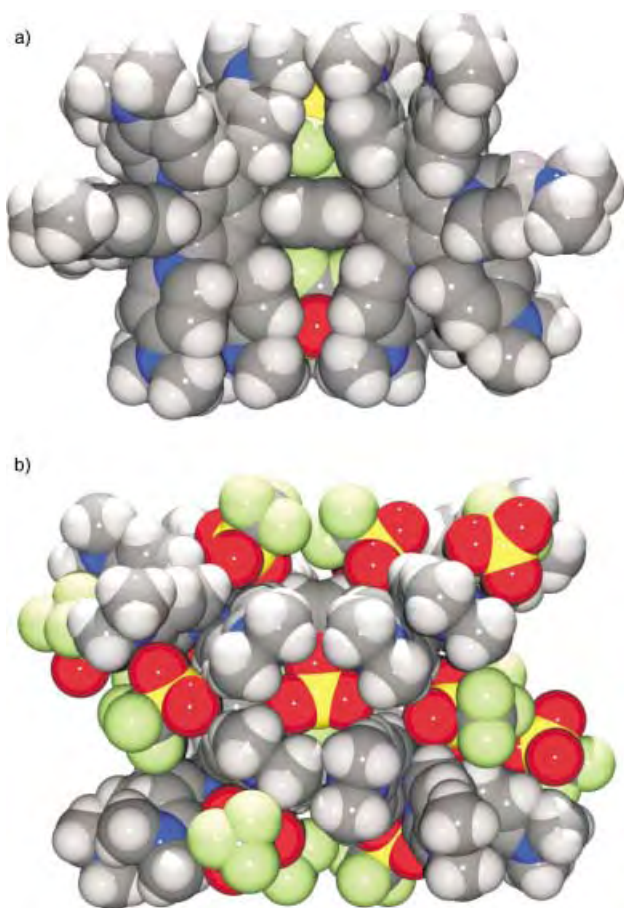


Figure 1. a) Cation of **5** with two centrally enclosed triflate ions (viewed parallel to the porphyrin plane). b) Cation of **5** with 16 triflate ions (viewed perpendicular to the porphyrin plane).

structure shown thus includes the icosakis(cation) and only 16 of the 20 triflate ions present (Figures 1 a and b).

The phenyl rings are twisted by 70–80° relative to the porphyrin framework; the dmap⁺ ligands are twisted relative to the phenyl rings by a similar angle. The resulting structure of the polycation in **5** is marked by the following characteristics:

- Large cavities are formed above and below the porphyrin π -electron system as a result of the four onio substituents at the 2,6-positions of the *meso* phenyl groups.
- There are four large indentations between the four pentakis(onio)phenyl groups.
- Vicinal onio ligands form many binding cavities on the periphery of the polycation.

A characteristic feature of the overall structure of the 1:20-electrolyte **5** is that the high positive potential of the polycation causes the 20 counterions to be massively attracted to it, resulting in discrete organic–inorganic ion clusters within the crystal. Thus each of the central cavities is filled by one anion, while each of the peripheral indentations contains two; spatial constraints cause the latter to be arranged alternately one above the other or next to each other. Aside from these ten anions within the cluster, six more were found to be within the local spheres of influence of the individual pentakis(onio-

phenyl groups; of these, four were within binding cavities between vicinal onio ligands. The four anions that were detected as diffuse electron densities occupied positions on the periphery of the ion cluster (Figures 1 a and b). Overall, **5** can be described as a “penetrated ion cluster”,^[10] in which we can qualitatively recognize a shell-like gradation of the electrostatic anion stabilization within the cluster.

A characteristic of the NMR spectrum of **5** is the upfield shift, on average by 0.5–0.9 ppm (see Experimental Section), of all of the proton signals of the eight dmap⁺ ligands bound at the 2,6-positions. This is as a result of the location of the ligands within the influence of the ring-current effect of the porphyrin π electrons (Figures 1 a and 1 b). Furthermore, **5** and **6** were analyzed by FAB mass spectrometry. Under these conditions, both ion clusters lose a triflate ion and are detected with high relative intensities as monocations with the expected m/z ratios of 5870 (**5**) or 1816 (**6**). This result is especially remarkable for **5**, and can be taken as direct evidence for the high stability of this type of discrete ion cluster.

The massive electrostatic effects of the onio substituents in **5** and **6** should significantly influence the redox potentials of the porphyrin framework. We looked into this by examining **5**.^[11] The half-wave potentials for *meso*-tetraphenylporphyrin (**7**), the perfluorinated analogue **1**, and the ion cluster **5**, which are summarized in Table 1, illustrate this influence.^[12] Usually,

Table 1. Redox potentials of selected porphyrin derivatives^[a]

	OX(2) [V]	OX(1) [V]	RED(1) [V]	RED(2) [V]
7 ^[b]	+ 1.34	+ 1.10	– 1.10	– 1.48
1 ^[c]	+ 1.54	+ 1.20	– 0.97	– 1.40
5 ^[b]	–	+ 1.90	– 0.26	– 0.72

[a] All values are reported relative to the standard calomel electrode. [b] In CH₃CN. [c] In CH₂Cl₂.

porphyrin derivatives have two oxidation and two reduction steps. We were unable to detect the second oxidation step (OX(2)) for **5**. The redox potentials for **5** are each shifted towards a more positive potential by about 800 mV relative to **7** (Table 1). This impressively demonstrates the electrostatic effect of the 20 cationic substituents in **5** on the central porphyrin π -electron system, and leads us to expect stable reduction products.

The results we have described herein open up a myriad of approaches for the variation of the structures of ion clusters based on porphyrins:

- by variation of the type, number, and arrangement of per- or partially fluorinated aryl substituents
- by exchange reactions of the resulting ion clusters with the assistance of protic nucleophiles H–Nu
- by anion metathesis
- by NH double deprotonation and synthesis of corresponding metal complexes.

We are close to being able to replace the porphyrin system with other organic and inorganic building blocks, thus opening routes for the rational design of new types of ion clusters. Further investigations are currently underway.

Experimental Section

All work was carried out under a nitrogen atmosphere with purified and dried solvents.

5: A solution of *meso*-tetrakis(pentafluorophenyl)porphyrin (94 mg, 0.10 mmol), DMAP (305 mg, 2.50 mmol), and Me₃SiOTf (0.40 mL, 2.20 mmol) in chlorobenzene (25 mL) was stirred at reflux for 4 days; a precipitate begins to form after 5 h. The precipitate was separated, washed with dichloromethane (5 × ≈ 5 mL), and dried at 0.05 Torr to yield an intensely violet powder (577 mg, 99%). ¹H NMR (400.05 MHz, CD₃NO₂): δ = −3.29 (s, 2H; NH porphyrin), 2.81 (s, 48H; CH₃ *o*-dmap), 3.30 (s, 48H; CH₃ *m*-dmap), 3.38 (s, 24H; CH₃ *p*-dmap), 6.16 (d, ³J(H,H) = 8.1 Hz, 16H; 3/5-*H o*-dmap), 7.06 (d, ³J(H,H) = 8.1 Hz, 16H; 3/5-*H m*-dmap), 7.15 (d, ³J(H,H) = 8.1 Hz, 8H; 3/5-*H p*-dmap), 7.86 (br d, ³J(H,H) = 7.9 Hz, 16H; 2/6-*H o*-dmap), 8.32 (d, ³J(H,H) = 8.1 Hz, 16H; 2/6-*H m*-dmap), 8.60 (br d, ³J(H,H) = 7.8 Hz, 8H; 2/6-*H p*-dmap), 9.95 ppm (br m, 8H, C-H porphyrin); ¹³C NMR (100.50 MHz, CD₃NO₂): δ = 41.37 (s; CH₃), 41.64 (s; CH₃), 41.68 (s; CH₃), 108.27 (s; *meso*-C porphyrin), 109.74 (s; C3/5 dmap), 110.85 (s; C3/5 dmap), 111.11 (s; C3/5 *p*-dmap), 122.00 (q, |¹J(C,F)| = 325.4 Hz; CF₃), 140.14 (s; phenyl), 140.58 (s; phenyl), 140.63 (s; C2/6 *p*-dmap), 141.54 (s; C2/6 dmap), 141.60 (s; C2/6 dmap), 142.26 (br s; porphyrin), 142.97 (s; phenyl), 144.72 (s; phenyl), 156.73 (s; C4 dmap), 156.96 (br s; C-H porphyrin), 157.60 (s; C4 dmap), 157.77 ppm (s; C4 dmap); UV/Vis (CH₃CN): λ_{max} (ε) = 300 (345 000), 437 (236 000), 525 (25 000), 595 nm (9000 mol^{−1} dm³ cm^{−1}); FABMS (NBA): *m/z*: 5870 [M-OTf]⁺, 5720 [M-HOTf-OTf]⁺, 5571 [M-HOTf-OTf-OTf]⁺, 2860 [M-2OTf]²⁺, 2786 [M-HOTf-2OTf]²⁺, 1808 [M-HOTf-3OTf]³⁺; elemental analysis (%): calcd. (M+6H₂O): C 39.99, H 3.65, N 10.06, S 10.46; found: C 40.12, H 3.66, N 9.90, S 10.32.

6: The same procedure as for **5**, but with **1** (128 mg, 0.13 mmol), PEt₃ (0.12 mL, 0.78 mmol), and Me₃SiOTf (0.12 mL, 0.65 mmol); reaction time: 2 days; precipitate formation after 1 h. Yield: 251 mg, 97%, intensely violet powder. ¹H NMR (400.05 MHz, CD₃NO₂): δ = −2.92 (s, 2H; NH Porphyrin), 1.63 (dt, ³J(H,H) = 7.6, ³J(H,P) = 20.8 Hz, 36H; CH₃), 3.07 (dq, ³J(H,H) = 7.6, ³J(H,P) = 19.8 Hz, 24H; CH₂), 9.36 ppm (br s, 8H, CH porphyrin); ¹³C NMR (100.50 MHz, CD₃NO₂): δ = 4.43 (d, ²J(C,P) = 5.5 Hz; CH₃), 15.32 (d, ¹J(C,P) = 47.8 Hz; CH₂), 101.54 (dt, |²J(C,F)| = 18.3, ¹J(C,P) = 70.5 Hz; C4 phenyl), 105.17 (s; *meso*-C porphyrin), 122.49 (q, |¹J(C,F)| = 321.7 Hz; CF₃), 129.06 (t, |²J(C,F)| = 19.3 Hz; C1 phenyl), 148.66 (dm, |¹J(C,F)| = 251.9 Hz; CF phenyl), 149.94 (dm, |¹J(C,F)| = 244.5 Hz; CF phenyl), 156.74 ppm (s; CH porphyrin); ³¹P NMR (161.70 MHz, CD₃NO₂): δ = 45.22 ppm (m); FABMS (NBA): *m/z*: 1818 [M-OTf]⁺, 1668 [M-HOTf-OTf]⁺, 1640 [M-C₂H₅-2OTf]⁺, 1552 [M+H-PEt₃-2OTf]⁺; elemental analysis (%): calcd. (M+2H₂O): C 43.16, H 3.72, N 2.80, S 6.40; found: C 43.08, H 3.70, N 2.71, S 6.43.

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Syntheses and Crystal Structures of the New Ag–S Clusters

[Ag₇₀S₁₆(SPh)₃₄(PhCO₂)₄(triphos)₄] and [Ag₁₈₈S₉₄(PR₃)₃₀]**

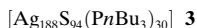
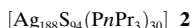
Xiu-Jian Wang, Timo Langetepe, Claudia Persau, Bei-Sheng Kang, George M. Sheldrick, and Dieter Fenske*

Dedicated to Professor Achim Müller on the occasion of his 65th birthday

Many investigations towards synthesis and structural characterization of large metal-rich clusters have been reported over the last few years. Particularly noteworthy are the oxometallates of molybdenum described by Müller et al.; only recently Na₄₈[H₃Mo₃₆₈O₁₀₃₂(H₂O)₂₄₀(SO₄)₄₈·*n* 1000H₂O (*x* ≈ 16; *n* ≈ 1000), the largest known derivative of a heteropolyacid was structurally characterized.^[1] Other examples of large cluster complexes are [Pd₁₄₅(CO)_x(PET₃)₃₀] (*x* ≈ 60) made by Dahl et al.^[2] and [Ga₃₄N(SiMe₃)₂]₂₀Li₆Br₂(thf)₂₀ reported by Schnöckel and Schnepf.^[3] The synthesis of the larger Ag–S cluster complexes [Ag₁₄S(SPh)₁₂(PPh₃)₈]^[4] and [HNet₃]₄–[Ag₅₀S₇(SC₆H₄tBu)₄₀]^[5] was recently achieved by Jin et al.

Over the last few years one of our major fields of interest was the synthesis of transition-metal clusters containing S, Se, Te, P, As, and Sb as bridging ligands, for example, copper-chalcogenide clusters stabilized by tertiary phosphane ligands.^[6] Reactions of transition-metal salts with Group 16 silyl derivatives E(SiMe₃)₂ or RESiMe₃ (R = alkyl- or aryl-; E = S, Se, Te) allows access to these clusters.^[7] Addition of tertiary phosphanes to these reactions prevents the formation of the thermodynamically stable binary phase.^[8]

Compounds obtained by this route include: [Cu₁₄₆Se₇₃–(PPh₃)₃₀],^[9] [Ag₁₇₂Se₄₀(SenBu)₉₂(dppp)₄]^[10] (dppp = bis(1,3-diphenylphosphanyl)propane), [Ag₃₈Te₁₃(TerBu)₁₂(dppe)₆] (dppe = bis(1,2-diphenylphosphanyl)ethane),^[11] [Au₁₈Se₈–(dppe)₆]Cl₂^[12], and [Zn₁₆Te₁₃(TePh)₆(tmeda)₅]^[13] (tmeda = tetramethylethylenediamine). Herein we report the synthesis of the Ag–S clusters **1**, **2**, and **3** containing 120 and 282 heavy atoms, respectively, in the cluster core.



The reaction of a suspension of silver benzoate and triphos [1,1,1-tris[(diphenylphosphanyl)methyl]ethane] with a mixture of S(Ph)SiMe₃ and S(SiMe₃)₂ (2:1) at –20 °C in diglyme produces a deep red solution from which small red needles of **1** [Eq. (1)], can be isolated.



Reaction of S(SiMe₃)₂ with silver trifluoroacetate and PnPr₃ at –40 °C in diglyme initially produces a red solution. After a few hours stirring, the reaction is allowed to warm up to room temperature. The solution becomes dark and black crystals of **2** are formed [Eq. (2)]. Employment of PnBu₃ in an analogous reaction produces black crystals of **3** [Eq. (2)]. Depending on the reaction conditions, **2** is often produced together with black amorphous Ag₂S. Attempts to recrystallize **2** and **3** from THF or CH₂Cl₂ failed and produced Ag₂S as the only isolatable material. The different colors of **1** and **2** (red and black) arise from quantum size effect, which result from the dependency of the band gap on particle size.^[14]



The molecular structures of complexes **1** and **2** in the solid-state were determined by X-ray crystallography.^[15] Compound **1** crystallizes in the space group *P* $\bar{1}$ with two molecules in the unit cell. The molecular structure is shown in Figure 1. The cluster core consists of an arrangement of 70 silver and 50 sulfur atoms protected by four triphos ligands and 34 phenyl rings of SPh[–] groups. Four benzoate ligands make up the additional charge to give a neutral cluster by coordinating by their oxygen centers to the surface of the cluster core.

The sulfur atoms are arranged in a highly distorted a layer substructure (Figure 2) with no bonding interactions. The sulfur atoms of the SPh[–] groups (S1–S34; yellow) are located on the surface of the cluster and S^{2–} ligands (S35–S50; orange) are part of the inner core. The four sulfur layers are highly corrugated with a pseudo S₄ axis through the midpoints of S39–S47 and S14–S45 (in Figure 2 from bottom to top). The top and bottom sulfur layers shown contain eight S atoms and are twisted by 90° relative to each other. Each of these layers contains two S^{2–} ligands (S39, S47 and S35, S45) and six SPh[–] ligands (S17, S18, S21, S24, S25, S30 and S4, S8, S11, S14, S16, S29, respectively). The two inner sulfur layers contain 17 S atoms each, six S^{2–} ligands (S36, S38, S40, S44, S46, S48 and S37, S41, S42, S43, S49, S50, respectively), which are surrounded by rings of 11 thiolato ligands (S1, S5, S7, S9, S10, S19, S20, S22, S27, S28, S34 and S2, S3, S6, S12, S13, S15, S23, S26, S31, S32, S33).

The S atoms in the SPh[–] ligands are μ₂-, μ₃-, and μ₄ bridging, whereas central S^{2–} ions act as μ₄ to μ₇ bridges between Ag

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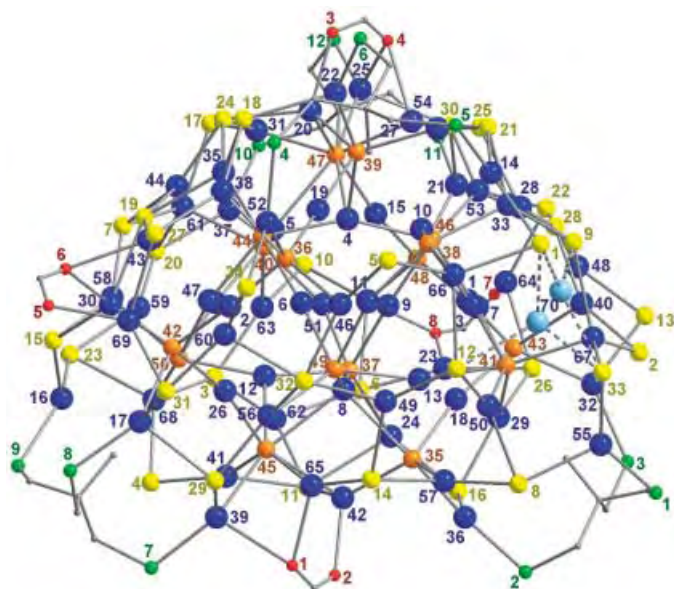


Figure 1. Molecular structure of **1** (phenyl rings of the phosphane, benzoate, and SPh[−] are omitted for clarity; P (green), S^{2−} ions (orange), S atoms of PhS[−] ligands (yellow), O (red), Ag (blue), both positions of Ag70 (light blue)). Selected bond lengths [± 0.5 pm] and angles [$\pm 0.2^\circ$]: Ag8–Ag13 288.9, Ag19–Ag22 338.0, Ag70–Ag70' 132.8, Ag1–S43 237.0, Ag7–S43 289.6, Ag13–S41 251.3, Ag17–S29 275.3, Ag17–S42 260.3, Ag22–S39 242.3, Ag28–S46 292.7, Ag39–S29 279.3, Ag46–S5 242.0, Ag64–S22 249.1, Ag64–S48 292.2, Ag67–S2 246.4, Ag69–S27 266.0, Ag69–S31 244.4, Ag36–P2 239.0, Ag52–P4 246.3, Ag34–O8 258, Ag43–O6 251, Ag64–O7 229, Ag69–O5 233, S43–Ag1–S48 174.8, S44–Ag4–S46 155.3, S38–Ag10–S46 160.4, S25–Ag28–S46 81.6, S28–Ag53–S46 89.2, S20–Ag59–S23 137.5, P6–Ag22–S39 147.8, P10–Ag37–S10 94.1, O8–Ag23–S6 89.5, O5–Ag69–S31 125.0, Ag41–S4–Ag68 92.4, Ag46–S5–Ag66 85.1, Ag23–S26–Ag29 70.2, Ag49–S32–Ag60 163.3, Ag67–S33–Ag70 66.0, Ag38–S36–Ag52 68.0, Ag4–S39–Ag10 61.5, Ag4–S39–Ag22 159.8, Ag13–S41–Ag67 164.6, Ag8–S45–Ag12 63.4, Ag26–S45–Ag42 158.2.

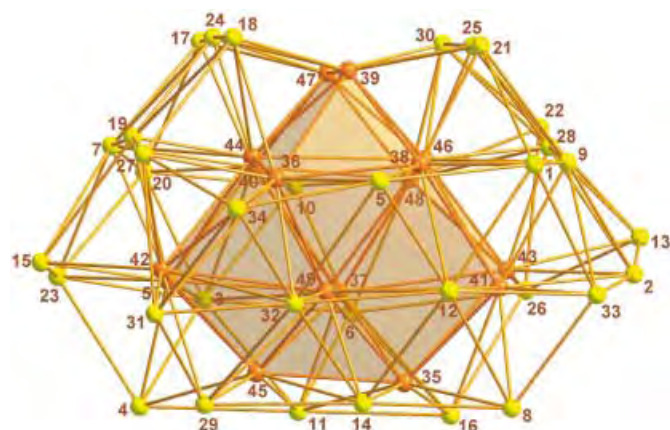


Figure 2. The sulfur substructure of **1** S atoms of PhS[−] (yellow) and polyhedral arrangement of S^{2−} ions (orange).

atoms. The P-bonded Ag atoms exhibit either a trigonal-planar (Ag14, Ag16, Ag22, Ag25, Ag32, Ag36, Ag37, Ag39, Ag52, Ag55) or a distorted-tetrahedral (Ag17, Ag21) coordination geometry. Ag atoms coordinated by O (benzoate) atoms have as analogous coordination geometry (trigonal planar for Ag23, Ag43, Ag54, Ag65, Ag69; tetrahedral for Ag20, Ag34, Ag42, Ag64). The remaining 49 Ag atoms are

solely coordinated by S^{2−} ligands and have coordination numbers from two to four. Observed S–Ag–S angles for the Ag atoms range from 137.5(2)–174.8(2) $^\circ$ (non-linear), 89.2(2)–160.4(2) $^\circ$ (trigonal planar with Σ S–Ag–S = 348.5–360.0 $^\circ$) and 81.6(2)–155.3(2) $^\circ$ (tetrahedral).

As a consequence of these different Ag coordination environments, significantly shorter Ag–S bonds (237.0(4)–251.3(4) pm) are observed for coordination number two in comparison to trigonal planar coordination (242.0(5)–289.6(4) pm) or tetrahedral coordination (246.4(7)–292.7(4) pm). Ag70 is disordered over two sites and is coordinated by S1, S33 and S9 or S12.

Assuming that in **1** only S^{2−}, SPh[−], and monoanionic benzoate ligands are present, all the Ag atoms have the formal charge +1 and thus have a d¹⁰ configuration. Ag–Ag separations within the cluster core are 288.9(2)–338.0(2) pm and indicate that there are no Ag–Ag interactions.

Compound **2** crystallizes in the space group $P\bar{1}$ with one molecule in the unit cell. The molecular structure shows **2** has an almost spherical structure with $\bar{1}$ symmetry (Figure 3). The surface is protected by 30 PnPr₃ ligands. The diameter of the Ag₂S core is 1.8–2.0 nm. On including the bound P atoms the diameter increases to 2.25–2.50 nm and when also the nPr groups are included the particle size is 3.2 nm. This size corresponds well with the hydrodynamic diameter of the particle determined by dynamic light-scattering measurements.

The structure of **2** is highly complex and in addition the Ag and S atoms in the cluster center are disordered. The extent of the disorder depends on the reaction conditions leading to the formation of **2** and on the temperature during data collection. Surprisingly, the disorder does not affect the atomic positions at the cluster periphery. In Ag₂S—an ionic conductor—a similar disorder of the Ag⁺ ions occurs at temperatures above 150 $^\circ$ C.^[16] In the solid-state structure of Ag₂S, however, only a few Ag⁺ ions show temperature-dependent disorder. Assuming that **2** is a nanoscopic section of the Ag₂S structure then it should not be surprising to make similar observations. It is, however, unusual that this observation can be made for a cluster of the size of **2**. To our surprise, it evolved that the structure of **2** cannot be interpreted as part of the Ag₂S structure. Related selenido and selenato complexes of silver (with less than 112 Ag atoms) are known to have structures composed of several shells, for example, [Ag₃₀Se₈(Se*t*Bu₁₄(PnPr₃)₈)] and [Ag₉₀Se₃₈(Se*t*Bu₁₄(PET₃)₂₂)].^[10] However, the Se atoms in [Ag₁₁₂Se₃₂(SenBu)₄₈(PrBu₃)₁₂] and [Ag₁₇₂Se₄₀(SenBu)₉₂(dppp)₄], the largest Ag₂Se cluster to be structurally characterized, adopt a distorted body-centered cubic arrangement in which the Ag atoms occupy the vacant positions and are surrounded by Se atoms in a distorted trigonal-planar or tetrahedral coordination environment. Disorder of Ag atoms, however, has also occurred in Ag₉₀[−], Ag₁₁₂[−], and Ag₁₇₂ clusters and seems to be a common feature in the structures of these clusters.

The structural change from complexes composed of several shells to structures that can be regarded as part of a solid-state structure of a binary compound very much depends on the size and properties of the cluster. These influences have already been discussed for ligand-protected M₂E clusters

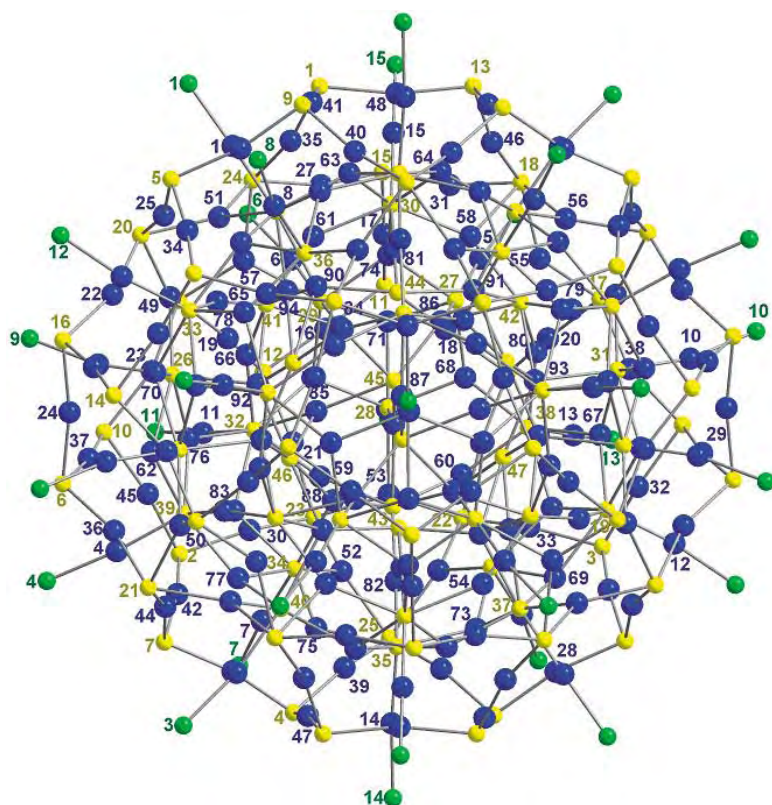


Figure 3. Molecular structure of **2** (*n*Pr groups atoms have been omitted for clarity P (green), S²⁻ ions (yellow), Ag (blue)). Selected bond lengths [± 0.8 pm] and angles [$\pm 0.3^\circ$]: Ag1–Ag25 307.3, Ag14–Ag47 287.2, Ag1–S37 244.3, Ag28–S9 239.2, Ag64–S39 265.1, Ag89–S47 242.1, Ag90–S41 272.7, Ag92–S47 280.2, Ag5–P5 236.5, Ag3–P3 241.2; S12–Ag16–S11 171.8, S21–Ag44–S7 162.0, S23–Ag53–S28 109.5, S18–Ag55–S17 137.1, P3–Ag3–S40 163.9, P11–Ag11–S32 176.1, Ag41–S1–Ag63 69.9, Ag16–S11–Ag17 99.9, Ag24–S16–Ag22 108.9, Ag77–S39–Ag76 130.4.

(E = S, Se, M = Cu, Cd).^[7–9,17,18] It is surprising in this context that the number of Ag₂E units present in a cluster does not allow any prediction of the structural change. Only recently we managed to demonstrate this for [Ag₁₂₄Se₉₇(SePrBu₂)₄Cl₆(*t*Bu₂P(CH₂)₃PrBu₂)₁₂] in which the Se substructure consists of a central Se atom surrounded by a distorted Se₁₆ Frank–Kasper polyhedron, which itself is surrounded by a Se₄₄ polyhedron as the second shell.^[18] Similar structural properties are found in **2**: 94 S atoms are distributed over three shells. The outer shell consists of 50 (S1–S25), the middle shell of 34 (S26–S42), and the inner shell of 10 (S43–S47) S atoms. Non-bonding S–S separations are in the range 450–500 pm.

Figure 4 shows the arrangement of the sulfur polyhedra in **2**. The S₅₀ polyhedron (bright yellow) consists of 30 twisted S₅ rings linked together by six S₃ triangles. The middle shell (dark yellow) forms a previously unknown Δ_3 polyhedron of 34 S atoms that itself contains an S₁₀ polyhedron (orange). However, because of the disorder, the structure of the S₁₀ polyhedron cannot be determined. During refinement comparatively high electron density remains within the cluster core; considering Ag–S bond lengths we believe that this observation can be explained by disordered Ag and S atoms. Hence, Ag atoms (Ag87–Ag94) in the vicinity of the S₁₀ polyhedron show high temperature factors. For these reasons, the formula of **2** has to be considered as idealized, but

coincides well with elemental analysis and also with interatomic distances commonly observed for Ag–S bonds. The edges of the S₅₀ outer shell are occupied by Ag atoms (Ag16–Ag48; Figure 5) which act as non-linear bridges between two S atoms (Ag–S 236.1(9)–244.2(8) pm, S–Ag–S: 155.3(2)–172.2(3) $^\circ$).

The shortest Ag–S separations are observed in the middle S₃₄ shell are in the range 333–388 pm. These very weak interactions could be the reason for the uncommon S–Ag–S bond angles in the outer shell. The broad range of Ag–E distances (E = S, Se, Te), generally complicates the structural discussion of Ag–chalcogenide clusters. The atoms Ag49–Ag57 are each coordinated by two outer-shell S atoms and act as bridging atoms between the outer shell (S₅₀ polyhedron) and the middle shell (S₃₄ polyhedron). Thus the atoms Ag49–Ag57 are surrounded by S atoms in a distorted trigonal-planar or tetrahedral fashion (S–Ag–S 104.3(2)–137.1(3) $^\circ$, Σ S–Ag–S 353.2–357.9 $^\circ$). The Ag–S bond lengths are between 247.2(8) and 283.5(8) pm. Additional weak interactions with outer-shell S atoms range from 301–309 pm.

Figure 5 shows an Ag₁₄S₅₀ polyhedron (Ag1–Ag57 and S1–S25) constructed from 30 Ag₅S₅-ten-membered rings. One Ag atom (Ag1–Ag15), stabilized by a phosphane (PnPr₃) ligand, caps each ring, these Ag atoms are not coordinated by S atoms of the S₅₀ shell but to 30 S atoms of the middle S₃₄ polyhedra. (Figure 6 shows the distorted linear coordination of Ag1–Ag15 by the S atoms the PnPr₃ ligands Ag–P 236.5(7)–241.2(7) pm, Ag–S 239.1(6)–244.7(5) pm, P–Ag–S 163.9(3)–176.1(2) $^\circ$). There are no interactions between Ag1–Ag15 and

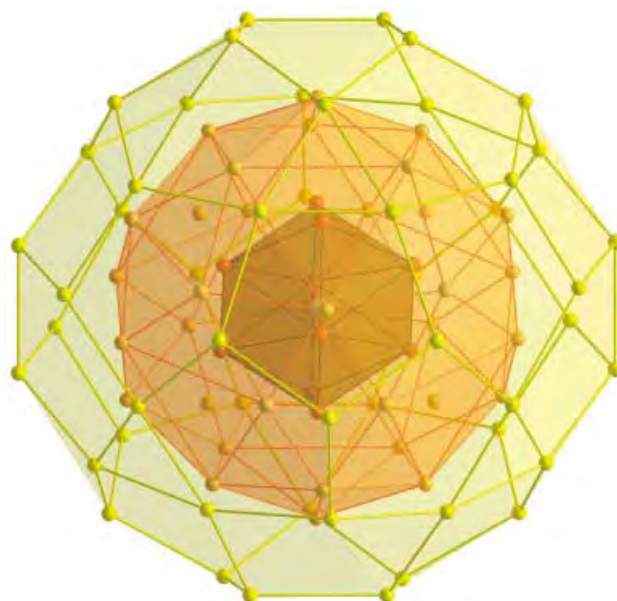


Figure 4. The sulfur substructure in **2**. The central S₁₀ polyhedron (orange) is surrounded by a S₃₄ polyhedron (dark yellow) which itself is encapsulated by a S₅₀ polyhedron (bright yellow).

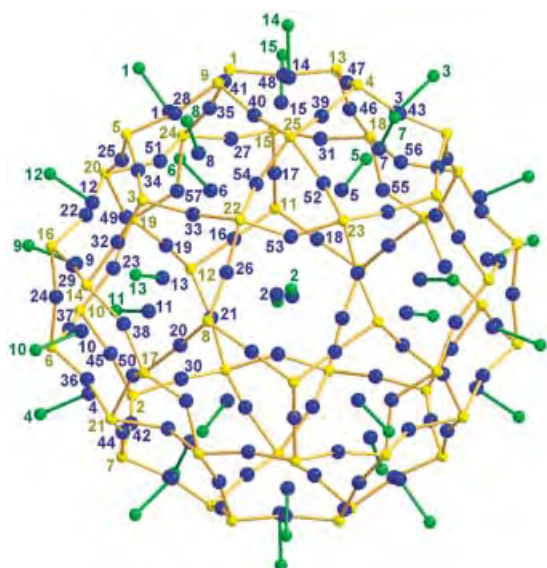


Figure 5. The outer shell of **2** consisting of 114 Ag atoms (blue), 50 S atoms (yellow), and P atoms (green; $PnPr_3$).

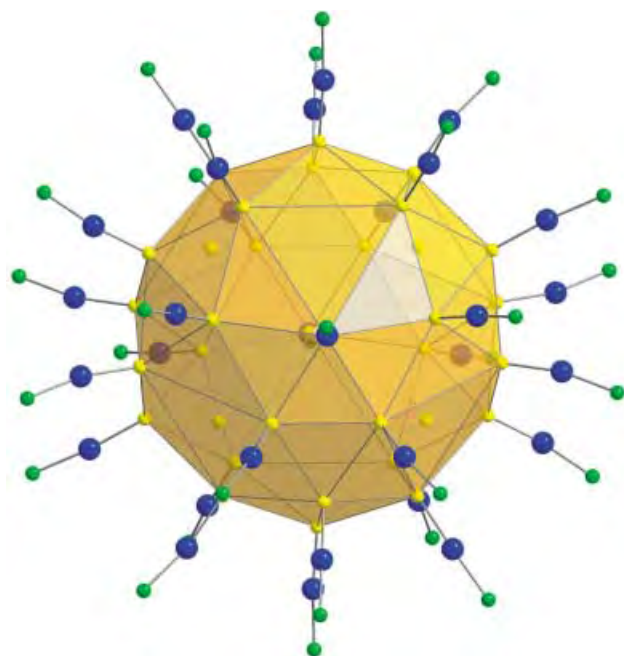


Figure 6. The middle shell in **2** consists of 34 S^{2-} ligands bound to P-coordinated Ag atoms; P (green), S^{2-} ions (yellow), Ag (blue).

the Ag atoms and S atoms located on the $Ag_{114}S_{50}$ cluster surface ($Ag \cdots Ag > 297$ pm, $Ag \cdots S$ 327–418 pm).

The atoms Ag58–Ag64 connect the outer with the middle shell. Each one of these Ag atoms is coordinated by one S atom of the outer S_{50} shell and two S atoms of the middle S_{34} shell and has a distorted trigonal-planar coordination geometry (Ag–S 258.1(6)–294.7(7) pm, S–Ag–S 102.3(2)–145.9(2)°, Σ S–Ag–S 358.5–360°). Ag62–Ag64 occupy vacant tetrahedral positions located between both S polyhedra (Ag–S 261.4(6)–293.9(6) pm). The atoms Ag65 and Ag66 are solely coordinated by S atoms of the middle S_{34} shell in a distorted linear fashion (Ag–S 250.7(5)–257.9(6) pm, S–Ag–S 147.8(2)–

161.4(2)°). Ag67–Ag80 are coordinated by three S atoms belonging to the middle S_{34} polyhedra and have a distorted trigonal-planar coordination geometry (Ag–S 256.1(6)–274.4(6) pm, S–Ag–S 101.6(2)–126.3(2)°, Σ S–Ag–S 336.5–349.8°).

Ag81–Ag94 act as bridging atoms between the middle S_{34} and the inner S_{10} polyhedron. Ag81 and Ag82 are coordinated by two S atoms (Ag–S 255.1(6)–262.4(6) pm, S–Ag–S 172.3(3)°) in a slightly bent arrangement. Ag83–Ag89 show a distorted trigonal-planar coordination (Ag–S 242.1(6)–287.1(8) pm, S–Ag–S 83.2(2)–163.6(3)°, Σ S–Ag–S 353.3–359.8°). Distorted tetrahedral coordination is observed for Ag90–Ag94 (Ag–S 251.7(9)–280.2(7) pm). As a result, the middle shell (diameter 1.1–1.5 nm) is formed by S26–S42, Ag58–Ag80, Ag81 and Ag83 and has the formula $Ag_{50}S_{34}$ (Figure 7). Ag82 and Ag84–Ag94 connect the middle shell with the inner S_{10} polyhedron. Ag49–Ag57 connect the $Ag_{114}S_{50}$ outer shell through Ag–S bonds with the $Ag_{50}S_{34}$ middle shell (Ag–S > 302 pm).

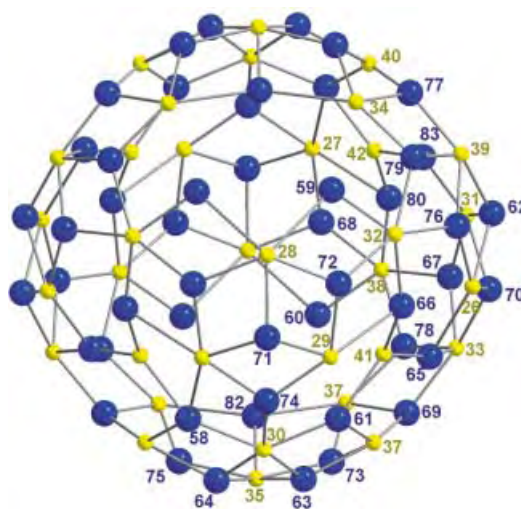


Figure 7. Spherical structure of the middle shell $Ag_{50}S_{34}$ S^{2-} ions (yellow), Ag (blue) in **2**.

The S^{2-} ions in **2** adopt various coordination modes. S1–S16 act as μ_3 bridging ligands coordinating three Ag^+ ions each (Ag–S–Ag 63.2(2)–115.5(3)°). S17–S25 are μ_4 bridging and each coordinate four Ag^+ ions of the outer $Ag_{114}S_{50}$ shell. Weak Ag–S interactions to Ag^+ ions belonging to the inner shell lead to distorted tetrahedral geometry for S1–S16 and distorted square-planar geometry for S17–S25 ((S1–S16) $\cdots$ Ag 290–312 pm, (S17–S25) $\cdots$ Ag 284–307 pm). The effect of these interactions is that the atoms S1–S25 are around 90–100 pm below the plane of the sulfur-bound Ag ions.

Of the 34 sulfide ions (S26–S42) of the middle S_{34} polyhedron 30 coordinate atoms Ag1–Ag15, each of these sulfide ions is surrounded by a distorted octahedron of six Ag^+ ions. The same coordination mode is found for S43, S44, and S46. Only S45 and S46 form μ_4 bridges.

So far we have assumed that Ag–S bonds are covalent. However, one must not overlook—the important!—ionic interactions between Ag^+ and S^{2-} ions. In an alternative

approach **2** could be described as an uncharacteristic nanoparticle of a crystal with the ionic Ag_2S structure. The formation of **2** instead of Ag_2S occurs because of the presence of the protecting ligand sphere.

Other silver chalcogenide clusters synthesized in our group all show the phenomenon of increased Ag disorder with increasing cluster size. This observation is in agreement with the fact that nanoparticles of the composition Ag_2E generally show a higher degree of Ag disorder than the corresponding binary crystalline phases. Similar disorder has also been observed in the isostructural cluster core of **3**. This suggests that the choice of cluster-stabilizing tertiary phosphane ligands does not effect the disorder within these Ag_2S clusters.

Experimental Section

All experiments were carried out under exclusion of oxygen and moisture in an atmosphere of dry nitrogen.

1: $\text{S}(\text{Ph})\text{SiMe}_3$ (0.10 mL, 0.50 mmol) and $\text{S}(\text{SiMe}_3)_2$ (0.04 mL, 0.25 mmol) is added a rapidly stirred suspension of PhCO_2Ag (silver benzoate; 230 mg, 1.00 mmol) and triphos (100 mg, 0.25 mmol) in diglyme (20 mL) at -20°C . The reaction was then allowed to slowly warm to 0°C . After 2 h at 0°C the reaction mixture was allowed to warm to room temperature. Storage of the reaction for one month produced tiny red needles of **1** (yield 27%).

2: $\text{CF}_3\text{CO}_2\text{Ag}$ (silver trifluoroacetate; 230 mg, 1.00 mmol), PnPr_3 (0.2 mL, 1.00 mmol), and $\text{S}(\text{SiMe}_3)_2$ (0.08 mL, 0.50 mmol) in diglyme (20 mL) were stirred at -40°C . After 2 h the reaction was allowed to warm to room temperature. Storage of the reaction mixture for seven days produced black crystals of **2** (33%). Changes to the reaction conditions causes precipitation of **2** and AgS as a black powder.

3: $\text{S}(\text{SiMe}_3)_2$ (0.08 mL, 0.50 mmol) was added to a suspension of $\text{CF}_3\text{CO}_2\text{Ag}$ (230 mg, 1.00 mmol) and PnBu_3 (0.25 mL, 1.00 mmol) in diglyme (25 mL) at -40°C . After 3 days at this temperature the deep red solution was allowed to warm to -20°C , then, after 1 day at this temperature, the reaction was allowed to warm to room temperature. Black crystals of **3** were formed on storing the reaction mixture at room temperature for 1 week.

Correct elemental analyses (C, H, O, P, Ag) for **1–3** were obtained.

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- [15] X-ray analysis: STOE-IPDS II (MoK_α); data collection and refinement (SHELX97, SHELXL93); empirical absorption correction (HABITUS). CCDC-187700 (**1**) and 187701 (**2**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk). **1:** $\text{C}_{376}\text{H}_{346}\text{Ag}_{70}\text{O}_8\text{P}_{12}\text{S}_{50}\cdot 2$ diglyme, triclinic, space group $\bar{P}1$ (no 2); $Z=2$, (150 K): $a=2546.0(5)$, $b=2915.6(6)$, $c=3946.0(8)$ pm, $\alpha=91.16(3)^\circ$, $\beta=96.63(3)^\circ$, $\gamma=113.93(3)^\circ$, $V=26522.5\times 10^6$ pm³, $\mu(\text{MoK}_\alpha)=2.8$ mm⁻¹, $2\theta_{\text{max}}=55^\circ$, of a total of 192662 reflections collected, 109402 were independent and 109317 reflections with $I>2\sigma(I)$, 3149 parameters (Ag, S, P anisotrope, O, C isotrope). Maximum residual electron density $2.8\text{ e}\cdot\text{\AA}^{-3}$, $R1=0.113$; $wR2=0.319$. **2:** $\text{C}_{270}\text{H}_{630}\text{Ag}_{188}\text{P}_{30}\text{S}_{94}\cdot 2$ diglyme, triclinic, space group $\bar{P}1$ (no 2), $Z=1$, (150 K): $a=2714.7(5)$, $b=2825.7(4)$, $c=28494(5)$ pm, $\alpha=119.05(2)^\circ$, $\beta=91.28(1)^\circ$, $\gamma=117.86(2)^\circ$, $V=15991.3\times 10^6$ pm³, $\mu(\text{MoK}_\alpha)=6.0$ mm⁻¹, $2\theta_{\text{max}}=57^\circ$, of a total of 118990 collected, 62257 were independent and 47327 reflections with $I>2\sigma(I)$, 2254 parameters (Ag, S, P anisotrope, C isotrope), Cancellation effects in the inside of the cluster were refined as Ag atoms (occupation 0.25). Maximum residual electron density $6.9\text{ e}\cdot\text{\AA}^{-3}$, $R1=0.098$; $wR2=0.241$. High residual electron density is located between S_{34} and S_{10} polyhedra and inside the S_{10} polyhedron. A more accurate allocation is impossible. These positions could be partially occupied by $\text{Ag}_{87}\text{–Ag}_{94}$.
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Targeted Synthesis of Ferromagnetically Coupled Complexes with Modified 1,3,5-Trihydroxybenzene Ligands**

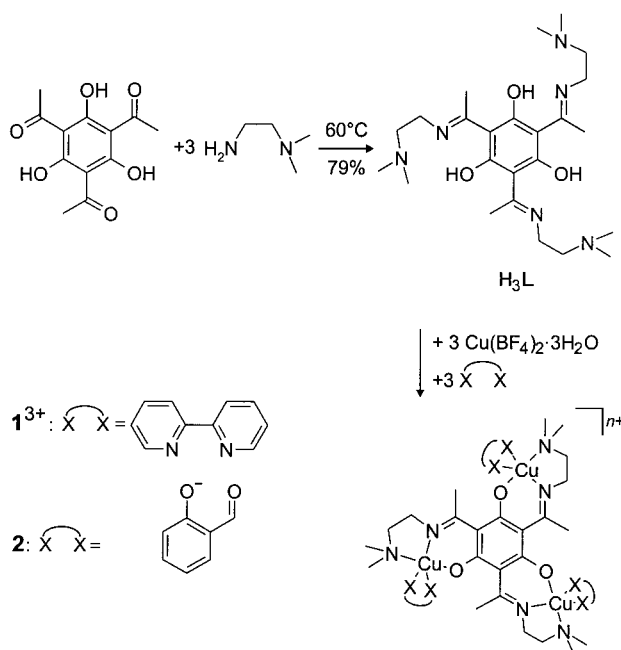
Thorsten Glaser,* Mareike Gerenkamp, and Roland Fröhlich

Dedicated to Professor Wieghardt on the occasion of his 60th birthday

The design and synthesis of molecule-based magnets has attracted considerable interest over the past decade. The synthetic efforts have focused on the assembly of molecular building blocks to form supramolecular magnetic materials.^[1] As Kahn emphasized, the design of molecular building blocks with *ferromagnetic* interactions between the paramagnetic centers is essential for the development of new types of molecule-based magnets.^[2] One strategy for synthesizing materials with ferromagnetic interactions is provided by the *m*-phenylene linkage of organic radicals, utilizing the spin-polarization mechanism.^[3] This concept was applied to binuclear transition metal complexes containing pyrimidine or resorcinol as bridging ligands.^[4] One trinuclear complex with 1,3,5-trihydroxybenzene (phloroglucinol) as bridging ligand was reported which exhibits ferromagnetic interactions between the three coordinated (Tp*)Mo^VOCl fragments (Tp* = tris((3,5-dimethylpyrazolyl)hydroborate)).^[5]

The synthesis of phloroglucinol-bridged trinuclear complexes with first-row transition metals is hindered because of the low stability of such complexes. To overcome this problem we have developed an approach in which the stability is enhanced by attaching pendant arms with additional coordinating groups in the 2,4,6-position of phloroglucinol. An analogous approach was used by Abrahams et al. with azophenyl groups in 2,4,6-position.^[6] Here we report on the phloroglucinol-based ligand H₃L and its ability to bridge three paramagnetic copper centers (Scheme 1) that are ferromagnetically coupled to give the highest possible spin ground state.

The ligand H₃L in reasonable yields was prepared by the condensation of 2,4,6-triacetyl-1,3,5-trihydroxybenzene with three equivalents of *N,N*-dimethylethylenediamine (Scheme 1). The reaction of H₃L with Cu(BF₄)₂·3H₂O in the presence of NEt₃ yielded a green solution that is typical of Cu^{II}-phenolato complexes. The coordination sphere of the three copper ions was completed by addition of three



Scheme 1. Synthesis of the ligand H₃L and the reaction to give complexes **1**³⁺ and **2**.

equivalents of a bidentate chelate ligand: the use of bipyridine (bpy) gave [L{Cu^{II}(bpy)}₃](BF₄)₃ (**1**-(BF₄)₃) and the use of salicylaldehyde (Hsal) gave [L{Cu^{II}(sal)}₃] (**2**). Large single crystals of **1**-(BF₄)₃·2 MeOH·HNMe₂·1.5 H₂O suitable for an X-ray structure analysis^[7] were grown by slow diffusion of *n*-pentane into the reaction solution. Figure 1a shows the structure of **1**³⁺ and illustrates the ability of the ligand L³⁻ to bridge three metal centers. Each of the three copper ions is coordinated by one phenolato oxygen and two nitrogen atoms of the ligand L³⁻, and two nitrogen atoms of bpy. The coordination geometry of the three copper ions is square pyramidal; however, Cu1 and Cu2 show considerable distortion towards trigonal bipyramidal. Based on the comparable characterization of **2** and **1**-(BF₄)₃ by elemental analysis, FT-IR, ESI-MS, UV/Vis/NIR absorption and EPR spectroscopy, and magnetic measurements complex **2** can be formulated as [L{Cu^{II}(sal)}₃].

Temperature-dependent magnetic susceptibility measurements (SQUID, 2–300 K, 1.0 T) on powdered samples of **1**-(BF₄)₃ and **2** revealed an increase of the effective magnetic moment (μ_{eff}) with decreasing temperature, indicative of ferromagnetic interactions between the metal centers (Figure 2). Below 4 K μ_{eff} decreases for **2** due to weak intermolecular antiferromagnetic couplings. The diamagnetic dilution by the three anions in **1**-(BF₄)₃ increases the distances between the trinuclear units and thus reduces these antiferromagnetic interactions. A Weiss constant ϑ was used in the fitting procedure to reflect these intermolecular couplings. Despite the small structural differences of the three copper centers in **1**-(BF₄)₃, a good fit to the experimental data was obtained with three equal *J* values ($H = -2J(S_1S_2 + S_2S_3 + S_3S_1) + \sum \mu_B g_i S_i B_i$). The best fit results in $J = +1.96 \text{ cm}^{-1}$ for **1**-(BF₄)₃ and $J = +3.31 \text{ cm}^{-1}$ for **2**. Both complexes exhibit ferromagnetic interactions between the copper centers. The

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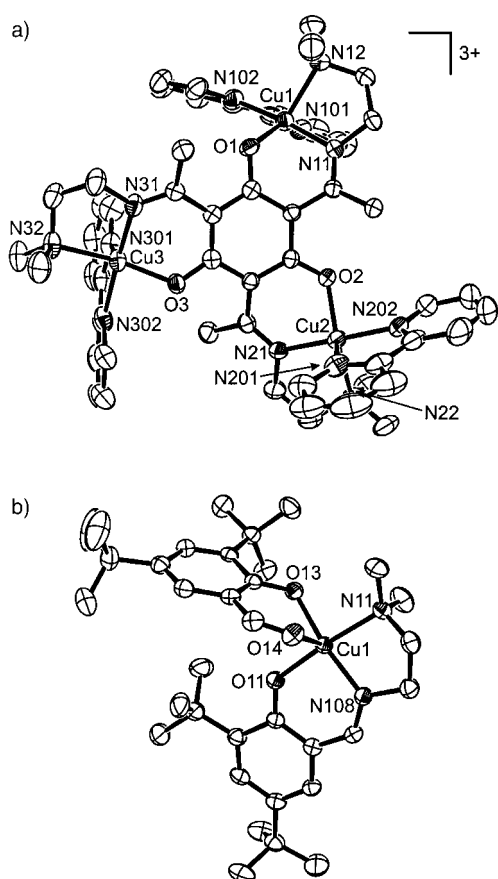


Figure 1. a) Molecular structure (50% probability; H atoms omitted) of 1^{3+} : Selected distances [Å]: Cu1–O1 1.932(4), Cu2–O2 1.937(4), Cu3–O3 1.930(4). b) Molecular structure (50% probability; H atoms omitted) of **3**: Selected distance [Å]: Cu1–O11 1.915(2).

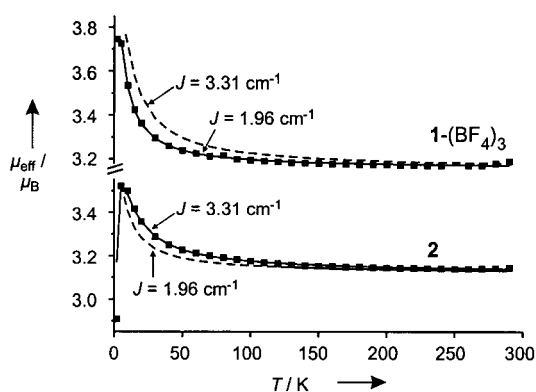


Figure 2. Temperature dependence of μ_{eff} for **1**-(BF₄)₃ and **2**. The solid lines represent the best fits ($J = 1.96 \text{ cm}^{-1}$, $g = 2.10$, $\chi_{\text{TIP}} = 246 \times 10^{-6} \text{ cm}^3 \text{ mol}^{-1}$, $\theta = -0.083 \text{ K}$ for **1**-(BF₄)₃; $J = 3.31 \text{ cm}^{-1}$, $g = 2.08$, $\chi_{\text{TIP}} = 100 \times 10^{-6} \text{ cm}^3 \text{ mol}^{-1}$, $\theta = -1.03 \text{ K}$ for **2**). The dashed lines represent simulations with interchanged J values to demonstrate the accuracy of the obtained values.

results show that complexes with ferromagnetic interactions can be constructed by using phloroglucinol as bridging ligand.

In analogy to a phloroglucin-bridged complex synthesized by Ung et al.,^[5] the spin-polarization mechanism should account for these ferromagnetic interactions (Scheme 2). The ferromagnetic interaction in **2** is somewhat larger than

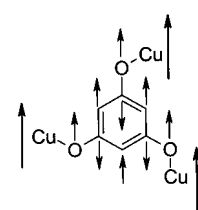
that in **1**-(BF₄)₃. We assume this reflects differences in the coordination geometry of the copper ions between the two complexes. To investigate this further, we synthesized complex **3**, a mononuclear analogue of **2**, which owing to the coordination of the sal[−] ligand displays a square-pyramidal structure (Figure 1b). In such a structure, the magnetic $d_{x^2-y^2}$ orbital is directed towards the orbitals of the oxygen donor atom of L^{3−} resulting in better overlap. The distortion to a trigonal-bipyramidal coordination environment in **1**-(BF₄)₃ rotates the magnetic orbital out of the basal plane and leads to a worse overlap with the orbitals of the oxygen donor atom of L^{3−} and consequently to weaker coupling.

In conclusion, the phloroglucinol-based ligand H₃L allows the bridging of three copper ions in a *m*-phenylene arrangement. The two copper complexes **1**-(BF₄)₃ and **2** exhibit ferromagnetic interactions between the paramagnetic copper centers, which are produced by the spin-polarization mechanism. In pursuit of new magnetic materials we aim to use this new class of ligands in two ways: 1) synthesis of trinuclear complexes with high local spin states and magnetic anisotropy through use of metal ions such as Mn^{III} and Cr^{III} as potential single-molecule magnets, and 2) synthesis of two-dimensional networks and magnetic dendrimers as candidates for molecule-based magnets.

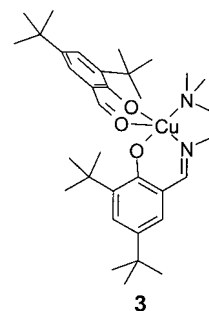
Experimental Section

1-(BF₄)₃: A solution of H₃L (0.127 g, 0.275 mmol) in methanol (15 mL) was added to a stirred solution of Cu(BF₄)₂·3H₂O (240 mg, 0.824 mmol) in methanol (20 mL) resulting in an olive-green solution. A solution of bpy (0.129 g, 0.824 mmol) and NEt₃ (83 mg, 0.824 mmol) in methanol (15 mL) was added dropwise. Upon slow diffusion of *n*-pentane into the filtered solution large black single crystals were obtained which were washed with diethyl ether and dried in vacuum. Yield: 170 mg (43%). ESI-MS (methanol) of **1**-(ClO₄)₃: m/z (%): 608.8 (28) [**1**-(ClO₄)₃−2ClO₄]²⁺, 530.7 (51) [**1**-(ClO₄)₃−bpy−2ClO₄]²⁺, 373.0 (100) [**1**-(ClO₄)₃−3ClO₄]³⁺; IR (KBr): $\tilde{\nu}$ = 1568 (m, br, (C=N)), 1341 (w, (C=O)), 1084 (w, bpy), 1058 (s, br, BF₄[−]), 778 cm^{−1} (m, bpy); UV/Vis/NIR (acetonitrile): λ_{max} (ϵ) = 243 (51 000), 304 (73 000), 322 (57 000), 468 (2700), 598 nm (1100); elemental analysis calcd for C₅₄H₆₇N₁₂O₃Cu₃B₃F₁₂ (%): C 45.83, H 4.77, N 11.88; found: C 45.63, H 4.42, N 11.67.

2: A solution of H₃L (147 mg, 0.318 mmol) in ethanol (12 mL) was added to a stirred solution of Cu(BF₄)₂·3H₂O (278 mg, 0.954 mmol) in ethanol (10 mL) resulting in an olive-green solution. After addition of a solution of Hsal (116 mg, 0.954 mmol) and NEt₃ (257 mg, 2.53 mmol) in ethanol (10 mL), the resulting solution was stirred for 4 h. Olive-green microcrystals separated which were washed with diethyl ether and dried in vacuum. Yield: 120 mg (37%). ESI-MS (methanol) of **2**: m/z (%): 802.3 (12) [**2**−2sal+CH₃O]⁺, 788.2 (19) [**2**−2sal+OH]⁺, 712.3 (12) [**2**−3sal-



Scheme 2. Schematic representation of the spin-polarization mechanism. The two large arrows represent the unpaired spin on each of the three Cu^{II} ions; the small arrows represent the direction of polarization of the electron clouds of the intervening atoms. Note that the spin densities of the Cu^{II} centers and the coordinated oxygen atoms have the same directions due to spin-delocalization.



sal+2CH₃O]⁺; 385.7 (11) [2–2sal]²⁺, 333.6 (100) [2–3sal+ OH]²⁺; IR (KBr): $\tilde{\nu}$ = 1645 (s, (C=O)), 1568 (m, br, (C=N)), 1352 (w, sal (C=O)), 1341 (w, L²⁻ (C=O)), 897 (w, sal), 762 cm⁻¹ (w, sal); UV/Vis/NIR (acetonitrile): λ_{max} (ϵ) = 238 (72000), 327 (47000), 445 (sh), 602 nm (600); elemental analysis calcd for C₄₅H₃₄N₆O₉Cu₃ (%): C 53.32, H 5.37, N 8.29; found: C 52.98, H 5.22, N 8.23.

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- [7] X-ray structure analysis data of **1**-(BF₄)₃·2MeOH·HNMe₂·1.5H₂O: formula C₅₅H₈₁N₁₃O_{6.5}Cu₃B₃F₁₂, M_r = 1515.41, black crystal 0.30 × 0.30 × 0.10 mm, a = 19.243(1), b = 16.521(1), c = 21.633(1) Å, β = 92.18(1)°, V = 6872.4(6) Å³, ρ_{calcd} = 1.465 g cm⁻³, μ = 10.10 cm⁻¹, empirical absorption correction by using SORTAV (0.751 ≤ T ≤ 0.906), Z = 4, monoclinic, space group $P2_1/n$ (no. 14), λ = 0.71073 Å, T = 198 K, ω and φ scans, 23777 reflections collected ($\pm h$, $\pm k$, $\pm l$), $((\sin\theta)/\lambda)$ = 0.62 Å⁻¹, 13898 independent (R_{int} = 0.032) and 9859 observed reflections ($I \geq 2\sigma(I)$), 756 refined parameters, R = 0.087, wR^2 = 0.256, max. residual electron density 1.68 (–1.12) e Å⁻³, close to the BF₄⁻, refinement with split positions did not improve the model, therefore the anions were refined with isotropic thermal displacement parameters, the solvent molecules (2 methanol, 1 dimethylamine, and 1.5 water) were refined with one common isotropic thermal parameter each, hydrogen atoms not localized, other calculated and refined as riding atoms. X-ray structure analysis data of **3**: formula C₃₄H₃₂N₂O₃Cu, M_r = 600.32, green-yellow crystal 0.25 × 0.15 × 0.03 mm, a = 9.382(1), b = 13.052(1), c = 13.789(1) Å, α = 87.25(1), β = 86.88(1), γ = 87.79(1)°, V = 1683.0(3) Å³, ρ_{calcd} = 1.185 g cm⁻³, μ = 6.82 cm⁻¹, empirical absorption correction by using SORTAV (0.848 ≤ T ≤ 0.980), Z = 2, triclinic, space group $P\bar{1}$ (no. 2), λ = 0.71073 Å, T = 198 K, ω and φ scans, 10380 reflections collected ($\pm h$, $\pm k$, $\pm l$), $((\sin\theta)/\lambda)$ = 0.62 Å⁻¹, 6793 independent (R_{int} = 0.052) and 5042 observed reflections ($I \geq 2\sigma(I)$), 375 refined parameters, R = 0.064, wR^2 = 0.142, max. residual electron density 0.98 (–0.54) e Å⁻³, hydrogen atoms calculated and refined as riding atoms. For data collection and programs used see H. P. Wu, R. Aumann, R. Fröhlich, E. Wegelius, *Eur. J. Org. Chem.* **2002**, 361–368. CCDC-181141 (**1**-(BF₄)₃·2MeOH·HNMe₂·1.5H₂O) and CCDC-181142 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit at ccdc.cam.ac.uk).

Supramolecular Engineering with Macromolecules: An Alternative Concept for Block Copolymers**

Bas G. G. Lohmeijer and Ulrich S. Schubert*

Block copolymers represent an important class of materials, which have received widespread attention because of their remarkable micro- and nanophase morphology. This morphology leads to unique properties compared to homopolymers or their blends. Classical examples of block-copolymer morphology are lamellae, hexagonal-packed cylinders and body-centered-cubic arrays of spheres.^[1] During the last decades, important advances have been made in the synthesis, characterization, and application of block copolymers. In particular, anionic polymerization has been successfully applied in their controlled synthesis.^[2] Several other routes have been realized as well, for example, controlled radical polymerization,^[3] cationic polymerization,^[4] group transfer,^[5] and metathesis,^[6] or combinations of such techniques. Nevertheless, block-copolymer synthesis remains a challenge for certain materials and several interesting combinations could not be realized to date. On the other hand, recent developments in the field of supramolecular chemistry have shown that small (self-)complementary building blocks can lead, through self-organization processes, to large, well-defined structures, which are held together by noncovalent interactions such as hydrogen bonds^[7] and metal-to-ligand coordination.^[8] Herein we present a new highly controlled and well-defined construction principle for block copolymers that utilize supramolecular interactions, in this case metal-to-ligand coordination. By this method new combinations of block copolymers can be prepared, which are not accessible, or have been very difficult to access to date. This allows a comparison of the new metallo-supramolecular compounds with classical well-documented covalent block copolymers. For this purpose we chose the terpyridine ligand as the central building unit, which is well-known for its outstanding ability to form stable bis complexes with a large variety of transition-metal ions (Figure 1).^[9] The main advantage of having a metal complex as the bridging unit is the possibility of cleavage at this junction point. Therefore new “smart materials” are accessible. Moreover, the metal ion being at the interface between the blocks may cause additional interesting features regarding morphology, thermal and mechanical as well as photophysical properties.

The construction of the supramolecular block copolymers works along the same principle as their covalent counterparts.

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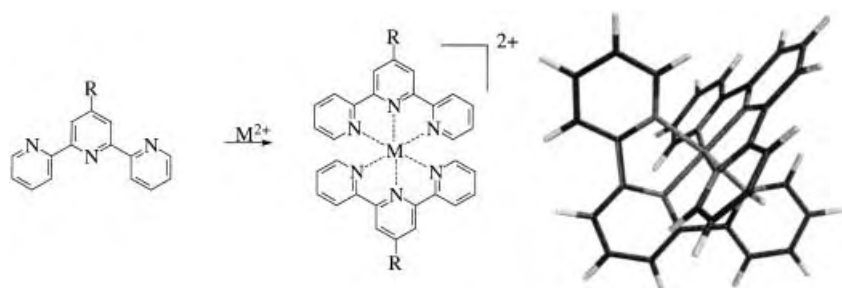


Figure 1. Bis(terpyridine) metal complex (left: schematic representation, right: results of the molecular modeling study).

First, defined oligomers of narrow polydispersities (<1.15) and with functional end groups (telomers) are formed by controlled polymerization methods. The terpyridine ligand is introduced at the chain end(s) of the telomers by simple organic reactions. Combining the different terpyridine-functionalized oligomers by self-organization processes directly leads to the desired block copolymers (Figure 2). An ex-

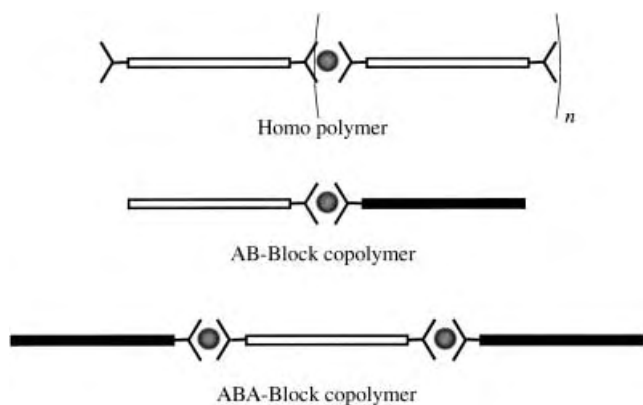


Figure 2. Modular engineering of A_n , AB-, and ABA-metallo-supramolecular block copolymers.

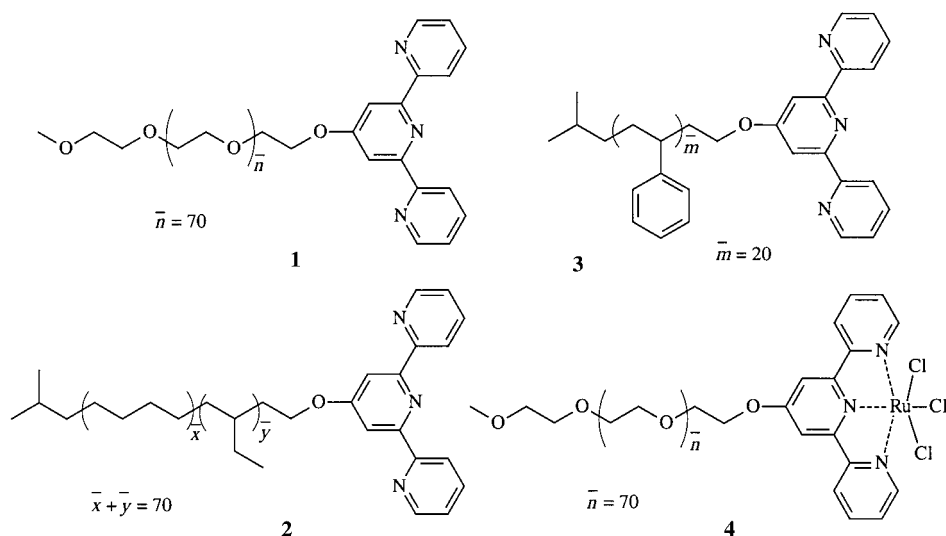
tremely powerful tool in the construction of well-defined supramolecular block copolymers is the ability of the terpyridine ligand to bind selectively only to a single transition-metal ion and form a “mono”-complex under specific conditions (1:1 ratio of ligand:metal ion).^[10] In particular, ruthenium ions have been used successfully in supramolecular chemistry to build up asymmetric complexes (Figure 2).^[11]

Herein we have used terpyridine-terminated polymers to engineer supramolecular AB, $(AB)_n$, and ABA block copolymers. To show the feasibility of this concept we chose well-known systems which also have covalent counterparts. Recently we demonstrated that the terpyridine ligand could be successfully introduced into hydroxy-functionalized oligomers of poly(ethyleneoxide) (PEO)

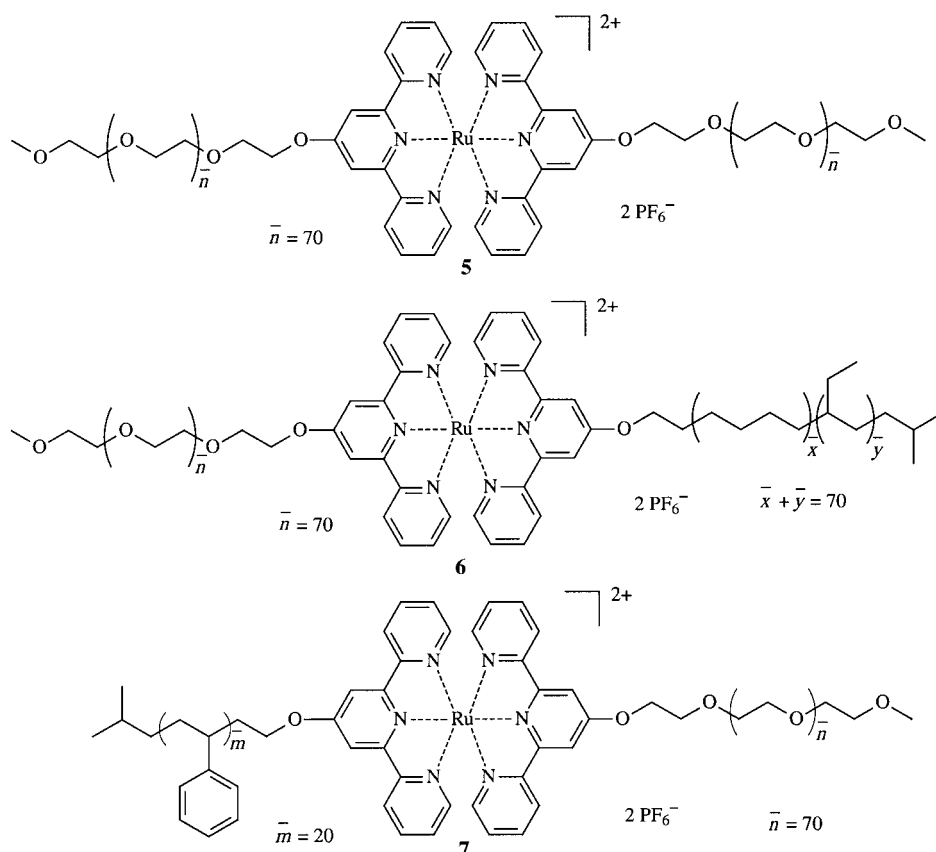
and poly(tetramethyleneoxide) (PTMO) in a suspension of KOH in DMSO.^[12] This strategy has now been extended to hydroxy-terminated polystyrene (PS)^[13] and poly(ethylene-*co*-butylene) (PEB; Scheme 1), by utilizing toluene as the solvent and using a crown ether to improve the base solubility. The terpyridine ligand could react in high yields through a Williamson type ether formation reaction. For this purpose, different reaction conditions were optimized for each class of polymers. The complete deri-

vativization of the prepolymers with terpyridine-moieties was demonstrated by ^1H NMR, ^{13}C NMR, UV/Vis, gel-permeation chromatography (GPC) and MALDI-TOF MS. To form AB-type polymer structures selectively, the poly(ethylenoxide) **1** was treated with Ru(III)Cl_3 , which resulted exclusively in the desired monocomplex **4** (simply isolated by precipitation). This compound was then further treated, in a self-organization step, with the terpyridine-functionalized polymers **1**, **2**, and **3**, respectively. In this approach, ethanol is utilized as the reducing agent and *N*-ethylmorpholine as the catalyst, to reduce the Ru^{III} ions to Ru^{II} ions. Subsequently, a bis complex was formed between the ruthenium-filled terpyridine unit and the uncomplexed terpyridine unit, which resulted in unsymmetrical dimers. After exchange of the counterions by addition of an excess of NH_4PF_6 , the supramolecular AB block copolymers **5**, **6**, and **7** were isolated by precipitation or extraction (Scheme 2). As an additional purification step, size-exclusion chromatography (BioBeads SX-1 in CH_2Cl_2) was applied. The low yields (35–50%) could be explained by the extensive purification procedures in conjunction with the small amounts we were working with to date. The corresponding model complexes were isolated in yields up to 97%.^[9b] Low selectivity was not an issue, because homopolymers (AA or BB) could not be isolated.

Characterization by UV/Vis spectroscopy revealed the characteristic metal–ligand charge-transfer (MLCT) band of the bis(terpyridine) ruthenium(II) complex at 490 nm, while



Scheme 1. Terpyridine-functionalized building blocks, poly(ethyleneoxide) **1**, poly(ethylene-*co*-butylene) **2**, polystyrene **3**, and poly(ethyleneoxide) treated with the $\text{Ru}^{\text{III}}\text{Cl}_3$ compound **4**.



Scheme 2. Isolated metallo-supramolecular block copolymers: PEO₇₀-[Ru]-PEO₇₀ (**5**), PEO₇₀-[Ru]-PEB₇₀ (**6**), and PS₂₀-[Ru]-PEO₇₀ (**7**).

the band at 390 nm—indicative of the mono(terpyridine) ruthenium(III) complex—has completely disappeared (Figure 3). This result is already unambiguous evidence for the successful formation of the block copolymers. In addition, because of the complexation of the ruthenium(II) ions, the signals arising from the terpyridine unit in both the ¹H and ¹³C NMR spectra have shifted when compared to the uncomplexed terpyridine-functionalized prepolymers. All signals can be assigned by a comparison with the corresponding low-

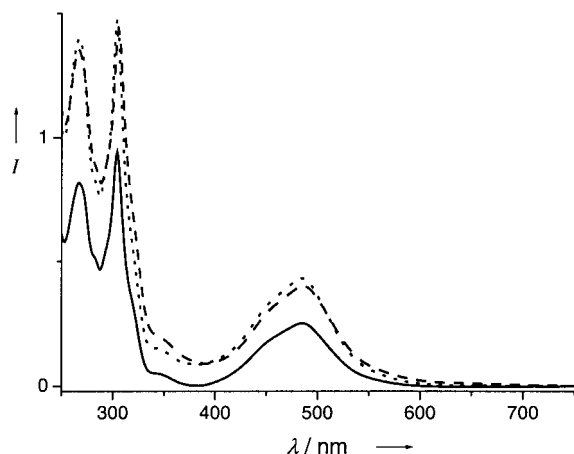


Figure 3. UV/Vis spectra of supramolecular block copolymers showing the metal-to-ligand charge-transfer band (MLCT) at 490 nm (in CH₃CN): — **5**, --- **6**, ··· **7**.

molar-mass model complexes. The integral ratio of the two polymer blocks was in good agreement with the expected ratio in all three cases. Also, this finding excludes the existence of any “homodimers”. MALDI-TOF MS revealed the presence of the different blocks in the supramolecular block copolymers, although the supramolecular connection seems to be partly broken during the MALDI process (as is known for this type of metal complex).

Size-exclusion chromatography (GPC), which applied a UV/Vis as well as a refractive-index (RI) detector, revealed a single signal. This clearly shows that the metallo-supramolecular block copolymer was formed and that no homopolymers are present (Figure 4). The similar molar masses of **5**, **6**, and **7** result in a similar elution volume. The absence of further peaks also shows that the compounds are stable on the GPC column. Moreover, by varying the pH value from 0 to 14 in water,

no changes in the UV/Vis spectrum could be observed, which indicates the unusual stability of the ruthenium complex. However, by utilizing redox processes or a large excess of a competitive chelator at higher temperatures (such as hydroxyethylethylenediaminotriacetic acid sodium salt, HEEDTA), the metal complex can be disassembled. Because the described A-[Ru]-B block copolymers represent amphiphilic materials, the formation of defined micelles is possible (see ref. [14] for the first examples). This opportunity will certainly be of interest for applications in supported catalysis and nanotechnology.

In conclusion, we have demonstrated that a supramolecular approach towards block copolymers is feasible. In particular, combinations of blocks that to date have been inaccessible, or accessible by established routes only with great difficulties, can be engineered utilizing the described approach. By introducing the terpyridine ligand at the chain end(s) of different polymers of various lengths, a large number of building blocks for block copolymers can be obtained (several hundreds of potential functional prepolymers and telechelic molecules are already commercially available). Applying the strategy employed herein and using different metal centers and counterions, the possibilities for assembling supramolecular block copolymers of the type described are virtually unlimited. This approach is highly suitable for the development of libraries of block copolymers by combinatorial methods, which vary the block properties systematically. Initial experiments of this type are currently in progress. In

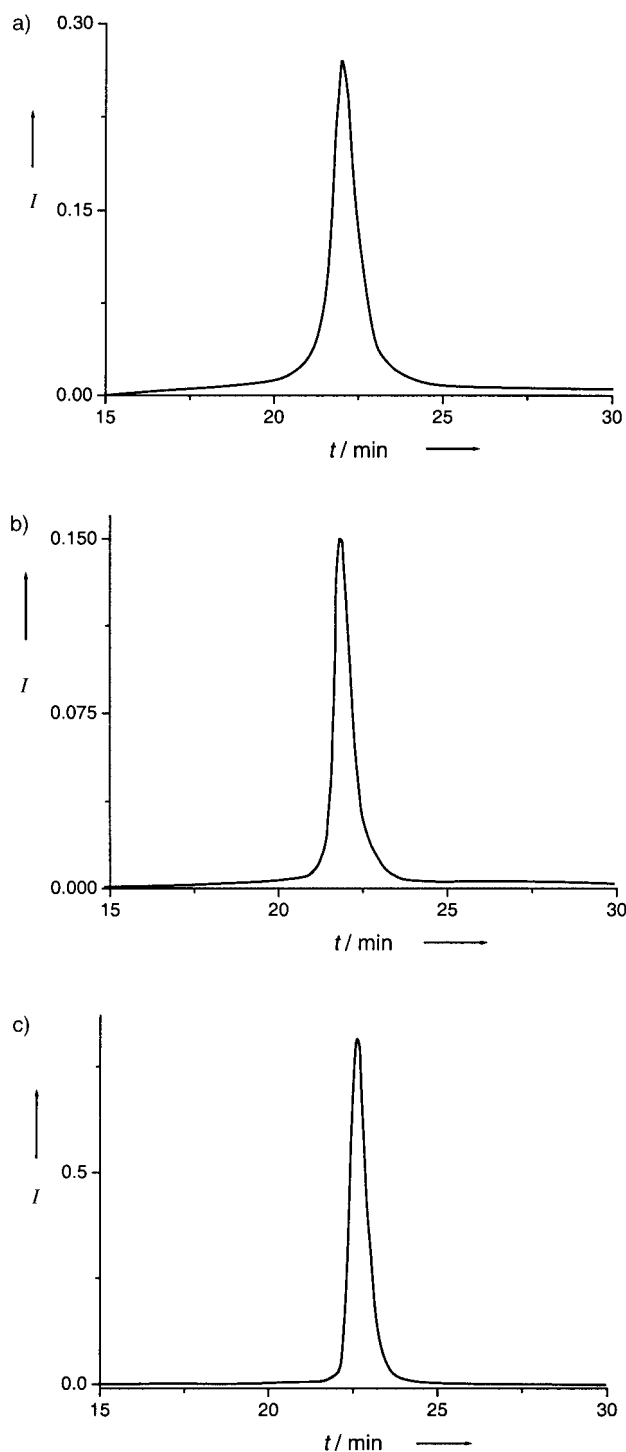


Figure 4. GPC traces of a) **5**, b) **6**, and c) **7** measured using a UV detector (eluant CHCl_3 , polystyrene calibration standards).

addition, the reversibility of the supramolecular connections opens up avenues for the construction of “switchable” materials. This can lead to new applications, for example, as intelligent glues or release-on-demand systems.

Experimental Section

General preparation of **1–3**: Powdered KOH and the prepolymer (3:1 ratio) were stirred under Ar in dry DMSO at 70 °C or dry toluene with [18]-

crown-6, heated under reflux. After 30 min, 4'-chloro-2,2':6',2''-terpyridine was added. The mixture was stirred for 24 h–48 h, then poured into cold water and extracted with CH_2Cl_2 . The combined organic layers were dried over Na_2SO_4 and the solvent removed in vacuo. All compounds were purified by preparative size-exclusion chromatography (BioBeads SX-1, CH_2Cl_2) and the compounds were subsequently precipitated by addition of a solvent in which they are insoluble. Compound **2** was further purified by column chromatography (silica, CH_2Cl_2 followed by $\text{CH}_2\text{Cl}_2:\text{Et}_3\text{N}$ 9:1). Yields were 9.75 g of **1** (95%), 3.9 g of **2** (46%), and 2.10 g of **3** (75%). Selected analytical data: **1**: ^1H NMR (400 MHz, CDCl_3 , 25 °C): δ = 8.68 (dt, J = 4.8, 2.0 Hz, 2H; H6, H6''), 8.61 (dt, J = 8.0, 2.0 Hz, 2H; H3, H3''), 8.04 (s, 2H; H3', H5'), 7.85 (td, J = 8.0, 2.0 Hz, 2H; H4, H4''), 7.34 (ddd, J = 8.0, 4.8, 2.0 Hz, 2H; H5, H5''), 4.40 (t, J = 5.2 Hz, 2H; tpyOCH_2), 3.93 (t, J = 5.2 Hz, 2H; $\text{tpyOCH}_2\text{CH}_2$), 3.83–3.45 (m, 280H; PEO backbone), 3.38 ppm (s, 3H; OCH_3); UV/Vis (H_2O): λ_{max} = 278, 234 nm; MALDI-TOF MS: M_n = 3436 g mol^{-1} ; GPC (RI): M_n = 2360, polydispersity index (PDI) = 1.21. **2**: ^1H NMR (400 MHz, CDCl_3 , 25 °C): δ = 8.69 (dt, J = 4.8, 2.0 Hz, 2H; H6, H6''), 8.62 (dt, J = 8.0, 2.0 Hz, 2H; H3, H3''), 8.01 (s, 2H; H3', H5'), 7.85 (td, J = 8.0, 2.0 Hz, 2H; H4, H4''), 7.32 (ddd, J = 8.0, 4.8, 2.0 Hz, 2H; H5, H5''), 4.25 (t, J = 6.4 Hz, 2H; tpyOCH_2), 1.58–0.68 ppm (m, 560H; PEB backbone); UV/Vis (CHCl_3): λ_{max} = 278, 243 nm; MALDI-TOF MS: M_n = 4151 g mol^{-1} ; GPC (UV): M_n = 4450, PDI = 1.19. **3**: ^1H NMR (400 MHz, CDCl_3 , 25 °C): signals are broad δ = 8.67 (bm, 2H; H6, H6''), 8.60 (bm, 2H; H3, H3''), 7.91 (s, 2H; H3', H5'), 7.83 (bm, 2H; H4, H4''), 7.31–6.39 (bm, 102H; C_6H_5 PS backbone; H5, H5''), 4.11–3.96 (bm, 2H; tpyOCH_2), 2.66, 2.18–1.10, 0.78 ppm (bm, 49H; CH_2 , CH PS backbone); UV/Vis (CHCl_3): λ_{max} = 278, 243 nm; MALDI-TOF MS: M_n = 2104 g mol^{-1} ; GPC (UV): M_n = 1850, PDI = 1.10.

Preparation of **4**: A solution of **2** (1.00 g, 0.29 mmol) in methanol (25 mL) was stirred at 60 °C. Then an equimolar amount of $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (0.076 g, 0.29 mmol) was added. Stirring was continued overnight. Subsequently, the reaction mixture was cooled to –20 °C. The resulting dark orange precipitate was collected by filtration and washed twice with ice-cold water, followed by diethyl ether, yielding 1.05 g of product (99%). ^1H NMR (400 MHz, CDCl_3 , 25 °C): δ = 3.92–3.46 (m, 280H; PEO backbone), 3.38 ppm (s, 3H OCH_3); UV/Vis (H_2O): λ_{max} = 272, 375 nm; MALDI-TOF MS: M_n = 3447 g mol^{-1} .

General procedure for the preparation of **5–7**: A solution of **1**, **2**, or **3** (1:1 ratio), respectively, and **4** in MeOH (5 mL) was stirred for 30 min, heating under reflux. A few drops of *N*-ethylmorpholine was added and the solution turned from orange to red. Heating under reflux was continued overnight, after which an excess of NH_4PF_6 (45 mg, 0.27 mmol) was added. The crude products were collected by filtration of the precipitate or extraction with CH_2Cl_2 after pouring them into water. Further purification was carried out by preparative size-exclusion chromatography (BioBeads SX-1, THF and/or CH_2Cl_2). Excess NH_4PF_6 was washed out with water by dissolving **5**, **6**, or **7** in CHCl_3 . Yields were 97 mg of **5** (50%), 76 mg of **6** (36%), and 40 mg of **7** (35%). Selected analytical data: **5**: ^1H NMR (400 MHz, CD_3CN , 25 °C): δ = 8.49 (dt, J = 8.0, 1.2 Hz, 4H; H3, H3''), 8.35 (s, 4H; H3', H5'), 7.91 (td, J = 8.0, 1.2 Hz, 4H; H4, H4''), 7.37 (dt, J = 5.6, 1.2 Hz, 4H; H6, H6''), 7.16 (ddd, J = 8.0, 5.6, 1.2 Hz, 4H; H5, H5''), 4.67 (t, J = 4.4 Hz, 4H; tpyOCH_2), 4.05 (t, J = 4.4 Hz, 4H; $\text{tpyOCH}_2\text{CH}_2$), 3.80–3.38 (m, 570H; PEO backbone), 3.31 ppm (s, 6H; OCH_3); UV/Vis (CH_3CN): λ_{max} = 486, 304, 267 nm; GPC (UV): M_n = 16780, PDI = 1.13; MALDI-TOF MS: M_n = 6627 g mol^{-1} . **6**: ^1H NMR (400 MHz, CDCl_3 , 25 °C): δ = 8.40 (dt, J = 7.2, 1.2 Hz, 2H; H3, H3''), 8.36 (dt, J = 8.0, 1.2 Hz, 2H; H3, H3''), 8.29 (s, 2H; H3', H5'), 8.17 (s, 2H; H3', H5', PEB), 7.81 (m, 4H; H4, H4'', PEB + PEO), 7.37 (m, 4H; H6, H6'', PEB + PEO), 7.18 (m, 4H; H5, H5'', PEB + PEO), 4.76 (t, J = 4.0 Hz, 2H; tpyOCH_2 , PEO), 4.58 (t, J = 4.8 Hz, 2H; tpyOCH_2 , PEB), 4.09 (t, J = 4.0 Hz, 2H; $\text{tpyOCH}_2\text{CH}_2$, PEO), 3.87–3.41 (m, 290H; PEO backbone), 3.38 (s, 3H; OCH_3), 1.68–0.80 ppm (m, 580H; PEB backbone); UV/Vis (CH_3CN) λ_{max} = 486, 304, 267 nm; GPC (UV): M_n = 12410, PDI = 1.10; MALDI-TOF MS: M_n = 7502 g mol^{-1} . **7**: ^1H NMR (400 MHz, CDCl_3 , 25 °C): δ = 8.36 (td, J = 8.0, 1.2 Hz, 2H; H3, H3''), 8.26 (s, 2H; H3', H5', PS), 8.17 (bm, 2H; H3, H3'', PS), 7.88–7.73 (bm, 6H; H3, H3''(PS), H3', H5' (PS), H4, H4'' (PEO)), 7.33–6.32 (m, 110H; C_6H_5 PS backbone and tpy signals), 4.74 (t, J = 3.6 Hz, 2H; tpyOCH_2 , PEO), 4.28–4.04 (m, 4H, $\text{tpyOCH}_2\text{CH}_2$ (PEO), tpyOCH_2 (PS)), 3.92–3.42 (m, 290H; PEO backbone), 3.38 (s, 3H; OCH_3), 1.72–0.60 ppm (m, 50H; CH_2 , CH PS

backbone); UV/Vis (CH₃CN): λ_{max} : 486, 305, 268 nm; GPC (UV): M_n = 7800, PDI = 1.08; MALDI-TOF MS: M_n = 5348 g mol⁻¹.

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Unusual P=C Bond Cleavage by Double Dichlorosilylene Transfer from Trichlorosilyltrimethylgermane to P-Phosphanyl Phosphaalkenes

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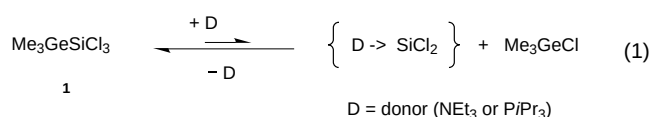
Dedicated to Professor Hans Bürger on the occasion of his 65th birthday

The major breakthroughs in the chemistry of stable carbenes and Group 14 carbene analogues in the last two decades were based on the use of sterically and electronically stabilizing substituents.^[1] Concerning short-lived dihalogenosilylenes, however, very little synthetic progress has been made even 30 years after the basic high-temperature and matrix studies of Timms et al.^[2,3] Oligomeric silanes of the empirical formula SiCl₂ are synthetically available, but they do not behave as sources of monomeric SiCl₂,^[4] the alternative use of Si₂Cl₆^[5] or HSiCl₃^[6] as precursors is very limited. Herein, we report the use of trichlorosilyltrimethylgermane (Me₃GeSiCl₃, **1**)^[7,8] as a new reagent for the transfer of SiCl₂ moieties to P-phosphanyl phosphaalkenes under very mild reaction conditions.

Pure **1**—a monomeric molecular compound in the gas phase—^[7c] is thermally stable; in the presence of tertiary amines and phosphanes, however, **1** partially decomposes to (Me₃Ge)₂Si(SiCl₃)₂, Me₃GeCl, and SiCl₄; this observation was explained by sequences of nucleophile-catalyzed transfers of Me₃Ge and SiCl₃.^[7,8] Alternatively, for the SiCl₃ transfer, the formation of (Me₃Ge)₂Si(SiCl₃)₂ may imply insertion reactions of nucleophile-coordinated dichlorosilylene (SiCl₂) into Si–Cl bonds.^[7,8] If nucleophiles such as Et₃N and *i*Pr₃P can really induce the α -elimination of chlorogermans from **1** [Eq. (1)],^[9] then trichlorosilylgermanes, such as **1**, would be important reagents for SiCl₂ transfer reactions.

Our first choice as SiCl₂ trapping reagents were the P-phosphanyl phosphaalkenes (Me₃Si)₂C=P–PRR' (**2a**: R, R' = *i*Pr; **2b**: R = *t*Bu, R' = *i*Pr).^[10] The dialkylphosphanyl groups within the reagent were intended to induce the desired α elimination at **1** [Eq. (1)] and coordinate intermediate SiCl₂, the adjacent P–P bonds may allow subsequent SiCl₂ insertion reactions, and the P=C bonds should be suitable for [2+1] cycloadditions with silylenes, similar to the known reactions of

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phosphaalkenes with phosphinidene precursors, to provide diphosphiranes.^[11]

When equivalent amounts of **1** and **2a** are stirred at room temperature in toluene, ³¹P NMR spectra confirm that **2a** is almost completely consumed within two hours to yield two main products **3a** and **4** (ca. 10:90) and traces of a third compound. In the ³¹P NMR spectrum the AX pattern of **3a** indicates the presence of an *i*Pr₂P group ($\delta^{31}\text{P} = 25.7$ ppm, d, $J(^{31}\text{P}, ^{31}\text{P}) \pm 183.6$ Hz) the P atom of which couples with another ³¹P nucleus a long way upfield ($\delta^{31}\text{P} = -113.3$ ppm).^[12] The NMR spectrum of compound **4** exhibits the two pseudotriplets of an AA'XX' spin system. One pseudotriplet can be assigned to *i*Pr₂P groups ($\delta^{31}\text{P} = 24.2$ ppm) and the other one a long way downfield ($\delta^{31}\text{P} = 577.5$ ppm) indicates phosphorus atoms of coordination number 2.^[13–15] This formulation was confirmed by a structure determination of **4** (Figure 1).^[16] In the solid state **4** is a centrosymmetric diphosphene that contains two silylphosphane groups. Intramolecular P⋯P=P⋯P contacts (P⋯P 3.449 Å) and steric crowding result in a lengthening of the P=P and P–Si bonds of **4** by about 3 pm, compared with related diphosphenes^[14,15] and silylphosphanes.^[8]

The reaction of **1** with the slightly bulkier phosphaalkene **2b** furnished, in addition to Me₃GeCl, a new compound **3b**, which shows in its ³¹P NMR spectrum a pattern closely related to that of **3a**. The analytical composition of pure **3b** and its spectroscopic data reveal that—surprisingly—**3b** is the product from the reaction of **2b** with *two* equivalents of SiCl₂. ¹³C, ²⁹Si, and ³¹P NMR spectra of **3b** at different magnetic field

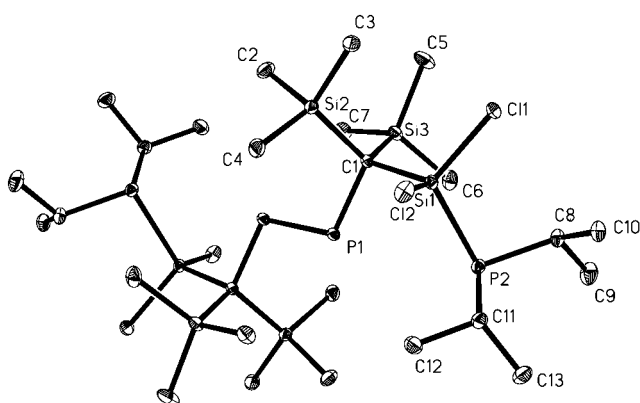
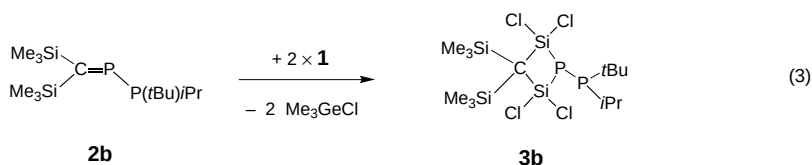
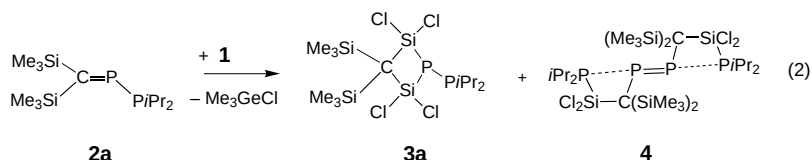


Figure 1. Molecular structure of diphosphene **4** (thermal ellipsoids set at 50% probability; H atoms omitted). Selected bond lengths [Å], angles and torsion angles [°]: P1–C1 1.8824(9), P1–P1* 2.0436(5), Si1–C1 1.8922(9), Si2–C1 1.9367(9), Si3–C1 1.9410(9), Si1–C11 2.0810(3), Si1–C12 2.0748(4), P2–Si1 2.2848(3), P2–C11 1.8780(10), P2–C8 1.8873(10), P1⋯P2 3.4490 (4); C1–P1–P1* 106.05(3), C11–P2–C8 105.15(4), C11–P2–Si1 103.05(3), C8–P2–Si1 99.85(3), C1–Si1–C12 111.15(3); P1*–P1–C1–Si1 174.83(3), C11–P2–Si1–C1 –125.21(4), C8–P2–Si1–C1 126.58(4), P2–Si1–C1–P1 42.94(4).

strengths lead to the conclusion that the upfield ³¹P doublet signals of **3a** and **3b** result from Si₂P fragments^[17] that are part of the novel 2-phospha-1,3-disiletane ring system [Eq. (2), (3)]. The NMR spectroscopic equivalence of the exocyclic SiMe₃ groups indicates (on the ¹H, ¹³C, and ²⁹Si NMR time scales) rapid inversion of the endocyclic phosphorus atom. This result is consistent with B3LYP/G-31 + G(d) calculations,^[18] which predict a barrier of 12.9 kcalmol^{–1} for the inversion of the endocyclic phosphorus atom of H₂C(μ-SiH₂)₂P–PH₂. In the transition state of this process, the C(μ-SiH₂)₂P ring is also planar. For the ring inversion itself, only a marginal barrier is expected.



Phosphasilirane intermediates with very bulky substituents on the silicon atom are known,^[12] but, in various reactions of **2a** and **2b** with **1**, were not detected by NMR spectroscopy, irrespective of the experimental conditions. The complete cleavage of the P=C bonds of **2a** and **2b** by spontaneous consecutive addition of two equivalents of SiCl₂ furnishing 2-phospha-1,3-disiletanes **3a** and **3b** is without precedence. Consecutive addition of two equivalents of photochemically generated dimesitylsilylene to *tert*-alkylphosphaalkynes has been observed by Weidenbruch et al.;^[19] these reactions, however, lead to 3-phospha-1,2-disiletanes, that is, a P=C bond of the starting material remains. Thermodynamically, H₂C(μ-SiH₂)₂P–PH₂, the simplified version of **3a** and **3b**, is 13.4 kcalmol^{–1} more stable than the isomeric 1,2-disiletane derivative (Figure 2).

Modeling the reaction paths of **2a** and **2b** with **1** will be an interesting challenge for computational methods. For the

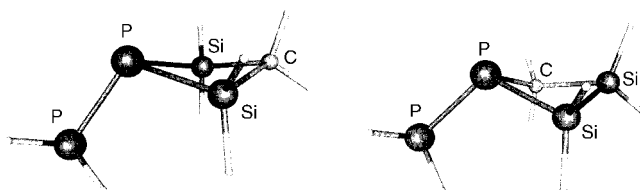


Figure 2. Geometries of calculated energy minima (B3LYP/6-31 + G(d) level) of H₂C(μ-SiH₂)₂P–PH₂ (left) and the 1,2-disiletane isomer (right) as model systems. Selected bond lengths [Å]: in H₂C(μ-SiH₂)₂P–PH₂: P–P 2.242, P–Si 2.289, Si–C 1.908; in the 1,2-disiletane isomer: P–P 2.242, P–Si 2.302, Si–C 1.917, Si–Si 2.348.

simultaneous formation of diphosphene **4** and **3a** [Eq. (2)] the attack of SiCl₂ molecules at the P=C bond of **2a** apparently competes with the SiCl₂ insertion into the P–P bond and the subsequent silyl-group migration.^[15,20] This hypothesis is supported by the observation, that with *two* equivalents of silylgermane **1**, phosphalkene **2a** furnishes predominantly the “2:1 product” **3a**. The formation of diphosphene **4**, however, cannot be suppressed completely. The reactive behavior of **1** towards **2a** and **2b** under very mild conditions gives rise to the expectation that finally, by using available trichlorosilylgermanes such as **1**,^[7,21] silylene-based products can be prepared which contain reactive Si–Cl bonds instead of protecting organic substituents.

Experimental Section

The experiments were carried out under dry nitrogen gas. NMR spectra were recorded using Bruker spectrometers AC 200, Avance 200, Avance 400 and AMX 300, with 85% H₃PO₄ and with SiMe₄ as external or internal standards. Elemental analyses: Institut für Pharmazeutische Chemie der TU Braunschweig.

3b: After stirring a mixture of silylgermane **1** (0.63 g, 2.5 mmol) and phosphalkene **2b** (0.40 g, 1.25 mmol) for 7 days at room temperature, ³¹P NMR spectra of the orange liquid showed that 90% of **2b** was consumed. Me₃GeCl and residual **1** were removed in vacuo and further **1** (0.13 g, 0.5 mmol) was added. After 10 days, consumption of **2b** was completed. Removal of all volatiles led to an orange residue of crude **3b** (0.6 g, 92%). Crystallization from toluene furnished pale yellow crystals, m.p. 143 °C. ¹H NMR (400 MHz, [D₈]toluene, δ(C₆D₆CHD₂) = 2.09): δ = 0.40 (d, *J*(P,H) = 0.8 Hz, 18H, Si(CH₃)₃); 1.06 (dd, *J*(P,H) = 11.2 and 0.9 Hz, 9H, C(CH₃)₃), 1.17 (ddd, *J*(P,H) = 19.0 and 1.3 Hz, *J*(H,H) = 7.1 Hz, 3H, CHCH₃), 1.19 (“t” d, *J*(H,H) = 7.1 Hz, *J*(P,H) = 7.1 and 1.3 Hz, 3H, CHCH₃), 1.74 ppm (sept-dd, *J*(H,H) = 7.1 Hz, *J*(P,H) = 4.1 and 2.9 Hz, 1H, CH(CH₃)₂); ¹³C NMR (101 MHz, [D₈]toluene, δ(C-1 of C₇D₈) = 137.44): δ = 5.6 (d, *J*(P,C) = 2.5 Hz, Si(CH₃)₃), 23.5 (dd, *J*(P,C) = 14.8 and 1.4 Hz, CHCH₃), 24.4 (dd, *J*(P,C) = 34.1 and 3.0 Hz, CHCH₃), 24.6 (dd, *J*(P,C) = 33.0 and 5.6 Hz, CH(CH₃)₂), 29.3 (dd, *J*(P,C) = 14.5 and 6.1 Hz, C(CH₃)₃), 32.6 (dd, *J*(P,C) = 28.6 and 8.7 Hz, C(CH₃)₃), 41.7 ppm (d, *J*(P,C) = 3.3 Hz, CSi₂); ²⁹Si NMR (39.8 MHz, C₆D₆): δ = 1.1 (d, *J*(P,Si) = 4.1 Hz; Si(CH₃)₃), 15.0 ppm (dd, *J*(P,Si) = 36.2 and 8.1 Hz, SiCl₂); ³¹P NMR (81.0 MHz, C₆D₆): δ = –113.5 (d, *J*(P,P) = 196.1 Hz, ²⁹Si satellites *J*(P,Si) = 36.2 Hz, PSi₂), 44.4 ppm (d, *J*(P,P) = 196.1 Hz, P₂Bu₄Pr); Cl-MS (NH₃, 150 °C): *m/z* 519 [(M+1)⁺]; elemental analysis (%): calcd for C₁₄H₃₄Cl₄P₂Si₄: C 32.43, H 6.61, Cl 27.35; found: C 31.62, H 6.98, Cl 26.43.

4: A mixture of phosphalkene **2a** (0.40 g, 1.31 mmol) and silylgermane **1** (0.32 g, 1.31 mmol) was stirred for 10 h at room temperature. NMR spectra of the orange solution indicated that **2a** had been consumed to 90% producing **4** and small amounts of **3a**. Removing all volatiles in vacuo gave an orange oil that was washed with small amounts of pentane. The remaining orange solid **4** (0.44 g, 83%) m.p. 112 °C is extremely sensitive towards moisture precluding satisfying analytical data. ¹H NMR (400 MHz, [D₈]toluene, δ(CHD₂) = 2.09): δ = 0.55 (br s, 36H, Si(CH₃)₃), 1.27 (dd, *J*(P,H) = 10.2 Hz, *J*(H,H) = 7.0 Hz, 12H, CH(CH₃)), 1.30 (dd, *J*(P,H) = 16.4 Hz, *J*(H,H) = 7.2 Hz, 12H, CH(CH₃)), 2.37 ppm (sept-d, *J*(P,H) = 1.6 Hz, *J*(H,H) = 7.1 Hz, 4H, CH(CH₃)); ¹³C NMR (101 MHz, [D₈]toluene, δ(C-1) = 137.44): δ = 5.6 (br “d”, splitting of 3.9 Hz, Si(CH₃)₃), 22.3 (d, *J*(P,C) = 6.7 Hz, CH(CH₃)₂), 23.9 (d, *J*(P,C) = 20.8 Hz, CH(CH₃)), 24.8 (d, *J*(P,C) = 20.0 Hz, CH(CH₃)), 43.6 ppm (br “t”, *N* = 42.4 ± 0.5 Hz, CSi₃P); assignment of isopropyl signals was by H,C-HSQC; ²⁹Si NMR (79 MHz, [D₈]toluene, virtual internal standard TMS): δ = 2.1 (m, Si(CH₃)₃); 21.6 ppm (d, *J*(P,Si) = 101.4 Hz, SiCl₂); ³¹P NMR (81 MHz, [D₈]toluene, virtual external standard H₃PO₄): δ = –23.4 (“t” (AA’XX’), *N* = 44.3 Hz, ²⁹Si satellites: *J*(P,Si) = 101.4 Hz, PSi); 577.5 ppm (“t” (AA’XX’), *N* = 44.3 Hz, P=P); elemental analysis (%) calcd for C₂₆H₆₄Cl₄P₄Si₆: C 38.61, H 7.98, Cl 17.31; found: C 33.45, H 7.68, Cl 15.86.

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area detector. Intensities were measured in the 2θ range 5–60°. Of a total of 33919 reflections, 6333 were independent ($R_{\text{int}} = 0.0468$). After absorption correction (multiple scan) the structure was solved by direct methods. All non-hydrogen atoms were refined anisotropically against F^2 (G. M. Sheldrick, SHELXS-97, University of Göttingen, Göttingen (Germany), 1997): $R_1 = 0.0222$, $wR_2 = 0.0630$ (all data). Methyl groups were refined as rigid groups, other hydrogen atoms by using a riding model. CCDC-175445 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit @ccdc.cam.ac.uk).

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Fluoroformic Acid Anhydride, FC(O)OC(O)F**

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Maximiliano Burgos Paci, and Gustavo A. Argüello*

*Dedicated to Professor Rüdiger Mews
on the occasion of his 60th birthday*

For many years new molecules, consisting only of fluorine, carbon, and oxygen atoms have been of fundamental interest.^[1–10] The view that such species are formed in atmospheric

degradation of HFCs and other CFC replacements^[11,12] has motivated further work in this field.^[13–16]

During our studies on radicals such as CF_3O ,^[17] CF_3OO ,^[18] $\text{CF}_3\text{OC(O)}$,^[19] FCO_2 ,^[20] and FC(O)OO ^[18] that are important intermediates in the atmospheric degradation of CFC replacements, as well as on the catalytic oxidation of CO by CF_3O_x radicals,^[21,22] we have also considered possible reaction products of these radicals, among them $\text{CF}_3\text{OC(O)OO-C(O)OCF}_3$.^[17] Correspondingly, the formation of fluoroformic acid anhydride, FC(O)OC(O)F (**1**), by a recombination of FCO and FCO_2 radicals is considered in principle as feasible. However both radicals have to be present in sufficiently high concentrations for a satisfactory yield. We now report on the synthesis and characterization of **1**. This fundamental acid anhydride is, to our knowledge the first example of a XC(O)OC(O)Y species, with X,Y=halogen and can be viewed as halogen dicarbonate. It is at the same time the last missing member in the family of $\text{FC(O)O}_x\text{C(O)F}$ molecules ($x=0$,^[23] **1** (this work), 2,^[1] 3,^[24]), which had not previously been isolated in pure form.

The analogous, well known compound bis(fluoroformyl) peroxide, FC(O)OOC(O)F , is readily synthesized by the reaction of CO with a F_2/O_2 mixture; O_2 , which must be present in large excess, acts as radical scavenger.^[1,25–27] Accordingly, it was considered that using a 2:4:1 mixture of $\text{F}_2/\text{CO}/\text{O}_2$ may provide a suitable route for the synthesis of **1** according to reaction (1).



However, since such mixtures tend to explode,^[26] for the synthesis of FC(O)OOC(O)F experiments with lower concentrations of oxygen, which would lead to higher concentrations of FCO radicals, have been avoided. Our approach to synthesize **1** focuses on the thermal decomposition of FC(O)OOC(O)F in the presence of CO. Gaseous mixtures of FC(O)OOC(O)F and CO (1:5 to 1:10) are kept at 60°C and the decay of the peroxide concentration is monitored by IR spectroscopy. We assume that the formation of **1** follows the reaction sequence given by Equations (2)–(4) then (1).



The initial unimolecular decomposition of FC(O)OOC(O)F [Eq. (2)] is followed by a further unimolecular decomposition^[20] [Eq. (3)] in which fluorine atoms are generated. These then react with CO to give FCO radicals [Eq. (4)]. In the final step FCO and FCO_2 radicals recombine to give the anhydride **1**, which is isolated from the reaction mixture after repeated trap-to-trap-condensation in vacuo. The gas-phase IR spectrum of **1** is depicted in Figure 1.

DFT calculations (B3LYP) with the 6-311+G(d) basis set^[28] predict the *syn-syn* conformer to be the most stable one for **1** (Figure 2). Calculated IR wavenumbers for this conformer are in good agreement with observed data (Table 1). By comparing observed and calculated band positions and

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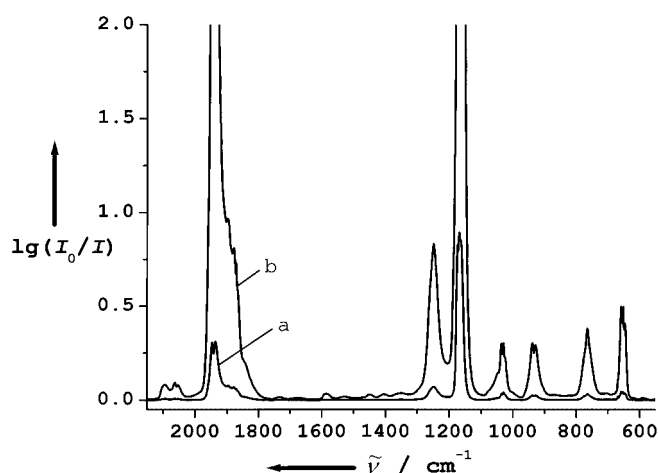


Figure 1. IR spectrum of **1** at 0.78 (a) and 7.95 mbar (b) (28°C; optical length 19.5 cm).

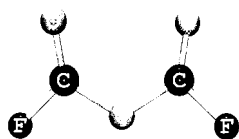


Figure 2. Structure of the most stable conformer of **1** (*syn-syn*) resulting from DFT calculations. Dihedral angles [°]: O=C-O-C 18.8, F-C-O-C 163.4; bond angles [°]: F-C-O 105.4, F-C=O 125.3, C-O-C 119.5; bond lengths [pm]: C-F 132.6, C-O 136.8, C=O 117.3.

intensities, the main absorption bands are attributed to the symmetric C=O (1941 cm⁻¹) and antisymmetric C-O-C (1168 cm⁻¹) stretching vibrations. The corresponding antisymmetric C=O and symmetric C-O-C vibrations are observed at 1870 and 938 cm⁻¹. The bands at 1249 and 1030 cm⁻¹ are assigned as C-F vibrations.

The ¹⁹F NMR spectrum shows a single signal at $\delta = -10.6$ and eight ¹³C satellites (Table 2). The ¹³C NMR spectrum exhibits besides a doublet for FC(O)OOC(O)F, which was used as solvent, a four-line signal for **1** which was centered at $\delta = 136.0$ ppm and thus is in a region, typical for a FC(O) moiety. The four lines in the ¹³C NMR spectrum and the eight ¹³C satellites in the ¹⁹F NMR spectrum are consistent with the ABX spin system expected for the isotopologue F¹³C(O)O¹²C(O)F. An evaluation analogous to that for the ABX system of F¹³C(O)¹²C(O)F,^[29] produces the coupling constants listed in Table 2. Comparing the ¹³C NMR spectra of FC(O)C(O)F^[29]

FC(O)OC(O)F, and FC(O)OOC(O)F^[30] reveals that the presence of an increasing number of bonds between the NMR-active atoms results in a decreasingly resolved multiplet (X-part of the ABX system). ¹³C and ¹⁹F NMR data of FC(O)OCF₃, which also contains a FC(O)OC moiety, are very similar to those of **1**.

Gas density measurements yielded a value of 109.7 g mol⁻¹ for the molar mass of **1**, which is in good agreement with the calculated value of 110.017 g mol⁻¹. The mass spectrum of **1** is also consistent with the expected fragmentation pattern for ionization at 70 eV (see Experimental Section). All findings strongly suggest that pure **1** was synthesized for the first time and that the IR bands observed in earlier experiments by Bednarek et al.^[31] and Wallington et al.^[32] appear to have been correctly assigned to **1**.

The UV spectrum (Figure 3) shows a structureless absorption band beginning at around 260 nm, similar to the band in FC(O)OOC(O)F^[33] and FC(O)OOC(O)F.^[24] The values reveal that **1** is a poor UV absorber, which should be photostable in the troposphere.

Compound **1** condenses as a colorless liquid at 19.2°C (extrapolated) and solidifies as a white solid at -46.2°C (triple point). The synthesis gave yields between 15 to 30% based on the conversion of FC(O)OOC(O)F. Side products are mainly COF₂, CO₂, SiF₄, and traces of two unidentified compounds with lower vapor pressures than **1**. The variation in yields depends on the condition of the surface of the reactor, since the decomposition of **1** is surface-catalyzed and

Table 1. Observed and calculated IR data of **1** in the gas phase.

$\tilde{\nu}_{\text{exp.}}$ [cm ⁻¹]	$I_{\text{rel.,exp.}}$ [%]	$\tilde{\nu}_{\text{calcd.}}$ [cm ⁻¹] ^[a]	$I_{\text{rel.,calcd.}}$ [%] ^[a]	Vibration (description)
1941	35	1985.5	54.4	$\nu_s(\text{C=O})$
1870	7	1909.9	10.5	$\nu_{\text{as}}(\text{C=O})$
1249	8	1230.9	6.1	$\nu_s(\text{C-F})$
1168	100	1143.0	100 ^[b]	$\nu_{\text{as}}(\text{C-O-C})$
1030	5	1027.9	8.8	$\nu_{\text{as}}(\text{C-F})$
938	3	929.1	4.1	$\nu_s(\text{C-O-C})$
765	4	770.1	4.7	$\delta(\text{FC(O)O})_{\text{oop, i.p.}}$
—	—	769.8	0.2	$\delta(\text{FC(O)O})_{\text{oop, o.p.}}$
—	—	707.7	0.4	$\delta_s(\text{FCO})$
652	5	651.6	3.7	$\delta_{\text{as}}(\text{FCO})$

[a] B3LYP functional with 6-311 + G(d) basis set. [b] Absolute intensity: 1227 km mol⁻¹.

Table 2. ¹⁹F and ¹³C NMR data of FC(O)C(O)F, **1**, FC(O)OOC(O)F, and FC(O)OCF₃.

	FC(O)C(O)F	1 ^[a]	FC(O)OOC(O)F	FC(O)OCF ₃ ^[b]
$\delta(^{19}\text{F})$ (FCO)	+23.8	-10.6 ^[c]	-34.1	-13.6
$^1\Delta^{19}\text{F}$ ^[d]	-0.133	-0.120		
$^2\Delta^{19}\text{F}$ ^[d]	-0.016	-0.001		
$\delta(^{13}\text{C})$ (FCO)	+143.2	+136.0 ^[e]	+142.3	+136.9
$^1J_{\text{C,F}}$ (FCO)	-366.3	-293.8	-301.1	295.1
$^2J_{\text{C,F}}$	+102.8			
$^3J_{\text{C,F}}$ (FC(O)OC)		+12.6		11.2
$^1J_{\text{C,C}}$	+126.1			
$^3J_{\text{F,F}}$	+50.6			
$ ^4J_{\text{F,F}} $		34.6		9.8
$ ^5J_{\text{F,F}} $			3.8	

[a] Measurements were carried out in CD₂Cl₂ at 223 K. Chemical shifts in ppm referenced to external CFCl₃ (¹⁹F) and to CD₂Cl₂ at $\delta = 53.7$ ppm (¹³C); coupling constants in Hz. [b] Ref. [17]. [c] ¹³C satellite signals: -10.17, -10.29, -10.55, -10.60, -10.67, -10.73, -11.22, -11.35 ppm. [d] Isotopic shifts $\Delta = \delta(^{13}\text{C}) - \delta(^{12}\text{C})$ of the ¹⁹F resonance in ppm.^[34] [e] ¹³C multiplet (X-part of the ABX system): 138.1, 137.9, 134.1, 133.9 ppm.

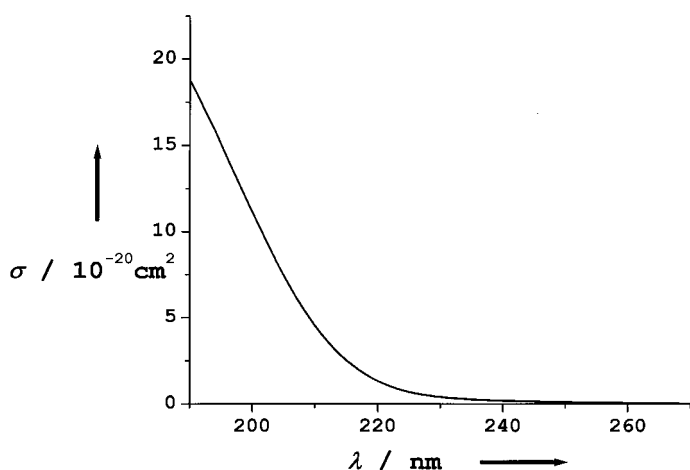


Figure 3. UV spectrum of **1**.

the compound reacts readily with moisture. After cleaning the reactor thoroughly and conditioning with FC(O)OOC(O)F, the yields of **1** are increased to 30 %. In a glass IR cell with a well conditioned surface, **1** is stable at room temperature for several days. At 50 °C **1** decomposes within hours to give COF₂, CO₂, and SiF₄.

Experimental Section

Caution: FC(O)OOC(O)F is potentially explosive if heated or brought in contact with oxidizable materials. It is recommended that appropriate safety precautions are thus taken when this compound is handled. Reactions involving FC(O)OOC(O)F should be carried out only in millimolar quantities.

1: In a typical reaction FC(O)OOC(O)F (ca. 2 mmol) and CO (20 mmol) were introduced into a clean, dry, and surface-conditioned (with 100 mbar FC(O)OOC(O)F, 1 h) 1-L glass bulb. This mixture was kept at 60 °C until most of the FC(O)OOC(O)F had disappeared (ca. 4 to 6 hours; the progress of the reaction was monitored by IR spectroscopy). After cooling to −196 °C and removal of the excess of CO in vacuo, the reaction mixture was separated by trap-to-trap-condensation (at −70, −120, and −196 °C). Compound **1** was collected together with unreacted peroxide in the trap at −120 °C. The −120 °C fractions of several synthetic runs were collected and **1** was separated from the peroxide by evaporating the peroxide from the mixture at −95 °C until a pure sample of **1** remained in the trap.

¹⁹F NMR: 282.40 MHz, −50 °C, CFCl₃; ¹³C NMR: 75.47 MHz, −50 °C, CD₂Cl₂.

MS (70 eV): *m/z* (%): 110 (1.5) [M⁺], 85 (trace) [CF₃O⁺], 69 (1) [CF₃⁺], 66 (14) [F₂CO⁺], 63 (trace) [FCO₂⁺], 50 (1) [CF₂⁺], 47 (43) [FCO⁺], 44 (100) [CO₂⁺], 33 (0.5) [F₂CO⁺⁺], 32 (2) [O₂⁺], 31 (2) [FC⁺], 28 (17) [CO⁺ or N₂⁺].

UV (gas): λ (σ in 10^{−20} cm² molecule^{−1}): 190 (18.79), 200 (11.14), 210 (4.54), 220 (1.32), 230 (0.40), 240 (0.19), 250 (0.11), 260 (0.05), 270 nm (0.02).

Vapor pressure curve (liquid phase): *p* [mbar], *T* [K], 274 K > *T* > 227 K: lg(*p*) = 9.767(0.015) − 1976.5(3.8)*T*^{−1}.

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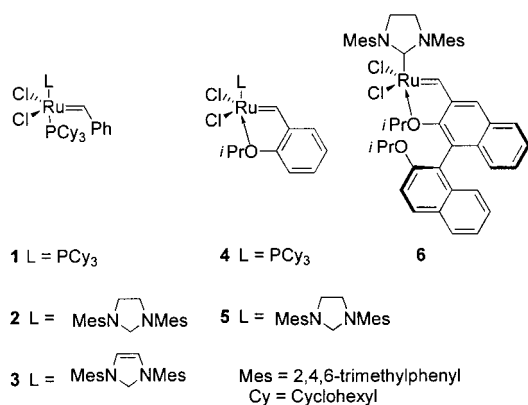
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A Self-Generating, Highly Active, and Recyclable Olefin-Metathesis Catalyst**

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As the world becomes more cost-conscious and environmentally aware, the pursuit of new transition-metal catalysts that are both active and recyclable has become increasingly important to synthetic organic chemists. Recently, the advent of efficient homogeneous ruthenium alkylidene precatalysts **1–6**^[1] have propelled the olefin-metathesis reaction to the



forefront of contemporary organic chemistry as a mild and efficient method for C–C-bond formation.^[2] Given this new-found significance, it is not surprising that the development of reusable catalysts has been the goal of a number of research groups.^[3,4]

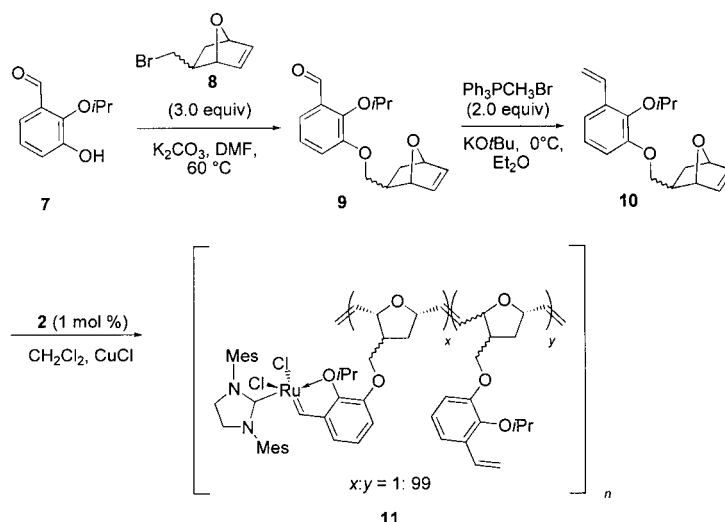
Various recycling strategies have been reported:

- Recovery of the homogeneous catalyst by chromatography of the crude reaction mixture^[1c,d]
- Filtration of the reaction mixture to separate the heterogeneous catalyst bound to a polymeric solid support^[3a–c,g–j]
- Selective precipitation of the homogeneous catalyst from solution after the reaction.^[3f]

Chromatographic recovery furnishes pure catalyst for reuse, but is time-consuming and generates considerable amounts of silica and solvent waste. Heterogeneous catalysts are easily recovered with minimal waste, however with one reported exception^[3i] these catalysts are much less active than their homogeneous counterparts. By employing a selective catalyst-precipitation strategy, one can

aspire to preparing ruthenium alkylidenes with reactivity profiles that correspond to those of homogeneous catalysts, combined with a facile recovery methodology that involves a simple change in the polarity of the solvent to allow easy separation of the catalyst from the substrate. The only previous report that involves this method detailed a variant of **4** attached to polyethylene glycol (PEG) chain which could be precipitated with diethyl ether.^[3f] The levels of residual ruthenium in the products is a critical issue in all heterogeneous systems. We report herein the design and preparation of a polymer-bound, homogeneous, recyclable, and highly efficient ruthenium catalyst. The polymer support also seems capable of scavenging ruthenium after the reaction, thus allowing the formation of metathesis products that contain extremely low ruthenium levels.

It is known that ring-opening-metathesis polymerization (ROMP) products of substituted oxanorbornene derivatives are often soluble in organic solvents with the notable exceptions of methanol, diethyl ether, or diethyl ether/hexane mixtures. This led us to postulate that a ruthenium alkylidene incorporated into these products could serve as a recyclable and easily assembled catalyst without the need for the purchase of and attachment to often expensive solid-phase resins. It was thus conceivable that **10** (Scheme 1) could serve



Scheme 1. Synthesis of catalyst **11**.

as a precursor for such a catalyst through consecutive (one-pot) ROMP and cross-metathesis (CM) attachment of the ruthenium moiety to the polymer. Compound **10** contains an isopropoxy styrene moiety necessary for catalyst formation and an oxanorbornene ring destined to become the polymer support after ROMP. Furthermore, the second ether linkage is positioned *ortho* to the chelating isopropoxy group. This is an important consideration: by correlation with catalyst **6** and from preliminary studies conducted in our laboratories, we were aware that the presence of alkoxy groups in this *ortho* position leads to catalysts that display strongly enhanced activity relative to **5**.^[1f]

Aldehyde **9** was readily prepared in good yield (76 %) by the action of the potassium salt of **7** on bromide **8** in *N,N*-

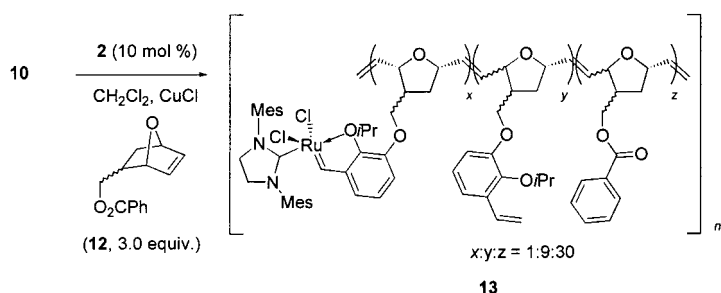
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dimethylformamide (DMF).^[5] Subsequent Wittig olefination gave styrene derivative **10** in 79% yield. Treatment of **10** with **2** (1 mol%) in CH₂Cl₂ at 20 °C in the presence of CuCl as a phosphane scavenger gave polymer-bound catalyst **11** (Scheme 1).

Catalyst **11** was tested in simple ring-closing-metathesis (RCM) reactions and gave encouraging results. Excellent conversions were obtainable for up to four consecutive cycles; however, long reaction times (7–12 h) were required for quantitative conversion. We speculated that the sluggish activity was in part due to the difficulty in forming the catalytically active 14-electron species^[6] in the presence of 99 equivalents of ligand and thus decided to lower the ligand/catalyst ratio by a factor of 10. To avoid a situation in which two catalyst moieties could exist in close proximity to one another, an oxanorbornene benzoate co-monomer **12** was added to act as a spacer. This was prepared from the same batch of alcohol used to prepare bromide **8**, and so had the same *endo/exo* isomer ratio (ca. 1:1) as styrene **10**. For ease and simplicity of catalyst preparation, no attempt was made to separate these *endo/exo* mixtures, which arise from the Diels–Alder reaction used to prepare **8**.^[5] In our experience, the rates of polymerization of these isomers do not differ greatly in any case. Thus, reaction of **2**, **10**, and **12** (1:10:30) at room temperature in CH₂Cl₂ gave quantitative polymerization of both oxanorbornene compounds **10** and **12** after 10 min to give a red solution, indicative of the presence of **2**. Addition of CuCl gave a green solution after heating at reflux for 1 h. Workup gave polymer-bound **13** in 93% yield (Scheme 2).



Scheme 2. Preparation of catalyst **13**.

Polymer **13** is soluble in most common organic solvents but not in diethyl ether and hexane. To our delight, the catalyst loading can be determined (typically in the range 0.08–0.1 mmol g^{−1}) by relative integration of the broad alkylidene signal at $\delta = 16.7$ ppm and the signal for the aromatic *ortho* proton ($\delta = 8.0$ ppm) of the benzoate moiety in the ¹H NMR spectrum (a 1:60 ratio of alkylidene/benzoate indicates quantitative ROMP and CM). Thus, expensive, time-consuming, and often inconvenient ruthenium analysis is not required. This loading indicates a high level of incorporation (i.e. efficient CM) of the ruthenium moiety onto the styrene-substituted polymer backbone, which was reproducible between polymer batches. ROMP-based catalyst **13** was found to have impressive activity in RCM, ROM-CM, and tandem metathesis reactions (Table 1).

With only 1 mol% (measurable by ¹H NMR spectroscopy) of **13** at 20 °C it was possible to generate five-, six-, seven-, and

Table 1. Activity of **13** in various metathesis reactions.

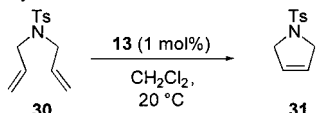
Substrate ^[a]	Product ^[b]	Conversion [%] ^[c]
 14	 22 (45)	> 98
 15	 23 (360)	> 98
 16	 24 (60)	> 98
 17	 25 (15)	> 98
 18	 26 (60)	> 98
 19	 27 (30)	> 98
 20	 28 (270)	> 98
 21	 29 (70)	> 98 ^[d]

[a] Conditions: **13** (1 mol%), CH₂Cl₂ (0.05 M), 20 °C. [b] Reaction times (min) in parentheses. [c] Determined by ¹H NMR spectroscopic analysis. [d] **13** (0.05 mol%), allyltrimethylsilane (1.0 equiv).

eight-membered rings **22–27** with quantitative conversion. The formation of trisubstituted olefin **23** and the compatibility of **13** with potentially chelating hydroxy- and amide-functionalized substrates **16** and **17** further underlines the synthetic utility of this catalyst. In all previous literature reports 2.5–5% of the polymer-bound catalyst and higher temperatures (usually 45 °C) were required to promote efficient metathesis.^[3] In the atom-economic and efficient ROM-CM reaction only 0.05 mol% of catalyst was necessary to give quantitative conversion of **21**.

Having established the reactivity of **13** under mild conditions, we then turned to the critical question of recyclability. It was found that after metathesis, **13** could be conveniently precipitated and filtered off by the addition of diethyl ether or hexane. In the RCM of *N*-tosyldiallylamine (**30**), **13** can be recycled easily under the conditions outlined previously in Table 1, with quantitative conversion for each of seven consecutive cycles (Table 2).

Table 2. Recyclability of **13** in the RCM of **30**.



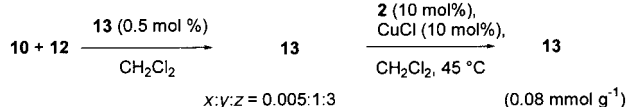
Cycle	<i>t</i> [h]	Conversion [%] ^[a]
1	1	> 98
2	1	> 98
3	1	> 98
4	1	> 98
5	1	> 98
6	2	> 98
7	4	> 98
8	72	75

[a] Determined by ¹H NMR spectroscopic analysis.

Total-reflection X-ray fluorescence (TXRF) analysis^[7] of the products after catalyst separation indicated that a maximum of 0.004 % ruthenium was present in each of the first four cycles. This value is approximately an order of magnitude lower than that of contemporary literature systems for the removal of ruthenium after the reaction^[3,8] and even two orders of magnitude lower than that of the best previously reported polymer-bound catalysts.^[3] It seems likely, therefore, that ruthenium remains attached to the polymer even after catalyst deactivation. Importantly, a ruthenium-saturated analogue of **13** (i.e. all styrene moieties loaded) was considerably less recyclable under these conditions, thus indicating that the recyclability of **13** is largely due to the presence of an excess of Lewis basic ligand, which captures the catalytically active species after the reaction. When the small amount of ruthenium used (1 mol% over seven cycles) is taken into account, **13** compares very favorably in terms of recyclability with literature systems.^[3] In addition to being more recyclable, **13** displayed a much enhanced metathesis activity relative to **5** in the RCM of **30**,^[9] and was comparable in terms of reaction rate to benchmark catalyst **2**. For example, in the RCM of **30** at high dilution (0.01 M, CH₂Cl₂, 20 °C, in air) the time taken to reach 80 % conversion to **31** was 65 min in the presence of **13**, whereas to 119 min were required when using non-polymer-bound catalyst **5**.^[9]

Given the mode of formation of **13**, it seemed likely that a high degree of self-generation of the polymer support would be possible. As expected, when just 0.5 mol % of **13** was added to a solution of **10** and **12** (1:3) in CH₂Cl₂, polymerization was complete after 10 min to afford **13** (off-white color) and no signal for the alkylidene was observed in the ¹H NMR spectrum. This ruthenium-deficient version of **13** could then be loaded with commercially available **2** to a preselected level under standard conditions (Scheme 3). It is envisaged that this development will allow greater control of the catalyst-loading process.

In summary, we have developed a highly efficient and recyclable ROMP-based catalyst,^[10] which combines good



Scheme 3. Self generation of the polymer support.

solution-phase activity with high and convenient recyclability without requiring the purchase of often expensive solid-support resins. The catalyst is prepared from inexpensive starting materials in a straightforward manner; the generation of the solid-support and attachment of the ruthenium moiety is possible in *one* convenient step through sequential ROMP and CM. The products from metathesis reactions involving these catalysts also contain unparalleled low levels of residual ruthenium. The conceptually novel catalyst **13** represents a balance between the high activity of suitably substituted analogues of **6**, and the recyclability of **5**; possible through ligand design and stoichiometry.

Studies on the exploitation of these flexible systems in new metathesis applications are underway. One example is the incorporation of a modified fluorescence marker into the catalyst to identify trace quantities of polymer in the reaction products. Investigation of the product by mass spectrometry is another option. The results of these and other investigations will be reported in due course.

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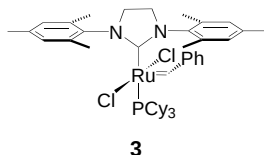
Synthesis of A,B-Alternating Copolymers by Ring-Opening-Insertion-Metathesis Polymerization**

Tae-Lim Choi, Isaac M. Rutenberg, and Robert H. Grubbs*

Alternating copolymers are normally formed by step growth polymerization of AA-BB monomers and in some special chain-growth reactions.^[1] Although recent developments in ring-opening-metathesis polymerization (ROMP)^[2] and acyclic-diene-metathesis polymerization (ADMET)^[3] have extended the versatility of both chain-growth and step-growth reactions, these metathesis polymerization reactions have not provided a general solution to alternating copolymerization. Examples of alternating copolymers by ROMP are rare as a result of the difficulty of finding systems in which there is an alternation in the affinity of the propagating metal carbene for the monomers.^[4] Although ADMET is a step-growth polymerization, examples of alternating copolymerization with two monomers by this mechanism have not been reported since most olefins studied have similar reactivity. Therefore, a general metathesis route toward A,B-alternating copolymers would open the way to the synthesis of new functional polymers.

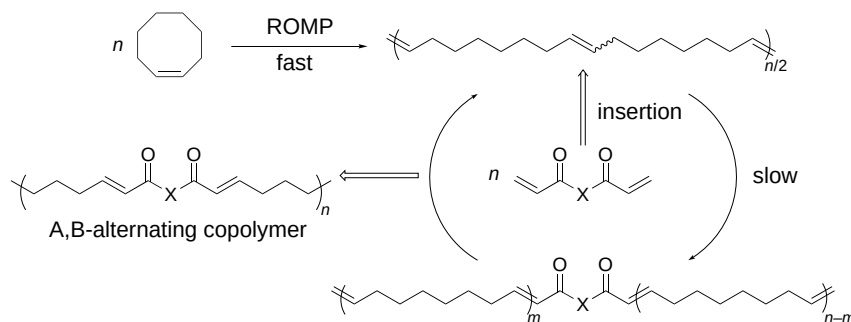
Although well-defined olefin-metathesis catalysts such as $[(\text{CF}_3)_2\text{MeCO})_2(\text{ArN})-\text{Mo}=\text{CH}(t\text{Bu})]$ (**1**) and $[\text{Cl}_2(\text{PCy}_3)_2\text{Ru}=\text{CHPh}]$ (**2**) have proven useful for the synthesis of polymers, the highly active catalyst **1** is sensitive to some polar functional groups^[5] and the highly functional-group-tolerant catalyst **2** shows decreased reactivity.^[6]

These disadvantages were recently addressed with the development of catalyst **3**, which exhibits high activity and remains tolerant of many functional groups.^[7] Furthermore, catalyst **3** promotes ring-closing metathesis and selective cross metathesis (CM) of α,β -unsaturated carbonyl olefins with high conversions,^[8] thereby expanding the scope of olefin metathesis in organic synthesis. This suggests that catalyst **3** should be able to produce polymers from α,β -unsaturated carbonyl



3

olefins. Also, if the coupling between internal olefins and α,β -unsaturated carbonyl olefins is selective, as is the case in cross metathesis, diacrylate monomers should be selectively inserted into ROMP polyolefins to yield alternating copolymers (Scheme 1). Herein we report the development of a new



Scheme 1. Proposed mechanism for ROIMP.

method for synthesizing A,B-alternating copolymers by ring-opening-insertion-metathesis polymerization (ROIMP).

Treatment of a 1:1 mixture of monomers A (diacrylates) and B (cycloalkenes) with catalyst **3**, indeed, yielded highly A,B-alternating copolymers in high yields. Examples of A,B-alternating copolymers from a variety of diacrylates and cycloalkenes are shown in Table 1. For example, with a total monomer/catalyst ratio of just 290:1, a 1:1 mixture of 1,4-butanediol diacrylate and cyclooctene gave a copolymer with up to 99% A,B-alternation and a molecular weight of $90\,100\text{ g mol}^{-1}$ (Table 1, entry 1). It is important to match the stoichiometry of cyclooctene because any excess of cyclooctene results in oligocyclooctene blocks, which lowers the A,B-alternation.

The extent of A,B-alternation could be easily determined by ^1H NMR spectroscopic analysis, since olefinic protons for A,B-alternating units have a distinct chemical shift from the starting materials and homocoupled units. *E*-Acrylate dimers produce a sharp singlet at $\delta = 6.9\text{ ppm}$ (Figure 1a), whereas polycycloalkenes display a multiplet at $\delta = 5.4\text{ ppm}$ (Figure 1c). On the other hand, A,B-alternating units produce a doublet of triplets at $\delta = 7.0\text{ ppm}$ and a doublet at $\delta = 5.8\text{ ppm}$ (Figure 1b). Therefore, the extent of A,B-alternation can be easily calculated by integrating these peaks. The sharp coupling patterns demonstrate a highly uniform polymer structure with *E* olefin isomer ($J = 15.9\text{ Hz}$). ^{13}C NMR spectroscopic analysis also shows high A,B-alternation, displaying only two olefinic carbon peaks for carbon atoms α and β to the carbonyl group (Figure 1d).

In support of the mechanism shown in Scheme 1, independently prepared polycyclooctene was treated with diacrylate and catalyst **3**, yielding A,B-alternating copolymer similar to the product of Table 1, entry 1. Furthermore, monitoring the reaction by ^1H NMR spectroscopy showed rapid and complete ROMP of cyclooctene followed by gradual appearance of peaks corresponding to A,B-alternating units. Furthermore, when a ROIMP reaction was terminated after 20 minutes, a polymer enriched in homopolycycloalkene olefin units was obtained. These results strongly suggest a

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Table 1. Examples of ROIMP products, their A,B-alternations, molecular weights, and distributions.

$\text{CH}_2=\text{CH}-\text{C}(=\text{O})-\text{X}-\text{C}(=\text{O})-\text{CH}=\text{CH}_2 + \text{Cycloalkene}^n \longrightarrow \left[\text{CH}_2-\text{CH}(\text{C}(=\text{O})-\text{X}-\text{C}(=\text{O})-\text{CH}_2) \right]_{n/2}$							
Entry	Diacrylate	Cycloalkene ^[a]	M/C ^[b]	Conc. [M] ^[c]	Yield [%] ^[d]	A,B-alt. [%] ^[e]	Mn/PDI [$\times 10^{-3}$ g mol ⁻¹] ^[f]
1			290	0.2	84	99	90.0/1.73
2			125	0.4	75	96	20.3/1.58
3			125	0.4	93	97	14.0/1.80
4			200	0.5	91	94	26.1/1.71
5			250	0.4	69	94.5	21.4/1.43
6			200	0.2	99	98.5	26.5/1.80
7			100	0.1	98	97	25.2/2.06

[a] 1.0 Equivalents of cycloalkene was used, except for cyclopentene (1.3 equiv). [b] Total monomer/catalyst ratio. [c] Concentration with respect to diacrylate. [d] Yields of isolated products after precipitation into hexane or methanol. [e] Determined by ¹H NMR spectroscopic analysis. [f] Determined by CH₂Cl₂ GPC relative to polystyrene standards.

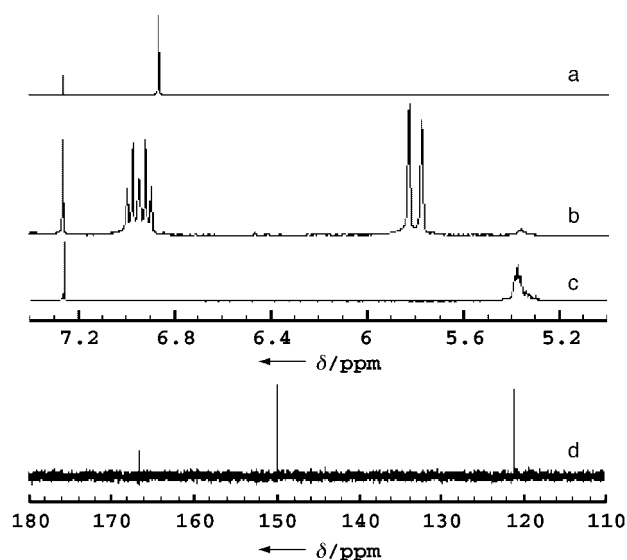


Figure 1. NMR spectra for a ROIMP product (Table 1, entry 1).

mechanism whereby ROMP of the cycloalkene initially produces an unsaturated polymer scaffold to which subsequent insertion of the diacrylate forms the final A,B-alternating structure.

Other cycloalkenes were also viable for ROIMP and yielded highly A,B-alternating polymers (Table 1, entries 2–4). However, substrates with particularly low ring strain, such

as cyclopentene and cycloheptene, required a lower monomer/catalyst ratio (125:1) as a result of the slow rate of ROMP.^[9] To obtain a high A,B-alternation (96%) with volatile cyclopentene (b.p. 44°C), a slight excess (1.3 equiv) of the cycloalkene relative to the diacrylate was used. Even with 2.0 equivalents of cyclopentene, a polymer with higher than 85% A,B-alternation was obtained. Also, treating an isolated polymer of lower A,B-alternation with catalyst **3** yielded a final polymer with higher A,B-alternation. These results suggest that the equilibrium for cyclopentene lies toward the cyclic form at 40°C; excess homopolycyclopentene units are degraded back to cyclopentene and lost from the system by evaporation.^[10]

Notably, various functional groups can be incorporated into ROIMP copolymers. 5-*tert*-Butyldimethylsilyloxycyclooctene proved to be a viable monomer, comparable to the parent cyclooctene (Table 1, entry 5). In this way, free alcohol groups could be installed into alternating monomer units upon simple deprotection. Further variations such as ethylene glycol and phenyl groups can be substituted into diacrylate units (Table 1, entries 6 and 7). These results demonstrate that the regioselective incorporation of functional groups is possible by the appropriate choice of monomers A and B, thus opening up a new class of polymers that can be synthesized by ROIMP.

ROIMP exhibits remarkable conversion and selectivity. Compared to ADMET, where high vacuum and elevated temperatures are required to drive the polymerization to high

conversion by removal of ethylene gas,^[3] ROIMP gives high conversion under gentle reflux conditions for two reasons. First, ROMP of monomer B is efficient in making the initial homopolycycloalkene chains. Second, the formation of 1,2-disubstituted α,β -unsaturated carbonyl compounds is thermodynamically favored by more than 3 kcal mol⁻¹ per bond.^[11] These enthalpic factors, combined with the loss of ethylene, drive the reaction to high conversion. Furthermore, the unfavorable oligomerization of diacrylates, in which the intermediate is an unstable enoic carbene, leads to high A,B-alternation.^[12] Therefore, ROIMP has benefits of both chain-growth and step-growth polymerization, leading to high molecular weight and high selectivity.

To optimize conversion, other polymerization conditions were investigated. It was found that 0.1–0.5 M solutions in CH₂Cl₂ at 40 °C give the best results. In contrast to ROMP, increasing the concentration beyond 0.5 M resulted in lower conversion. Switching to toluene or 1,2-dichloroethane as solvent also gave lower conversion at either 40 °C or 60 °C. Although there is precedence for CH₂Cl₂ being the best solvent for cross metathesis of functionalized olefins,^[12] the concentration dependence for ROIMP is somewhat surprising, since concentrations of 0.1–0.5 M are considered dilute conditions for conventional step-growth-polymerization reactions.

Controlling the molecular weight of polymers is a very important issue since polymers with different molecular weights often exhibit different properties. For alternating copolymers produced by ROIMP, molecular weight can be roughly controlled by changing the relative stoichiometry of the two monomers. For example, using 0.96 equivalents of cyclooctene to 1.0 equivalent of hydroquinone diacrylate gave a copolymer of 17 800 g mol⁻¹ with 98 % A,B-alternation (PDI = 1.64), whereas a copolymer of 45 200 g mol⁻¹ and 95.5 % A,B-alternation (PDI = 1.69) was obtained by increasing the cyclooctene to 1.06 equivalents. These results show that when compared with the 1:1 case (Table 1, entry 7), an excess of hydroquinone diacrylate shortens the polymer chain, but an excess of cyclooctene gives higher molecular weight as a result of the oligomeric blocks of polycyclooctene.

In conclusion, we have demonstrated a new general method for synthesizing highly alternating copolymers by olefin metathesis. The high conversion and degree of alternation arise from the thermodynamically driven selective bond formation between diacrylates and cycloalkenes.

Experimental Section

Full procedures and characterization data are given in the Supporting Information.

Representative procedure (Table 1, entry 1): Catalyst **3** (2.7 mg) and cyclooctene (65 μ L, 0.45 mmol) were added to a flask charged with 1,4-butanediol diacrylate (90 mg, 0.45 mmol) in CH₂Cl₂ (2 mL). Quick degassing by dynamic vacuum was conducted and the flask was fitted with a condenser and heated at reflux under argon for 6 h. The product (108 mg, 84 %) was precipitated into methanol. ¹H NMR (300 MHz, CDCl₃): δ = 6.93 (dt, J = 7.2, 15.9 Hz, 1 H), 5.77 (d, J = 15.9 Hz, 1 H), 4.13 (br s, 2 H), 2.12 (m, 2 H), 1.73 (m, 2 H), 1.43 (m, 2 H), 1.30 ppm (m, 2 H); ¹³C NMR (75 MHz, CDCl₃): δ = 166.8, 149.6, 121.3, 64.0, 32.5, 29.3, 28.2, 25.8 ppm.

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Polymerase Recognition of Unnatural Base Pairs*

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The storage and replication of genetic information requires bases that pair stably and selectively in duplex DNA and are also good substrates for DNA polymerases. Though the four natural bases pair by hydrogen bonding, there is no reason to assume that the pairing of two unnatural bases could not be driven by other intermolecular interactions, for example, those based on hydrophobicity.^[1,2] To investigate this issue, a wide variety of hydrophobic base pairs has been characterized.^[3,4] For example, ICS (see Figure 1) and its derivative PICS, with a propynyl group at C7, form self-pairs in duplex DNA that are as stable as natural base pairs. The unnatural triphosphates are also inserted opposite themselves in the

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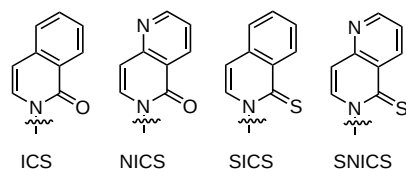


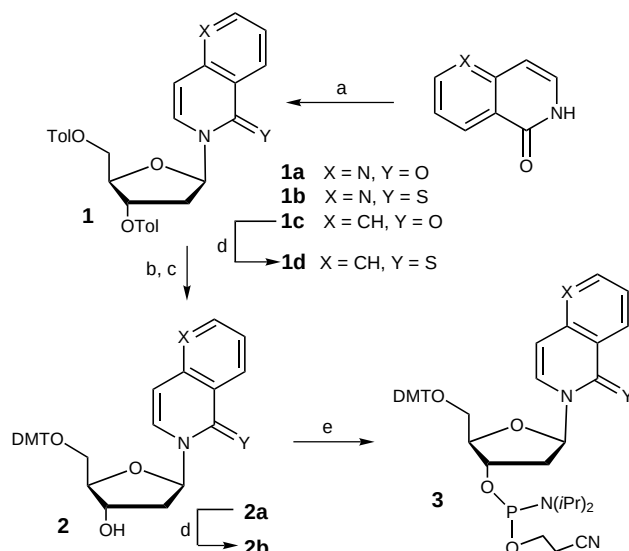
Figure 1. Representation of the unnatural nucleobases used.

template (self-pair synthesis) with reasonable efficiency and selectivity by polymerases.^[4] However, with all of the polymerases and nucleobases examined to date, replication has been limited by inefficient continuation of primer extension after synthesis of the unnatural self-pair.^[4] One solution to this problem is to use a binary polymerase system where different polymerases mediate incorporation and extension.^[3] Alternatively, if nucleobases are to be generated that can be incorporated and extended by a single polymerase, ultimately in vivo, the determinants of efficient base pair incorporation and extension must be better understood. To this end, we have synthesized and analyzed several ICS analogues and herein report three that efficiently form self-pairs and are also more efficiently extended than the ICS self-pair by the exonuclease-deficient Klenow fragment of DNA polymerase I from *E. coli* (KF).

To find an improved substrate for DNA replication, we synthesized three analogues of ICS with heteroatom substitutions (Figure 1). The effects of a permanent dipole oriented along the long axis of the ICS scaffold was examined with NICS. To further vary the polarizability as well as the hydrogen bond acceptor substituent at C10, we synthesized the sulfur-containing analogues SICS and SNICS.

Each nucleoside was synthesized as shown in Scheme 1 (see also the Supporting Information). The starting 1,6-naphthyridin-5(6H)-one was synthesized based on a published four-step protocol.^[5] For the 6-aza analogues, the Lewis acid catalyzed N-glycosidic bond formation was found to proceed more efficiently with a stoichiometric loading of SnCl₄, possibly because of chelation of the catalyst by the N6 atom. Compound **1a** was obtained as a mixture of β and α anomers which were separated by preparative TLC after protection of the hydroxy group at C5 with di(*p*-methoxyphenyl)phenylmethyl chloride (DMT). The analogues SICS and SNICS, which contain a thio group at C10, were synthesized from the corresponding lactams using Lawesson's reagent.^[6,7] The synthesis of ICS has already been described.^[4] Each DMT-protected nucleoside was converted into the corresponding phosphoramidite and incorporated into oligonucleotides with an ABI 392 DNA/RNA synthesizer. The corresponding triphosphates were synthesized as described.^[4]

The thermal stability of the ICS analogues was evaluated by determining the melting temperature (T_m) of duplex DNA containing the SICS: SICS, NICS:NICS, or SNICS:SNICS self-pairs (Table 1). As reported previously, the ICS self-pair is as stable as a dA:dT pair in the same sequence



Scheme 1. Synthesis of the unnatural nucleobases. a) Bis-TMS acetamide, RT, **4**, then chloroglycoside, SnCl₄, 0°C; b) 0.5 M NaOMe, MeOH, RT; c) DMTCl, pyridine, RT; d) Lawesson's reagent, toluene, reflux; e) diisopropylchlorophosphoramidite, Hünig's base, CH₂Cl₂, 0°C. DMT = di(*p*-methoxyphenyl)phenylmethyl, Tol = *p*-methylbenzoyl, TMS = trimethylsilyl.

context ($T_m = 59.3$ and 59.2°C for ICS:ICS and dA:dT, respectively). Thio substitution at C10 results in a 5.5°C decrease in T_m for the SICS self-pair. Aza-substitution at position 6 of the ICS framework leads to only a 3.2°C destabilization for the NICS self-pair (relative to the ICS self-pair). Surprisingly, the SNICS analogue containing both heteroatom substitutions forms a self-pair that is more stable than either analogue with a single substitution. The SNICS self-pair was only 2.2°C less stable than the ICS self-pair. The thermal selectivity of each self-pair is also high.

The ICS, SICS, NICS, and SNICS phosphoramidites were incorporated into a 45-mer oligonucleotide and used with the corresponding triphosphates to investigate the KF-mediated synthesis of the unnatural self-pairs under steady-state conditions (Table 2).^[4] The ICS self-pair is synthesized with an efficiency (k_{cat}/K_M) of $2.0 \times 10^4 \text{ M}^{-1} \text{ min}^{-1}$, which agrees well with previously reported data.^[4] Relative to ICS, replacement of C6 with nitrogen in NICS resulted in about a twofold decrease in insertion efficiency. However, thio substitution at C10 provided a marked increase in efficiency; the SICS self-pair was synthesized 80-fold more efficiently than ICS. The

Table 1. Denaturation temperatures (T_m) for NICS, SICS, and SNICS.^[a]

X	Y	T_m [°C]	5'-dGCGTACXCATGCG 3'-dCGCATGYGTACGC					
			X	Y	T_m [°C]	X	Y	T_m [°C]
NICS	NICS	56.1 ± 0.14	SICS	SICS	53.8 ± 0.01	SNICS	SNICS	57.1 ± 0.14
NICS	dA	52.4 ± 0.68	SICS	dA	52.0 ± 0.03	SNICS	dA	51.8 ± 0.03
NICS	dT	51.0 ± 0.03	SICS	dT	52.5 ± 0.03	SNICS	dT	52.3 ± 0.14
NICS	dC	47.5 ± 0.52	SICS	dC	48.3 ± 0.04	SNICS	dC	49.4 ± 0.13
NICS	dG	48.6 ± 0.03	SICS	dG	48.6 ± 0.02	SNICS	dG	50.2 ± 0.18

[a] The values for T_m were determined under the following conditions: 10 mM piperazine-*N,N'*-bis(2-ethanesulfonic acid) (PIPES), 10 mM MgCl₂, 100 mM NaCl, pH 7.

Table 2. The efficiency of incorporation of unnatural and natural triphosphates opposite unnatural bases in the template.

5' -dTAATACGACTCACTATAGGGAGA
3' -dATTATGCTGAGTGATATCCCTCT**X**GCTAGGTTACGGCAGGATCGC

↓ dYTP

5' -dTAATACGACTCACTATAGGGAGAY
3' -dATTATGCTGAGTGATATCCCTCT**X**GCTAGGTTACGGCAGGATCGC

X	Y	k_{cat} [min ⁻¹]	K_{M} [μM]	$k_{\text{cat}}/K_{\text{M}}$ [M ⁻¹ min ⁻¹]
ICS	ICS	1.7 ± 1.1	86 ± 27	2.0 × 10 ⁴
	A	0.04 ± 0.01	7.7 ± 2.7	5.7 × 10 ³
	C	n.d. ^[a]	n.d. ^[a]	5.9 × 10 ¹
	G	0.2 ± 0.1	95 ± 32	2.3 × 10 ³
	T	0.5 ± 0.2	147 ± 39	3.5 × 10 ³
NICS	NICS	0.8 ± 0.3	76 ± 3	1.1 × 10 ⁴
	A	0.20 ± 0.04	26 ± 6	7.7 × 10 ³
	C	0.27 ± 0.01	2.7 ± 1.8	1.0 × 10 ⁵
	G	0.32 ± 0.08	62 ± 7	5.2 × 10 ³
	T	2.1 ± 0.2	129 ± 56	1.6 × 10 ⁴
SICS	SICS	5 ± 1	3.2 ± 3.1	1.6 × 10 ⁶
	A	1.6 ± 0.6	45 ± 2	3.7 × 10 ⁴
	C	n.d. ^[a]	n.d. ^[a]	1.3 × 10 ²
	G	13 ± 3	85 ± 9	1.5 × 10 ⁵
	T	2.7 ± 1.2	194 ± 66	1.4 × 10 ⁴
SNICS	SNICS	3.8 ± 1.0	3.4 ± 3.2	1.1 × 10 ⁶
	A	1.31 ± 0.06	18 ± 10	7.4 × 10 ⁴
	C	0.11 ± 0.02	72 ± 40	1.5 × 10 ³
	G	0.9 ± 0.1	35 ± 8	2.5 × 10 ⁴
	T	0.6 ± 0.1	97 ± 40	6.1 × 10 ³

[a] n.d. = not determined. The reaction was too inefficient to obtain accurate measurements.

presence of N6 and thio substitution at C10 together in SNICS resulted in an unnatural base pair that is also efficiently synthesized with $k_{\text{cat}}/K_{\text{M}} = 1.1 \times 10^6 \text{ M}^{-1} \text{ min}^{-1}$ (100-fold increase relative to NICS). The SICS and SNICS self-pairs are synthesized 30- to 50-fold less efficiently than a natural base pair in the same sequence context. The enhanced insertion efficiency imparted by thio substitution at C10 in SICS and SNICS resulted from modest increases in k_{cat} (3- to 5-fold) and more substantial decreases in K_{M} (ca. 25-fold).

The fidelity of unnatural self-pair synthesis was also determined by measuring the efficiency of insertion of each natural triphosphate opposite the unnatural bases in the template. In agreement with previously reported data, the most efficiently synthesized mispair with ICS came from the insertion of dATP ($k_{\text{cat}}/K_{\text{M}} = 5.7 \times 10^3 \text{ M}^{-1} \text{ min}^{-1}$), which resulted in a selectivity of only 3.5-fold. The slightly decreased efficiency of NICS self-pair synthesis, along with the efficient insertion of dCTP opposite the base ($k_{\text{cat}}/K_{\text{M}} = 1.0 \times 10^5 \text{ M}^{-1} \text{ min}^{-1}$), provided poor selectivity for the NICS self-pair. The triphosphate dGTP was efficiently inserted opposite SICS ($k_{\text{cat}}/K_{\text{M}} = 1.5 \times 10^5 \text{ M}^{-1} \text{ min}^{-1}$), but less so than d(SICS)TP ($k_{\text{cat}}/K_{\text{M}} = 1.6 \times 10^6 \text{ M}^{-1} \text{ min}^{-1}$), resulting in an 11-fold increase in selectivity for this self-pair. The highest fidelity was found for the SNICS self-pair, which

showed an efficiency that was at least 15-fold greater than that of all possible mispairs.

The unnatural phosphoramidites were also incorporated into a 24-mer primer as the 3'-terminal nucleotide (Universal solid support, Glen Research). The primer was used, in conjunction with the 45-mer template, as a substrate for DNA synthesis (Table 3). The efficiency and selectivity of KF-mediated insertion of dCTP opposite dG (correct extension) was determined under steady-state conditions.^[4] The ICS self-pair is extended inefficiently ($k_{\text{cat}}/K_{\text{M}} = 1.8 \times 10^3 \text{ M}^{-1} \text{ min}^{-1}$, compared to $5.4 \times 10^7 \text{ M}^{-1} \text{ min}^{-1}$ for a dA:dT pair in the same sequence context). Relative to ICS, replacement with N6 and thio substitution at C10 each enhanced extension, resulting in an increase in the efficiency of dCTP insertion of 2.0 and 3.5-fold, respectively, for the NICS and SICS self-pairs. Modification of the ICS scaffold at both positions resulted in a SNICS self-pair that was extended with an efficiency of $2.2 \times 10^4 \text{ M}^{-1} \text{ min}^{-1}$, a 12-fold increase over that for the ICS self-pair. While the SNICS self-pair is extended less efficiently than is a natural base pair, this represents significant progress toward a replicable ICS scaffold.

The origins of the enhanced extension efficiency were different for each heteroatom substitution. Both 6-aza substitution in NICS and C10-thio substitution in SICS resulted in an elevated k_{cat} (7- to 10-fold) relative to the ICS self-pair; however, the K_{M} for dCTP was also increased (3-fold in each case). The effects of the substitutions were quite different when combined in the SNICS unnatural base. The self-pair was extended with both an increased k_{cat} and a decreased K_{M} (5- and 2.5-fold, respectively) relative to the ICS self-pair. In all cases, insertion of dGTP, dATP, and dTTP opposite dG was found to be negligible ($k_{\text{cat}}/K_{\text{M}} < 5 \times 10^2 \text{ M}^{-1} \text{ min}^{-1}$), demonstrating that extension of unnatural base pairs proceeds with reasonable fidelity.

The SNICS self-pair represents significant progress toward expansion of the genetic alphabet. Moreover, the thermodynamic and kinetic data presented above aid in the determination of unnatural base pair properties that mediate their stability and facilitate their replication. The stability of the self-pairs formed between the ICS derivatives are all reduced relative to that of the ICS self-pair, though only marginally in the case of SNICS. The decreased stability is unlikely to be the result of solvation effects as each position is expected to be fully accessible to solvents in either single-stranded or duplex

Table 3. The efficiency of the correct extension of unnatural self-pairs.^[a]

5' -dTAATACGACTCACTATAGGGAGAX
3' -dATTATGCTGAGTGATATCCCTCT**X**GCTAGGTTACGGCAGGATCGC

↓ dCTP

5' -dTAATACGACTCACTATAGGGAGAXC
3' -dATTATGCTGAGTGATATCCCTCT**X**GCTAGGTTACGGCAGGATCGC

Unnatural self-pair	k_{cat} [min ⁻¹]	K_{M} [μM]	$k_{\text{cat}}/K_{\text{M}}$ [M ⁻¹ min ⁻¹]
ICS	0.15 ± 0.06	82 ± 22	1.8 × 10 ³
NICS	1.0 ± 0.2	257 ± 155	3.7 × 10 ³
SICS	1.5 ± 0.3	242 ± 78	6.3 × 10 ³
SNICS	0.76 ± 0.04	34 ± 16	2.2 × 10 ⁴

[a] Incorporation of dCTP opposite dG in the template. The extension with an incorrect natural dNTP was in every case less than $3 \times 10^2 \text{ M}^{-1} \text{ min}^{-1}$.

DNA (through the duplex major groove or minor groove).^[8] Increased polarizability of the nucleobase is also unlikely to result in the destabilization as it is expected to enhance interbase stacking.^[8] The observed destabilization may result from unfavorable dipole–dipole interactions with flanking bases in the case of NICS, and increased steric repulsion between the opposing sulfur atoms of the self-pairs of SICS and SNICS.

Sulfur substitution in SICS and SNICS results in self-pairs that are synthesized two orders of magnitude more efficiently than ICS and NICS. As described above, this increase in efficiency resulted from a modest increase in k_{cat} (3- to 5-fold) and a more substantial decrease in unnatural triphosphate binding (25-fold). Speculation about the potential origins of these effects may be based on the available structures of the type I DNA polymerases from *B. stearothermophilus* and *T. aquaticus*.^[9,10] These polymerases are highly homologous to KF, both structurally and functionally. In these structures the triphosphate hydrogen bond acceptor, located at a position analogous to that of the C10 sulfur atom in the unnatural bases, interacts with the template base as well as a water molecule. Based on the structures, the aromatic ring of the unnatural triphosphate is also expected to pack with Tyr 766. It therefore seems likely that sulfur substitution may increase the binding of the unnatural substrate through favorable sulfur–sulfur interactions or through electronic effects which favor hydrophobic packing.

The crystal structures also reveal information that may be relevant to the extension rates that are increased by an order of magnitude. The nucleobase at the primer terminus packs against the base of the incoming triphosphate, and along with the template base is tightly packed by hydrophobic side chains of the protein, which is thought to exert a geometrical selection against the aberrant structures of mispaired bases. The structures also reveal sequence-independent hydrogen bonds between the polymerase and the purine N3 or pyrimidine O2 atoms of the natural bases at the primer terminus. Failure of the unnatural DNA base pair to suitably engage the protein by any of these interactions may result in a misaligned 3'-OH primer terminus which is unable to act as an efficient nucleophile during the extension step. The higher extension efficiency that results from C10-thio substitution may therefore derive from improved packing interactions, structural or electronic changes owing to interpair sulfur–sulfur interactions, or altered hydrogen bonding with protein side chains in the developing minor groove.

Replication of DNA containing unnatural base pairs requires that the base pairs be stable as well as efficiently synthesized and then extended by a DNA polymerase. We have demonstrated that both of these steps may be optimized by heteroatom substitution. The SNICS self-pair is synthesized 55-fold more efficiently and 5-fold more selectively and is extended 12-fold more efficiently than its parent ICS self-pair. Not only does this represent significant progress towards a replicable unnatural base pair, it implies that further improvement in insertion and extension should be possible with further modification of the bases.

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Hierarchically Ordered Silica Mesophases Using Mixed Surfactant Systems as Templates**

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Since the discovery of silica mesophases,^[1,2] surfactant-templated syntheses based on the hydrolysis and crosslinking of inorganic precursors (I) at the surfaces of supramolecular surfactant (S) assemblies have been used to prepare a variety of hexagonal, cubic, or lamellar mesophases through five pathways: S^+I^- , S^-I^+ , $S^+X^-I^+$, $S^-M^+I^-$, and S^+I^0 (or N^0I^0) (X^- = counterion, M^+ = metal ion, N = polyethylene oxide).^[3–16] Several methods are now available for the preparation of ordered structures at different length scales, such as micro-, meso-, and macroporous materials.^[17,18] However, the preparation of hierarchically ordered structures in a single body, such as seen in diatoms in nature, has remained an experimental challenge.^[17]

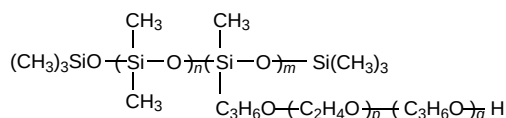
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A number of models were proposed to explain the formation of the silica mesophases.^[2,4] However, these models rarely consider the effect of the configuration of the supra-molecular chain on the mesophase formation and are insufficient for establishing the mechanistic understanding needed for a better control of the synthetic process, which is key to improving this exciting new class of mesophases or adding to it. Stucky and co-workers presented a more detailed model to explain the formation and morphologies of surfactant/silica mesophases based on the experimental results.^[19] However, formation of oxide mesophases and structure selection have not been well understood to date. On the basis of experimental data, we present here a detailed model of the oxide mesophase formation process, which explains presently known experimental data and successfully predicts conditions needed for the synthesis of desired mesostructures from the consideration of the chain configuration.

A new class of silicone-based surfactants was designed to direct the assembly of surfactant/oxide mesophases. The amphiphilic silicone surfactant is composed of a polydimethylsiloxane (PDMS) backbone and a side chain of poly(ethylene oxide)-*block*-poly(propylene oxide) (PEO-PPO) (Scheme 1). Silicone surfactants (denoted MD_n(D'E_pP_q)_mM, where M = (CH₃)₃SiO_{1/2}, D = (CH₃)₂SiO, D' = CH₃(C₃H₆O)-SiO, E_p = (C₂H₄O)_p, and P_q = (C₃H₆O)_qH) are amphiphilic, cheap, nontoxic, and biodegradable, and they have lower glass transition temperatures and higher surface activities than conventional hydrocarbon surfactants.^[20,21] The silicone surfactants (purity > 95%) were prepared by hydrosilylation addition reactions, as found elsewhere.^[20]



Scheme 1. Primary structure of the polyether-modified polysiloxanes used in our study.

Lamellar surfactant/silica powders (denoted ZSU-L) were prepared by hydrolysis of tetraethylorthosilicate (TEOS) in the presence of pure silicone surfactants in acidic media or at neutral pH. The lamellar character of the ZSU-L products is clearly seen from the transmission electron microscopy (TEM) image of an ultrathin section of an as-prepared sample that was prepared under strong acidic conditions (Figure 1). The ZSU-L products are planar bilayers sandwiched by thick silica platelets that are arranged parallel to each other. The interlayer distance, as measured from the TEM images is 200(±10) nm, which is much greater than those of all previously synthesized and natural layered materials.^[7–16] The splitting of silica walls visible in the image is the result of ultrathin sectioning. TEM observation of the ZSU-L sample under various tilting angles did not show evidence for any framework topology other than lamellae. Even when the concentration of the silicone surfactant and HCl is substantially changed, the lamellar structure is retained, suggesting that silicone surfactants favor the formation of layered materials (see for example Figure 1 of the

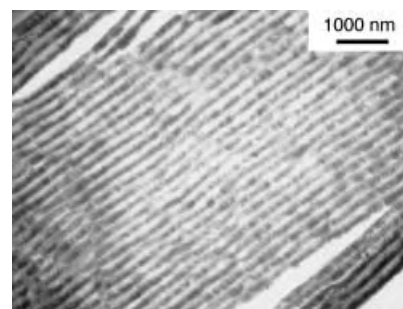


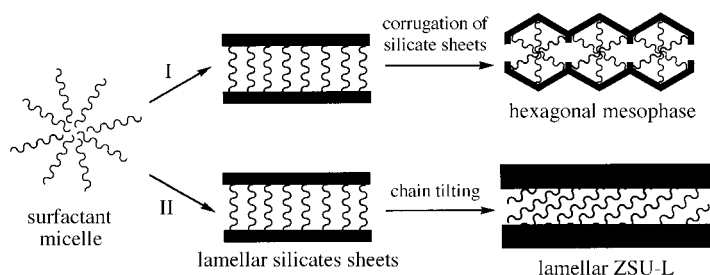
Figure 1. TEM image of an ultrathin section of an as-prepared lamellar ZSU-L product obtained using MD₁₀₈(D'E₁₆P₁₆)₈M as the template in 2 M HCl.

Supporting Information for a composite obtained at neutral pH). Lamellar silica were obtained no matter whether the silicone surfactant was of low or high molecular weight (M(D'E₁₀OH)M, M(D'E₁₂H)₂M, MD₂₈(D'E₁₂H)₃M, MD₃₄(D'E₁₂P₁₂)₆M, MD₇₀(D'E₁₅P₁₅)₉M, MD₁₀₃(D'E₁₈P₁₈)₁₀M).

At low concentrations (~1 wt % for the preparation of ZSU-L powders), silicone surfactants form isotropic micelles with no long-range order.^[20] Under our reaction conditions, the initial dilute solutions were completely clear and devoid of phase-segregated planar bilayer structures of the size observed for the mesostructure obtained later. No lamellar phase was observed by freeze-fracture electron microscopy analysis in the initial surfactant solution. Phase segregation and planar bilayer formation did not occur until TEOS was added to the solution of the silicone surfactant. This indicates that the formation of the ZSU-L powders is not templated by the pre-existing bilayers and vesicle templates or liquid crystal phases previously thought to be responsible for lamellar organic/inorganic adducts.^[7–9,15,16]

The dimensionless effective surfactant packing parameter $g = V/a_0l_c$ determines the mesostructure of the product;^[19,22,23] V is the chain volume, l_c the chain length, and a_0 the optimal headgroup area of a surfactant molecule. The governing role of the headgroup area (a) in the selection of a particular mesostructure has already been confirmed in water-surfactant systems: the favored mesophase is that which permits a to be close to its optimum value a_0 , while maintaining favorable packing of the hydrophobic surfactant chains.^[19]

During freeze-dry kinetic experiments with silicone surfactant templating, we observed the lamellar mesophase after reaction times in the order of 5 min in strong acidic media; this phase remained as the reaction proceeded. We conclude that, in the early stage of the reaction, coassembly of organic and inorganic species leads to the formation of lamellar surfactant/silicate sheets. As crosslinking and condensation of the silicate species proceed, the organic-inorganic interfacial area increases and the number of silanol groups decreases, so that a_0 increases. To accommodate this change, Stucky and co-workers proposed^[19] that silica condensation leads to an increase in interfacial area through corrugation of the lamellar surfactant/silicate sheets (pathway I in Scheme 2). This corrugation progresses until connection between the sheets is made at the cusps, which ultimately results in the formation of a hexagonal mesophase. In contrast, we always obtained layered silica mesophases when silicone surfactants



Scheme 2. Comparison of the templating pathways for conventional surfactants with a restrictive hydrocarbon chain configuration and silicone surfactants with an unrestricted siloxane chain configuration. Pathway I: transformation from lamellar surfactant/silicate sheets to a hexagonal mesophase templated by CTA⁺, as proposed by Stucky et al.^[19] Pathway II: formation of ZSU-L templated by silicone surfactants.

were used. Therefore, we suggest that the formation of lamellar ZSU-L is governed by the supramolecular chain configuration. PDMS chains are more flexible than the hydrocarbon chains in alkyltrimethylammonium ions (like CTA⁺) or Pluronics (PEO-PPO-PEO), because the bond angle (Si-O-Si, ~143°) is significantly larger and the bond length (Si-O, 0.165 nm) significantly longer than for comparable C-C-C (109°, 0.140 nm) and C-O-C (114°, 0.142 nm) units. Thus, the obstacle to rotation is very low (rotation barrier: 0.8 kJ mol⁻¹) and the Si-O bond can freely rotate and tilt.^[20,21] This is the reason why even very long PDMS chain surfactants are in the liquid state at room temperature. In contrast, hydrocarbon surfactants tend to be in the solid state at room temperature since Krafft temperatures for surfactants with long and linear hydrocarbon chains are high.^[20,21]

Hill showed that the behavior of the “linear” trisiloxane surfactant MDM'E₈OH in the aqueous phase is essentially identical to that of the “branched” version, M(D'E₈OH)M. This was unexpected, as the shape of the two molecules should be quite different (see p. 30 in ref. [20]). The observation illustrates the important role of the flexibility of the Si-O chain for the behavior of silicone surfactants: the siloxane group tends to adopt a configuration that allows it to accommodate the preferred cross-sectional area of the polar group—in this case the coil of the hydrated PEO chain. This indicates that the flexible chain configuration enables a silicone surfactant to increase its *a* value toward *a*₀ through rotation or tilting of the Si-O chains, while maintaining a planar structure. In this case, the wall thickness simultaneously increases to keep the silicone surfactant/SiO₂ volume ratio constant. Polymerization normal to the interface substantially thickens the walls even in strong acidic media, though this was previously not expected because of the high positive charge on the silicate species in strong acidic media.^[19] Thus, unrestricted supramolecular chain configurations always led to the formation of lamellar mesophases, and lamellar-to-hexagonal mesophase transformations have never been observed using silicone surfactants as the template. We suggest that silica polymerization leads to an increase in interfacial area through tilting of the siloxane chains, as indicated by pathway II in Scheme 2.

We propose that the formation of oxide mesophases is governed by the chain configuration of the supramolecular

template. This enables us to predict which chain configurations favor lamellar structures and which favor other mesophases. For example, a lamellar mesophase should be formed when silicone surfactants are used as templates. To test this model, we prepared silica and TiO₂ films by the sol-gel method^[24] in conjunction with the dip-coating process using silicone surfactants as templates. Highly ordered long-range lamellar structures of silica and TiO₂ films were clearly observed (see Figure 2 in the Supporting Information). Their interlayer spacing measured from TEM images was 160(±10) and 320(±20) nm, respectively. The results demonstrate that silicone surfactants with unrestricted chain configurations are responsible for the formation of lamellar mesostructures. Yang et al.^[25] prepared a variety of hexagonal metal oxide mesophases using EO₂₀PO₇₀EO₂₀ (P123) as the template in nonaqueous solutions. However, with silicone surfactants as templates, we obtained only lamellar forms of metal oxides such as TiO₂ and ZrO₂ by the same method (see Figure 3 in the Supporting Information). Their lattice constants were 210(±10) and 160(±10) nm, respectively. These results further support our proposal that the structure of oxide mesophases is governed by the chain configuration of the supramolecular template, that is, unrestricted chain configurations (such as those of silicone surfactants) are responsible for the formation of zero-curvature (planar) lamellar silica mesophases, and restricted chain configurations (such as those of the Pluronics family, CTA⁺) are responsible for high-curvature hexagonal mesophases.^[19]

Hierarchically ordered silica (denoted ZSU-4) was prepared using a mixture of silicone surfactant and P123 as the template. Figure 2A shows that lamellar silica similar to that observed in the ZSU-L product is retained in the ZSU-4 product. Previously, in systems with a member of the Pluronics family, C_nEO_m (polyethylene oxide), CTA⁺, or their mixtures serving as templates, a single mesophase such as hexagonal mesoporous silica has been prepared.^[26–29] Surprisingly, we find here that hexagonal pore channels were formed in the silica walls of ZSU-4 (Figure 2B). Both the lamellae and the hexagonal mesophase are assembled in a single body, representing a complex mesostructure. No X-ray diffraction (XRD) peaks are observed for the ZSU-L product (Figure 3). However, a high degree of mesoscopic order (at least three *p6mm* XRD peaks) is observed for the calcined ZSU-4 (Figure 3). It is obvious that the lamellar mesophase and the hexagonal mesoporosity in the walls were separately templated by the silicone surfactant and P123 in the mixed templating system, and thus hierarchically ordered silica formed, although both structures exist in a single system. The presented examples further supply strong evidence that the structure of oxide mesophases is governed by the chain configuration of the supramolecular template.

The N₂ sorption isotherm and the corresponding BJH (Barret–Joyner–Halenda) pore size distribution curve of the calcined ZSU-4 product are shown in Figure 4A and B, respectively. The N₂ isotherm of calcined ZSU-4 is a type IV isotherm with a large type H₂ hysteresis loop. This is in contrast to the isotherms of SBA-15 and MCM-41, which indicates that ZSU-4 has a three-dimensional network of mesopores.^[30,31] The calcined ZSU-4 product, prepared using

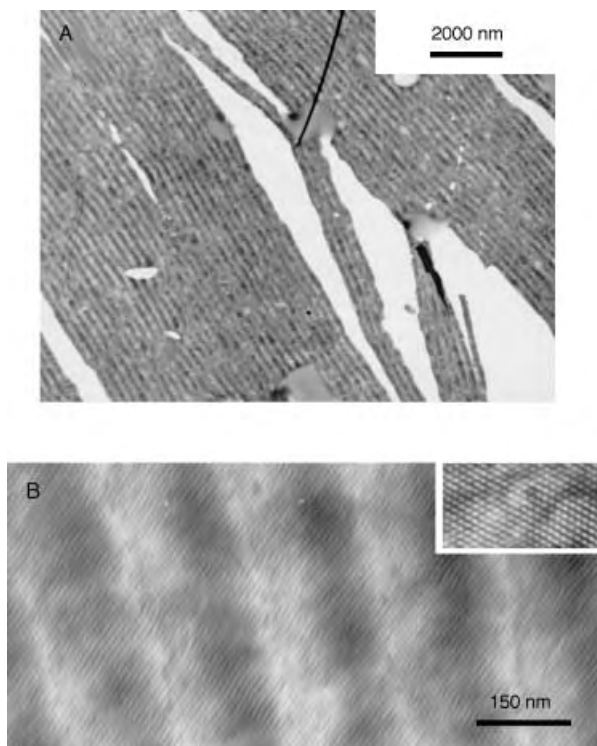


Figure 2. TEM images of an ultrathin section of the hierarchically ordered silica mesostructure ZSU-4 obtained with a mixture of silicone surfactant and P123 as the template. A) Low-magnification TEM image of the as-prepared ZSU-4; B) higher-magnification TEM image (recorded along the [110] zone axis). The inset in (B) is recorded along the [001] zone axis and shows highly ordered hexagonal mesopores.

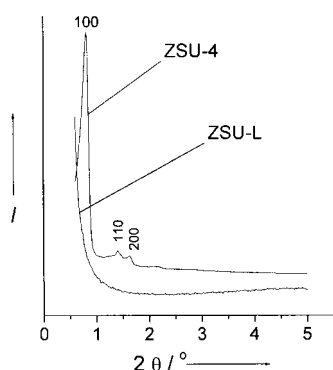


Figure 3. Powder XRD patterns of the as-prepared ZSU-L product and the ZSU-4 product (calcined at 560 °C in air for 6 h).

the mixture of silicone surfactant and P123 as the template, has a high BET surface area of 841 m²g⁻¹. The BJH analyses show that calcined ZSU-4 exhibits pore sizes of 8.1 nm (Figure 4B).

In conclusion, highly ordered lamellar hybrid oxides with large interlayer spacings were obtained using silicone surfactants as templates under a wide range of synthetic conditions. We found that silicone surfactants with unrestricted chain configuration are responsible for the formation of lamellar mesophases. The addition of copolymers can create hexagonal mesophases in the layered walls, which provides a simple route to the design of complex mesostructured materials. Coassembly of organic and inorganic species, and the fact that

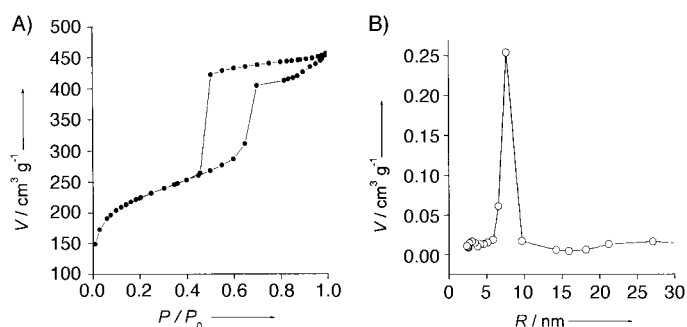


Figure 4. A) N₂ adsorption and desorption isotherms for ZSU-4 calcined at 560 °C for 6 h. B) Corresponding BJH pore size distribution curve determined from the N₂ adsorption isotherm. Prior to measurement the sample was evacuated at 523 K and 10⁻⁶ Torr for 16 h.

silicone surfactants prefer planar structures, results in the formation of highly regular lamellar structures. We believe that this novel route is universal and offers significant overall benefits for the controlled design of a wide range of materials with complex mesostructures. Oxide materials with hierarchically ordered mesostructures are of interest from the viewpoint of biomineralization, and may find wide applications in catalysis, adsorption, separation, etc. We believe that our findings provide new insights into the mechanistic issues involved in the formation of this interesting class of mesostructured materials. Further investigation, however, will be required in order to adequately elucidate the actual mechanisms of the formation of these unusual lamellar structures.

Experimental Section

Lamellar silica powders (ZSU-L) were prepared by hydrolysis of TEOS in the presence of pure silicone surfactants under a wide range of acidic conditions or at neutral pH. In a typical synthesis, silicone surfactant MD₁₀₈(D'E₁₆P₁₆)₈M (1 g) was dissolved in 2 M HCl (60 mL), then TEOS (4.16 g) was added while stirring. The reaction mixture was stirred at room temperature for 24 h to obtain the ZSU-L powder.

Complex silica mesostructures (ZSU-4) were prepared using a mixture of a silicone surfactant and P123 as the template. In a typical synthesis, MD₁₀₈(D'E₁₆P₁₆)₈M (0.8 g) and P123 (1 g) were dissolved in 2 M HCl (60 mL), then TEOS (4.16 g) was added while stirring. The reaction mixture was stirred at 35 °C for 24 h and subsequently heated for 24 h to 90 °C. The precipitate was recovered by filtration, washed with water, and air-dried. The surfactant was removed by calcination at 560 °C for 6 h in air. XRD analysis was performed on a Rigaku Rotaflex diffractometer equipped with a rotating anode and CuK_α radiation. TEM images were obtained with a JEOL 100CX operated at 100 kV. The samples were embedded in epoxy resin and ultramicrotomed for the TEM measurements. N₂ adsorption measurements were performed at 77 K using a Micromeritics ASAP 2010 system. The surface area was obtained by Barrett-Emmett-Teller (BET) calculations for the adsorption branch of the isotherm, the pore size distribution by BJH calculations.

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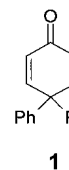
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4,4-Diphenyl-2,5-cyclohexadienone: Four Polymorphs and Nineteen Crystallographically Independent Molecular Conformations**

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Polymorphism is the existence of the same chemical substance in at least two different crystalline arrangements of molecules.^[1] The existence of polymorphism implies that free energy differences between different crystalline forms are small (1–2 kcal mol⁻¹) and that kinetic factors are important during crystal nucleation and growth.^[2] Molecular conformations, packing arrangements, hydrogen bond syntheses, and lattice energies of the same molecule in different crystalline environments can be compared in polymorphic structures. Polymorphs represent special situations for the study of structure–property relationships with a minimum number of variables, since differences arise from crystal packing effects and not because of the presence of a different chemical species. A proper understanding of polymorphism is important in crystal engineering^[3] because the unexpected occurrence of a new polymorph can well demolish the best of crystal design strategies. Getting the correct polymorph^[4] is of the utmost importance in the synthesis of drugs, pharmaceuticals, explosives, dyes, pigments, flavors, and confectionery products.

We describe here four X-ray crystal structures of 4,4-diphenyl-2,5-cyclohexadienone (**1**) that exhibit conformational polymorphism,^[5] conformational isomorphism,^[5] and concomitant polymorphism^[6]



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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

in the same system. While there are examples wherein only one of these phenomena occurs for a particular molecule,^[7] their simultaneous occurrence for the same molecule is rare.^[8] Initially, crystallization of **1** from EtOAc/hexane appeared to afford two concomitant polymorphs as characterized by single-crystal X-ray diffraction: a monoclinic form **A** in space group $P2_1$ ($Z=2$) and a triclinic form **B** with four molecules in the asymmetric unit ($P\bar{1}$, $Z=8$).^[9] When data were collected on another crystal, a large triclinic cell ($P\bar{1}$, $Z=24$, form **C**) was indexed^[10] that could not be refined to better than $R=0.11$ despite a satisfactory data/parameter ratio of 7.5. The solvent system was modified (CH_2Cl_2 was added to EtOAc/hexane) in the hope of getting bigger crystals for better quality data. To our surprise, the structure solution and refinement proceeded routinely this time but in space group $Pbca$ ($Z=16$).^[10] Yet another polymorph of **1**, form **D**, had been discovered.

We have thus characterized 19 crystallographically independent molecules of **1** in four crystal structures (**A–D**) that may be classified as conformational polymorphs.^[11] Furthermore, forms **A**, **B**, and **C** are concomitant polymorphs because they crystallize from the same flask, and forms **B**, **C**, and **D** are conformational isomorphs because they have multiple conformations of **1** within the same crystal. There are only three examples known of systems with four polymorphs: pyrazinamide, sulfathiazole, and sulfapyridine.^[12] A trimorphic system^[13] with seven conformations of the molecule and a hexamorphic system^[14] of conformational polymorphs with one symmetry-independent molecule in each crystal structure have been reported.

Form **A** consists of linear chains of $\text{C–H}\cdots\text{O}$ hydrogen bonds ($d(\text{H}\cdots\text{O})$, $\angle(\text{C–H}\cdots\text{O})$: 2.52 Å, 163.9°; 2.61 Å, 129.9°; neutron-normalized geometry) such that each molecule of **1** (A_i , Table 1) is bonded to four screw axis related molecules through phenyl hydrogen donors (Figure 1). There are four symmetry-independent molecules in crystal **B**. Molecules B_{ii} and B_{iii} engage in centrosymmetric $\text{C–H}\cdots\text{O}$ dimers with the quinone carbonyl group of different molecules (synthon **I**, 2.33 Å, 169.2°; 2.49 Å, 123.4°). Similarly molecules B_i and B_{iv} have distinct occurrences of centrosymmetric (Ph) $\text{C–H}\cdots\text{O}$ synthon **II** through the *para* hydrogen donor (2.64 Å, 137.9°; 2.75 Å, 121.5°; Figure 2). Each symmetry-independent molecule of form **B** (B_i – B_{iv}) is a different conformer of the title compound (Table 1). Polymorph **C** has 12 molecules in the asymmetric unit (C_i , C_{ii} , ..., C_{xii}). The structure has a complex and intricate crystal packing (not shown) mediated by multiple occurrences of $\text{C–H}\cdots\text{O}$ hydrogen bonded synthons **I** and **II** (Table 1). In the orthorhombic form **D**, D_i molecules are connected by $\text{C–H}\cdots\text{O}$ hydrogen bonds (2.36 Å, 138.0°;

Table 1. The conformation of 19 symmetry-independent molecules in tetramorphs of **1** (forms **A–D**).

Polymorph (space group)	Torsion angle ^[a]		Crystallographic molecular designation	Intermolecular hydrogen bond synthon	Graph set notation
	τ_1 [°]	τ_8 [°]			
A ($P2_1$)	12.6(7)	12.5(8)	A_i	$\text{C–H}\cdots\text{O}$	$C(8)$
B ($P\bar{1}$)	11.5(3)	17.7(3)	B_i	II	$R_2^2(20)$
	12.3(3)	16.0(3)	B_{ii}	I	$R_2^2(8)$
	14.9(3)	23.6(3)	B_{iii}	I	$R_2^2(8)$
	19.1(3)	31.8(3)	B_{iv}	II	$R_2^2(20)$
C ($P\bar{1}$)	20.1	31.5	C_i	II	$R_2^2(20)$
	20.9	30.8	C_{ii}	II	$R_2^2(20)$
	18.4	32.3	C_{iii}	II	$R_2^2(20)$
	12.1	22.7	C_{iv}	I	$R_2^2(8)$
	15.2	22.0	C_v	I	$R_2^2(8)$
	18.3	28.2	C_{vi}	I	$R_2^2(8)$
	12.8	16.0	C_{vii}	I	$R_2^2(8)$
	14.0	16.7	C_{viii}	II	$R_2^2(20)$
	10.2	21.0	C_{ix}	II	$R_2^2(20)$
	14.9	15.1	C_x	I	$R_2^2(8)$
	11.9	16.7	C_{xi}	I	$R_2^2(8)$
	11.5	17.4	C_{xii}	II	$R_2^2(20)$
D ($Pbca$)	18.5(2)	36.8(2)	D_i	$\text{C–H}\cdots\text{O}$	$C(10)$
	8.4(2)	16.5(2)	D_{ii}	III	$R_2^2(16)$

[a] The estimated standard deviation (esd) of the torsion angle is given in parentheses. The esd values are not provided for form **C** because the R factor is high (0.11). A difference of more than 3° in the torsion angle ($\geq 3 \times \text{esd}$) may be taken as representing different conformations.

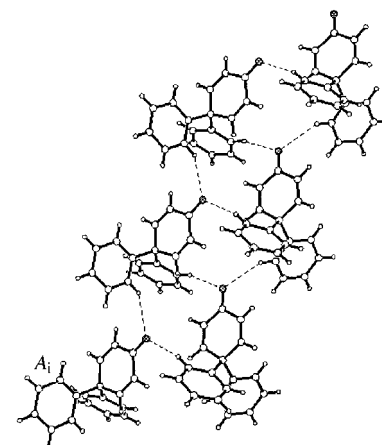
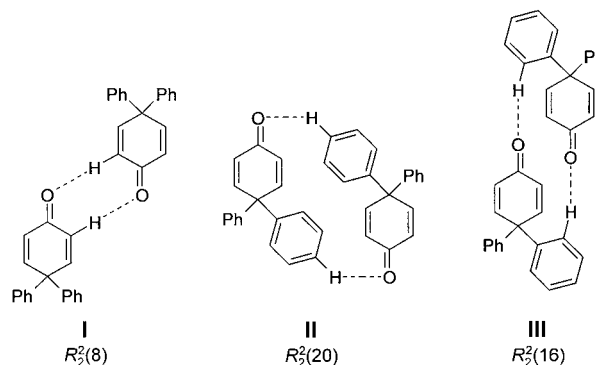


Figure 1. Helices of $\text{C–H}\cdots\text{O}$ hydrogen bonds ($C(8)$ graph set) between 2_1 -related molecules in form **A** (conformer A_i).

2.55 Å, 166.9°; Figure 3a) and D_{ii} molecules are connected as centrosymmetric dimers through synthon **III** (2.57 Å, 144.6°); such dimers are in turn connected by $\text{C–H}\cdots\text{O}$ bonds



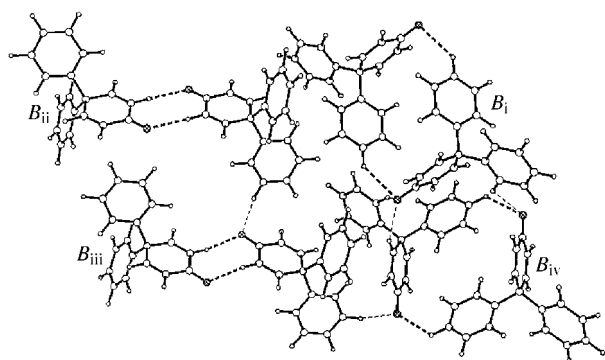


Figure 2. Centrosymmetric C–H...O synthons **I** (B_{ii} , B_{iii} ; $R_2^2(8)$ motif) and **II** (B_i , B_{iv} ; $R_2^2(20)$ motif) in form **B** shown as bold dotted lines. The C–H...O interactions are shown as normal dotted lines.

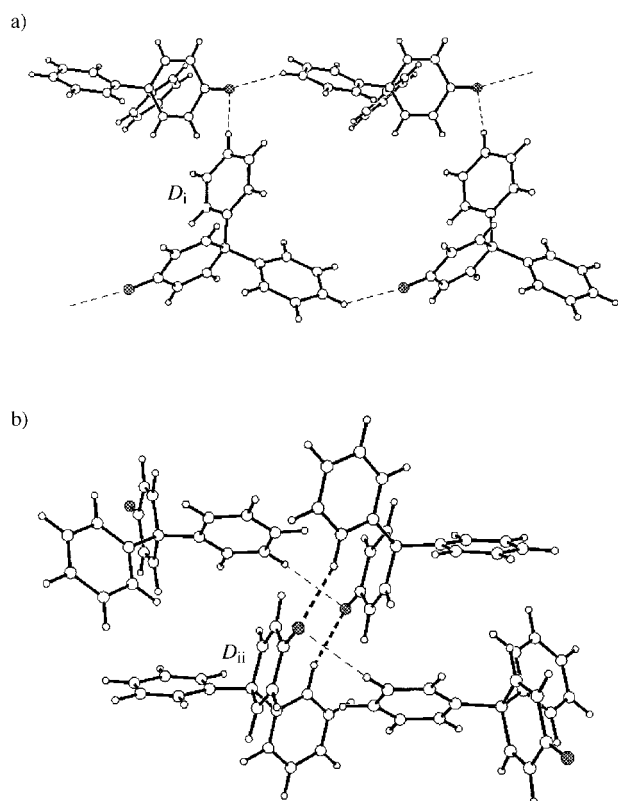


Figure 3. a) C–H...O hydrogen bonds between D_i molecules in form **D**. These molecules are related by a translation (left–right, $C(10)$ chain) and a screw axis (bottom–top). b) Centrosymmetric C–H...O synthon **III** between D_{ii} molecules (bold dotted lines, $R_2^2(16)$ motif) and C–H...O interactions (normal dotted lines).

(2.76 Å, 145.2°; Figure 3b). From the viewpoint of conformational polymorphism and conformational isomorphism, D_i and D_{ii} adopt new conformations (Table 1). To summarize, the tetramorphic crystal structures of **1** are stabilized by different arrangements of C–H...O hydrogen bonds.^[15] The supramolecular synthon^[16] description and graph set notation^[17] of these motifs are given in Table 1.

The 19 crystallographically independent molecules of **1** differ in rotation about the C–C bond between the quinone and the phenyl ring. These different conformations may be classified through eight possible torsion angles (τ_1 , τ_2 , ..., τ_8). We have selected τ_1 and τ_8 , taken from a single asymmetric

unit of the eight-dimensional torsion angle space, as the torsion parameters to map the conformational surface in these 19 molecules (Figure 4a). Similar scatter plots are obtained if other appropriate pairs of torsion angles are used. There are two populations of conformers (Figure 4b): $\tau_1 = 8.0$ – 16.0° , $\tau_8 = 12.0$ – 24.0° and $\tau_1 = 18.0$ – 22.0° , $\tau_8 = 27.0$ – 38.0° . The motion of the phenyl rings in these conformations is correlated, that is, a change in the conformation of one phenyl ring leads to a conformational change in the second ring. Such a gearing of geminal phenyl rings has been noted earlier.^[18] Notwithstanding that conformational change about a C–C single bond is a flexible (soft) parameter and that small differences in torsion parameters (2–3°) may not be chemically meaningful, it is clear that in our case there are two populations of conformers with mean values of $\tau_1 = 12^\circ$, $\tau_8 = 18^\circ$ and $\tau_1 = 20^\circ$, $\tau_8 = 32^\circ$.

A particular conformation is associated with a specific hydrogen bond synthon even if the molecules are present in different polymorphs. For example, B_i and C_{xii} molecules have nearly identical conformations and they engage in synthon **II** ($R_2^2(20)$ motif) in their respective crystal structures. Similarly, other conformations in forms **B** and **C** that are part of the same cluster in the τ_1 – τ_8 scatter plot engage in synthons **I** and **II**. All this suggests that each of these conformations plays a specific structural role in the crystallization of these polymorphs. The two triclinic crystals present snapshot pictures at different stages of crystallization, from an evolving array of

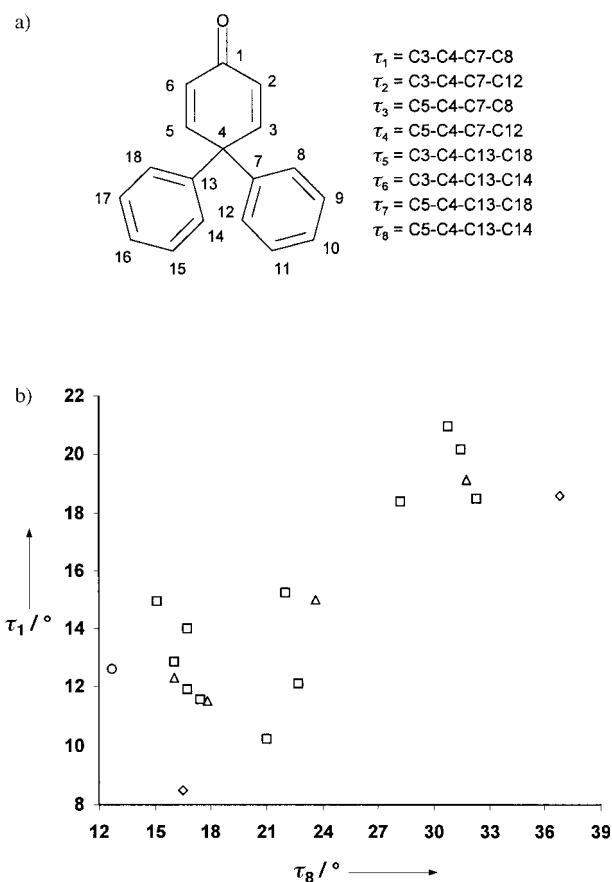


Figure 4. a) Definition of the torsion angles τ_1 – τ_8 in **1**. b) The scatter plot of τ_1 versus τ_8 . Note the two clusters of conformations and the near linear correlation. Absolute values of torsion angles are used. Symbols for the polymorphs: **A** = $\circ$, **B** = $\triangle$, **C** = $\square$, **D** = $\diamond$.

ordered molecules in many conformations (form **C**, $Z' = 12$) to a more compact lattice (form **B**, $Z' = 4$). Their similarity may be judged from the calculated powder X-ray diffraction trace (Cerius²,^[19] see the Supporting Information). A frequently posed question about conformational polymorphs is the following:^[20] Does molecular conformation determine crystal packing or vice versa? We show herein that the flexible conformations of **1** result in different crystal packing arrangements through the hydrogen bond synthons and graph set patterns listed in Table 1. The chemical basis for the simultaneous occurrence of conformational polymorphism and concomitant polymorphism is that the energy scale of these two events are comparable ($1\text{--}2\text{ kcal mol}^{-1}$). The difference between the two extreme values of Z' ($\Delta Z' = 11$) in tetramorphs of **1** is the highest known to date.^[21] Despite the presence of different Laue symmetries, there is no compromise in crystal compactness because the density of these forms is about the same ($1.23\text{--}1.25\text{ g cm}^{-3}$).

To conclude, polymorphism in compound **1** is significant for several reasons. This is the first example of four polymorphs with 19 crystallographically independent conformations of the same molecule to be characterized by low-temperature X-ray diffraction. Such systems may serve as an accurate benchmark for the refinement of atom–atom potentials in crystal structure prediction programs.^[22] In addition to being an example of conformational polymorphism, **1** also exhibits conformational isomorphism (forms **B**, **C**, and **D**) and concomitant polymorphism (forms **A**, **B**, and **C**). Further studies on temperature- or pressure-mediated phase transition, kinetic and thermodynamic measurements, and molecular and lattice energies as well as the search for new polymorphs^[23] and characterization of their morphology are the focus of continuing experiments with **1**.

Experimental Section

Compound **1**^[24] was crystallized from EtOAc/*n*-hexane (5/95) at ambient temperature. Three types of morphologies were observed: needle, block, and plate. The needle-shaped crystals correspond to the **A** polymorph as verified by the space group determination of ca. 10 different crystals. Forms **B** and **C** crystallize concomitantly with **A** from the same flask. Crystals of form **D** were obtained by adding CH_2Cl_2 to the above solvent system. The experimental powder X-ray diffraction trace of the bulk material matches with the simulated trace of the monoclinic form **A**^[10] (see the Supporting Information).

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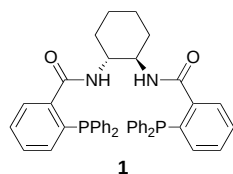
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Heterogeneous Pd-Catalyzed Asymmetric Allylic Substitution Using Resin-Supported Trost-Type Bisphosphane Ligands**

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For economic, environmental, and social reasons, the trend towards the application of optically pure compounds is undoubtedly increasing. Among the various methods to produce single enantiomers, asymmetric catalysis is one of the most attractive from the atom-economic point of view of.^[1] Over the last thirty years, numerous catalytic reactions allowing the enantioselective formation of C–H, C–C, C–O, C–N, and other bonds have been discovered. A number of homogeneous chiral catalysts have gained wide acceptance owing to their efficiency and selectivity, and some of them are even used on an industrial scale.^[2] However, in spite of the huge amount of work devoted to this subject in both academic and industrial fields, the contribution of asymmetric catalysis in the overall production of chiral chemicals is much lower than originally expected. One of the major drawbacks of homogeneous catalysis is the need for separating the relatively expensive catalysts from the reaction mixture at the end of the process. One of the most promising solutions to this problem seems to be the anchoring of effective soluble catalytic systems to an insoluble matrix, ideally without any reduction of catalytic performance with respect to the homogeneous phase.^[3]

In our continuing effort to develop efficient heterogeneous chiral catalysts,^[4] we became interested in the immobilization of Trost-type bisphosphane ligands such as **1**, which have proven to be extremely useful in palladium(0)-catalyzed asymmetric allylic substitutions.^[5] In spite of the versatility of this class of chiral ligands, the catalytic system provides relatively low turnover numbers and frequencies, and both ligand **1** itself and palladium are quite expensive. Thus, it would be highly desirable to develop heterogeneous analogues that could be

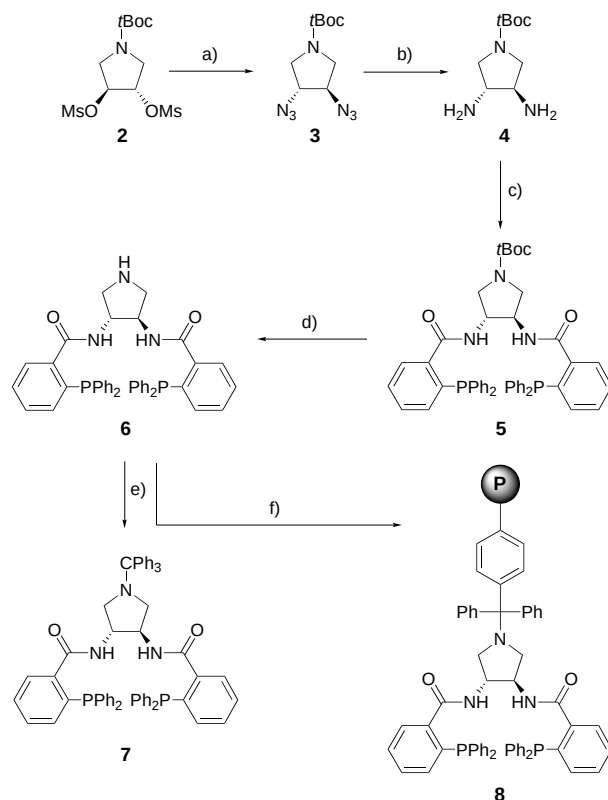


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readily recovered from the reaction mixture and offer the possibility of reusing both components. Surprisingly, to the best of our knowledge, there has been no report so far on the use of a heterogeneous analogue of ligand **1** for asymmetric allylic substitutions.^[6]

We present here the supported bisphosphane ligands **8a** and **8b**, which are polymeric analogues of the Trost-type ligand **1** and exhibit excellent activity and enantioselectivity (up to 99% *ee*) in Pd-catalyzed desymmetrization reactions. These ligands can be reused for consecutive reactions without any further addition of a Pd source. The immobilized ligands **8** were designed with the following criteria: 1) The molecular structure of the monomeric moiety should mimic precisely the optimum structure of ligand **1**; 2) the monomeric moiety should be attached by a single flexible linkage to the polymer support to minimize detrimental changes in the conformational preference of the reactant–catalyst intermediates; and 3) the morphology of the resin should be such that no limitation on mass transfer arises, with all active sites freely accessible.

The polymeric ligands **8** and their homogeneous analogue **7** were synthesized by the route depicted in Scheme 1. The



8a: Polystyrene-based resin (0.152 mmol g^{−1})
8b: JandaJEL (0.174 mmol g^{−1})

Scheme 1. Synthesis of the polymer-bound ligands **8**. a) NaN₃, DMF, 85 °C, 24 h, 78%; b) 10% Pd/C, H₂ (50 psi), MeOH, 99%; c) DPPBA, DCC, DMAP, CH₂Cl₂, RT, 24 h, 70%; d) BF₃·Et₂O, CH₂Cl₂, 0 °C → RT, 1 h, 98%; e) trityl chloride, Et₃N, DMAP, CH₂Cl₂, RT, 1 h, 96%; f) polymer-bound triphenylchloromethane (cross-linked with 1% DVB) for **8a** or JandaJEL trityl chloride for **8b**, Et₃N, DMAP, CH₂Cl₂, RT, 14 h. Boc = *tert*-butoxycarbonyl, DCC = dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, DPPBA = 2-diphenylphosphanylbenzoic acid, DVB = divinylbenzene, Ms = methanesulfonyl.

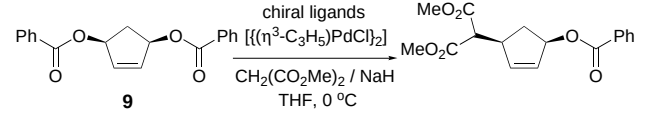
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catalytic reduction of *N*-*t*Boc-(3*R*,4*R*)-3,4-diazidopyrrolidine (**3**), which was obtained by azide substitution of *N*-Boc-(3*S*,4*S*)-3,4-bis(methanesulfonyloxy)pyrrolidine (**2**),^[7] followed by reaction of the resulting diaminopyrrolidine **4** with 2-diphenylphosphanylbenzoic acid (DPPBA) in the presence of dicyclohexylcarbodiimide (DCC) afforded the monomeric moiety **5**. After deprotection^[8] of the *t*Boc group of **5** with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in CH_2Cl_2 , the resulting monomeric ligand **6** was allowed to react with polystyrene-based trityl chloride resin^[9] and JandaJEL trityl chloride^[10] in the presence of triethylamine in dichloromethane to give the pale yellow polymeric ligands **8a** and **8b**, respectively. The trityl chloride is relatively inert to the formation of the phosphonium salt during the anchoring of **6** to the polymer support. The polymeric chloride moieties that remained were capped with methoxy groups^[11] (see the Experimental Section). Nitrogen analysis of **8a** and **8b** indicated that 0.152 and 0.174 mmol g⁻¹ of the monomeric moiety **6** were incorporated, respectively. To compare the catalytic efficiency in homogeneous and heterogeneous reactions, the homogeneous analogue **7** was also prepared by the reaction of **6** with trityl chloride.^[12]

The catalytic efficiency of the polymeric ligands **8** was examined with the Pd-catalyzed desymmetrization^[13] of *cis*-1,4-bis(benzoyloxy)cyclopent-2-ene (**9**) with dimethylmalonate nucleophile (Table 1) and the intramolecular cyclization

Table 1. Results of the Pd-catalyzed desymmetrization of **9** with dimethylmalonate nucleophile.^[a]

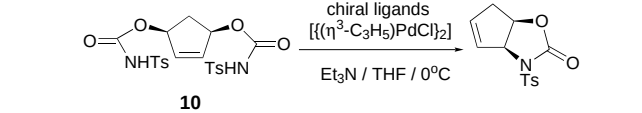
					
Entry	Ligand	Time	Yield [%] ^[b]	<i>ee</i> [%] ^[c]	Config.
1	7	1 h	98	98	1 <i>S</i> ,4 <i>R</i>
2	8a	15 h	73	84	1 <i>S</i> ,4 <i>R</i>
3	8b	30 min	98	96	1 <i>S</i> ,4 <i>R</i>

[a] All reactions were carried out on a 0.2-mmol scale based on substrate **9** at 0 °C. The molar ratio of $[(\eta^3\text{-C}_3\text{H}_5)\text{PdCl}]_2$:ligand:**9**:NaH(95%):dimethylmalonate was 0.025:0.15:1:1.8:1.5. [b] Yields of isolated product. [c] Determined by HPLC using Chiralcel OJ column with *i*PrOH/hexane (15/85), flow rate: 1.0 mL min⁻¹; elution times: 15.8 min (1*S*,4*R*), 21.5 min (1*R*,4*S*).

of biscarbamate **10** (Table 2). The catalytic activity and enantioselectivity of the monomeric analogue **7** was first investigated as a control experiment. We were pleased to find that this ligand showed high activity and enantioselectivity (up to 99% *ee*) in the Pd-catalyzed desymmetrization reactions of **9** and **10** (entry 1, Tables 1 and 2). This result indicates that the homochiral pyrrolidine diamine moiety is an appropriate chiral scaffold for the catalyst.

With these results in hand, we turned to studying polymer-bound **8a** and **8b**. The activity and enantioselectivity of the polystyrene-based catalyst **8a** (entry 2, Tables 1 and 2) were slightly lower than those obtained with **7**. However, the JandaJEL-based catalyst **8b** (entry 3, Tables 1 and 2) was nearly as effective (up to 99% *ee*) as **7**. The JandaJEL resin is a polystyrene resin containing flexible tetrahydrofuran-derived cross-linkers, and is therefore reported to swell much better

Table 2. Results of the Pd-catalyzed intramolecular cyclization of biscarbamate **10**.^[a]

					
Entry	Ligand	Time [min]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]	Config.
1	7	20	99	99	1 <i>S</i> ,4 <i>R</i>
2	8a	30	98	97.5	1 <i>S</i> ,4 <i>R</i>
3	8b	20	99	99	1 <i>S</i> ,4 <i>R</i>
4 ^[d]	8b	20	99	98.2	1 <i>S</i> ,4 <i>R</i>
5 ^[d]	8b	40	99	97.7	1 <i>S</i> ,4 <i>R</i>
6 ^[d]	8b	60	99	97.1	1 <i>S</i> ,4 <i>R</i>
7 ^[d]	8b	180	95	94.7	1 <i>S</i> ,4 <i>R</i>

[a] All reactions were carried out on a 0.2-mmol scale based on biscarbamate **10** at 0 °C. The molar ratio of $[(\eta^3\text{-C}_3\text{H}_5)\text{PdCl}]_2$:ligand:**10**: NEt_3 was 0.025:0.075:1:1; Ts = *p*-toluenesulfonyl. [b] Yields of isolated product. [c] Determined by HPLC using Chiralpak AD column with *i*PrOH/heptane (15/85), flow rate: 1.0 mL min⁻¹; elution times: 24.4 min (1*S*,4*R*), 27.3 min (1*R*,4*S*). [d] The reaction was carried out with the **8b**-Pd complex recovered from the previous run without further addition of $[(\eta^3\text{-C}_3\text{H}_5)\text{PdCl}]_2$.

than Merrifield resin.^[14] This characteristic of the JandaJEL support is envisaged to give the bulky ligand greater degrees of freedom and, as a result, to act more like a homogeneous catalyst.

After the successful first run of the intramolecular cyclization of **10** (entry 3, Table 2), the reaction mixture was filtered off under an argon atmosphere and the catalyst-resin complex was rinsed with dry THF (3 × 5 mL). The ³¹P NMR spectrum of the recovered orange resin showed a signal at $\delta = +26.0$ ppm (85% H_3PO_4 external reference). This remarkable downfield shift indicates that the phosphanyl group of **8b** in the recovered resin is coordinated to palladium. Finally, the recovered Pd complex of **8b** was subjected to further catalytic reactions without any further addition of a Pd source. The recovered catalyst could be recycled with only a slight loss in activity and enantioselectivity (from 99% *ee* in the first run to 94.7% *ee* in the fifth run; entries 3–7, Table 2). These results demonstrate that in addition to highly facilitated workup procedures, the JandaJEL-bound catalyst **8b** offers the advantage of easy recovery and reutilization in consecutive heterogeneous asymmetric desymmetrization reactions.

In summary, we have prepared a promising class of polymer-bound chiral ligands for heterogeneous asymmetric allylic substitution reactions. In particular, the JandaJEL-bound ligand **8b** exhibited excellent activity and enantioselectivity in Pd-catalyzed asymmetric desymmetrizations. To the best of our knowledge, this is the first successful work on heterogeneous asymmetric desymmetrization reactions in which Trost-type ligands were used. Studies to optimize the reaction conditions for continuous processing are currently in progress.

Experimental Section

8b: Compound **6** (288.7 mg, 0.426 mmol) and Et_3N (89 μL , 0.639 mmol) were added to a suspension of polymer-bound triphenylchloromethane (JandaJEL; 2.0 g, 1.42 mmol) in CH_2Cl_2 (50 mL), and the mixture was stirred at ambient temperature for 14 h under a nitrogen atmosphere. The resin was filtered and washed with CH_2Cl_2 (160 mL), water (150 mL), and

methanol (200 mL) and then dried under vacuum. To cap the unchanged chloride moieties with methoxy groups, the resin was stirred for 15 min in CH_2Cl_2 /methanol (1/1, v/v; 15 mL) containing an excess of Et_3N (383 μL , 2.75 mmol). The resin was filtered and washed with CH_2Cl_2 (50 mL), water (150 mL), and methanol (200 mL). To remove any traces of unchanged chiral monomer **6** in the resin, **8b** was then continuously extracted in a Soxhlet device with THF for 24 h and dried under vacuum. Solid-state ^{31}P NMR (85% H_3PO_4 external reference): $\delta = -11.6$ ppm (brs).

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Noncovalent Chemistry of Nitrous Oxide: Interactions with Secondary *cis* Amides in Solution**

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The environmental impact of nitrous oxide (N_2O) is enormous. As one of the most abundant components of the atmosphere, N_2O plays a critical role in the destruction of the ozone layer and contributes to the greenhouse effect.^[1] Emission of N_2O into the atmosphere has already reached 13 million tons and is constantly growing. The widespread use of nitrogen-containing fertilizers and the industrial manufacture of nylon are critical contributors to this amount. The major natural suppliers of N_2O are enzyme-supported nitrification/denitrification processes in soils in which this gas is the key intermediate.^[2] N_2O is also involved in a number of biochemical processes, especially related to anesthesia.^[3] Together with O_2 and CO , N_2O belongs to the family of blood gases.

The chemistry of N_2O is limited, although it is considered to be a reliable and nontoxic source of oxygen for catalysis.^[4] It is commonly known as a noncoordinating gas and as a very poor ligand. Although several metal complexes react with N_2O , $[\text{Ru}(\text{NH}_3)_5(\text{N}_2\text{O})]^{2+}$ is the *only* characterized complex to date.^[5]

The rules governing reversible interactions between N_2O and various receptor sites, which usually precede the covalent fixation and are also responsible for the biochemical action, are still poorly understood. We report herein the previously unnoticed noncovalent interactions between secondary amides and N_2O in apolar solutions. N_2O frequently circulates in biological fluids,^[2,3] and its rather weak dipole–dipole interactions with hydrophobic fragments of proteins has been noticed.^[6] At the same time, the possibility of its involvement in hydrogen bonding with proteins and enzymes has been routinely ignored.

Hydrogen bonding is one of the most important forces in Nature and is responsible for self-assembly and enzyme selectivity.^[7] In chemistry, it has been used in the design of effective receptors for polar neutral molecules and anions in the gas phase, in solution, and in the solid state.^[8] Molecules of gases are known to form hydrogen bonds in the gas phase. Among the typical examples are the adducts of acidic HF, HCl, HBr, and HCN with N_2 , CO , CO_2 , and OCS ,^[9] and weak $\text{PhOH}\cdots\text{Ar}$ (N_2 , CO) molecular clusters.^[10] At the same time,

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surprisingly little is known about hydrogen bonding with gases in solution. Nature employs hydrogen bonds for the complexation of blood gases by heme proteins.^[11] In the crystal structures, the amino acid residues on the distal porphyrin face of hemoglobin and myoglobin are seen in close proximity to the metal-bound O₂, thus indicating their involvement in hydrogen bonding with O₂. Surprisingly, solution spectroscopic studies with hemes and their synthetic models only very recently confirmed such hydrogen bonding.^[12,13]

We found that secondary *cis* amides interact with N₂O in apolar solutions, but *trans* amides do not. Whereas the ¹H NMR spectra of a number of alkyl and aryl *trans* amides^[14] remained unchanged upon saturation with N₂O (in CDCl₃), ϵ -caprolactam **1** (a typical *cis* amide) exhibited modest but reproducible complexation-induced spectral changes. Specifically, upon saturation of a 5×10^{-2} M CDCl₃ solution of ϵ -caprolactam **1** with N₂O,^[15] the singlet assigned to NH shifted from $\delta = 6.31$ ppm to $\delta = 6.08$ ppm ($\Delta\delta = 0.23$, 295 ± 2 K) (Figure 1). Similar shifts were obtained upon addition of H₂O, a hydrogen-bonding solvent: the signal for NH shifted from $\delta = 6.31$ ppm to $\delta = 6.05$ ppm ($\Delta\delta = 0.26$, 295 ± 2 K). In [D₆]benzene, the singlet for NH shifted from $\delta = 8.20$ ppm to $\delta = 7.95$ ppm ($\Delta\delta = 0.25$) upon saturation with N₂O. These modest but reproducible shift changes imply N–H...N₂O bonding. Caprolactam (**1**) is a self-complementary molecule and weakly aggregates in CDCl₃ solution with a dimerization constant (*K_D*) of ~ 3 M⁻¹.^[16] Apparently, interaction with N₂O (and H₂O) introduced a new equilibrium into the system and interrupted the self-association.^[17]

Secondary *cis* amides are generally not synthetically available, but some exceptions are known. We prepared the hindered amide, *N*-(*n*-octanoyl)-2,4,6-tri-*tert*-butylaniline (**2**),^[18] which exists as an equilibrated mixture of two stereoisomers (*E*)-**2** and (*Z*)-**2** (inseparable under standard conditions), with *cis* and *trans* amide group arrangements, respectively.^[19] These have two distinct ¹H NMR spectra and thus offer a unique opportunity to compare them simultaneously upon interaction with N₂O.

The (*E*)-**2**/(*Z*)-**2** ratio is $\sim 1:8$ at 295 ± 2 K in CDCl₃ and [D₆]benzene. Two bulky *t*Bu groups in *ortho* positions to the NH–C(O) fragment place the amide group perpendicular to the plane of the benzene ring. The steric hindrances block the C=O oxygen atom and prevents self-aggregation of the (*Z*)-**2** amide group. In contrast to typical secondary amides, the singlet for the NH group of (*Z*)-**2** remains concentration-independent within 2×10^{-1} – 1×10^{-3} M range. In the (*E*)-**2** amide group, the carbonyl oxygen atom and the NH group are not shielded; the signal for NH is concentration-sensitive as a result of self-aggregation.^[20]

A solution of amide (*Z*)-**2** produced no visible changes in the ¹H NMR spectrum upon saturation with N₂O, but amide (*E*)-**2** appeared to interact with N₂O (Scheme 1, Figure 2). Upon saturation of the 3×10^{-2} M solution of (*E*)-**2** with the gas, the NH singlet shifted from $\delta = 7.04$ ppm to $\delta =$

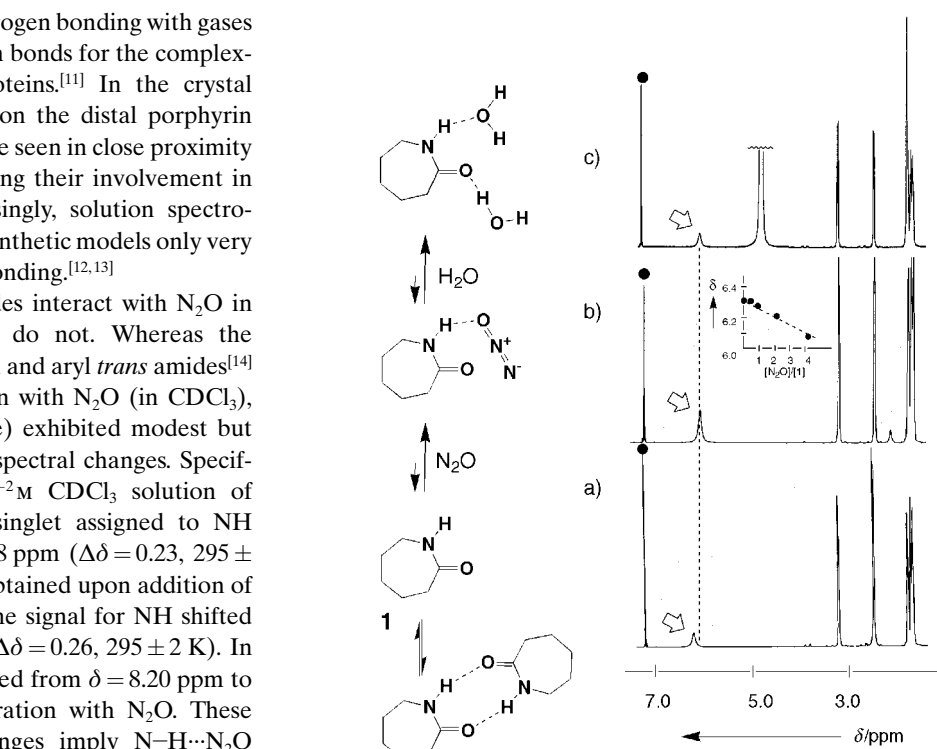
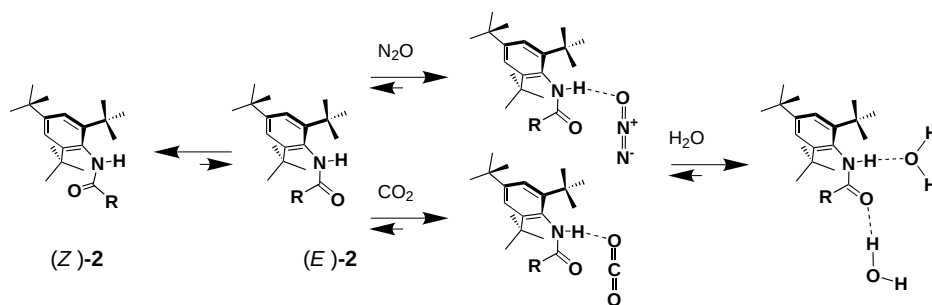


Figure 1. Complexation-induced changes in the ¹H NMR spectrum (500 MHz, CDCl₃, 295 ± 2 K) of ϵ -caprolactam **1**: a) solution of **1**, 5×10^{-2} M; b) same, after saturation with N₂O; c) same, after saturation with H₂O. In two independent experiments, saturation of both **1** and **1**:N₂O solutions with H₂O gave identical spectra. An arrow marks the NH signal. The residual CHCl₃ signal is marked ●.

6.81 ppm ($\Delta\delta = 0.23$, 295 ± 2 K). Upon saturation of the same solution with H₂O, the singlet for NH shifted to $\delta = 6.76$ ppm ($\Delta\delta = 0.28$, 295 ± 2 K).

The rational explanation of the binding events and the differences between *cis* and *trans* amides may be obtained from molecular modeling, ab initio and semi-empirical calculations,^[21] and the limited literature data on the gas-phase noncovalent aggregates of N₂O.^[22] A complementary receptor site for N₂O should contain both a hydrogen donor and an acceptor separated by ~ 2 Å, and the *cis* amide HN–C=O fragment satisfies such a requirement (Figure 3).

Cis amides exhibit amphiphilic properties in both dipolar and hydrogen-bonding interactions. The C=O oxygen atoms are dipole donors and hydrogen acceptors, whereas the NH groups are dipole acceptors and hydrogen donors. Ab initio, MP2/6-31 + G* calculations of the complex between simple



Scheme 1. Complexation of N₂O, CO₂, and H₂O by *cis* amide (*E*)-**2**.

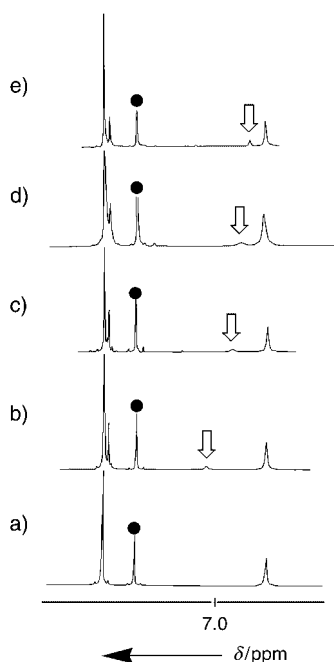


Figure 2. Complexation-induced changes in the ^1H NMR spectrum (500 MHz, CDCl_3 , 295 ± 2 K) of amides **2** at 3×10^{-2} M: a) (*Z*)-**2** obtained immediately after dissolution; b) a mixture of (*Z*)-**2** and (*E*)-**2** (8:1), equilibrated over 20 h; c) solution of (*Z*)-**2** and (*E*)-**2** after saturation with N_2O ; d) solution of (*Z*)-**2** and (*E*)-**2** after saturation with CO_2 ; e) solution of (*Z*)-**2** and (*E*)-**2** after saturation with H_2O . The signal for the NH proton of the (*E*)-**2** amide is marked by an arrow. The signal for NH of the (*Z*)-**2** amide is at $\delta = 6.66$ ppm. Both singlets for the aromatic H atoms ($\sim 8:1$ ratio) are situated at $\delta \sim 7.4$ ppm. The residual CHCl_3 signal is marked $\bullet$.

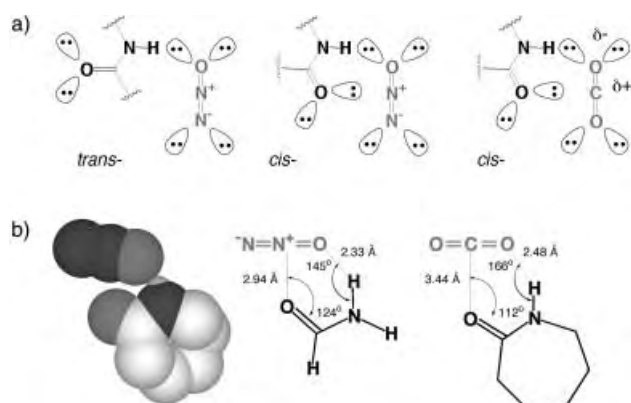


Figure 3. a) Proposed binding motif between a secondary *cis* amide and N_2O and CO_2 . b) Computer-generated structures of: **1**· N_2O (PM3), $\text{H-C(O)-NH}_2\cdot\text{CO}_2$ (MP2/6-31+G*), and **1**· CO_2 (MP2/6-31+G*). The CH hydrogen atoms and long alkyl chains are omitted for clarity.

formamide (HC(O)-NH_2 , which possesses a *cis* amide arrangement) and N_2O indicates that a hydrogen bond is possible between the amide N–H hydrogen atom (+0.43 e) and the partially negatively charged (−0.62 e) oxygen atom of the gas molecule. The $\text{N-H}\cdots\text{O}=\text{N}^+=\text{N}^-$ distance is 2.33 Å, and the $\text{N-H}\cdots\text{O}$ and $\text{N}^+=\text{O}\cdots\text{H}$ angles are 145° and 119°, respectively (Figure 3). This places the basic C=O oxygen atom of the amide group (−0.58 e) directly in front of the central, electron-deficient nitrogen (+0.68 e) of the N_2O molecule. There is an electrostatic attraction between the

former lone pair and the latter partial positive charge. The $\text{C=O}\cdots\text{N}^+$ distance is 2.94 Å, and the $\text{C=O}\cdots\text{N}^+$ angle is 124°. Taken together, a two-point noncovalent interaction occurs. Semi-empirical, PM3 calculations with caprolactam (**1**) and N_2O gave similar results. The $\text{C=O}\cdots\text{N}^+$ distance appeared to be 3.26 Å, and the $\text{C=O}\cdots\text{N}^+$ angle is 128°. The $\text{N-H}\cdots\text{O}=\text{N}^+=\text{N}^-$ distance is 1.9 Å, and the $\text{N-H}\cdots\text{O}$ angle is 165°.

As saturation with N_2O interrupts dimerization of *cis* amides ($K_D = 5 \text{ M}^{-1}$), this sets the lower limit for the described N_2O complexation to be $\Delta G^{295} \sim 0.9 \text{ kcal mol}^{-1}$, which is typical for weak interactions in apolar solutions. This estimate was further confirmed by dilution experiments with amides **1** and (*E*)-**2**, and N_2O in CDCl_3 . The association constant values of $K_{\text{ass}} = 5 \pm 3 \text{ M}^{-1}$ were obtained for 1:1 complexes **1**· N_2O and (*E*)-**2**· N_2O ; $\Delta G^{295} = 0.8 \pm 0.4 \text{ kcal mol}^{-1}$.^[23,24]

Similar conclusions can be drawn from the modeling and calculations with CO_2 , which is isoelectronic with N_2O (Figure 3). Indeed, we confirmed this experimentally. When the 3×10^{-2} M solution of (*E*)-**2** amide was saturated with CO_2 , the NH singlet shifted from $\delta = 7.04$ ppm to $\delta = 6.77$ ppm ($\Delta\delta = 0.27$, 295 ± 2 K). Neither amide (*Z*)-**2** nor any other *trans* amides interacted with CO_2 .^[25,26]

Addition of H_2O to the CDCl_3 solutions of complexes **1**· N_2O , (*E*)-**2**· N_2O and also (*E*)-**2**· CO_2 destroyed them, and the formation of **1**· H_2O and (*E*)-**2**· H_2O species was clearly observed (for example, Figure 2e). The latter complexes were also independently obtained upon addition of H_2O to the CDCl_3 solutions of **1** and (*E*)-**2**.

In conclusion, noncovalent interactions between *cis* amides and N_2O (and CO_2) have been detected in apolar solutions for the first time. It is proposed that both hydrogen bonding and electrostatic interactions play a role in the binding event. This finding opens novel possibilities to construct receptors, sensors, and membranes for N_2O (and CO_2) that are based on the molecular recognition principles. Synthesis of fluorescent and UV/vis-active hydrogen-bonding receptors for N_2O , and also *cis*-amide-functionalized catalytic systems for its chemical fixation is underway. In the meantime we are also looking at the complexation between *cis* peptide bonds and N_2O in biological systems. In the absence of strong self-aggregation and competing water molecules, such interactions could be responsible for a certain biological activity of this important gas.

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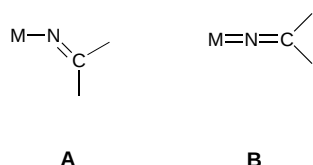
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- [15] In a typical procedure, N_2O vapor was passed through the NMR samples for 2 h at 295 ± 2 K. To compensate for losses caused by evaporation, the solvent level was adjusted with CDCl_3 saturated with N_2O . The ^1H NMR spectra were recorded immediately and also after standing for 12, 24, and 48 h. All experiments were performed at least in triplicate. The solubility of N_2O in CHCl_3 is 2.2×10^{-1} M at 293 K; see: W. Gerrard, *Solubility of Gases and Liquids*, Plenum, New York, **1976**, chap. 8. Commercial CDCl_3 was used in all experiments. Saturation of CDCl_3 with N_2 prior to measurements did not affect the reported chemical shifts. Solubility of N_2 in CDCl_3 is 6×10^{-3} M.
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- [18] **2**: *n*-Octanoyl chloride (1.1 mmol) was added to a magnetically stirred solution of 2,4,6-tri-*tert*-butylaniline (0.26 g, 1 mmol) and a catalytic amount of DMAP in pyridine (10 mL). The reaction mixture was heated at reflux for 48 h, cooled down, and poured onto ice water (50–100 mL). The pH value was adjusted to 2, and the product was extracted with EtOAc (3×50 mL). The organic layer was washed twice with water, then with brine, dried over Na_2SO_4 , and evaporated under reduced pressure. The residue was treated with hexanes (40 mL), and the formed precipitate was filtered off, washed with hexane, and dried. Upon dissolving in CDCl_3 , exclusively (*Z*)-**2** isomer is detected by NMR spectroscopy, which slowly equilibrates over 12 h. (*Z*)-**2** (*trans*-isomer): yield 60%; mp 240°C (hexane); ^1H NMR (500 MHz, CDCl_3 , 25°C , TMS): $\delta = 7.39$ (s, 2H; arom), 6.66 (br s, 1H; NH), 2.35–2.4 (m, 2H; CH_2), 1.7–1.8 (m, 2H; CH_2), 1.38 (s, 2×9 H; CH_3), 1.3–1.4 (m, 10H; CH_2), 1.29 (s, 9H; CH_3), 0.88 ppm (t, $^3J(\text{H,H}) = 6.8$ Hz, 3H; CH_3); ^{13}C NMR (CDCl_3): $\delta = 172.9$, 149.5, 148.3, 130.9, 123.3, 38.1, 36.4, 35.1, 32.1, 31.8, 31.5, 29.7, 29.1, 25.1, 22.7, 14.2 ppm; MS (EI): m/z [$M - t\text{Bu}$] $^+$: calcd: 330.5; found: 330.3. (*E*)-**2** (*cis*-isomer): ^1H NMR (CDCl_3): $\delta = 7.38$ (s, 2H; arom), 7.04 (br s, 1H; NH), 2.3–2.35 (m, 2H; CH_2), 1.38 (s, 2×9 H; CH_3), 1.3–1.4 (m, 10H; CH_2), 1.17 (s, 9H; CH_3), 0.82 ppm (t, $^3J(\text{H,H}) = 6.9$ Hz, 3H; CH_3). Experiments with gases were performed only after the equilibration.
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- [20] Upon dilution of (*E*)-**2** from 2×10^{-1} M to 3×10^{-3} M, the singlet for the NH group shifted upfield from $\delta = 8.1$ ppm to $\delta = 6.8$ ppm, with significant broadening; the dimerization constant of $K_D \sim 5\text{ M}^{-1}$ was obtained.
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- [24] Preliminary binding studies were performed at 295 ± 2 K with a constant concentration of amides **1** (5×10^{-2} M) and (*E*)-**2** (3×10^{-2} M) and varied (0 – 2×10^{-1} M) concentration of N_2O . The association constants were estimated from the changes in the chemical shifts for the amide NH at different concentrations of N_2O considering $\sim 20\%$ loss of the amide concentration as a result of dimerization. Nonlinear regression gave a fit for a 1:1 model. Detailed thermodynamic studies will be published in a full paper.
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- [26] The Lewis basic C=O group is known as a “ CO_2 -phile”. While this manuscript was under review, the two-point interaction between sugar acetates and CO_2 was proposed, which involved both the acetate C=O $\cdots\text{CO}_2$ electrostatic interactions and C–H $\cdots\text{O}_2\text{C}$ hydrogen bonding; see: P. Raveendran, S. L. Wallen, *J. Am. Chem. Soc.* **2002**, *124*, 7274–7275.

Insertion and Cycloaddition Reactivity of a Transition-Metal *N*-Metalloimine**

Eva Hevia, Julio Pérez,* Víctor Riera, and Daniel Miguel

Dedicated to Professor Maurice Brookhart on the occasion of his 60th birthday

The presence of electron-releasing main-group-metal substituents on the nitrogen atom increases the reactivity of imines **A** towards dipolar reagents such as isocyanates^[1] and ketenes.^[2] We speculated that, in addition to this inductive



effect, a low-oxidation transition-metal substituent would contribute a destabilizing interaction between the lone pair on the nitrogen atom and the filled metal d orbitals.^[3]

However, all structurally characterized $M(N=CR_2)$ complexes have essentially linear M-N-C geometries^[4] as a result of π donation of the lone pair on the nitrogen atom to empty metal orbitals. Thus, these azavinylidene^[5] complexes **B** are more related to alkylideneammonium cations than to imines.^[6]

Herein we report the synthesis, structure, and a preliminary account of the reactivity of an *N*-metalloimine (type **A**) which contains a transition-metal fragment.

The reaction of $KN=CPh_2$ with $[Re(OTf)(CO)_3(bpy)]$ ($bpy = 2,2'$ -bipyridine) afforded the complex $[Re(N=CPh_2)(CO)_3(bpy)]$ (**1**), which was characterized spectroscopically and by X-ray diffraction (Figure 1a). For comparison, the structure of the imine complex $[Re(HN=CPh_2)(CO)_3(bpy)]^+$ (**2**), synthesized as its triflate salt by reaction of **1** with HOTf, was also determined (Figure 1b). The Re-N-C angle ($133.9(4)^\circ$) for the alkylideneamido group of **1**, even smaller than the Re-N-C angle ($138.9(2)^\circ$) of **2**, indicates the absence of N-to-Re π donation. The larger deviations from linearity in previously known azavinylidene complexes ($152.9(4)^\circ$ and $157.2(4)^\circ$ for $[OsCl(=N=CMe_2)(=CCH_3)(P^iPr_3)_2][OTf]$ ^[7] and $[OsCl(=N=CMe_2)(=CHPh)(P^iPr_3)_2]$ ^[8] respectively) can be related to the presence of bulky ancillary ligands, whereas such effects are absent in **1**. The Re-N CPh_2 distance ($2.113(4)$ Å) in **1** is comparable to the Re-N(H) CPh_2 distance

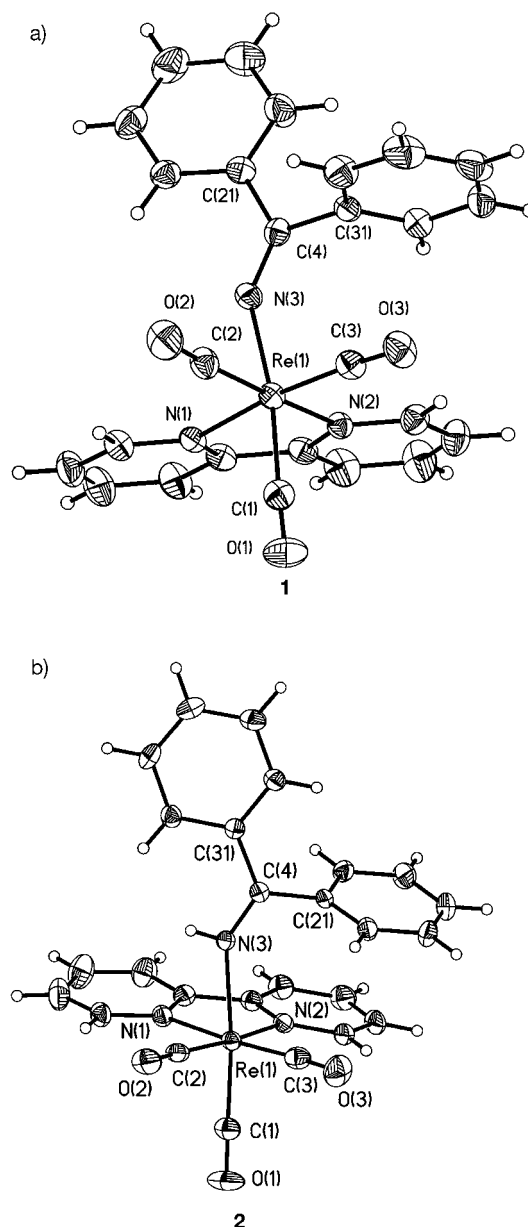


Figure 1. Thermal ellipsoid (30%) plots of **1** (a) and **2** (b). See Supporting Information for further details.

($2.192(3)$ Å) in **2**, which is in agreement with the lack of multiple-bond character of the Re-N bond.^[9]

Despite the structural similarity, the spectroscopic data of **1** and **2** are very different. Values of ν_{CO} even lower than those found for the related alkoxo^[10] and amido^[11] complexes reflect the strongly donor character of the alkylideneamido ligand in the neutral complex **1**, whereas the higher wavenumbers of **2** are consistent with its cationic nature. ^{13}C NMR spectroscopy data indicate that the two phenyl groups of **1** are equivalent. Given the angular geometry of the alkylideneamido group, this should result from a fast exchange of the position of the metal atom between the two electron pairs at the alkylideneamido nitrogen atom.^[12]

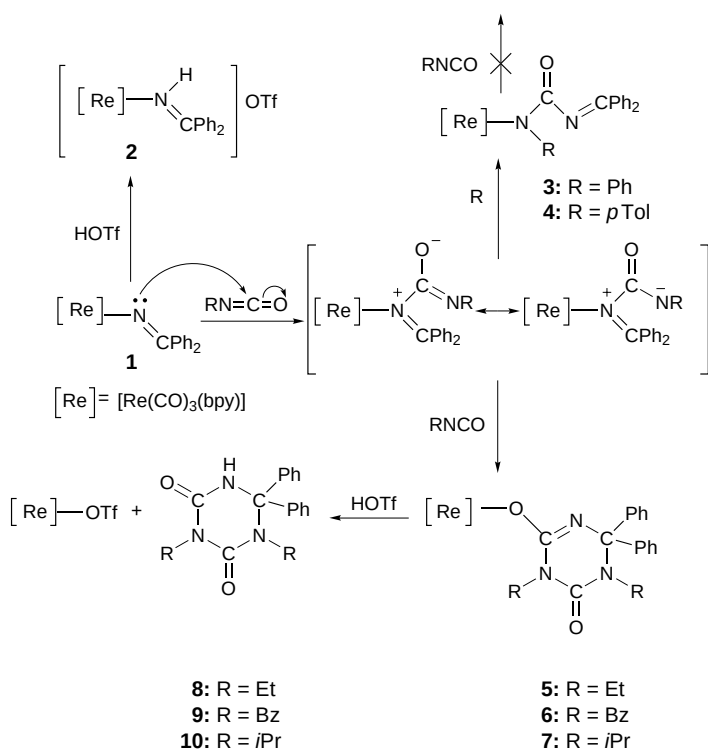
Complex **1** acts as a nucleophile towards isocyanates. Thus, its reactions with $RNCO$ ($R = Ph, pTol$; Scheme 1) afford the products (**3** and **4**, respectively) of formal isocyanate insertion

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

Scheme 1. Reaction of complex **1** as a nucleophile with isocyanates

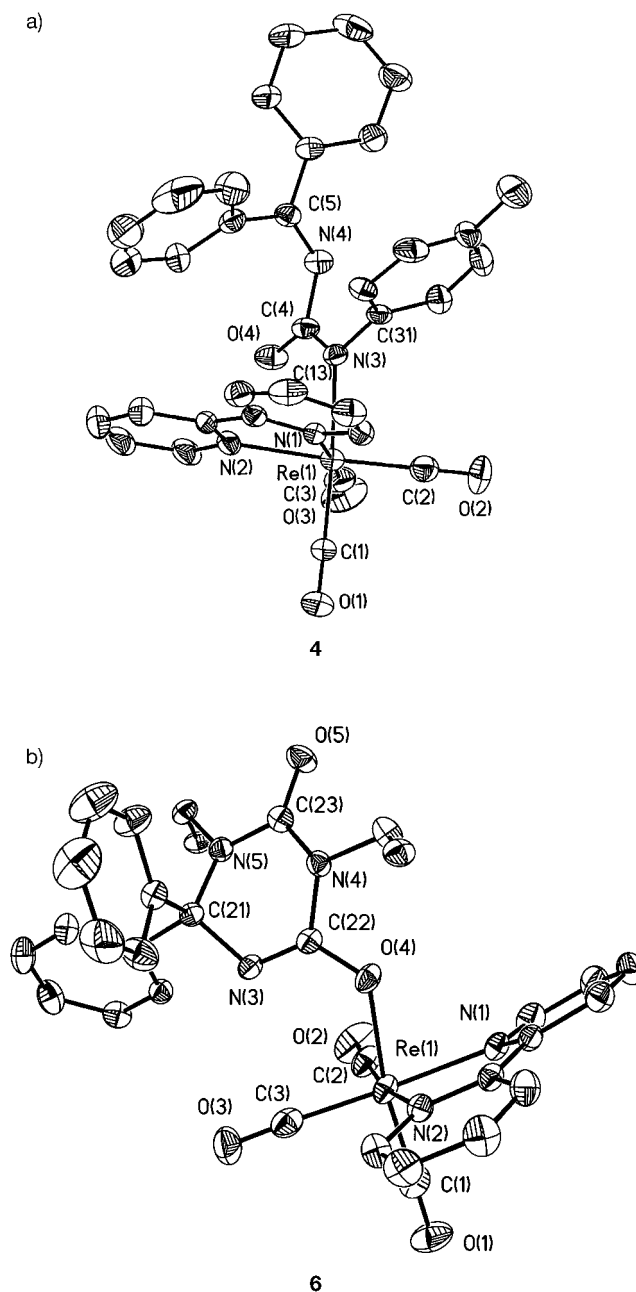
into the Re–N bond, as confirmed by an X-ray crystal structure determination of **4** (Figure 2a). This parallels the proposed first step of the reactions of isocyanates towards either late-transition-metal nucleophilic amido complexes^[13] or N-silylimines.^[1,14] The rhenamine **1** is more reactive than N-silylimines; the reaction with arylisocyanates, instantaneous at room temperature with **1**, takes 8 h with $\text{Me}_3\text{SiN}=\text{C}(\text{H})\text{Ph}$.^[1]

Complex **1** reacts with 2 equivalents of alkylisocyanates, as shown in Scheme 1. The products (**5**, **6**, and **7**) were characterized spectroscopically and (for **6**) by X-ray diffraction (see Figure 2b). The six-membered cyclic ligands present in **5–7** should result from [4+2] cycloaddition of a second molecule of RNCO to the 1,3-diaza-1,3-butadiene moiety formed in a previous step of formal RNCO insertion into the Re–N bond, similar to that leading to the formation of compounds **3–4**. Attempts to detect the proposed intermediate were unsuccessful, and only mixtures of **5–7** and unreacted **1** were obtained in the reaction of equimolar amounts of **1** and alkyl isocyanates.

Compounds **3** and **4** are unreactive (12 h in refluxing THF) towards either PhNCO or EtNCO. We suspect that the formation of the intermediate 1,3-azabutadiene required for the cycloaddition to take place is precluded for R = aryl by the stability of the Re–N species **3** and **4**.

The reactions of **5–7** with HOTf cleanly demetallate the 1,3,5-triazine-2,4-diones and allow an efficient recycling of the metal auxiliary as the triflate complex $[\text{Re}(\text{OTf})(\text{CO})_3(\text{bpy})]$ (Scheme 1).

In summary, we have unambiguously characterized a transition-metal N-metalloimine; that is, an alkylideneamido complex that is *not* an azavinylidene.^[15] Accordingly, the

Figure 2. Thermal ellipsoid (30%) plots of **4** (a) and **6** (b) (phenyl rings on the benzyl groups are omitted for clarity). See Supporting Information for further details.

nucleophilicity of the nitrogen atom dominates its reactivity. Studies of the reactivity of **1** towards ketenes are in progress in our laboratories.

Experimental Section

All manipulations were performed under a nitrogen atmosphere by using Schlenk techniques. Correct C, H, N analyses were obtained for all the new complexes. Full experimental details can be found in the Supporting Information. CCDC-184784–184787 contain the supplementary crystallographic data for the structures reported in this paper (**1**, **2**, **4**, and **6**, respectively). These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

1: A solution of $\text{K}[\text{NCPH}_2]$ (0.094 mmol) in THF (10 mL) was transferred to a solution of $[\text{Re}(\text{OTf})(\text{CO})_3(\text{bpy})]$ (0.050 g, 0.086 mmol) in THF (15 mL) at -78°C . The color changed from yellow to dark green. After reaching room temperature, 15 min stirring, solvent evaporation, extraction (CH_2Cl_2 , 2×10 mL), filtration, evaporation of the solvent, crystallization from THF/hexane yielded **1** in (0.045 g, 87%). IR (THF): $\tilde{\nu} = 1999$, 1898, 1880 cm^{-1} ; ^1H NMR (200 MHz, CD_2Cl_2): $\delta = 8.80$, 8.37, 8.11, 7.44 (m, 2H each; bpy), 7.24 (m, 6H; Ph), 6.96 ppm (m, 4H; Ph); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.46 MHz, CD_2Cl_2): $\delta = 158.10$ [$\text{N}=\text{C}$], 157.14, 155.30, 143.25 [bpy], 142.30, 128.94, 127.53, 126.14 [2Ph], 125.54, 121.79 ppm [bpy].

Reaction of 1 with pTolNCO: pTolNCO (9.0 μL , 0.082 mmol) was added to a solution of **1** (0.050 g, 0.082 mmol) in THF (15 mL). Evaporation of the solvent, followed by crystallization from CH_2Cl_2 /hexane yielded **4** (0.053 g, 87%). IR (CH_2Cl_2): $\tilde{\nu} = 2014$, 1913, 1887, 1716 cm^{-1} ($\text{C}=\text{O}$); ^1H NMR (200 MHz, CD_2Cl_2): $\delta = 8.80$, 8.74, 8.16 (m, 2H each; bpy), 7.54–7.05 (m, 24H; bipy, Ph), 6.66, 6.64, 6.51, 6.48 (qAA'BB', 4H; pTol), 2.05 ppm (s, 3H; CH_3 , pTol).

Reaction of 1 with BzNCO: BzNCO (20 μL , 0.164 mmol) was added to a solution of **1** (0.050 g, 0.082 mmol) in THF (15 mL) and the mixture was stirred for 15 min. Workup as for **4** afforded orange crystals of **6** (0.060 g, 84%). IR (THF): $\tilde{\nu} = 2019$, 1917, 1890, 1669, 1623 cm^{-1} ($\text{C}=\text{O}$ and $\text{C}=\text{N}$); ^1H NMR (200 MHz, CD_2Cl_2): $\delta = 8.83$, 7.84, 7.75 (m, 2H each; bpy), 7.39–6.79 (m, 44H; bpy, Bz, Ph), 4.49 (s, 2H, CH_2), 4.29 ppm (s, 2H; CH_2).

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An Iridaborane Reaction Cycle Driven by PMe_3 and $\text{BH}_3\cdot\text{THF}$: Synthesis and Characterization of $[\text{Cp}^*\text{IrB}_3\text{H}_7(\text{PMe}_3)]$ and $[\text{Cp}^*\text{IrB}_2\text{H}_6(\text{PMe}_3)]^{**}$

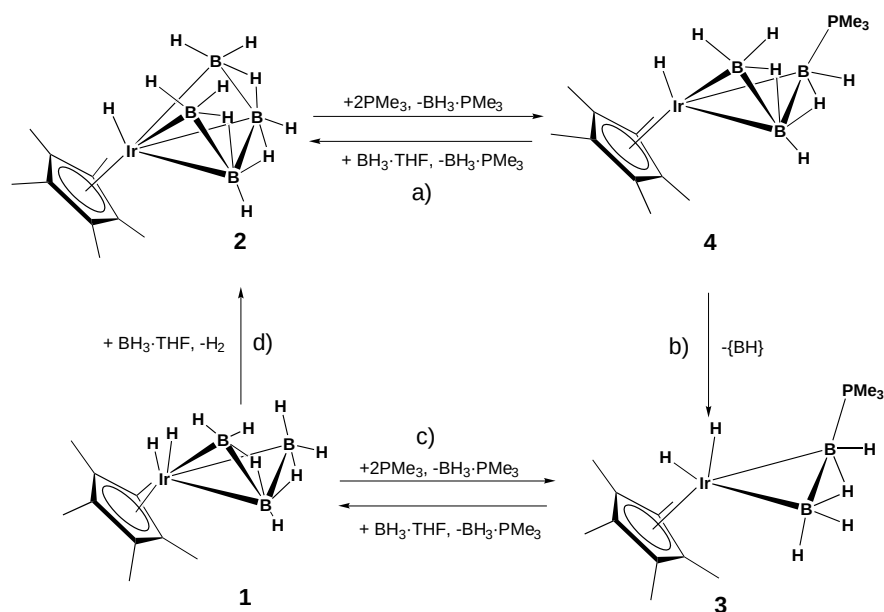
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Polyhedral boron-containing compounds show an extensive structural chemistry that exhibits clear interconnections with organometallic and other p-block transition-element compounds.^[1,2] However, until recently, limitations of synthetic methods have precluded systematic study of metallaboranes, and as a result their reactivity has remained largely unexplored relative to that of organometallic compounds.^[3–6] This changed significantly with the development of a general route to a class of metallaboranes in which the metal can be varied from Group 5–9.^[7] The results to date show that although metallaborane chemistry does overlap with organometallic chemistry, the former exhibits reactivities without parallel in other areas.^[8,9]

The chemistry of the environment and of living organisms is often reversible and based on catalytic and stoichiometric cycles. Industrial chemistry is also highly reliant on the use of catalytic and stoichiometric cycles. The importance of such systems has provided much of the impetus for research in organometallic chemistry.^[10,11] Even though significant examples exist,^[12–14] polyhedral boron chemistry shows a marked lack of reaction cycles either catalytic or stoichiometric. Herein we report a novel stoichiometric cycle in which the iridaboranes, $[\text{1-(Cp}^*)\text{-1-(H)}_2\text{-arachno-1-IrB}_3\text{H}_7]$ (**1**)^[15] and $[\text{1-(Cp}^*)\text{-1-H-arachno-1-IrB}_4\text{H}_9]$ (**2**)^[15] ($\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$) are interconverted via novel phosphane-substituted derivatives (Scheme 1). The chemistry is driven by acid/base chemistry of PMe_3 ($\text{Me} = \text{CH}_3$) and borane.

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Scheme 1. a) C_6D_6 solution, PMe_3 (forward) and $\text{BH}_3\cdot\text{THF}$ (reverse), room temperature; b) solid state or solution, room or lower temperatures; c) C_6D_6 solution, PMe_3 (forward) and $\text{BH}_3\cdot\text{THF}$ (reverse), room temperature; d) THF solution, excess of $\text{BH}_3\cdot\text{THF}$, 60°C .

PMe_3 reacts at room temperature with **1** to give BH_3PMe_3 and the new three-vertex iridatriborane, $[\text{1-(Cp}^*)\text{-1-(H)}_2\text{-arachno-1-IrB}_2\text{H}_4\text{-2-(PMe}_3)]$ (**3**). By contrast, **2** reacts with the PMe_3 to give $[\text{1-(Cp}^*)\text{-1-(H)-arachno-1-IrB}_3\text{H}_6\text{-2-(PMe}_3)]$ (**4**), which decomposes slowly in solution (and the solid state) to give **3** (Scheme 1). Compound **4** has been characterized by NMR spectroscopy and mass spectrometry. The $^{11}\text{B}\text{-}\{^1\text{H}\}$ NMR spectrum shows three signals with a relative intensity ratio of 1:1:1: the signal at the highest field being a doublet. Accordingly, the $^{31}\text{P}\text{-}\{^1\text{H}\}$ NMR spectrum shows a broad quartet indicating a B-PMe_3 bond. ^1H NMR spectroscopy demonstrates the existence of three B-H terminal hydrogen atoms, two B-H-B bridging hydrogen atoms, and one Ir-H hydride as well as the presence of a Cp^* ring and a PMe_3 ligand. The proposed structure of **4** (Scheme 1) is that of well-known metal “borallyl” complexes such as **1**,^[15] $[(\text{PPh}_3)_2(\text{CO})\text{-HIrB}_3\text{H}_7]$,^[16] $[(\text{Cp}^*)\text{Co}(\text{CO})\text{B}_3\text{H}_7]$,^[17] and Group 10 metal-tetrahaboranes.^[18–23]

An X-ray diffraction analysis of **3** shows that the molecular structure^[24] (Figure 1) is analogous to that of previously reported metallatriboranes of formulation, $\text{K}[\text{M}(\text{CO})_4(\eta^2\text{-B}_2\text{H}_5)]$ ($\text{M}=\text{Fe}, \text{Ru}, \text{Os}$) and $[\text{M}(\eta^5\text{-C}_5\text{H}_5)(\text{CO})_2(\eta^2\text{-B}_2\text{H}_5)]$ ($\text{M}=\text{Fe}, \text{Ru}$).^[25] The PMe_3 group is bound to the boron atom B2 of the $\{\text{IrB}_2\}$ triangle *trans* to the $\eta^5\text{-C}_5\text{Me}_5$ ligand; a configuration probably driven by steric effects. The B2–B3 bond length in compound **3** is significantly longer than that in $[(\eta^5\text{-C}_5\text{H}_5)(\text{CO})_2\text{Fe}(\eta^2\text{-B}_2\text{H}_5)]$ (1.815(4) versus 1.773(8) Å). In addition, the B–B bridging hydrogen atom H6 is asymmetrically bound to the boron atoms B2 and B3; that is, the distance to the PMe_3 -substituted boron atom B2 is 0.15 Å shorter. These structural distortions presumably reflect the unsymmetrical electronic distribution imposed by the phosphane ligand in the substituted metalladiboranes compared with the distribution in the unsubstituted analogues.

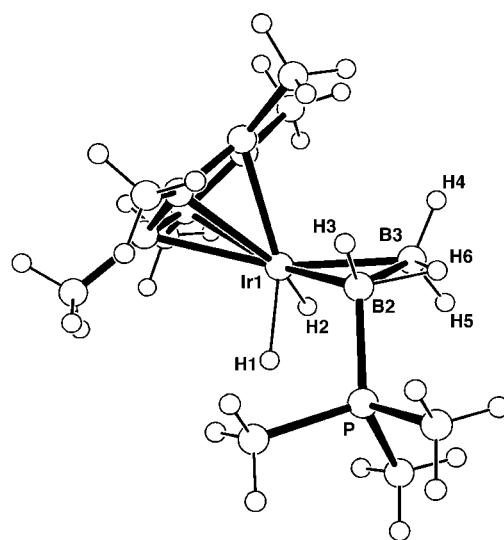


Figure 1. Molecular structure of compound **3**. Selected bond lengths [Å] and interatomic angles $^\circ$: Ir1–B2 2.146(3), Ir1–B2 2.157(3), P–B2 1.931(3), B2–B3 1.815(4); B2–Ir1–B3 49.89(10), B3–B2–P 119.76(18), B3–B2–Ir1 65.38(12), P1–B2–Ir1 115.22(13).

Similarly, compound **4** reacts with $\text{BH}_3\cdot\text{THF}$, yielding the five-vertex *arachno*-metallaborane **2** (Scheme 1). This type of reactivity suggests that the use of BH_3PMe_3 as a leaving group in **3** and **4** may permit, for example, the insertion of different Lewis acids in the cluster framework of the iridaboranes.

Monitoring the reactions by NMR spectroscopy shows that the cleavage of **1** and **2** by PMe_3 is fast and quantitative at room temperature. Likewise, the regeneration of **1** and **2** upon addition of $\text{BH}_3\cdot\text{THF}$ to solutions of **3** and **4** takes place quantitatively in a few minutes at ambient temperature. By contrast, the decomposition of **4** to give **3** is slow in solution under the same conditions with a measured half-life of four

days. To our surprise, in the solid state the half-life is four hours.

The cleavage of polyboranes and metallaboranes by abstraction of BH_3PR_3 with formation of phosphane derivatives has considerable precedent.^[26] Particularly relevant here is the generation of *nido*- $[\{\text{Cp}^*\text{Ru}\}_2(\text{PR}_3)_2\text{B}_2\text{H}_6]$ ($\text{PR}_3 = \text{PMe}_3$, PMe_2Ph) from the reaction of PR_3 with the five-vertex *nido*- $[\{\text{Cp}^*\text{Ru}\}_2\text{B}_3\text{H}_9]$.^[27] Here the phosphane ligand is found coordinated to the ruthenium center rather than to a boron atom. Indeed, the thermal decomposition of the PMe_2Ph derivative generates benzene to give *nido*- $[\{\text{Cp}^*\text{Ru}\}_2-(\mu\text{-PMe}_2)(\text{B}_2\text{H}_5)]$. By contrast, in **3** and **4** PMe_3 is preferentially bound to a boron atom rather than to an iridium center. In the case of an osmahexaborane, $[(\text{PPh}_3)_2(\text{CO})\text{OsB}_5\text{H}_9]$, reaction with PPh_3 generates $[(\text{PPh}_3)_2(\text{CO})\text{OsB}_4\text{H}_7(\text{BH}_2\text{PPh}_3)]$ in which a pendant BH_2PPh_3 group is bound to a basal boron atom. On heating, the original starting osmahexaborane is formed, or it decomposes to give $[(\text{PPh}_3)_2(\text{CO})\text{OsB}_4\text{H}_8]$ and BH_3PPh_3 .^[28] These differing behaviors reflect the influence of the metal fragments. As with organometallic chemistry, the reactivity of a bound polyborane is strongly affected by the metal, thereby demonstrating the potential of similarly effective control of the chemistry with metal properties.

Experimental Section

Reaction of **1** and **2** with PMe_3 : A mixture of **1** and **2** (1:5 ratio; 15 mg, 0.04 mmol) was treated with PMe_3 in $[\text{D}_6]$ benzene. Compound **1** gave rise to **3** (minor component), whereas **2** afforded **4** (major component). Compound **4** decomposed in solution (and in the solid state) to give **3**. **3**: ^{11}B NMR ($[\text{D}_6]$ benzene, 22 °C, 128 MHz): $\delta = -19.1$ (t, $^1J(\text{B,H}) = 103$ Hz; $\{^1\text{H}\}$, s, 1B), -24.7 ppm (td, $^1J(\text{B,H}) + ^1J(\text{B,P}) = 107$ Hz, $^1J(\text{B,H}) = 42$ Hz; $\{^1\text{H}\}$, d, $^1J(\text{B,P}) = 98$ Hz, 1B); ^1H NMR ($[\text{D}_6]$ benzene, 22 °C, 400 MHz): $\delta = 3.05$ (d, 20 Hz, 1H, B-H), 2.83 (s, 1H; B-H), 2.13 (s, 15H; C_5Me_5), 1.59 (m, $J = 10$ Hz, 1H; B-H), $+0.69$ (d, $^2J(\text{H,P}) = 11$ Hz, 9H, PMe_3 ; $\{^{31}\text{P}\}$, s), -6.36 (quintet, 9 Hz, 1H; B-H-B), -17.06 (s, 1H; Ir-H), -19.04 ppm (d, $^3J(\text{H,P}) = 17$ Hz, 1H, Ir-H; $\{^{31}\text{P}\}$, s); ^{31}P NMR ($[\text{D}_6]$ benzene, 22 °C, 162 MHz): $\delta = -16.3$ ppm (quartet, $^1J(\text{B,P}) = 95$ Hz, PMe_3); IR (KBr): $\tilde{\nu} = 2407, 2373$ (B-H); 2153 cm^{-1} (Ir-H); HR-MS(EI): m/z calcd for $\text{C}_{13}\text{H}_{28}\text{B}_2\text{P Ir}$: 430.17478, $[M^+ - \text{H}_2]$; found 430.17317; elemental analysis (%) calcd for $\text{C}_{13}\text{H}_{30}\text{B}_2\text{P Ir}$: C 36.21, H 7.01; found: C 36.40, H 6.99.

4: ^{11}B ($[\text{D}_6]$ benzene, 22 °C, 128 MHz): $\delta = -5.3$ (d, $^1J(\text{B,H}) = 134$ Hz; $\{^1\text{H}\}$, s, 1B), -12.9 (t, $^1J(\text{B,H}) = 109$ Hz; $\{^1\text{H}\}$, s, 1B), -20.1 ppm (t, $^1J(\text{B,H}) + ^1J(\text{B,P}) = 112$ Hz; $\{^1\text{H}\}$, d, $^1J(\text{B,P}) = 103$ Hz, 1B); ^1H ($[\text{D}_6]$ benzene, 22 °C, 400 MHz): $\delta = 3.96$ (s, 1H; B-H), 3.07 (s, 1H; B-H), 2.45 (dd, $J = 19, 7$ Hz; B-H), 2.11 (s, 15H; C_5Me_5), 1.99 (s, 1H; B-H), 0.63 (d, $^2J(\text{H,P}) = 11$ Hz, 9H, PMe_3 ; $\{^{31}\text{P}\}$, s), -4.32 (s, 1H; B-H-B), -4.78 (dq, 1H, $J = 19.4, 6.3$ Hz, B-H-B), -18.50 ppm (d, $^3J(\text{H,P}) = 21$ Hz, 1H, Ir-H; $\{^{31}\text{P}\}$, s); ^{31}P ($[\text{D}_6]$ benzene, 22 °C; 162 MHz): $\delta = -9.7$ ppm (quartet, $^1J(^{11}\text{B},^{31}\text{P}) 10.0$ Hz; PMe_3); IR (hexane): $\tilde{\nu} = 2518, 2472, 2425$ (B-H); 2282 cm^{-1} (Ir-H); LR-MS (EI): m/z calcd for $\text{C}_{18}\text{H}_{31}\text{B}_3\text{IrP}$: 444, $[M^+]$; found envelop with cut-off at 445 and maximum at 442; the isotopic pattern suggests that the ions $[M^+]$ and $[M^+ - \text{H}_2]$ are overlapped with a major contribution of the latter.

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A Crystalline β -Hairpin Peptide Nucleated by a Type I' Aib-D-Ala β -Turn: Evidence for Cross-Strand Aromatic Interactions**

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Recent progress in the design of β -hairpin peptides^[1] and β -sheet models has been based on the ability to nucleate reverse turns of the appropriate stereochemistry. D-Pro-Gly^[2] and to a lesser extent Asn-Gly^[3] segments have been shown to facilitate formation of type I' and II' β -turns, which are most often found at the site of sharp polypeptide chain reversal, that is, β -hairpins in proteins.^[4,5] The prime turns, I' and II', can exert differing influences on the relative twist of the antiparallel strands. The I' turn has the sense of twist that matches the twisting of adjacent β -strands in proteins. In contrast, the II' turn results in a more "planar arrangement" with the hairpin flattening to a considerable degree.^[4a,e] The D-Pro-Xxx segment can in principle adopt both II' and I' turn conformations as ψ (D-Pro) values of $+30^\circ$ and -120° are energetically favorable.^[1a,5]

To develop a definitive approach towards the design of I' turn nucleated β -hairpins, we have been investigating Aib-D-Xxx nucleating segments. The achiral α -aminoisobutyric (Aib) residue is overwhelmingly constrained to adopt either right-handed α_R ($\phi = -60^\circ$, $\psi = -30^\circ$) or left-handed α_L ($\phi = +60^\circ$, $\psi = +30^\circ$) helical conformations.^[1a,6,7] The incorporation of a D-residue is intended to favor formation of a type I' β -turn, with the D-residue adopting a preferred α_L conformation. Alternative β -turn conformations such as types I, II, and II' are expected to be energetically less favorable as one of the two prospective turn residues will have to adopt disfavored conformations.^[5] We report here the crystallographic characterization of a type I' turn nucleated β -hairpin in the designed octapeptide Boc-Leu-Phe-Val-Aib-D-Ala-Leu-Phe-Val-OMe (**1**; Boc = *tert*-butoxycarbonyl).

Figure 1 shows a view of the molecular conformation of peptide **1** in the crystal, while Table 1 summarizes the observed backbone torsion angles. Three strong cross-strand intramolecular hydrogen bonds are observed between Val(3)-

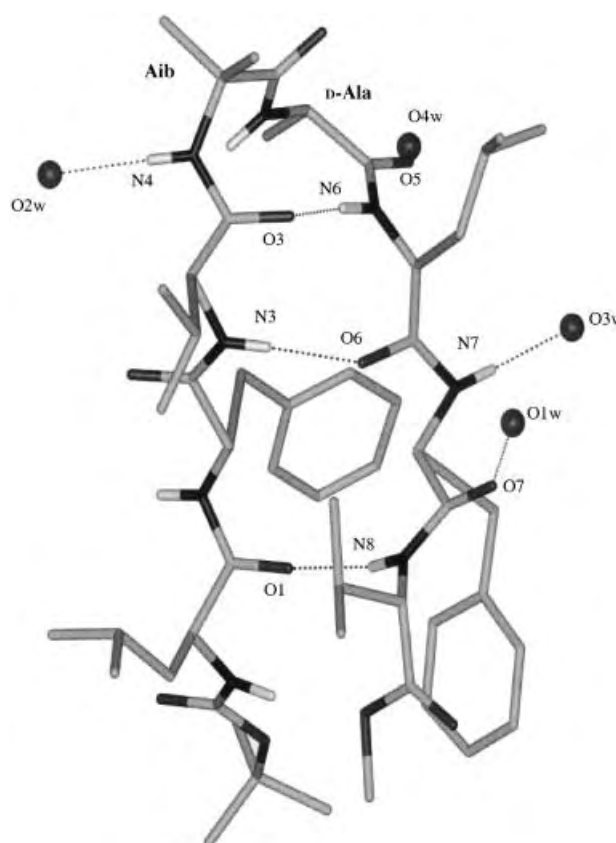


Figure 1. Molecular conformation of peptide **1** in the crystal. All the intramolecular hydrogen bonds and hydrogen bonds to the solvent molecules are shown as dotted lines.

CO...HNLeu(6) ($N\cdots O$ 2.958 Å, $\angle N-H\cdots O$ 159.95°), Val(3)NH...OCLeu(6) ($N\cdots O$ 2.853 Å, $\angle N-H\cdots O$ 162.23°), and Leu(1)CO...HNVal(8) ($N\cdots O$ 2.913 Å, $\angle N-H\cdots O$ 167.84°). Peptide **1** adopts a β -hairpin structure with a type I' β -turn formed at the Aib-D-Ala segment. Of the four anticipated cross-strand hydrogen bonds in an idealized β -hairpin, the terminal interaction Leu(1)NH...OCVal(8) is disrupted by a large reorientation about the C^α -CO bond of Val(8) ($\psi = -57.3^\circ$). Such fraying at hairpin termini is not uncommon.^[8c] Residues Leu(1), Phe(2), Val(3), and Leu(6) adopt ϕ and ψ values characteristic of β -sheets, while some distortion is observed at Phe(7), which takes up a "polyproline-like" conformation ($\phi = -69.9^\circ$, $\psi = +140.5^\circ$). The molecules are held together in the crystal by a network of water-mediated hydrogen bonds. Four water molecules bridge CO and NH groups in symmetry-related molecules that do not participate in intramolecular hydrogen bonds ($N4\cdots O2w$ 2.909, $N7\cdots O3w$ 2.955, $O1w\cdots O7$ 2.867, $O4w\cdots O5$ 2.842, and $N5\cdots O1w$ 3.048 Å (symmetry-related by $x+1, y, z$); $O1w\cdots O2$ 3.193 Å (symmetry-related by $x-1, y, z$); $O2w\cdots O4$ 2.763 Å (symmetry-related by $-x+1, y+1/2, -z+1/2$)). A single interpeptide hydrogen bond $N(2)\cdots O(8)$ of 2.957 Å (symmetry-related by $x+1, y, z$) is also observed. The retention of the β -hairpin conformation of peptide **1** in solution has been demonstrated by ^1H NMR spectroscopic studies in methanol (data not shown). The characteristic distribution of C^α and NH chemical shifts and interstrand NOEs as observed in

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Table 1. Torsion angles^[a] of peptide **1**.

Residue	ϕ [deg]	ψ [deg]	ω [deg]	χ^1 [deg]	χ^2 [deg]
Leu(1)	-124.0 ^[b]	133.4	-178.3	-173.9	72.3, -166.6
Phe(2)	-125.3	137.4	177.3	-67.3	73.8, -106.8
Val(3)	-128.2	125.9	179.8	-61.9, -179.6	
Aib(4)	56.4	34.13	173.2		
D-Ala(5)	83.2	4.3	-174.9		
Leu(6)	-115.8	139.6	178.6	-65.8	-59.9, 170.8
Phe(7)	-69.9	140.5	174.4	-174.1	73.0, -104.1
Val(8)	-117.7	-57.3 ^[c]	-179.5 ^[d]	-57.8, 178.9	

[a] The torsion angles for rotation about bonds of the peptide backbone (ϕ , ψ , and ω) and about bonds of the amino acid side chains (χ^1 and χ^2) as suggested by the IUPAC-IUB Commission on Biochemical Nomenclature.^[16] [b] Estimated standard deviation $\approx 1^\circ$. [c] N8-C⁸-C⁸-O(OMe). [d] C⁸-C⁸-O(OMe)-C(OMe).

related peptide β -hairpins^[8] confirmed that the conformation determined in the crystal is also robust in solution.

Figure 2 shows the far-UV CD spectrum of peptide **1** in methanol. It is clear that the observed CD is anomalous and possibly the consequence of interaction between the two aromatic Phe chromophores, which occur at facing positions across the antiparallel strands. Indeed, anomalous CD bands have been demonstrated for the related peptide Boc-Leu-Phe-Val-D-Pro-Gly-Leu-Phe-Val-OMe in a study which demonstrated the utility of vibrational CD as compared to electronic CD.^[9] The CD spectrum of the related peptide Boc-Leu-Val-Val-Aib-D-Ala-Leu-Val-Val-OMe (**2**) is also shown in Figure 2 for comparison. Notably, the CD spectrum of peptide **2** closely resembles that observed for well-characterized β -hairpins, with a strong negative CD band at

approximately 220 nm. In contrast, the CD spectra of peptide **1** reveals positive bands at 223 and 203 nm, negative bands at 238 and 212 nm, and an intense negative band below 195 nm. This abnormal pattern is likely to be a consequence of the interaction of the two aromatic chromophores. This interpretation is supported by the absence of unusual CD bands in the spectra of model peptide hairpins which contain a single Phe residue^[9] or of hairpins which have two Phe residues in nonfacing positions (unpublished results).

The inset in Figure 2 shows the approximately orthogonal disposition of the two phenyl rings, with the closest interatomic distance of 3.91 Å for Phe(7)CD1...CZPhe(2) and a centroid-to-centroid distance of 5.52 Å. The positive and negative bands observed at 223 and 212 nm may be tentatively assigned to the exciton split π - π^* transition centered at 217 nm. Such orthogonal arrangements of aromatic rings have been observed in proteins and are suggested to be a source of stabilization of tertiary structures. In proteins, the centroid-to-centroid distance for interacting phenyl pairs shows a peak in the distribution at approximately 5.5 Å.^[10]

The ability to generate peptide hairpin structures nucleated by I' and II' β -turns permits a comparison of the effects of turn conformation on antiparallel strand orientation. Figure 3 shows a superposition of two octapeptide β -hairpin segments—namely, peptide **1** and Leu-Phe-Val-D-Pro-Gly-Leu-Phe-Val-OMe^[11]—which contain the same strand residues but differ in the constitution and conformation of the β -turn units. For the superposition, only the C α carbon atoms of the backbone have been used. The flattened nature of the type II' turn is evident. More pronounced twisting and divergence of the strands in the I' turn nucleated hairpin is observed, as

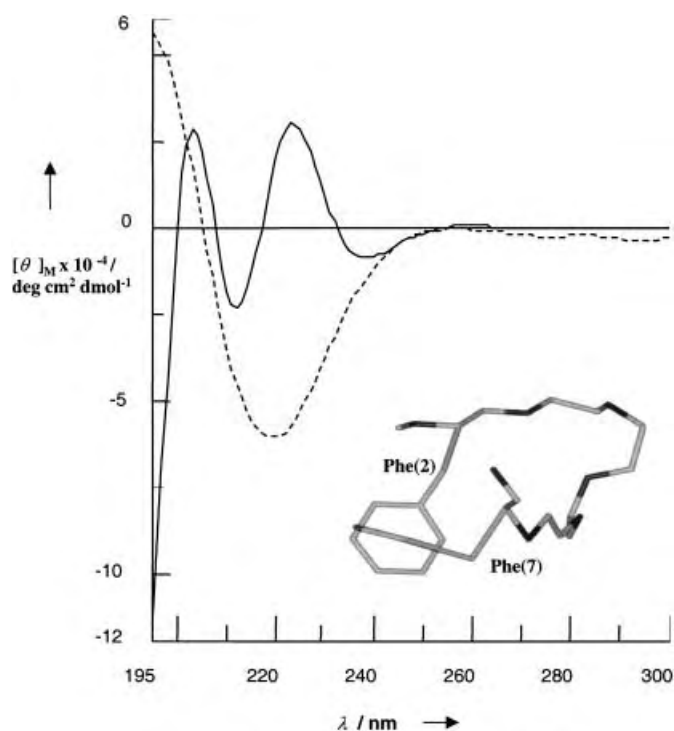


Figure 2. Electronic CD spectra of peptides **1** (—) and **2** (---) in the far-UV region in methanol. $[\theta]_M$ is the molar ellipticity. The inset shows the proximity of the aromatic rings of Phe(2) and Phe(7), which are approximately perpendicular to each other.

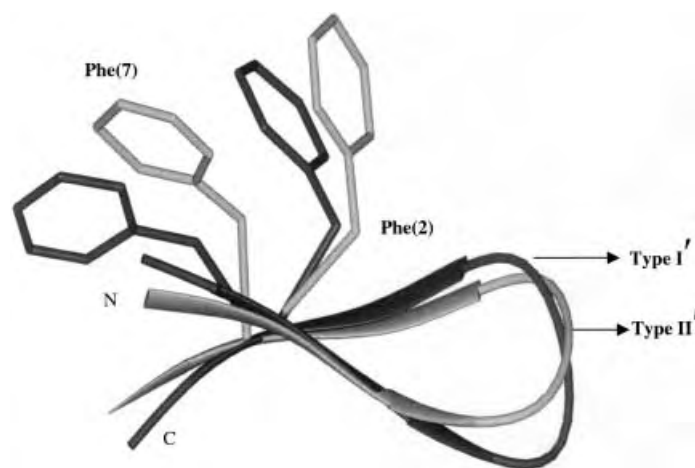


Figure 3. Superposition of peptide **1** (black) and the octapeptide segment Leu-Phe-Val-D-Pro-Gly-Leu-Phe-Val-OMe (gray) from the crystal structure of a 17-residue helix-hairpin peptide.^[11] Only the side chains of the Phe residues are shown. This representation was generated using the program MolMol.^[15] The virtual torsion angle^[4d] ($\theta = C^{\alpha}3-C^{\alpha}4-C^{\alpha}5-C^{\alpha}6$) is -56.2° for peptide **1** and -20.7° for the octapeptide segment.

compared to the II' counterpart. It must be noted that the use of only C α atoms avoids the distortion at the C-terminus observed in peptide **1**.

This study establishes the utility of an Aib-D-Xxx sequence in generating a type I' β -turn, which in turn facilitates nucleation of β -hairpin structures incorporating an appreciable degree of strand twisting. Enhancing the degree of the strand twist in synthetic hairpins may be critical in the design of twisted multistranded structures in de novo approaches to β -barrels.^[12] The conformationally constrained Aib residue has been extensively employed for the nucleation of helical structures in designed peptides.^[1a,6,7] An Aib-L-Ala type II' β -turn has been characterized in the crystal structure of the disulfide-bridged hairpin peptide Boc-Cys-Val-Aib-Ala-Leu-Cys-NHMe.^[13] However, in the absence of the covalent S–S bond, the S-protected precursor favors a helical conformation in apolar solvents.^[13c] The present study demonstrates that in conjunction with adjacent D-residues, Aib, and by extension related α,α -dialkyl residues, can be used to generate β -hairpin structures in de novo design strategies.

Experimental Section

Peptide **1** was synthesized by conventional solution-phase procedures using a fragment condensation strategy. Boc and methyl ester groups are used as N- and C-terminal protecting groups, respectively. Peptide couplings were mediated by *N,N'*-dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole.^[8b] The peptide was purified by reverse-phase, medium-pressure liquid chromatography (C18, 40–60 μ) using methanol/water gradients. The peptide was characterized by 500 MHz ¹H NMR spectroscopy and MALDI mass spectrometry ($M + Na^+_{\text{obs}} = 1030.6$; $M_{\text{calcd}} = 1007.22$).

Crystal structure analysis: Crystals of peptide **1** were grown by slow evaporation from a solution in isopropanol/water. A single crystal (0.5 $\times$ 0.3 $\times$ 0.2 mm) was mounted on a capillary with a small amount of the mother liquor. The X-ray data were collected at room temperature on a Bruker AXS SMART APEX CCD diffractometer using MoK α radiation ($\lambda = 0.71073$ Å), ω -scans ($2\theta = 53.8^\circ$), for a total of 13913 independent reflections. Space group *P*212121, $a = 10.004(4)$, $b = 13.724(5)$, $c = 51.214(19)$ Å, $V = 7023(4)$ Å³, $Z = 4$ for chemical formula C₅₃H₈₂N₈O₁₁·4H₂O, with one molecule per asymmetric unit; $\rho_{\text{calcd}} = 1.012$ g cm^{−3}, $\mu = 0.074$ mm^{−1}, $F(000) = 2304$, $R_{\text{int}} = 0.14$. The structure was obtained by direct methods using SHELXS-97.^[14a] The four water molecules were located from a difference Fourier map. Refinement was carried out against F^2 with full-matrix least-squares methods using SHELXL-97.^[14b] All non-hydrogen atoms were refined isotropically. The R value at the end of isotropic refinement was 0.178, and dropped to 0.12 after anisotropic refinement. The hydrogen atoms were fixed geometrically in the idealized position and refined in the final cycle of refinement as riding over the atoms to which they are bonded. The final R value was 0.0958 ($wR2 = 0.246$) for 5055 observed reflections ($F_0 \geq 4\sigma(F_0)$) and 686 variables, where the data to parameter ratio is 7.4:1.0 and $S = 0.857$. The largest difference peak and hole were 0.47 and -0.23 e Å^{−3}, respectively. The standard deviations in bond lengths and bond angles are approximately 0.01 Å and 1°. CCDC-184575 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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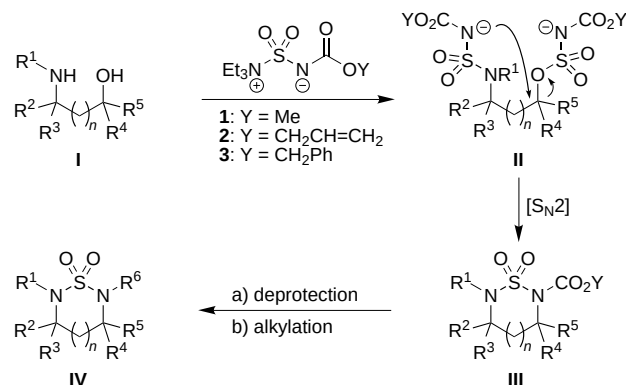
A New Method for the Synthesis of Nonsymmetrical Sulfamides Using Burgess-Type Reagents**

K. C. Nicolaou,* Deborah A. Longbottom, Scott A. Snyder, Annie Z. Nalbanadian, and Xianhai Huang

Within the realm of proven pharmacophores, the sulfamide functional group (thiadiazine-1,1-dioxide) stands out as one of the most important structural motifs found in high affinity protein ligands and pharmaceutically useful agents. Indeed, a survey of the recent patent literature reveals several hundred proprietary documents illustrating that the incorporation of a sulfamide group within a suitable scaffold, often cyclic, leads to compounds with an impressive and diverse array of biological activity.^[1] Among the numerous applications of sulfamides, these agents have proven to be particularly effective as inhibitors of key enzymes including HIV protease^[2] and serine protease,^[3] and have demonstrated utility as both agonists and antagonists of critical molecular receptors such as those used to regulate endogenous levels of serotonin^[4] and histamine.^[5] Beyond their clear significance in the treatment of disease, cyclic sulfamides have also been employed with considerable success as chiral ligands and auxiliaries,^[6] and constitute an increasingly popular set of building blocks within the field of supramolecular chemistry.^[7]

Despite the indisputable utility of these compounds, existing routes for their synthesis, particularly in a cyclic setting, are far from ideal. For example, typical procedures to fashion cyclosulfamides rely upon the reaction of a diamine with either SO₂Cl₂ or H₂NSO₂NH₂ at elevated temperatures,^[8] conditions which often lead to a low yield of product as a result of the concomitant formation of polycondensation side-products. Equally problematic is the relative scarcity of suitable diamines for these reactions from commercial sources^[9] and the difficulties associated with their laboratory preparation. While these issues have led to the development of several alternative protocols for sulfamide synthesis,^[10] these additional synthetic technologies have proven amenable only to specific substrate classes and have not yet alleviated

the need for multistep protocols. Most significantly, none of these methods has enabled the efficient and selective synthesis of nonsymmetrical *N,N'*-disubstituted cyclosulfamides (**IV**, Scheme 1), perhaps the most versatile class of these compounds for generating pharmaceutically relevant molecular diversity. Herein, we provide a general and widely applicable solution for the synthesis of these diverse classes of sulfamides, which enables for the first time the reliable and efficient formation of this highly desirable structural moiety (**IV**).



Scheme 1. Proposed conversion of amino alcohols (**I**) into cyclic sulfamides (**III**) using Burgess (**1**) and related reagents (**2** and **3**) and further elaboration leading to nonsymmetrically substituted, structurally diverse products (**IV**).

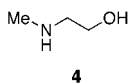
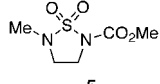
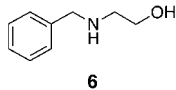
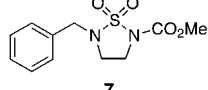
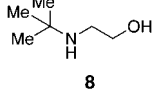
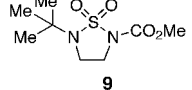
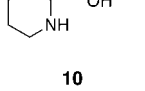
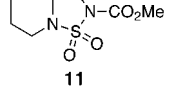
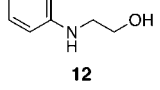
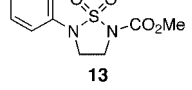
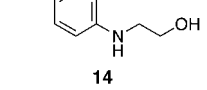
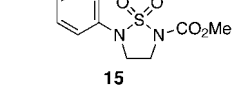
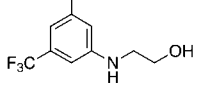
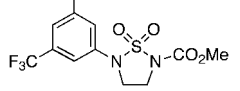
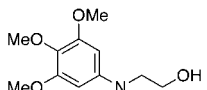
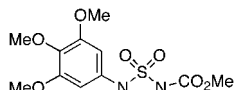
Drawing insight from our recent discovery^[11] that β -amino alcohols can be smoothly synthesized with excellent chiral integrity from precursor diols through a novel cyclization reaction initiated by the Burgess reagent (**1**, Scheme 1)^[12] and related compounds (**2** and **3**),^[11] we anticipated that application of this protocol to an amino alcohol starting material (**I**) would result in a monoprotected, nonsymmetrical cyclic sulfamide (**III**) in a single, stereocontrolled operation through the delineated mechanism (Scheme 1). Assuming that this reaction course could be successfully realized in preference to the typical rearrangement/dehydration pathways promoted by these reagents,^[13] subsequent deprotection of the carbonate in **III**, followed by substitution with an appropriate electrophile, would then provide access to an assorted collection of sulfamides (**IV**) with the potential to incorporate diversity at all possible sites.

To test this attractive hypothesis, a representative set of commercially available secondary β -amino alcohols was investigated. Most gratifyingly, exposure of all substrates listed in Table 1 to excess Burgess reagent (**1**) in refluxing THF for 8 h led to the formation of the desired cyclic sulfamide product in high yield, regardless of the nature of the group attached to the amine. Of particular note is that neither placement of the amine in a hindered cyclic setting (entry 4) nor addition of a bulky *tert*-butyl substituent (entry 3) retarded product formation. This latter substrate constitutes a particularly effective test for the power of this synthetic technology, as starting materials bearing this functionality have generally proven recalcitrant to sulfamide formation with currently available methods.^[4] Of equal importance, all

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Table 1. Synthesis of five-membered nonsymmetrical cyclic sulfamides from precursor secondary β -amino alcohols using Burgess reagent (**1**): initial investigations.

$\begin{array}{c} \text{R}^1\text{NH} \\ \\ \text{CH}_2\text{OH} \\ \\ \text{R}^2 \end{array} \xrightarrow[\text{THF, } \Delta, 8 \text{ h}]{\text{Burgess reagent (1)}} \begin{array}{c} \text{O} \\ \parallel \\ \text{R}^1\text{N}-\text{S}-\text{N}-\text{CO}_2\text{Me} \\ \quad \\ \text{R}^2 \end{array}$			
Entry	Starting material	Product	Yield [%]
1			75
2			85
3			81
4			77
5			92
6			75
7			82
8			69

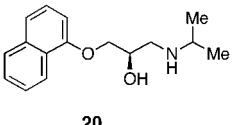
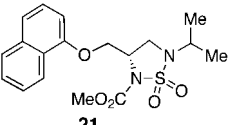
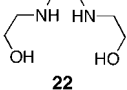
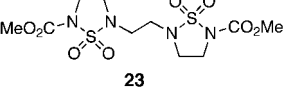
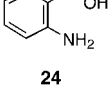
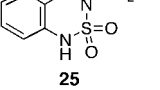
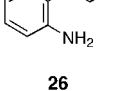
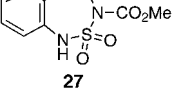
relatively hindered context **20**, failed to engender any particular difficulties (although extension of the reaction time beyond the standard 8 h of heating was required to optimize yields), and led to **21** with clean inversion of configuration. A double cyclization seeking to generate a bis-sulfamide (**23**, entry 2) was also smoothly effected. The reduced yield in this case was solely a consequence of difficulties encountered during isolation of this polar product. Finally, following optimization of the reaction conditions, extension of the sulfamide cyclization to ring sizes beyond the five-membered products formed in the previous examples also proved to be possible. Initial efforts in this regard focused on **24** (entry 3), wherein commencing the reaction at 0 °C for 1 h and then warming to ambient temperature for 5 h led to the desired product (**25**) in 45% yield. All other conditions examined provided no improvement on this yield; they gave only greater amounts of decomposition and led us to conclude that the activated primary benzylic alcohol was responsible. Fundamentally, however, the formation of other sulfamide-containing rings should not prove to be as problematic if a non-benzylic alcohol is employed instead. For this reason, alcohol **26** was examined and, to our delight, the seven-membered ring analogue (**27**, entry 4) was readily generated in 90% yield through a cyclization reaction that is less favorable both enthalpically and entropically than that to form a six-membered ring. The smooth generation of **27** is additionally significant because this bicyclic product is analogous to the benzodiazepine motif, a molecular scaffold that has been the subject of intensive biological investigations and the source of several clinically employed agents.^[15]

Based on the successful cyclization of the latter two primary aryl amine substrates in Table 2, we were hopeful that primary aliphatic amino alcohols would perform equally well as both sides of the resultant sulfamide product could then be substituted in turn, thus leading to greater structural diversity. Unfortunately, all four substrates examined within this class (Table 3, entries 1–4) gave rather disappointing yields of sulfamide products which led either to decomposition or to

aniline-derived systems (entries 5–8) proved readily amenable to the cyclization process regardless of the electron-withdrawing (entries 6 and 7) or -donating (entry 8) properties of the appended aromatic ring; these results are indicative of the versatility of this intramolecular Burgess-mediated cyclization.^[14]

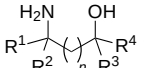
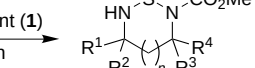
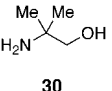
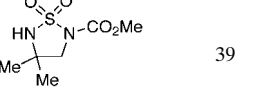
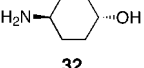
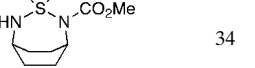
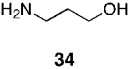
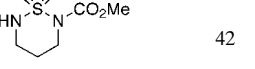
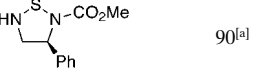
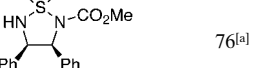
While certainly satisfied by this initial success in which the two nitrogen atoms of the sulfamide product had been effectively differentiated, we next sought to more fully probe the limits of the Burgess-mediated sulfamide synthesis by exploring more challenging substrates. As shown in Table 2, the use of a chiral secondary alcohol (entry 1), even in a

Table 2. Synthesis of nonsymmetrical cyclic sulfamides from precursor amino alcohols using Burgess reagent (**1**): exploration of additional substrate classes and development of optimized reaction conditions.

Entry	Starting material	Product	Yield [%]
1			89 ^[a]
2			55 ^[b]
3			45 ^[c]
4			90 ^[d]

[a] THF, Δ , 21 h. [b] THF, Δ , 8 h. [c] 0 °C, 1 h, then 25 °C, 5 h. [d] THF, Δ , 2 h.

Table 3. Synthesis of monoprotected cyclic sulfamides from precursor primary amino alcohols using Burgess reagent (**1**).

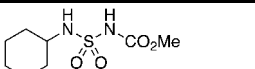
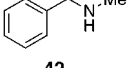
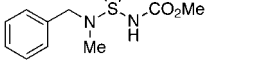
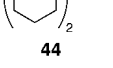
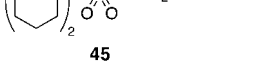
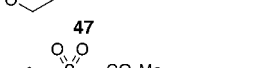
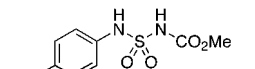
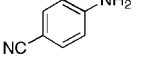
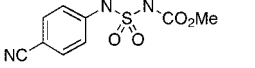
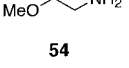
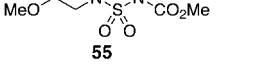
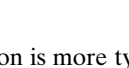
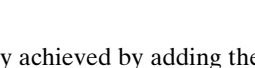
Entry	Starting material	Product	Yield [%]
1			62
2			39
3			34
4			42
5			90 ^[a]
6			76 ^[a]

[a] 0 °C, 1 h, then 25 °C, 5 h.

the formation of side-products resulting from undesired rearrangements. In retrospect, however, the poor performance of these substrates in an intramolecular cyclization relative to their secondary amine counterparts is not so surprising, as in the absence of an additional alkyl or aryl substituent, the nitrogen atom is less nucleophilic, and requires a longer reaction time and provides a greater opportunity for decomposition/rearrangement. The modest yields observed in these examples, however, do not really constitute a limitation in strategy as the quantitative debenzoylation of **7** (Table 1, entry 2) using Pearlman's catalyst provided a route to the same product **29** (Table 3, entry 1), thus alleviating the need to start with ethanolamine (**28**). As such, this approach provides a tactic to sequentially substitute both sides of any cyclic sulfamide product, if so desired. Finally, in contrast with the results in the rest of Table 3, the utilization of primary aliphatic amines in conjunction with a secondary benzylic alcohol (Table 3, entries 5 and 6) led to good product yields when the reaction was performed at low temperature. As such, these unanticipated results suggest that there is a subtle interplay between substrate structure and particular reaction conditions to facilitate sulfamide formation in synthetically useful yield.

Beyond the synthesis of cyclic sulfamides, we have also verified that Burgess reagent (**1**) can smoothly effect the generation of nonsymmetrical, linear sulfamides from all classes of amines in excellent yield (Table 4). While this same

Table 4. Synthesis of nonsymmetrical linear sulfamides from precursor amines using Burgess reagent (**1**).

Entry	Starting material	Product	Yield [%]
1			83
2			91
3			82
4			87
5			73
6			97
7			66
8			98 ^[a]

[a] –10 to 25 °C, 24 h.

conversion is more typically achieved by adding the amine to an appropriate chlorosulfonylisocyanate derivative,^[5,16] the present conditions provide a mild alternative which avoids the use of these rather toxic and corrosive agents directly on the reaction substrate.

Finally, we should note that since all of the preceding examples of sulfamide synthesis in Tables 1–4 led to products with methyl carbamate protection we tested the ability of our recently reported novel benzyloxycarbonyl (Cbz) and allyloxycarbonyl (Alloc) Burgess-type reagents (**2** and **3**, Scheme 1)^[11,17] to perform the same transformations. Most gratifyingly, in all cases examined, these reagents provided the desired product in yields that were equivalent to those obtained with the original Burgess reagent (**1**). As such, this method of sulfamide synthesis, whether for cyclic or linear systems, can be tailored with a variety of protecting groups to fit the particular needs of the test molecule. In line with several reports,^[18] our own studies have revealed that subsequent deprotection (Table 5) is easily achieved with conventional procedures and readily followed by substitution of appropriate electrophiles. Thus general and efficient syn-

Table 5. Deprotection of cyclic sulfamides to yield nonsymmetrical, monosubstituted sulfamides.

Entry	Starting material (Yield [%]) ^[a]	Product	Yield [%]
1	 17	 56	99 ^[b]
2	 7	 57	99 ^[b]
3	 58 (75)	 59	97 ^[c]
4	 60 (82)	 61	98 ^[c]
5	 62 (82)	 63	84 ^[d]
6	 64 (75)	 65	87 ^[d]

[a] Yield in parentheses is that for synthesis of the starting material. [b] NaOH, MeOH:H₂O (2:1), 25°C, 2 h. [c] Pd(OAc)₂ (10 mol %), 3,3',3''-phosphinidynetris(benzenesulfonic acid) trisodium salt (20 mol %), HNEt₃ (40 equiv), MeCN:H₂O (1:1), 25°C, 15 min. [d] 10% Pd/C, H₂, EtOH:EtOAc (4:1), 25°C, 2 h.

thesis of compounds represented by structure **IV** (Scheme 1) has been realized.

In conclusion, we have developed a practical and high-yielding method for the efficient, one-step synthesis of diverse classes of *N,N'*-differentiated sulfamides from a wide range of amino alcohols and simple amines using Burgess-type reagents. This synthetic technology constitutes a marked improvement over those currently in the literature, and should extend the potential applications of sulfamides not only within chemical biology and medicinal chemistry, but also in the fields of asymmetric synthesis and supramolecular chemistry. At a more fundamental level, this methodology, in conjunction with additional applications currently under development in these laboratories, serves to delineate new pathways in which the power of the Burgess reagent and its relatives can be applied to effect transformations of critical importance in chemical synthesis.

Experimental Section

Representative procedure: The desired Burgess reagent (**1–3**, 1.25 mmol, 2.5 equiv) was added in one portion to a stirred solution of amino alcohol (0.5 mmol, 1.0 equiv) in THF (2 mL). The reaction mixture was then subjected to the conditions defined in the Tables. Upon completion, the reaction was diluted with CH₂Cl₂ (20 mL) and washed with 1N HCl

(30 mL). The aqueous phase was re-extracted with CH₂Cl₂ (2 × 20 mL) and the combined organic phase was dried (Na₂SO₄), filtered, and concentrated. Flash column chromatography on silica gel then provided the desired products in the yields quoted.^[18]

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[Os^{III}(tpy)(Cl)(NCCH₃)(NSAr)]: Reversible Reduction of Acetonitrile by Os^{III}–Sulfilimido Complexes**

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Earlier reports have revealed an extensive electron–proton, reversible redox chemistry based on the Os^{V/IV} couples [Os^V(tpy)(Cl)₂{NN(CH₂)₄O}]⁺/[Os^{IV}(tpy)(Cl)₂{N(H)–N(CH₂)₄O}]⁺ (tpy = 2,2':6,2''-terpyridine, N(CH₂)₄O is a morpholide),^[1] [Os^V(tpy)(Cl)₂{NS(3,5-C₆H₃Me₂)}]⁺/[Os^{IV}(tpy)(Cl)₂{NS(H)(3,5-C₆H₃Me₂)}]⁺,^[2] and [Os^V(Tp)(Cl)₂(NPEt₂)]/[Os^{IV}(Tp)(Cl)₂(NP(H)Et₂)] (Tp = tris(pyrazolyl)borate).^[3] These couples are reminiscent of oxo/hydroxo/aqua couples such as *cis*-[Ru^{IV}(bpy)₂(py)(O)]²⁺/*cis*-[Ru^{III}(bpy)₂(py)(OH)]²⁺ and *cis*-[Ru^{III}(bpy)₂(py)(OH)]²⁺/*cis*-[Ru^{II}(bpy)₂(py)(H₂O)]²⁺ (bpy = 2,2'-bipyridyl, py = pyridyl), where the change in proton content between oxidation states is a consequence of differences in proton acidity of several orders of magnitude.^[4]

We report here the existence of a related electron–proton chemistry, but based on the reversible two-electron reduction of a nitrile ligand and the couples [Os^{III}(tpy)(Cl)(N≡CCH₃)(NSAr)] / [Os^{III}(tpy)(Cl)(NH=CHCH₃)(NSAr)] (Ar = C₆H₅, 4-MeC₆H₄, 3,5-Me₂C₆H₃). At more negative potentials, the Os^{III}–imino complexes undergo further reduction and solvolysis to give [Os^{III}(tpy)(Cl)(NCCH₃)(NSAr)] and CH₃CH₂NH₂.

A rapid reaction occurs when *cis*-[Os^{VI}(tpy)(Cl)₂(N)]⁺ ([1]⁺) and aromatic thiols (C₆H₅SH, 4-MeC₆H₄SH, or 3,5-Me₂C₆H₃SH) are mixed in CH₃CN under N₂ at room temperature [Eq. (1)]. The products are *cis*-

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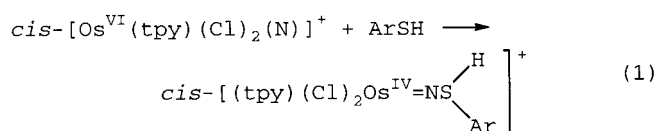
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$[Os^{IV}(tpy)(Cl)_2[NS(H)Ar]]^+$ (Ar = C₆H₅ ([**2A**]⁺), 4-MeC₆H₄ ([**2B**]⁺), 3,5-Me₂C₆H₃ ([**2C**]⁺)).^[5]

Addition of a small amount of water to [**2**]⁺ in CH₃CN causes solvolysis and deprotonation to give the monosolvento complexes $[Os^{IV}(tpy)(Cl)(NCCH_3)(NSAr)]^+$ (Ar = C₆H₅ ([**3A**]⁺), 4-MeC₆H₄ ([**3B**]⁺), 3,5-Me₂C₆H₃ ([**3C**]⁺)) on a time scale of minutes and the corresponding disolvento complexes $cis-[Os^{IV}(tpy)(NCCH_3)_2(NSAr)]^{2+}$ on a time scale of hours.^[6] The mononitrile complexes were isolated as their PF₆[−] salts and characterized by elemental analysis and cyclic voltammetry as well as ¹H NMR, infrared, and UV/Vis spectroscopies.^[5]

Crystals of [**3B**]PF₆ were grown by slow diffusion of Et₂O into a solution in CH₃CN.^[7] The structure shows that the distorted octahedral arrangement of ligands at Os in the *cis* parent nitrido complex is retained (Figure 1).^[7] The Os–N(tpy) bond lengths range from 1.948(6) to 2.078(7) Å with the shortest one *trans* to the Os–N(CH₃CN) bond. The Os–N(sulfilimido) and N4–S1 bond lengths of 1.899(8) and 1.535(9) Å, respectively, are consistent with multiple bonding.^[8–10] The angle N4–S1–C16 is 107.9(6)° and thus indicates pseudo sp³ hybridization at the S atom of the sulfilimido ligand. The Os–N(sulfilimido) bond length, the bent angle Os1–N4–S1 of 129.3(5)°, and the diamagnetism of the complexes (as shown by ¹H NMR spectroscopy) are all consistent with d⁴ spin-paired Os^{IV}. There are structural similarities with related complexes such as $[Os^{IV}(tpy)(Cl)(NCCH_3)-\{NN(CH_2)_4O\}]^+$,^[11] $cis-[Os^{IV}(tpy)(NCCH_3)_2\{NN(CH_2)_4O\}]^{2+}$,^[12] and $trans-[Os^{IV}(tpy)(NCCH_3)_2(NSC_6H_4Me)]^{2+}$.^[7]

Cyclic voltammograms of [**3C**]⁺ in dry CH₃CN (5.0 × 10^{−3} M) containing 0.1 M NBu₄PF₆ show the following couples: Os^{VIV} at +1.56 V, Os^{IV/III} at +0.65 V, and Os^{III/II} at −0.79 V (versus SSCE). These couples are shifted to more positive

potentials compared to those for *cis*-[Os^{IV}(tpy)(Cl)₂[NS(H)-C₆H₃Me₂]]⁺ with +1.21 V for Os^{VIV}, −0.09 V for Os^{IV/III}, and −1.24 V for Os^{III/II}. The more negative potentials result from the exchange of the electron-donating Cl[−] ligand for CH₃CN. The corresponding couples for *cis*-[Os^{IV}(tpy)(NCCH₃)₂-(NSC₆H₃Me₂)]²⁺ appear at +1.94 V for Os^{VIV}, +0.98 V for Os^{IV/III}, and +0.09 V for Os^{III/II}.^[6]

The cyclic voltammetric characteristics of [**3C**]⁺ in H₂O/CH₃CN (1/1, v/v; I = 1.0 M in NH₄PF₆) are strikingly different from those in CH₃CN (Figure 2).^[13] Besides the electrochemi-

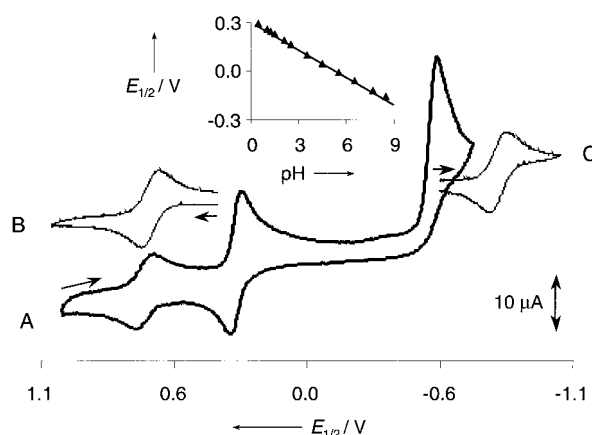
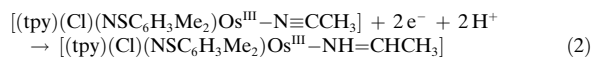


Figure 2. A) Cyclic voltammogram of [**3C**]⁺ in CH₃CN/H₂O (1/1, v/v) at pH 0.48 and I = 1.0 M in NH₄PF₆ (V versus SSCE). B) The Os^{IV/III} couple in 0.2 M CH₃CN/NBu₄PF₆. C) The Os^{III/II} couple under the same conditions as in (B). Inset: The pH dependence of $E_{1/2}$ for the Os^{IV/III} couple of [**3C**]⁺ in CH₃CN/H₂O from pH 0.48 to 8.50. A line of slope 57 mV/pH unit is shown drawn through the data.

cally reversible Os^{IV/III} wave at 0.67 V, a reversible, pH-dependent two-electron wave appears at $E_{1/2}$ = +0.29 V at pH 0.48 and an irreversible, multiple-electron reduction wave is seen at E_{pc} = −0.54 V. The peak-to-peak separation for the two-electron, reversible wave is 37 mV, which is half that of the Os^{IV/III} wave (73 mV) and consistent with a two-electron process. Comparison of relative peak currents confirms that the couple at $E_{1/2}$ = 0.29 V is a two-electron couple.

Measurements of $E_{1/2}$ as a function of pH value show that in the case of [**3C**]⁺ the $E_{1/2}$ value for the two-electron wave decreases by 57 mV/pH unit from pH 0.48 to 8.50 (Figure 2, inset). This is consistent with the chemically and electrochemically reversible 2e[−]/2H⁺ couple shown in Equation (2). Similar results have



been obtained for [**3A**]⁺ and [**3B**]⁺ with the 2e[−]/2H⁺ waves appearing at 0.31 V and 0.30 V, respectively, at pH 0.48.

The reduced Os^{III}-imino product shown in Equation (2) was electrochemically generated in CH₃CN/H₂O (1/1, v/v; pH 2.5, I = 0.5 M NH₄PF₆) at E_{app} = −0.35 V with *n* = 2. Once formed, [Os^{III}(tpy)(Cl)-(NH=CHCH₃)(NSC₆H₃Me₂)] undergoes air oxidation

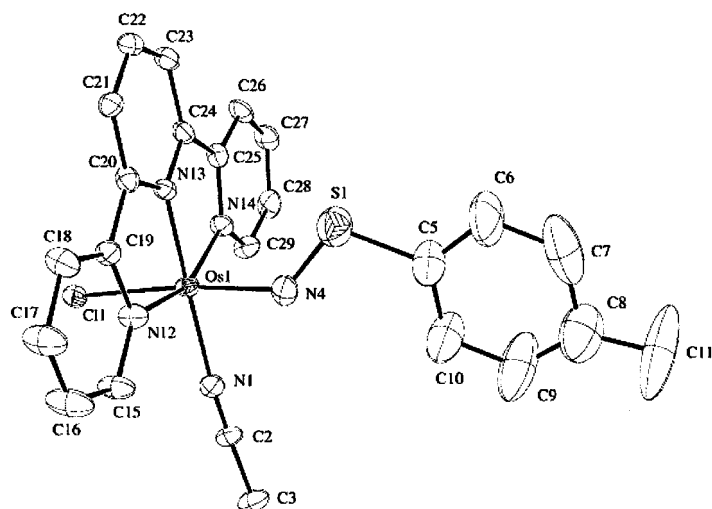
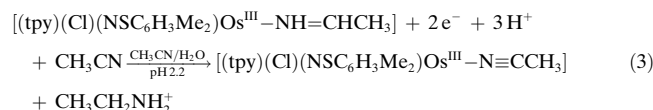


Figure 1. ORTEP diagram (30% ellipsoids) for [**3B**]PF₆.

to $[\text{Os}^{\text{IV}}(\text{tpy})(\text{Cl})(\text{NH}=\text{CHCH}_3)(\text{NSC}_6\text{H}_3\text{Me}_2)]^+$ within minutes and then to $[\mathbf{3C}]^+$ in about 1 h.^[14] The imine complex was isolated as the PF_6^- salt and characterized by elemental analysis as well as UV/Vis, ^1H NMR, and infrared spectroscopies.^[5] We have so far been unsuccessful at growing a suitable crystal for X-ray structure analysis.

The pH dependence of the irreversible, multiple-electron wave was also investigated in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (1/1, v/v). The E_{pc} values for this wave decrease by 55 mV/pH unit from $E_{\text{pc}} = -0.57$ V at pH 0.48 to $E_{\text{pc}} = -0.69$ V at pH 2.5.^[5] Above pH 2.5, the peak current falls by a factor of 4, and E_{pc} becomes pH-independent. Electrolysis of $[\mathbf{3C}]^+$ at $E_{\text{app}} = -0.85$ V in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ at pH 2.2 at $n = 4$ followed by investigation with GC-MS reveals ethylamine as a product. The retention of the initial cyclic voltammogram at the end of the electrolysis and the appearance of ethylamine are consistent with $2e^-/2\text{H}^+$ reduction followed by rapid solvolysis as shown in Equation (3). Reduction of the



nitrile complex is catalytic at -0.85 V, but changes occur in the complex upon electrolysis for extended periods of time, as shown by electrochemical measurements. The underlying chemistry remains to be investigated in detail.

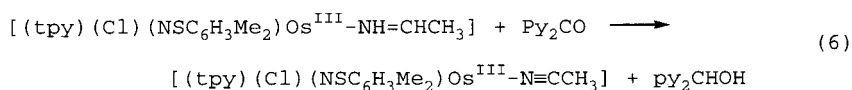
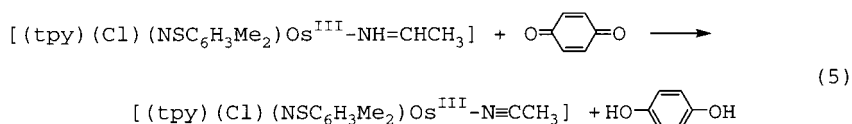
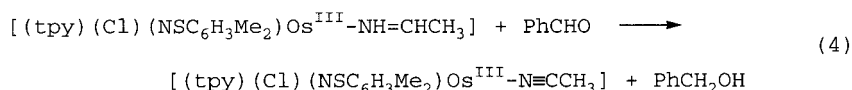
There is literature precedence for the reduction of coordinated acetonitrile ($-\text{N}_\alpha=\text{C}_\beta-\text{CH}_3$) to acetimidoyl ($\eta^2-\text{N}(\text{H})=\text{C}-\text{CH}_3$; bonded through N_α and C_β), ethylenimido ($\eta^2-\text{N}=\text{CH}-\text{CH}_3$; bonded to M through N_α and to M' through the double bond),^[15] azavinylidenyl ($-\text{N}=\text{CH}-\text{CH}_3$),^[16] imino ($-\text{NH}=\text{CH}-\text{CH}_3$),^[16–17] ethylimido ($\equiv\text{N}-\text{CH}_2-\text{CH}_3$),^[18] ethylamido ($-\text{NH}-\text{CH}_2-\text{CH}_3$),^[16] and aza-allylic ($\eta^3-\text{CH}_2-\text{CH}-\text{NH}_2$)^[19] ligands. In these reactions, hydrogen^[20] and/or hydride (H^- ,^[21] NaBH_4 ,^[22] LiHBEt_3 ,^[16] and LiAlH_4)^[22] are the reductants.

There is also evidence for the protonation of neutral acetonitrile complexes, either diprotonation at C_β by HCl or monoprotection at N_α and C_β by $\text{HBF}_4\cdot\text{Et}_2\text{O}$. At electron-rich metal centers, protonation is accompanied by oxidation of the metal center to form ethylimido^[23] or imino complexes.^[19] There are also examples of hydride formation at the metal.^[24]

Our result is the first example of reversible $2e^-/2\text{H}^+$ reduction of the acetonitrile ligand to the corresponding imine. It may presage an extensive proton-coupled electron transfer or hydride transfer chemistry analogous to that of $\text{Ru}^{\text{IV}}=\text{O}^{2+}/\text{Ru}^{\text{II}}-\text{OH}_2^{2+}$ couples but with proton and electron acceptor sites on the two-atom nitrile ligand ($\text{Os}^{\text{III}}-\text{N}\equiv\text{CCH}_3/\text{Os}^{\text{III}}-\text{NH}=\text{CHCH}_3$).

Initial experiments show that $[\text{Os}^{\text{III}}(\text{tpy})(\text{Cl})(\text{NH}=\text{CHCH}_3)(\text{NSC}_6\text{H}_3\text{Me}_2)]$ undergoes hydrogen transfer with reduction of an organic carbonyl compound. The imino

complex acts as an electron–proton donor in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (3/1, v/v; pH 1.8, $I = 0.5$ M in NH_4PF_6) toward 1) benzaldehyde with reduction to benzyl alcohol [$k_{\text{PhCHO}}(25.0 \pm 0.1^\circ\text{C}) = (1.03 \pm 0.01) \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$, Eq. (4)], 2) benzoquinone with



reduction to hydroquinone [$k_{\text{O}}(25.0 \pm 0.1^\circ\text{C}) = (3.63 \pm 0.01) \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$, Eq. (5)], and 3) dipyriddy ketone with reduction to the corresponding alcohol [$k_{\text{Py}_2\text{CO}}(25.0 \pm 0.1^\circ\text{C}) = (1.07 \pm 0.01) \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$, Eq. (6)]. The reduced products in the $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ reaction mixtures were quantitatively determined by GC-MS.^[25]

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- reported are those measured in the mixed solvents and are the same to within experimental error of those measured in CH₃CN/H₂O.
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The Ability of the α,α' -Diiminopyridine Ligand System to Accept Negative Charge: Isolation of Paramagnetic and Diamagnetic Trianions**

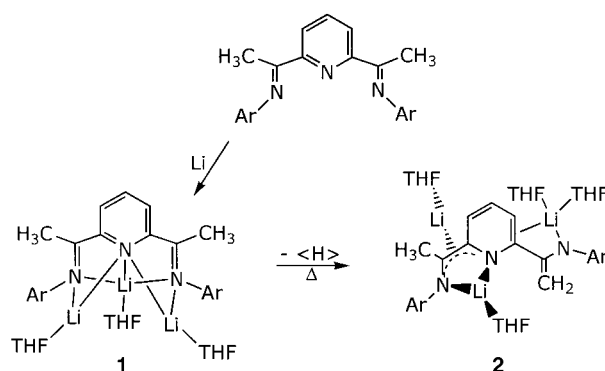
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Recent work, both in this research group and elsewhere, has shown that the α,α' -diiminopyridine ligand [α,α' -{2,6-(iPr)₂PhN=C(Me)}₂(C₅H₃N)]₂, well known for its ability to form highly active polymerization catalysts,^[1] can be involved

in the organometallic transformations of metal centers. Alkylating agents may attack not only the imino function^[2] but also all of the pyridine ring carbon atoms^[3,4] and even the nitrogen atom.^[5] In addition, dimerization may be achieved by imine reductive coupling^[4] or by the cycloaddition of two pyridine rings to form a tricyclic system.^[4] In parallel with all of these transformations, either one or both of the CH₃ groups attached to the imine functions may be partly deprotonated.^[4,5] In this unusual variety of transformation, the metal center coordinated to the ligand may engage in redox reactions and may either lower or even increase its oxidation state.^[3,6,7] This behavior illustrates the unique ability of this ligand system to a) accept negative charge with preferential spin-density localization on the imine groups and on the pyridine N and C_{para} atoms, and b) to engage in internal redox processes with the coordinated metal. The ability of the ligand to accept or to donate negative charge to the metal is paramount to the fine-tuning of the redox potential of the metal, and of its Lewis acidity which, in turn, determines the catalytic behavior of the metal complex.

Given the above scenario, we became interested in clarifying the ability of this remarkable ligand system to accept negative charge. For this purpose, we have carried out the reduction of [α,α' -{2,6-(iPr)₂PhN=C(Me)}₂(C₅H₃N)]₂ with strong reductants such as Li and [Li(naphthalenide)], in the absence of transition metals. Herein we describe our findings.

The reactions were carried out by treating a solution of [α,α' -{2,6-(iPr)₂PhN=C(Me)}₂(C₅H₃N)]₂ with either metallic Li under argon or [Li(naphthalenide)] under nitrogen in THF. Regardless of the stoichiometric ratio, the reduction with Li afforded a mixture of [α,α' -{2,6-(iPr)₂PhN=C(Me)}₂(C₅H₃N)]₂[Li(thf)]₃ (**1**) and [α,α' -{2,6-(iPr)₂PhN=C(Me)}₂]-{ α' -[2,6-(iPr)₂PhN-C(=CH₂)]C₅H₃N}]₂[Li(thf)]₂[Li(thf)₂] (**2**) through a readily reproducible process. Both species contain a trianionic ligand (Scheme 1). Separation of the two ex-



Scheme 1.

tremely air-sensitive species was possible because of their relative solubilities in hexane. However, we observed that reactions carried out at low temperature with 3 equiv of [Li(naphthalenide)] afforded **2** as the only isolated compound (67%) and no evidence for the presence of **1**.

The connectivity of **1** was elucidated by an X-ray crystal structure (Figure 1). The complex contains the intact ligand, which adopts the usual chelating tridentate conformation

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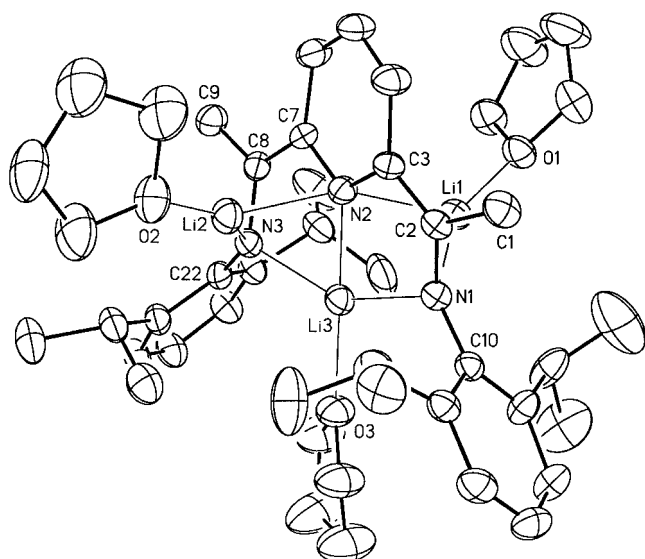


Figure 1. Thermal ellipsoid plot of **1**. Relevant bond lengths [Å] and angles [°]: C1–C2 1.522(4), C2–C3 1.373(4), C3–N2 1.421(4), C3–C4 1.481(4), C4–C5 1.407(5), C8–C9 1.512(4), Li3–N1 2.203(6), Li3–N2 1.993(6), Li3–N3 2.276(6), Li1–N1 1.994(6), Li1–N2 2.077(6), Li1–C2 2.138(6), Li2–C8 2.146(7), Li2–N2 2.049(6), Li2–N3 1.989(6); Li1–N2–Li2 154.6(3), Li3–N2–C3 119.1(3), Li3–N2–C7 121.2(2).

around the first Li atom which is, in turn, coordinated to one molecule of THF, with an overall distorted square-planar geometry. Two additional Li atoms, each solvated by one molecule of THF, are symmetrically placed on either side of the plane defined by the central Li atom and the three donor atoms. Each of these Li atoms is coordinated to a $N_{py}CCN_{im}$ fragment in a geometry reminiscent of metal–diene complexes. As a result, the pyridine N atom is pentacoordinated, and displays a near-regular trigonal bipyramidal geometry. The two out-of-plane Li atoms occupy a trigonal planar environment, with respect to the N and O donor atoms.

Complex **1** is a rare example of a paramagnetic organolithium complex that displays a magnetic moment ($\mu_{eff} = 1.30 \mu_B$) which is lower than expected for a complex with one unpaired electron per molecule. The presence of anti-ferromagnetic exchange between the radical anions is a reasonable expectation. The ESR spectrum shows a single resonance peak at $g = 2.001$ with a hyperfine pattern appearing as a complex 25 line spectrum.

Density functional theory calculations (B3LYP)^[8–11] on model complex **1a** (with the aryl substituents replaced by hydrogens) indicated the presence of a rather substantial SOMO–LUMO gap (approximately 2.3 eV) which accounts for the low-spin electronic configuration. The SOMO and HOMO are essentially identical to the LUMO and LUMO + 1 of the free ligand. Both orbitals (see Figure 2) are antibonding in the pyridine ring and between the C and N atoms of the imine moiety; the HOMO has substantial density at the N and C_{para} atoms of the pyridine moiety, whereas the SOMO has a nodal plane through these atoms. This behavior is in good agreement with the bond lengths displayed in the crystal structure, where the C–C bond formed between the *ortho* and *meta* C atoms are essentially single

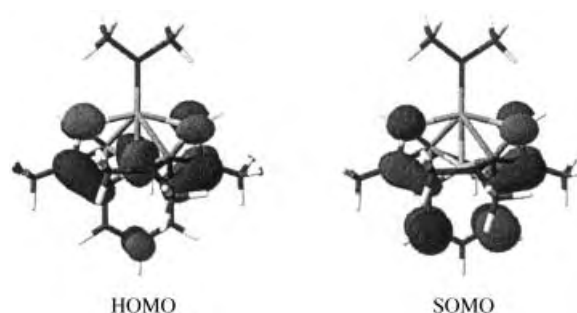


Figure 2. Pictorial drawing of the HOMO and SOMO of **1a**.

bonds whereas the C–C bonds formed by the *para* C atom are substantially shorter.

Although complex **2** originates from the same reaction and contains the same ligand skeleton, its structure is remarkably different. From the formal point of view it can also be regarded as a rare example of an organotrillithium complex. The loss of a proton from one of the methyl groups leads to the formation of a double bond with the adjacent C atom (Figure 3). The olefinic function is rotated approximately 30° out of the plane of the pyridine ring. One Li atom displays

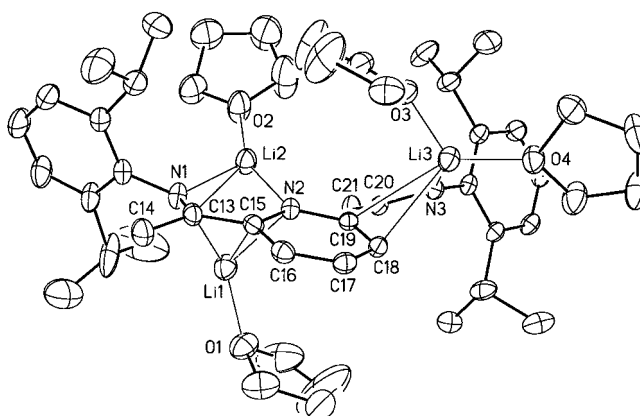


Figure 3. Thermal ellipsoid plot of **2**. Relevant bond lengths [Å] and angles [°]: C20–C21 1.366(4), C20–N3 1.364(3), C20–C19 1.526(4), C19–C18 1.374(4), C18–C17 1.442(4), C17–C16 1.352(4), C16–C15 1.446(4), C15–N2 1.451(4), C13–C15 1.394(4), C13–C14 1.514(4), Li1–N1 2.017(6), Li1–C13 2.156(6), Li1–C15 2.171(6), Li1–N2 2.121(6), Li2–N1 1.989(6), Li2–C13 2.779(6), Li2–N2 1.956(6), Li3–N3 1.958(5), Li3–C18 2.528(6), Li3–C19 2.754(6), C27–N3–Li3 129.7(2), C20–N3–Li3 110.1(2), C20–N3–C27 118.4(2), C19–C20–C21 119.2(3), N3–C20–C21 128.1(3).

normal chelation to the iminopyridine moiety, while the second sits above the ring plane and binds to the $N_{py}CCN_{im}$ fragment in much the same way as the out-of-plane lithium atoms of **1**; both of these Li atoms are coordinated to one THF molecule. The third Li atom is σ -bound to the dangling enamide nitrogen atom and coordinated to two THF molecules. The pattern of bond lengths indicates substantial localization in the sense of the resonance structure depicted in Scheme 1.

The loss of a H atom from one of the two methyl groups of the imine carbon atom during the formation of **2** was conclusively demonstrated by NMR. The spectrum shows

the presence of the two CH₂ protons at 2.04 and 3.01 ppm, coupled to each other and to the same carbon atom (66.39 ppm); their identity as CH₂ protons was confirmed from a DEPT experiment. The spectrum also displayed a remarkable upfield shift of the three pyridine resonances, two distinct phenyl rings, and two sets of *i*Pr groups.

In agreement with the observed diamagnetism of **2**, the conversion of **1** to **2** implies the loss of one hydrogen atom which corresponds to a formal one-electron oxidation. This might explain why a stronger reducing agent, such as metallic Li, is necessary for the formation of **1** while a milder reducing agent ([Li(naphthalenide)]) may favor the formation of **2**. In addition, the basicity of [Li(naphthalenide)] may play a role by promoting competition between reduction and hydrogen abstraction during its reaction with the free ligand. Finally, we have observed that **1** is thermally unstable and completely converts to **2** upon heating in toluene.

In conclusion, we have established that the popular [α,α' -{2,6-(*i*Pr)₂PhN=C(Me)}₂(C₅H₃N)}] ligand can accommodate up to three electrons in the antibonding orbitals of the imino unit and the pyridine ring in a low-spin configuration. Assuming that upon alkylation similar metal-to-ligand charge-transfer also occurs in the transition-metal complexes formed with this ligand, the observed variety of transformations may be easily explained. The localization of spin density on the *meta* C atoms of the pyridine group explains the cycloaddition observed in the related Cr complex,^[4] while the formation of a double bond explains the reductive coupling observed with Mn.^[4,6] The charge localization at the *para* position of the pyridine ring accounts for both the lithiation^[5a] and for the possibility of transferring alkyl groups directly from the metal center to any position of the pyridine ring.^[3–5] What remains to be unveiled is how this ligand supports a high level of catalytic activity with various metals. The ability of the large π -system to accommodate negative charge might concurrently lead to increased Lewis acidity of the metal center, which has an obvious positive impact on catalytic performance. On the other hand, it may also help the stabilization of electron-rich, low-valent metals, as is often observed during the alkylation of these derivatives, and whose ability to promote polymerization is still controversial.^[7]

Experimental Section

1: Freshly cut fragments of lithium foil (0.14 g, 21 mmol) were washed with hexanes, dried, and suspended in THF (100 mL). [α,α' -{2,6-(*i*Pr)₂PhN=C(Me)}₂(C₅H₃N)}] (1.0 g, 2.1 mmol) was added to the reaction vessel. The mixture was stirred for 48 h under an argon atmosphere during which the color of the solution changed from light yellow to dark red/brown. Excess lithium was removed through a glass filter. THF was evaporated from the reaction mixture in vacuo without heating and the dark-brown residue was suspended in pentane (20 mL). Compound **2** was isolated as an insoluble, brown microcrystalline powder which was present even after filtration and additional washing with pentane (0.618 g, 38%). The filtrate was concentrated to give a 15-mL solution and then cooled to –35°C. Dark-red crystals of **1** (0.14 g, 0.2 mmol, 10%) were isolated from the pentane solution. The extreme air-sensitivity of this compound, combined with the spontaneous loss of solvent, prevented any meaningful analytical data being obtained.

2: A solution of [Li(naphthalenide)] in THF (10 mL) was prepared by stirring a solution of naphthalene (0.8 g, 6.2 mmol) and freshly cut fragments of lithium foil (0.05 g, 6.6 mmol). The resulting dark-green

solution was diluted with additional THF (50 mL) and subsequently treated with [α,α' -{2,6-(*i*Pr)₂PhN=C(Me)}₂(C₅H₃N)}] (1.0 g, 2.1 mmol). An instant color change from dark green to dark brown occurred. The reaction was stirred for an additional 10 min and the solvent was then removed in vacuo. The dry residue was left under dynamic vacuum overnight at room temperature to remove most of the naphthalene. The residual solid was then washed with cold pentane (30 mL), filtered, and isolated as an insoluble, brown diamagnetic powder (1.1 g, 1.4 mmol, 67%). Crystals of **2** suitable for X-ray diffraction were grown by cooling a saturated solution in hexane to –35°C. ¹H NMR (500 MHz, [D₈]THF, 23°C): δ = 6.88 (2H, m; CH_(aromatic)); 6.75 (2H, m; CH_(aromatic)); 6.63 (1H, m; CH_(aromatic)); 6.36 (1H, m; CH_(aromatic)); 5.49 (1H, brs; CH_(pyridine)); 5.34 (1H, brs; CH_(pyridine)); 4.68 (1H, brs; CH_(pyridine)); 3.67 (12H, m; THF); 3.40 (4H, 2 overlapping septets; CH_(*i*Pr)); 3.01 (1H, brs; CH₂); 2.04 (1H, brs; CH₂); 1.76 (12H, m; THF); 1.38 (3H, s, CH_(imino)); 1.19, 1.17, 1.09, 1.08 ppm (24H, 6 overlapping doublets; Me_(*i*Pr)). ¹³C NMR (125.72 MHz, [D₈]THF, 23°C): δ = 167.52, 165.96, 157.98, 155.66, 154.80 (C_(quaternary)); 144.24, 143.82 (CH_(pyridine)); 123.01, 122.83, 119.76, 119.38, 115.38 (CH_(aromatic)); 114.35 (CH_(pyridine)); 112.66 (CH_(aromatic)); 108.31 (C_(quaternary)); 83.09 (CH_(pyridine)); 67.75 (THF); 66.39 (CH₂); 35.55, 32.57 (CH_(*i*Pr)); 25.44 (THF); 24.99, 24.93, 24.50, 23.56 (Me_(*i*Pr)).

Crystal data for **1**: C₄₅H₆₇N₃Li₃O₃, *M*_r = 718.84, monoclinic, space group C2/c, *a* = 21.2094(11), *b* = 11.5121(7), *c* = 37.855(2) Å, β = 103.279(2)°, *V* = 8995.7(9) Å³, *Z* = 8, *T* = 233 K, *F*₀₀₀ = 3128, *R* = 0.0789, *wR*² = 0.2220, GOF = 1.043. **2**: C₄₉H₇₄N₃O₄Li₃, *M*_r = 789.93, monoclinic, space group P21/c, *a* = 15.0732(16), *b* = 18.855(2), *c* = 17.9425(19) Å, β = 105.170(2)°, *V* = 4921.6(9) Å³, *Z* = 4, *T* = 203°K, *F*₀₀₀ = 1720, *R* = 0.0759, *wR*² = 0.1971, GOF = 1.067. CCDC-189630 and -189631 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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Room-Temperature Synthesis in Acidic Media of Large-Pore Three-Dimensional Bicontinuous Mesoporous Silica with *Ia3d* Symmetry**

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Since the discovery of a new family of mesoporous silicate materials, denoted M41S and including MCM-41, MCM-48, and MCM-50, by researchers at Mobil,^[1] major developments have been made in this field. A great variety of mesostructures has been obtained, including mesoporous silica, metal oxides, metals, carbon, and hybrid organosilicates.^[2] Up to now, the main research efforts have concentrated on the MCM-41 silica structure, which consists of a hexagonal packing of one-dimensional (1D) channels (*p6mm*), and fewer investigations have been reported on mesoporous MCM-48, which has a 3D bicontinuous mesostructure (*Ia3d*). This may result from the small domain of this cubic phase (*Ia3d*) of MCM-48 in phase diagrams. Several methodologies have been developed for the syntheses of mesoporous silica MCM-48 by using a cationic alkylammonium surfactant,^[1,3] mixed cationic/anionic surfactants,^[4] or cationic/non-ionic surfactants as templates.^[5] Generally, these syntheses were carried out under the severe conditions of high-temperature ($\geq 100^\circ\text{C}$) hydrothermal synthesis in alkaline aqueous media. Relatively expensive ionic surfactants were employed, and the resulting mesostructures have a limited range of small pore sizes (pore diameter 1.5–4.5 nm). These restrictions may limit the potential applications of 3D bicontinuous mesoporous materials as adsorbents, separators, and catalysts.

Here we report the synthesis of large-pore 3D bicontinuous mesoporous silica (designated FDU-5) at room temperature in acidic media by using a commercial nonionic triblock copolymer as template and an organosiloxane or organic compound as additive. To the best of our knowledge, this is the first preparation of *Ia3d* mesostructured material at room temperature under acidic conditions. The FDU-5 products have uniform large pores (4.5–9.5 nm). Such mesoporous materials with large 3D bicontinuous pores could have applications in sorption and transport, especially of large molecules.

Large-pore 3D bicontinuous mesoporous FDU-5 was synthesized at room temperature in ethanol solution by a solvent-evaporation method. Triblock poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-poly(ethylene oxide) copolymer (EO₂₀PO₇₀EO₂₀, P123) was used as template, tetraethyl orthosilicate (TEOS) as silica source, and a small amount of 3-mercaptopropyltrimethoxysilane (MPTS), benzene, or a benzene derivative (methyl-, ethyl-, dimethyl-, or trimethylbenzene) as additive.

Transmission electron microscopy (TEM) images and corresponding Fourier diffractograms recorded along the [100], [111], [110], and [331] directions of calcined FDU-5 silica prepared with P123 as template and MPTS as additive in acidic medium at room temperature are shown in Figure 1. These images clearly show that the products have large domains of ordered 3D bicontinuous mesostructure. The two principal directions displaying continuous pores are [100] and [111] (Figure 1 a,b), and two types of hexagonally packed dots with different sizes and darkesses (Figure 1 b) are clearly observed. The images shown in Figure 1 are beautiful representative packing patterns for bicontinuous cubic mesostructures (*Ia3d*).^[6,7] The cell parameter *a* calculated from these TEM images is 18.0 nm. On the basis of these TEM

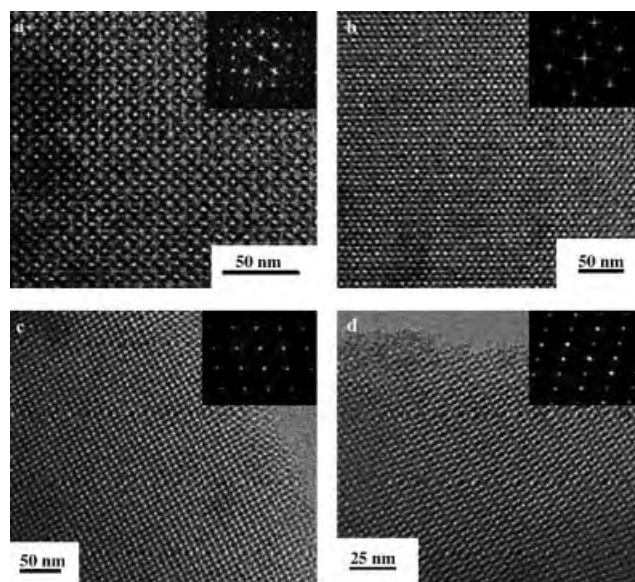


Figure 1. TEM images and corresponding Fourier diffractograms of calcined FDU-5 prepared at room temperature under acidic conditions with triblock copolymer P123 as template and MPTS as additive. The images were recorded along the directions [100] (a), [111] (b), [110] (c), and [331] (d).

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images, corresponding Fourier diffractograms, and the results of simulations,^[6] we assign the mesoporous silica a 3D cubic *Ia3d* mesostructure.

X-ray powder diffraction (XRD) patterns (Figure 2) further confirm the cubic *Ia3d*-type mesostructure of FDU-5 prepared in acidic medium at room temperature. Although only two diffraction peaks can be observed for the as-made sample (Figure 2a), their *d*-spacing ratio is exactly 0.866,

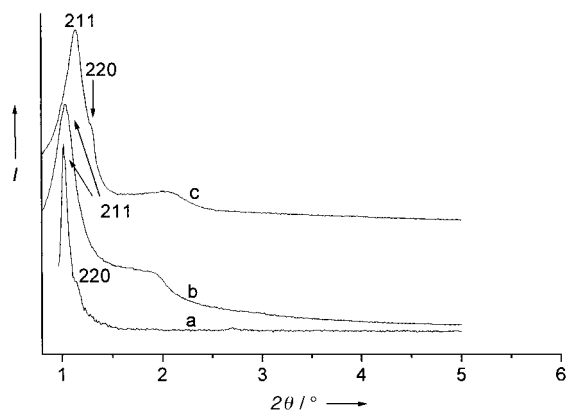


Figure 2. XRD patterns for a) as-made, b) ethanol-extracted, and c) calcined mesoporous FDU-5 synthesized at room temperature under acidic conditions with P123 as template and MPTS as additive.

which implies that these two peaks can be indexed as (211) and (220) diffraction peaks of mesoporous bicontinuous cubic space group *Ia3d*. The unit cell parameter *a* of the as-made sample, calculated from XRD data, is as large as 21.1 nm. After extraction by ethanol, the two diffraction peaks merge into one broad reflection peak. The additional broad diffraction peak in the range of $2\theta = 1.5\text{--}2.2$ may arise from overlapping of (321), (400), (420), and (332) diffraction peaks of the *Ia3d* space group. The XRD pattern of the calcined sample (Figure 2c) features one high-intensity Bragg peak and a shoulder peak, which can be indexed as (211) and (220) and show a typical pattern for *Ia3d* mesostructures. Similar to that observed for the extracted sample, a broad diffraction peak in the range of $2\theta = 1.7\text{--}2.4$ is also observed. The cell parameter *a* of the calcined sample was calculated to be 18.2 nm, in good agreement with the value estimated from TEM images, and suggests that the mesoporous silica FDU-5 has a bicontinuous cubic *Ia3d*-type mesostructure.

Nitrogen adsorption–desorption isotherms (Figure 3) for both extracted and calcined samples show type IV curves with typical H_1 hysteresis loops, and this implies that the samples have large 3D bicontinuous mesopores without windows or necks. The calcined mesoporous FDU-5 has a narrow pore size distribution with a mean value of 8.1 nm, a BET surface area of $804\text{ m}^2\text{g}^{-1}$, and a pore volume of $1.04\text{ cm}^3\text{g}^{-1}$. The ethanol-extracted mesoporous FDU-5 has also a narrow pore size distribution, but with a relatively small mean value of 5.9 nm, a BET surface area of $399\text{ m}^2\text{g}^{-1}$, and a pore volume of $0.55\text{ cm}^3\text{g}^{-1}$. The relatively small pore diameter, surface area, and pore volume of the extracted sample may result from the organic functional groups that remain in the channels.

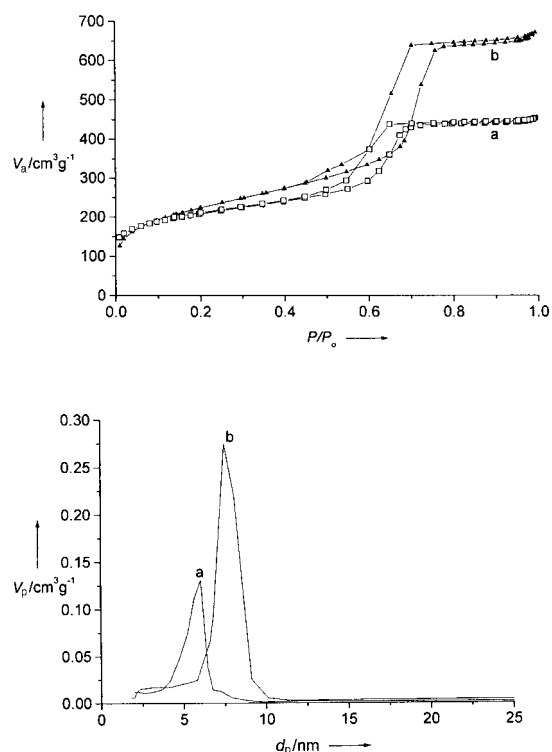


Figure 3. Nitrogen adsorption–desorption isotherms (top) and pore size distribution curves (bottom) calculated from the adsorption branch of the isotherms for a) extracted and b) calcined FDU-5 synthesized at room temperature under acidic conditions with P123 as template and MPTS as additive. The pore size was calculated by Barrett–Joyner–Halenda (BJH) analysis. V_a : volume adsorbed, V_p : pore volume, d_p : pore diameter.

The organosiloxane or organic additive plays an essential role in the formation of *Ia3d*-type mesostructures under acidic conditions at room temperature. With MPTS as additive, mesoporous FDU-5 is formed only for an MPTS/TEOS molar ratio of 0.046–0.058. Without organosiloxane, 2D hexagonal (*p6mm*) mesostructure is obtained from TEOS as sole silica source.^[8] With MPTS/TEOS ratios smaller than 0.046, the products consisted of a mixture of hexagonal (*p6mm*) and cubic (*Ia3d*) mesostructured phases (see Supporting Information), and this suggests that a phase transition occurs. The addition of organosiloxane or small organic molecules may increase the hydrophobic/hydrophilic ratio and result in a transition of the cooperatively assembled inorganic–organic mesostructure from high-curvature hexagonal *p6mm* to low-curvature bicontinuous cubic *Ia3d*.^[9,10] An analogous phase transition was also observed in previous syntheses of *Ia3d* mesostructured MCM-48 in an aqueous system during hydrothermal treatment owing to the increase in the hydrophobic portion caused by the hydrophobicity of organic co-solvents such as alcohols.^[3a,c,e,f,11] Moreover, high-curvature cubic *Pm3n* mesostructures can be transformed into low-curvature hexagonal *p6mm* mesostructures by increasing the hydrophobic/hydrophilic ratio in an aqueous reaction system by addition of co-solvents.^[3e,12] However, previous methodologies^[3a,c,e,f,11] for obtaining *Ia3d* mesostructures by phase transition required high-temperature processes ($\geq 100^\circ\text{C}$) and alkaline media. In our procedure, such a conversion can

be attained economically (cheap template) with the aid of an additive under mild conditions (low temperature).

The solid-state ^{29}Si magic-angle spinning (MAS) NMR spectrum (see Supporting Information) of as-made mesoporous FDU-5 prepared by using MPTS as an additive under acidic conditions at room temperature exhibits four signals corresponding to T_2 ($\delta = -53$), T_3 ($\delta = -66$), Q_3 ($\delta = -101$), and Q_4 ($\delta = -111$ ppm), where T_2 and T_3 represent the species $\text{RSi}(\text{OSi})_2\text{OH}$ and $\text{RSi}(\text{OSi})_3$, and Q_3 and Q_4 correspond to $\text{Si}(\text{OSi})_3\text{OH}$ and $\text{Si}(\text{OSi})_4$ moieties. The results suggest that large-pore 3D bicontinuous mesoporous material with functional organic groups can be formed in one step under acidic conditions at room temperature. The $(T_3 + Q_4)/(T_2 + Q_3)$ ratio of 3.77 suggests a high degree of framework cross-linking.^[13] The amount (4.6%) of organic moieties incorporated in the mesostructure, calculated by the ratio $T/(T + Q)$ ($T = T_2 + T_3$, $Q = Q_3 + Q_4$), is in accordance with that calculated from the initial composition (5.1%).

In summary, 3D bicontinuous cubic $1a3d$ -type mesoporous silica has been synthesized for the first time in acidic medium at room temperature by using a nonionic triblock copolymer as template. The resulting FDU-5 materials have extra-large pores (4.5–9.5 nm) with narrow size distributions. Such materials could have promising applications for the sorption, transport, and separation of large molecules.

Experimental Section

Typical synthesis of FDU-5: P123 (1 g, $M_w = 5800$, Aldrich) was dispersed with HCl solution (0.1 g, 2 M) and H_2O (0.9 g) in EtOH (10 g). After stirring vigorously at room temperature for 2 h, MPTS (0.106 g, 5.4 mmol) was added. After a further 2 h of stirring, TEOS (2.08 g, 10 mmol) was added. Then the mixture was stirred for 1 h. The resulting solution was dried in air for 2 d, and a solid white product was obtained. The surfactant P123 was removed from the as-synthesized material by washing with ethanol under reflux for 40 h or by calcining the product at 823 K for 6 h. The molar composition of the reaction mixture $\text{TEOS}/\text{P123}/\text{HCl}/\text{H}_2\text{O}/\text{EtOH}/\text{additive}$ was $1/0.015\text{--}0.020/0.018\text{--}0.096/2.44\text{--}6.97/11\text{--}52/x$, where x varied in the ranges of 0.046–0.058, 0.048–0.66, 0.042–0.60, 0.035–0.54, and 0.030–0.47 for MPTS, benzene, methylbenzene, 1,4-dimethylbenzene, and 1,3,5-trimethylbenzene as additive, respectively.

Characterization: TEM photographs were obtained on a JEOL 2010 microscope operated at 200 kV. XRD patterns were obtained on a Bruker D4 X-Ray diffractometer with $\text{Cu}_{K\alpha}$ radiation. Nitrogen adsorption-desorption isotherms were acquired on a Micromeritics Tristar 3000 system at 77 K. ^{29}Si NMR experiments were performed on a Bruker DSX300 spectrometer with a frequency of 59.63 MHz, a recycling delay of 600 s, and a radiation frequency intensity of 62.5 KHz.

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Transmembrane Signalling**

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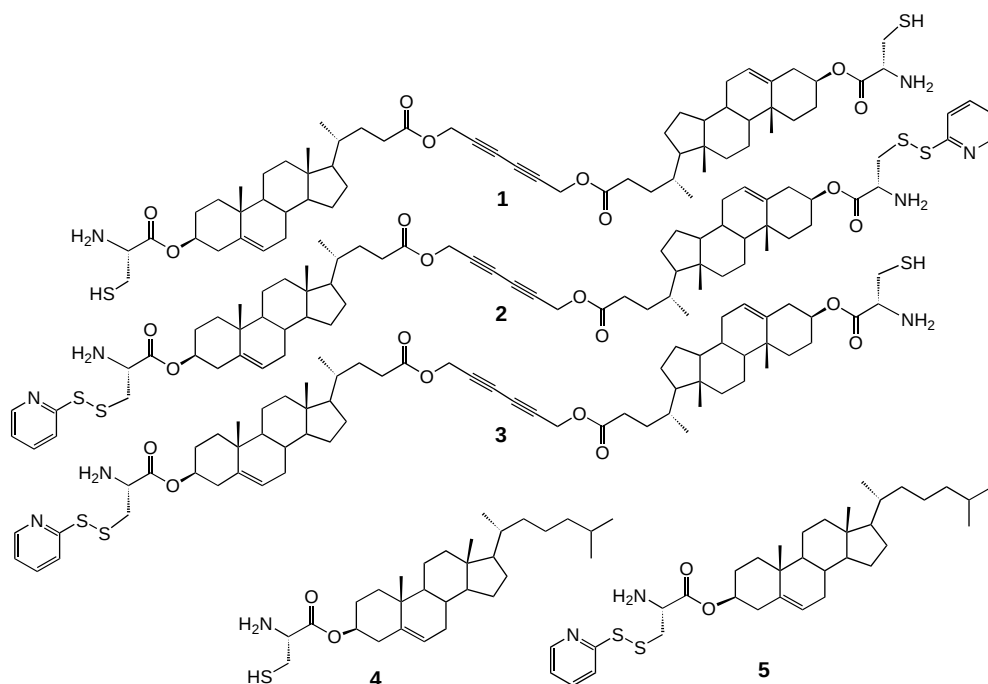
Cells are separated from their surroundings by a lipid bilayer membrane, yet their survival depends on their ability to sense and respond to changes in the environment such as the levels of extracellular hormones, growth factors, cytokines, nutrients, and pathogens. One way in which these molecular signals can change the intracellular chemistry is by being transported into the cell through active transport or pores in the membrane. To date, synthetic approaches to communication across lipid membranes have relied on mimicking this direct physical transport of the molecular signal across the

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Scheme 1. Membrane-spanning molecules **1**, **2**, and **3**, with the control compounds **4** and **5**.

membrane. However, this approach means that the external and internal chemistry are not separated and that the message and response have to be intimately linked.^[1–3] An alternative biological mechanism is to transduce the signal with proteins that span the cellular membrane, as exemplified by G-protein-coupled receptors and tyrosine kinase receptors; for example, an external ligand can make tyrosine kinase receptors dimerize; the dimer then autophosphorylates its intracellular domain, which initiates a cascade of events inside the cell.^[4] This cascade provides a mechanism for coupling but separating the chemistry on the inside and outside of the cell—in contrast to transport mechanisms, the message and signal can be chemically unrelated and potentially harmful messenger molecules are excluded. Here we describe a synthetic system capable of molecular signal transduction without physical transport of the messenger across the membrane.

Our approach is based on the mode of action of the tyrosine kinase receptors described above and uses synthetic compounds to send and transform a signal across a unilamellar vesicle membrane. The signal-transducing molecule must

span the lipid-bilayer membrane with sensor units directed towards the outside of the vesicle and signalling units on the inside. Compounds **1**, **2**, and **3** were designed for the assembly of such a system (Scheme 1). To construct the transmembrane section, we used cholenic acid, a naturally occurring bifunctional steroid from which tail-to-tail cholesterol dimers can be synthesized. Cholesterol inserts well into membranes, and the straight, relatively rigid dimer structure should favor a transmembrane conformation, leading to strong coupling between the locations of the external and internal head groups. The sensor and signalling units both exploit thiol–disulfide chemistry, allowing construction of an unsymmetrical signal transduction system from relatively simple symmetrical compounds.^[5–7] The amino acid cysteine provides an ideal charged headgroup that has a thiol functional group and can be readily attached to the cholesterol dimer (Scheme 1). The sensing event is the oxidation of the thiol group to a disulfide group on the outside of the membrane, which induces dimerization of the signal-transducing molecules (Figure 1). The signalling event is the reaction of a thiol

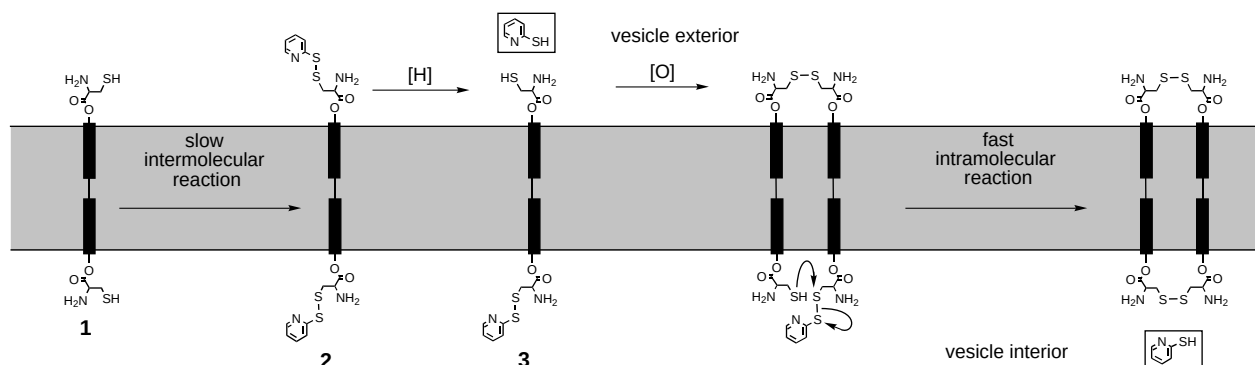


Figure 1. Chemical scheme showing the sensing and signalling reactions.

moiety on the inside of the membrane with an activated disulfide group, which releases a colored species, pyridine-2-thiol, detectable by UV/Vis absorption spectroscopy. The idea is that the intermolecular reaction should be slow, but following dimerization of the external sensing groups, the internal signalling groups are brought into close proximity, which gives rise to fast intramolecular reaction (Figure 1).

The first requirement is clearly the identification of a thiol/disulfide pair that is unreactive under dilute conditions but can be forced to react at higher concentrations in the lipid membrane. A series of model compounds were prepared from cholesterol and cysteine, and **4** and **5** exhibited the desired behavior. Unilamellar 200 nm egg yolk phosphatidylcholine vesicles containing **4** and **5** were prepared by extrusion of a mixture of the lipid and the cholesterol derivatives through 200 nm polycarbonate membranes.^[8,9] At pH 5.5 and a membrane loading of 2.5 mol %, no release of pyridine-2-thiol was observed by UV/Vis absorption spectroscopy over a period of hours. The integrity of the functional groups was confirmed by adding external reagents: addition of 2,2'-dipyridyl disulfide led to an increase in the UV/Vis absorption at 341 nm, caused by the release of pyridine-2-thiol, which confirmed the presence of reactive thiol groups in the (**4** + **5**) vesicles;^[10] addition of dithiothreitol also led to the release of pyridine-2-thiol, which confirmed the presence of reactive disulfide groups in the (**4** + **5**) vesicles.^[11] In both cases, the magnitude of the response indicated that little reaction had taken place between **4** and **5** in the course of vesicle preparation. Thus **4** and **5** can be incorporated intact into bilayer membranes and, once inserted, they do not react under dilute conditions.

Compound **1** was synthesized from cholenic acid in four steps. The key step was formation of the propargyl ester of cholenic acid to give an analogue of cholesterol, from which tail-to-tail dimers could be prepared using Glaser–Hay coupling.^[12] The dialkyne linker provides the rigidity required for close coupling of the locations of the internal and external cholesterol units. Cysteine units were attached to both ends of the dimer to give **1**. Derivatization with 2,2'-dipyridyl disulfide converted **1** into **2** (Scheme 1). Unilamellar 200 nm egg yolk phosphatidylcholine vesicles containing **1** and **2** were prepared by extrusion of a mixture of the lipid and the cholesterol derivatives. This procedure favors a membrane-spanning conformation over insertion of compounds from solution after vesicle preparation.^[13] The integrity of the functional groups was again checked by adding 2,2'-dipyridyl disulfide to test for thiol groups, and dithiothreitol to test for disulfide groups, as before, and showed that both **1** and **2** were incorporated into the vesicles intact. As with the model compounds, no release of pyridine-2-thiol was observed over a period of hours, which indicates that the assembly is stable, and that no reaction takes place between **1** and **2** in the membrane.

The active signal transduction system was then revealed by deprotection of the external disulfide units using tris(3-sulfonatophenyl)phosphane, a charged reducing agent which does not cross the lipid membrane.^[14] This phosphane selectively reduces the external disulfide groups, converting **2** into **3** so that the unsymmetrical product is oriented across

the membrane with all of the remaining disulfide units located on the inside of the vesicle (Figure 1). Exposure of these (**1** + **3**) vesicles to potassium ferricyanide, an external oxidant that is incapable of crossing the vesicle membrane, gave an increase in the UV/Vis absorption at 341 nm, which corresponds to the release of pyridine-2-thiol on the inside of the vesicle.^[15] The change in absorption is not accompanied by an increase in turbidity, which would originate from vesicle aggregation.

Thus the system appears to function in the desired manner: the inside of the vesicle responds to the presence of an external messenger molecule, ferricyanide, with the release of a second messenger, pyridine-2-thiol. The complete experiment is illustrated in Figure 2. The (**1** + **2**) vesicles can be prepared and stored with no reaction (resting, Figure 2c). These vesicles are equipped with a safety catch, the external disulfide, that renders them insensitive to the messenger molecule. Thus, addition of ferricyanide to (**1** + **2**) vesicles causes no change in the UV/Vis absorption spectrum (safety catch on, [O], Figure 2a,c). Release of the safety catch by external reduction (addition of the phosphane) causes a rapid increase in the absorbance at 341 nm over a period of about 10 min, caused by the release of pyridine-2-thiol on the outside of the vesicles ([H], Figure 2a,c). This reduction generates the active (**1** + **3**) vesicles, and when these are exposed to the messenger molecule (ferricyanide), a further jump in the absorption at 341 nm is observed, caused by the production of a second messenger molecule ("internal" pyridine-2-thiol) inside the vesicles (safety catch off, [O], Figure 2).

As a control, the (**4** + **5**) vesicles were subjected to the same conditions. The only difference between the (**1** + **2**) and (**4** + **5**) vesicles is that the connection between the inside and outside steroid units has been severed. As with the "safety catch on" (**1** + **2**) vesicles, the (**4** + **5**) vesicles are stable (resting, Figure 2c) and insensitive to oxidation by the messenger ferricyanide (control 1, [O], Figure 2b). External reduction generates pyridine-2-thiol over a period of 10 min as before ([H], Figure 2), but now addition of external oxidant causes no further change in the UV/Vis absorption spectrum (control 2, [O], Figure 2c). The failure of the messenger to trigger a response in this system is caused by the absence of a covalent connection across the membrane, so that the inside of the vesicles is isolated from the outside, and no signal transduction is possible.

In conclusion, a simple synthetic system has been constructed which successfully mimics biological signal transduction. The system consists of two membrane-spanning molecules embedded in egg yolk phosphatidylcholine vesicles. A safety catch renders the system unresponsive until it is released by addition of an external reducing agent. The vesicles then respond to the presence of an external oxidant by releasing a colored second messenger molecule on the inside of the vesicle. Thus, molecular communication is possible across the membrane without direct contact between the species involved. The flexibility inherent in our synthetic methodology will allow us to adapt both the sensor and signalling modules, retaining the same molecular framework for signal transduction, and this opens the way for the

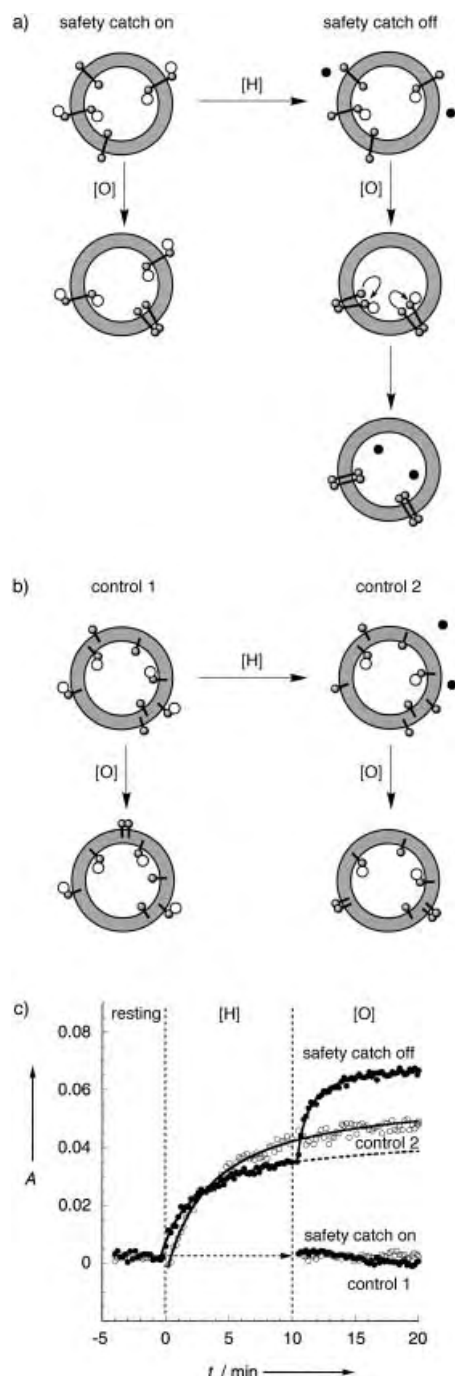


Figure 2. Mechanism of action and optical signals observed for compounds **1–5** embedded in vesicle membranes, for details see text. a) **1** and **2** embedded in the membrane. b) The control experiment using **4** and **5**. c) Change in absorbance at 341 nm, which indicates the release of pyridine-2-thiol (membrane-spanning molecules ●, control compounds ○). The resting period before reagents are added shows that no reaction takes place between the membrane embedded thiols and disulfides. At $t=0$, tris(3-sulfonatophenyl)phosphane [H] was added. For both the control compounds and the membrane-spanning molecules, an increase is observed caused by the release of extravesicular pyridine-2-thiol. The kinetics of release could be fit using the same second-order rate constant $k=100\text{ M}^{-1}\text{ s}^{-1}$ for both systems (theoretical lines shown). After 10 minutes, potassium ferricyanide [O] was added. The membrane-spanning molecules (safety catch off) generated a new signal, but no further change was observed for the control compounds. If oxidant were added without releasing the safety catch, no signal was observed for the membrane-spanning molecules (safety catch on) or the control compounds. Instantaneous jumps in absorbance caused by addition of reagents are not shown.

development of novel sensing and controlled-release technology for a wide range of messenger molecules.

Experimental Section

All compounds were made using standard synthetic procedures and gave satisfactory spectroscopic data (see Supporting Information).

Vesicles were prepared to give a final lipid concentration of 2 mM in all cases. Egg yolk 1- α -phosphatidyl choline was dissolved in HPLC grade chloroform. A chloroform solution of the dopant compound was added to the lipid solution so that the concentration in the final vesicular solution was 50 μM . The lipid was deposited as a thin film by removal of the solvent under reduced pressure, followed by freeze-drying. Buffer (50 mM morpholine ethanesulfonate (MES), pH 5.5, 1 mL) was added to the thin film and the mixture stirred with a vortex mixer. The resulting suspension was passed through a 200 nm polycarbonate filter in an Avestin Lipofast extrusion apparatus 19 times, to give 200 nm diameter unilamellar vesicles.

This solution was added to a cuvette, and left to equilibrate for 10 min at 25°C before any external reagents were added.

Changes in absorbance were monitored as a function of time at 341 nm (the absorbance wavelength of the pyridine-2-thiol leaving group) using a Cary3 UV spectrophotometer. Multiple wavelength scans were taken before and after each experiment to ensure that the changes taking place were caused by the product chromophore, and not by changes in the turbidity of the solution.

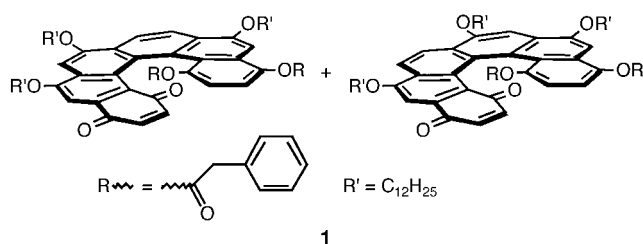
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Electric-Field-Modulated Circular-Difference Effects in Second-Harmonic Generation from a Chiral Liquid Crystal**

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Nonracemic chiral structures do not need to be subjected to such demanding procedures as acentric crystallization, electric-field poling, optical poling, or Langmuir–Blodgett film construction to obtain the noncentrosymmetrical materials required for the observation of second-order nonlinear optical (NLO) effects.^[1,2] Indeed, nonracemic calamitic mesophases assembled in tilted smectic phases, and nonracemic helical discotic materials in columnar arrays have produced substantial second-harmonic generation (SHG).^[3,4] When such systems are excited by circularly polarized light, the harmonics are dependent upon the direction of light polarization; the circular-difference (CD) effects are opposite in sign for the two enantiomers.^[5,6] Here we show that the CD effects are also reversed in sign for a liquid-crystalline substrate of fixed handedness when the polarity of an orienting electric field is reversed. A chiral discotic nematic phase has been studied, consisting of a mixture of the isomeric nonracemic (*M*)-(-)-helicenes **1** and dodecane. It is known that compounds such as



1, when dissolved in dodecane, aggregate into helical columns and form discotic nematic liquid-crystalline phases. The columns, whose orientations can be affected by electric fields, have dipole moments parallel to their long axes.^[7,8] The experiments described below show that the material also exhibits a significant second-order NLO response in the absence of an orienting electric field, and a markedly increased response under the influence of such a field.

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Samples were prepared by placing solutions of (*M*)-(-)-helicene (**1**, 20 wt % dissolved in dodecane) into rubbed 4 μm LC cells at room temperature.^[9] For the SHG experiments, a Q-switched Nd:YAG laser beam (1064 nm, 5 ns pulses, 100 Hz repetition frequency, beam diameter of 2 mm) was directed onto the sample at an angle of 45°, and the second-harmonic light was detected in the transmitted direction. Half- and quarter-wave plates were used to control the polarization of the irradiating fundamental beam, and the second-harmonic light was resolved into *p*- and *s*-polarized components.^[10] The second-harmonic signals arise from the quadratic response of the sample to the fundamental laser beam. This response is represented by the nonlinear polarization given in Equation (1), where *ijk* are Cartesian coordinates, $E_j(\omega)$ and $E_k(\omega)$ are components of the optical field at the fundamental frequency, $\chi_{ijk}^{(2)}$ is a component of the second-order susceptibility tensor, and $P_i(2\omega)$ is a component of the nonlinear source polarization at the second-harmonic frequency.

$$P_i(2\omega) = \sum_{jk} \chi_{ijk}^{(2)} E_j(\omega) E_k(\omega) \quad (1)$$

First, samples were studied in the absence of an orienting electric field. To analyze their symmetry, they were irradiated with *s*- and *p*-polarized fundamental light incident at 45°. They were then continuously rotated around their surface normals so that the *s*- and *p*-polarized second-harmonic components could be measured. The only second-harmonic signal detected was the *p*-*s* signal (*p*-polarized fundamental, *s*-polarized second-harmonic), and its magnitude was independent of the rotational angle. This implies that the planes within the samples are isotropic and that their symmetry is D_{∞} .^[11] This observation is in agreement with a previous report, which suggested that compounds such as this give discotic nematic phases that are not oriented by rubbed surfaces.^[8] For such disordered systems, only the $\chi_{xyz}^{(2)}$ susceptibility components can differ from zero. It should be noted that these are apolar components; they do not vanish in samples that have no polar order. Furthermore, because they are only finite in chiral samples, they are often referred to as chiral components. A comparison of the SHG signals from the samples and from a quartz reference ($d_{11} = 0.3 \text{ pm V}^{-1}$) showed that $\chi_{xyz}^{(2)} = 0.13 \text{ pm V}^{-1}$.^[12] The result is notable because it shows for the first time that significant second harmonics can be generated from disordered phases.^[13]

An electric field was then applied to the cell, perpendicular to the sample plane. The effect on an initially birefringent sample, sandwiched between crossed polarizers and viewed through an optical microscope, was to extinguish the light that passed through the cell (Figure 1). This phenomenon has also been observed in a related material.^[8] Both this result and the NLO response showed that such samples are isotropic in the plane, but the single SHG signal observed before the electric field was applied is now replaced by three signals: *p*-*p*, *p*-*s*, and *s*-*p*. These observations suggest that polar order is imposed on the material by the helical columns orienting themselves parallel to the electric field. A consequence of the resulting C_{∞} symmetry is that more susceptibility components

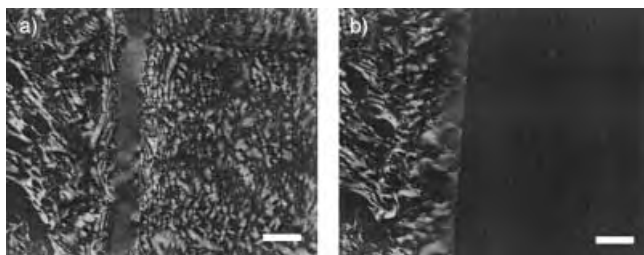


Figure 1. Microscopic images of the same section of a solution of **1** (20 wt %) in dodecane contained within a 4 μm thick electrooptic cell sandwiched between crossed polarizers: a) in the absence of an applied electric field; b) with an applied electric field of 9 V μm⁻¹. The electrode covers only the right side of the field of view. The length of the scale bar is 100 μm.

are required: $\chi_{xyz}^{(2)}$, $\chi_{xxz}^{(2)}$, $\chi_{zxx}^{(2)}$, and $\chi_{zzz}^{(2)}$. The last three of these, which are polar components, are finite only in media that have net polar order. Since they can contribute to any sample, chiral or achiral, they often are referred to as achiral components. A series of polarization measurements yielded the relative magnitudes and phases of the susceptibility components and, when calibrated against a quartz reference, the following values: $\chi_{xyz}^{(2)} = (-0.68 + i0.16)$ pm V⁻¹, $\chi_{xxz}^{(2)} = 0.51$ pm V⁻¹, $\chi_{zxx}^{(2)} = (0.59 + i0.03)$ pm V⁻¹, and $\chi_{xyz}^{(2)} = (1.22 + i0.1)$ pm V⁻¹.^[12,14] Although these values are not large enough for commercial NLO applications, their magnitudes are sufficient to indicate the potential of the material. The applied electric field was +10 V μm⁻¹.

The response of a sample to the electric field is shown in Figure 2. The second-harmonic signal was monitored as a function of time. When the field of +10 V μm⁻¹ was applied the signal suddenly increased by a factor of 3.5. When the field was switched off the system relaxed to its original state over a period of several minutes. It is noteworthy that the signal falls to zero when the field is switched on or off, a consequence of interference between the additional susceptibility components that arise in the orienting field.

Reversing the polarity of the applied electric field to -10 V μm⁻¹ has a profound effect on the values of the

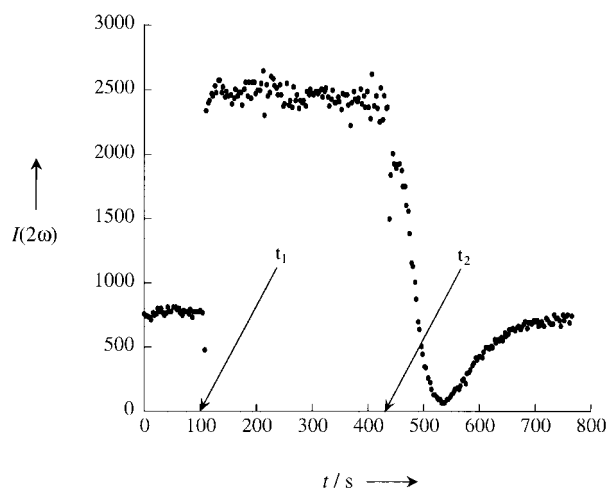


Figure 2. Plot of the second-harmonic signal intensity from **1** ($I(2\omega)$, in arbitrary units) versus time t . At time t_1 a field of 10 V μm⁻¹ was applied, and at time t_2 the field was switched off.

susceptibility components. Within experimental error (typically around 10 % for the xyz , zxx , and xxz components, and approximately 35 % for the zzz component) their magnitudes are unaffected and the apolar (or chiral) component is unchanged, but the signs of the polar (achiral) components are reversed: $\chi_{xyz}^{(2)} = (-0.64 + i0.15)$ pm V⁻¹, $\chi_{xxz}^{(2)} = -0.47$ pm V⁻¹, $\chi_{zxx}^{(2)} = (-0.58 - i0.002)$ pm V⁻¹, and $\chi_{zzz}^{(2)} = (-0.78 - i0.015)$ pm V⁻¹. These results are important because the ability to reverse the sign of susceptibility components allows the use of quasi-phase matching to prepare efficient frequency-conversion devices.^[15]

Finally, the CD effects were analyzed by examining the transmitted second-harmonic light. The samples were illuminated with left- and right-handed circularly polarized light, and the s -polarized component of the resulting second-harmonic light was detected. In general, CD effects in SHG can be expressed as given in Equation (2);^[5]

$$\frac{\Delta I(2\omega)}{I(2\omega)} = \frac{2(I(2\omega)_{\text{left}} - I(2\omega)_{\text{right}})}{I(2\omega)_{\text{left}} + I(2\omega)_{\text{right}}} \quad (2)$$

where $\Delta I(2\omega)/I(2\omega)$ is the normalized second-harmonic intensity difference and $I(2\omega)_{\text{left}}$ and $I(2\omega)_{\text{right}}$ are the second-harmonic intensities excited by left- and right-handed circularly polarized fundamental light. The CD has its origin in the interference of the chiral and achiral susceptibility components. For example, for an experimental configuration in which the fundamental laser beam is incident on the sample at 45° and the p -polarized second-harmonic component is measured in transmission, the CD response is given in Equation (3);^[16]

$$\frac{\Delta I(2\omega)}{I(2\omega)} = \frac{-4\sqrt{2}Im(\chi_{xyz}^{(2)}\chi_{xxz}^{(2)*})}{|\chi_{xyz}^{(2)}|^2 + 2|\chi_{xxz}^{(2)}|^2} \quad (3)$$

This expression implies that for CD effects to be observed in the SHG, the chiral and achiral component must differ from zero, which is in agreement with the experimental observation that for unoriented samples, second-harmonic efficiency does not vary with the helicity of the incoming light. There is only one nonzero susceptibility component, and $\Delta I(2\omega)/I(2\omega)$ is zero. However, when the samples are oriented, the achiral xxz component becomes apparent, and CD effects are therefore observed. Furthermore, the sign of the CD response changes when the polarity of the orienting field is reversed. For example, for the s -polarized component of the second-harmonic field, the experimental CD response changes from -43 to +45 %. This extraordinary observation (the handedness of the sample remains unchanged) can be explained, as indicated in the above expression for $\Delta I(2\omega)/I(2\omega)$, by the change in sign of the achiral susceptibility components, with respect to the chiral components. There is, to our knowledge, only one other example in which optical activity effects have been altered by a method that does not involve a change in the chirality of the sample; in that case alteration was induced by the reversal of a magnetic field.^[17] The change reported here is induced by the reversal of an electric field. Possible applications could include optical switches, phase-shifters, and quasi-phase matching. Note that the effect cannot be observed in

linear optics since it would require the refractive index to change sign.

In conclusion, we have shown that a chiral discotic nematic liquid crystal in the absence of an orienting electric field is apolar and has only one second-order NLO susceptibility component. In the presence of an orienting electric field, it becomes polar and displays four significant susceptibility components. In the unoriented state, there are no CD effects on second-harmonic efficiency, even though the linear circular dichroisms and optical rotations are large. In the oriented state, such CD effects are seen, and they change sign when the polarity of the orienting field is reversed.

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Diastereoselective Lithiation of (η^6 -Arene)dicarbonyltriphenylphosphane Chromium(0) Oxazoline Complexes—Direct Preparation of Enantiopure Complexes Having Planar Chiral Fragments of Either Configuration**

Larry E. Overman,* Carolyn E. Owen, and G. Greg Zipp

Planar chiral η^6 -arene chromium(0) complexes are finding increasing application in the synthesis of enantioenriched compounds by serving as enantiopure starting materials or ligands for catalytic asymmetric processes.^[1,2] Whereas early methods of generating enantiopure 1,2-disubstituted η^6 -arene chromium(0) complexes relied on resolution of racemates,^[3] many methods have been developed recently for asymmetric synthesis of these molecules.^[1] One powerful strategy employs an enantiopure chiral lithium reagent (or an achiral lithium reagent plus a chiral additive) to elaborate a prochiral complex by either enantioselective ring lithiation followed by trapping with an electrophile,^[4] or enantioselective nucleophilic addition followed by abstraction of hydride.^[5] Another strategy involves diastereoselective lithiation of a monosubstituted η^6 -arene chromium(0) complex containing a chiral, nonracemic substituent that is capable of directing *ortho* lithiation.^[6]

We recently introduced chiral ferrocenyl oxazoline palladacycles as catalysts for the asymmetric addition of external (that is, not bound to a metal) nucleophiles to prochiral alkenes.^[7] To further explore this general catalyst architecture, we became interested in the synthesis of related η^6 -arene chromium(0) complexes. The precursors of the ferrocenyl catalysts were prepared by diastereoselective *ortho* lithiation of enantiopure chiral ferrocenyl oxazolines with alkyl lithium reagents.^[8] Unfortunately, this convenient approach cannot be used to prepare (η^6 -arene)tricarbonylchromium(0) complexes, as lithium reagents are known to add to such complexes containing strong acceptor substituents such as imines or oxazolines.^[1c,5,9] Herein we report that less electron deficient (η^6 -arene)dicarbonyl(triphenylphosphane) chromium(0) oxazoline complexes undergo *ortho* lithiation, rather than addition, upon exposure to either *sec*- or *n*-butyllithium, and that, depending on the presence or absence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA), either diastereomer

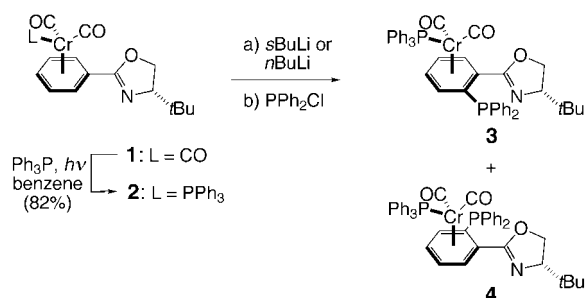
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of the 1,2-disubstituted arene chromium(0) complex can be prepared with high selectivity.^[10]

Photolytic replacement of a carbonyl ligand^[11] of complex **1**^[12] by triphenylphosphane provided complex **2** as a crystalline red solid in good yield (Scheme 1). Reaction of **2** with



Scheme 1. Synthesis of oxazolines **3** and **4** by metalation of **2** and quenching with PPh₂Cl. Diastereoselectivity (**3**:**4**): in Et₂O (−78 °C), 18:1; in Et₂O/TMEDA (−78 °C), 1:50.

1.5 equiv of *n*-butyllithium at −78 °C in Et₂O, followed by warming to −30 °C and quenching with chlorodiphenylphosphane provided the chromium(0)-complexed aryl phosphane oxazolines **3** and **4** in a 10:1 ratio. The diastereoselectivity of this transformation was improved when the lithiation was conducted with *sec*-butyllithium at −78 °C and the intermediate organolithium species was trapped at this temperature. By this procedure, diastereomers **3** and **4** were produced in an 18:1 ratio and 59 % yield.^[13,14] As summarized in Table 1, varying the electrophile allows a variety of related 1,2-disubstituted η⁶-arene chromium(0) complexes to be prepared in useful chemical yields and high diastereoselectivities (18–50:1).

Table 1. Metalation of **2** with *s*BuLi in Et₂O.

Product	E	EX	yield [%]	d.r.
3	PPh ₂	Ph ₂ PCl	59	18:1
5	SePh	PhSeSePh	59	22:1
6	CO ₂ Me	MeO ₂ CCl ^[a]	56	18:1
7	I	I(CH ₂) ₂ I	66	20:1
8	CH(OH)Ph	PhCHO	68	13:1 ^[b]
9	Me	MeI	48	50:1 ^[c]
10	TMS	TMSCl	63	25:1 ^[c]

[a] The ketone product resulting from double aryl lithium addition was not observed. [b] A 1:1 mixture of alcohol epimers was obtained. [c] Reaction was maintained at 4 °C for 18 hours before quenching.

Complexes possessing a planar chiral moiety of the opposite absolute configuration can be formed with high selectivity by a simple modification of the lithiation conditions. Thus, addition of 1.5 equiv of *n*-butyllithium to a solution of oxazoline **2**, TMEDA (1.5 equiv), and Et₂O at −78 °C, followed by quenching at this temperature with chlorodiphenylphosphane provided **4** and **3** in a 50:1 ratio and

81 % yield.^[13] By using this procedure, various 1,2-disubstituted (η⁶-arene)chromium(0) complexes were prepared in excellent chemical yield and diastereoselectivity (10:1–50:1) (Table 2). In some cases, diastereoselection was improved slightly when the reaction mixture was warmed to −30 °C prior to adding the electrophile. Interestingly, although benzylic alcohol **8** was generated as a 1:1 mixture of alcohol epimers (Table 1), diastereomer **14** was produced as a single alcohol epimer (Table 2).

Table 2. Metalation of **2** with *n*BuLi-TMEDA in Et₂O.

Product	E	EX	T [°C]	yield [%]	d.r.
4	PPh ₂	Ph ₂ PCl	−78	81	50:1
			−30	86	25:1
11	SePh	PhSeSePh	−78	82	16:1
			−30	78	22:1
12	CO ₂ Me	MeO ₂ CCl ^[a]	−78	60	13:1
			−30	75	17:1
13	I	I(CH ₂) ₂ I	−78	69	20:1
			−30	76	13:1
14	CH(OH)Ph	PhCHO	−30	78	10:1 ^[b]
15	Me	MeI	4	38	15:1
16	TMS	TMSCl	4	81	14:1

[a] The ketone product resulting from double aryl lithium addition was not observed. [b] Produced as a single alcohol epimer.

The relative configuration of (η⁶-arene)chromium(0) complex **7** was determined by single-crystal X-ray analysis^[15] (Figure 1) and that of **10** and **16**^[16] by chemical correlation of the latter with the dextrorotatory *S*_p enantiomer of tricarbonyl(η⁶-2-trimethylsilylbenzaldehyde)chromium(0).^[17,18] The relative configurations of other complexes reported in Tables 1 and 2 were assigned by analogy.

Steric interactions between the oxazoline *tert*-butyl substituent, the chromium tripod, and the base should determine

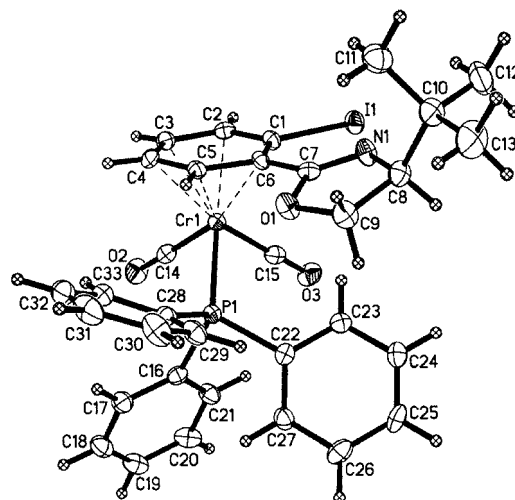
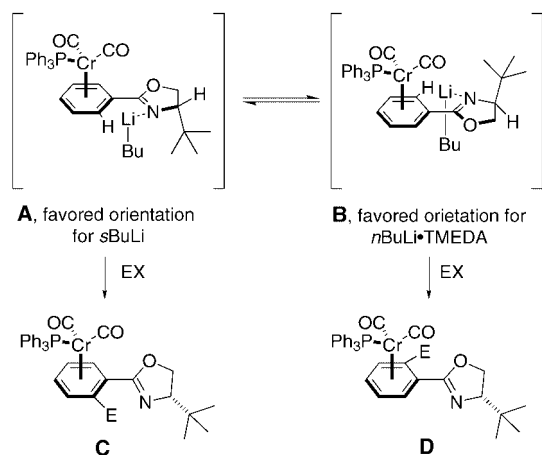


Figure 1. ORTEP representation of the molecular structure of iodide **7**. Torsion angle C6–center of arene–Cr1–P1: 53.9°.

which of the diastereotopic *ortho* hydrogen atoms of **2** is abstracted by lithiation (Scheme 2).^[12,19–21] When deprotonation is performed with an alkyl lithium base in Et₂O, destabilizing interactions between the bulky chromium tripod



Scheme 2. Proposed interactions governing the diastereoselectivity of the metalation reactions.

and the *tert*-butyl group apparently favor lithiation in the sense depicted in ensemble **A**.^[22] The solid-state structure of iodide **7** provides some indication of the considerable steric bulk of the [CrPPh₃(CO)₃] unit (Figure 1).^[23] If, as has been suggested, the addition of TMEDA increases the effective size of the base,^[21a] deprotonation by the *n*BuLi-TMEDA complex might preferentially proceed via ensemble **B**, in which orientation of the oxazoline substituent towards the chromium tripod allows the bulky nitrogen-coordinated base to approach unhindered from the opposite direction.

In summary, (η^6 -arene)dicarbonyltriphenylphosphane chromium(0) oxazoline complexes, in contrast to (η^6 -arene)-tricarbonyl chromium(0) oxazoline complexes, undergo *ortho* lithiation, rather than addition, upon reaction with alkyl lithium bases in Et₂O. As diastereoselection in this deprotonation can be regulated by the presence or absence of TMEDA, either diastereomer of a variety of enantiopure 1,2-disubstituted (η^6 -arene)chromium(0) oxazoline complexes can be prepared in one simple synthetic step. Numerous potential applications of this now readily available family of chiral enantiopure (η^6 -arene)chromium(0) complexes are readily envisaged.

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- [14] a) At –78°C, *n*-butyllithium does not deprotonate **2** at a convenient rate. Stereoselectivity in forming **3** and **4** was unchanged when **2** was deprotonated with *s*-butyllithium at –78°C and the reaction warmed to –30°C prior to quenching; b) deprotonation of **1** with *sec*-butyllithium at –78°C followed by trapping with Ph₂PCl gave a complex product mixture; the product of lithiation-trapping was not

detected by ESMS analysis of this mixture. Deprotonation of **1** with *n*-butyllithium/TMEDA at -78°C followed by trapping with Ph_2PCl at -30°C provided the product of *ortho* lithiation–trapping in low yield.

- [15] Crystal structure analysis of **7**: Bruker CCD platform diffractometer, 168(2) K, MoK_{α} radiation, $\lambda = 0.71073 \text{ \AA}$, the structure was solved by direct methods (SHELXTL; G. M. Sheldrick, SHELXTL Version 5.10, Bruker Analytical X-Ray Systems, Inc.; Madison, WI, 1999); full-matrix least-squares refinement on F^2 (SHELXTL), structure presentation: crystal dimensions $0.22 \times 0.18 \times 0.08 \text{ mm}^3$, orange crystals, space group $P2_12_12_1$, orthorhombic, $a = 10.0557(5) \text{ \AA}$, $b = 17.7209(8) \text{ \AA}$, $c = 19.4695(9) \text{ \AA}$, $V = 3469.4(3) \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calc}} = 1.481 \text{ Mg m}^{-3}$, $2\theta_{\text{max}} = 56.58^{\circ}$, 42399 measured, 8460 independent reflections, $R = 0.0343$, $wR = 0.0667$, residual electron density = $0.652 \text{ e \AA}^{-3}$, hydrogen atoms were included using a riding model. CCDC-187068 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
- [16] Diastereomers **10** and **16** could be separated by silica gel chromatography.
- [17] Sequential treatment of **16** with a) MeOTf , b) NaBH_4 , and c) aqueous oxalic acid^[18a] provided (Sp)-tricarboxyl(η^6 -2-trimethylsilylbenzaldehyde)chromium(0), $[\alpha]_{\text{D}}^{25} = +151$ ($c = 0.14$ in CHCl_3).^[18b,c]
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- [23] The effective size of this fragment would obviously depend on the orientation of the Ph_3P ligand. It is interesting to note that the torsion angle measured from the center of the arene to C6 and Cr1 to P1 is 53.9° (see Figure 1).

Enantioselective Synthesis of Substituted Pyrrolidines by Dynamic Resolution**

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The formation of enantiomerically enriched products from chiral organolithium species is a highly efficient and selective approach for organic synthesis.^[1] The majority of examples involve the selective asymmetric deprotonation of a prochiral hydrogen atom adjacent to an oxygen or nitrogen atom, such as the method developed by the groups of Hoppe and Beak in which *sec*-butyllithium and (–)-sparteine is used as the chiral base.^[2] However, an alternative mode of asymmetric induction exists, in which the chiral, racemic organolithium species is formed and complexed with a chiral ligand to promote asymmetric substitution. We report here the first highly enantioselective substitution of nonactivated organolithium species at ambient temperature.

Asymmetric substitution requires, for high yields, a dynamic resolution^[3] in which the reacting chiral center can invert under the reaction conditions. Success has been achieved with lithiated allylic or benzylic substrates in the presence of a chiral ligand through either a dynamic thermodynamic or a dynamic kinetic resolution pathway.^[4–7] Examples with α -thio and α -seleno organolithium species have also been reported,^[8] however, to our knowledge there are no reports of dynamic resolution, followed by addition of an electrophile, of other nonactivated lithiated species. This may be a consequence of the common perception that organolithium species should be generated and treated at low temperature (typically -78°C); under these conditions, although allylic, benzylic, α -thio and α -seleno organolithium species undergo racemization,^[9] non-activated chiral organolithium species do not normally racemize. For example, α -amino organolithium species display configurational stability at low temperature.^[10] We have found, however, that the formation of α -amino organolithium species and their racemization is possible at room temperature.^[11] We therefore set out to substitute racemic α -amino organolithium species asymmetrically in the presence of a chiral ligand.

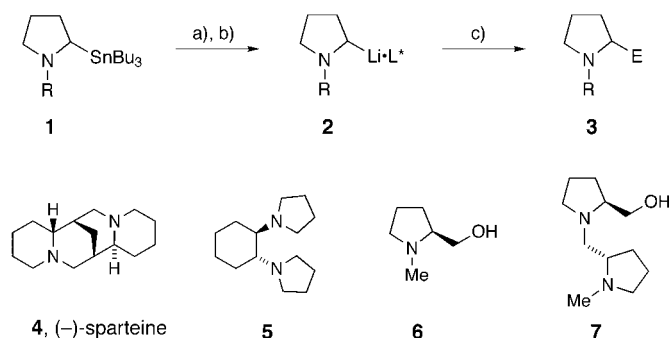
Extending our work on intramolecular carbolithiation,^[11,12] we studied the dynamic resolution of chiral 2-lithiopyrrol-

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idines (Scheme 1). We tested a variety of N-substituted pyrrolidines and chiral ligands to effect the asymmetric substitution of the organolithium species **2**, generated at room temperature by transmetalation of the racemic stannanes **1**.

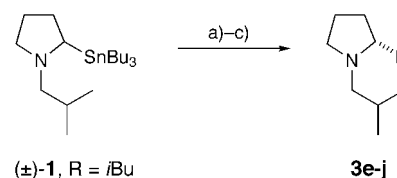


Scheme 1. a) *n*BuLi (1.2 equiv), hexane/Et₂O (4:1), 22°C, 1 h; b) chiral ligand L* (1.5 equiv), 30 min; c) –10°C, electrophile E⁺, see Tables 1 and 2.

The stannanes **1** (R = alkyl) were prepared from the known stannane **1** (R = CO₂*t*Bu).^[10c,11,13] Treatment with *n*BuLi and addition of the chiral ligands **4–7** (ligands **6** and **7** were pretreated with *n*BuLi in Et₂O), followed by an electrophile, gave the products **3**, as described in Table 1. Regarding the various N-substituents, greater steric bulk enhanced the enantioselectivity, although the rate of transmetalation was noticeably reduced with larger substituents. There was no enantioselectivity when the derivative **1** (R = CO₂*t*Bu) was used.

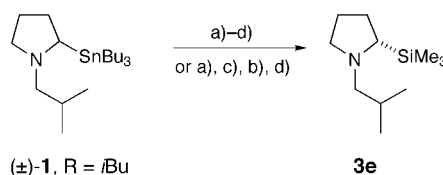
The ligand (–)-sparteine (**4**) provided the products **3** with reasonable enantioselectivity, but we have not yet been able to improve this selectivity with a variety of N-substituents. Interestingly, the major enantiomer has the configuration opposite from that formed by asymmetric deprotonation/electrophile addition of *N*-Boc pyrrolidine with (–)-sparteine (Boc = *tert*-butoxycarbonyl).^[10c] Bis-(oxazoline) ligands^[14] gave no isolable products other than tetrabutyltin, so we turned to chiral diamine or amino alcohol ligands. The ligands **5** and **6** promoted low enantioselectivity (Table 1). However, the commercially available prolinol derivative **7** gave excellent asymmetric induction. Thus, by using the ligand **7**, a selection of 2-substituted pyrrolidines **3** was prepared (Scheme 2, Table 2). In each case the products were formed with > 95:5 enantiomeric ratio.

It is clear that an asymmetric substitution reaction is taking place with dynamic resolution of the intermediate organolithium species. Cooling the organolithium species to –78°C



Scheme 2. a) *n*BuLi (1.2 equiv), hexane/Et₂O (4:1), 22°C, 1 h; b) **7** (1.5 equiv, pretreated with *n*BuLi), Et₂O, 30 min; c) –10°C, E⁺.

prior to addition of the chiral ligand and then the electrophile results in the formation of a racemic mixture of the pyrrolidine products **3**. However, addition of the chiral ligand *before* cooling to –78°C provides the products **3** with high enantioselectivity (Scheme 3). These results suggest that a dynamic thermodynamic resolution is operating.^[3a]



Scheme 3. a) *n*BuLi (1.2 equiv), hexane/Et₂O (4:1), 22°C, 1 h; b) –78°C; c) **7** (1.5 equiv, pretreated with *n*BuLi, 1.8 equiv), Et₂O, 30 min; d) Me₃SiCl (4 equiv). Sequence a–d: product **3e**, yield 77%, e.r. 50:50; sequence a,c,b,d: product (*S*)-**3e**, yield 74%, e.r. ≥ 96:4

In dynamic thermodynamic resolution, the ratio of enantiomers of the product results from the ratio of the intermediate diastereomeric complexes, which interconvert slowly in comparison with the rate of reaction with the electrophile. To determine which of these complexes reacts faster with the electrophile, the organolithium–ligand complex **2** (50:50

Table 1. Formation of pyrrolidines **3** by using chiral ligands **4–7**.

R	Ligand	"E ⁺ "	E	Product	Yield [%]	e.r. ^[a]	Config. ^[b]
Et	4	Me ₃ SiCl	SiMe ₃	3a	81	73:27	(<i>R</i>)
<i>n</i> Pn	4	CO ₂ /LiAlH ₄	CH ₂ OH	3b	83	81:19	(<i>S</i>)
<i>n</i> Oct	4	Me ₃ SiCl	SiMe ₃	3c	50	75:25	(<i>R</i>)
CH ₂ <i>t</i> Bu	4	Me ₃ SiCl	SiMe ₃	3d	30	80:20	(<i>R</i>)
<i>i</i> Bu	4	Me ₃ SiCl	SiMe ₃	3e	78	85:15	(<i>R</i>)
<i>i</i> Bu	4	PhNCO	CONHPh	3f	57	82:18	(<i>S</i>)
<i>i</i> Bu	5	Me ₃ SiCl	SiMe ₃	3e	49	60:40	(<i>R</i>)
<i>i</i> Bu	6	PhNCO	CONHPh	3f	76	59:41	(<i>R</i>)
<i>i</i> Bu	7	PhNCO	CONHPh	3f	61	97:3	(<i>R</i>)

[a] The enantiomer ratio was determined by either HPLC or NMR spectroscopy. [b] The absolute configuration of the major enantiomer was determined by comparison with an authentic sample prepared from (*S*)-**1** (R = Boc).

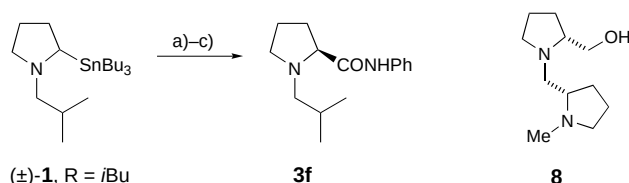
Table 2. Formation of pyrrolidines **3** (R = *i*Bu) by using chiral ligand **7**.

"E ⁺ "	E	Product	Yield [%]	e.r. ^[a]	Config. ^[b]
Me ₃ SiCl	SiMe ₃	3e	75	≥ 96:4	(<i>S</i>)
PhNCO	CONHPh	3f	61	97:3	(<i>R</i>)
Me ₂ CO	C(OH)Me ₂	3g	54	≥ 96:4	(<i>R</i>)
Bu ₃ SnCl	SnBu ₃	3h	71	96:4	(<i>S</i>)
Me ₂ SO ₄	Me	3i	65 ^[c]	≥ 96:4	(<i>S</i>)
<i>p</i> -MeOC ₆ H ₄ CHO	CH(OH)C ₆ H ₄ OMe	3j	70 ^[c,d]	97:3	(<i>anti</i>)
				97:3	(<i>syn</i>)

[a] The enantiomer ratio was determined by HPLC, NMR spectroscopy, or specific rotation. [b] The absolute configuration was determined by comparison with an authentic sample prepared from (*S*)-**1** (R = Boc). [c] E⁺ added at –78°C. [d] *anti*:*syn* = 1:1.

mixture of diastereomeric complexes, formed by adding the ligand **7** after cooling to -78°C was treated with 0.3 molar equivalents of the electrophile TMSCl. The product **3e** was formed as a mixture of enantiomers in the ratio 61:39 (*R*:*S*) (opposite enantioselectivity) which indicates that the minor diastereomeric complex reacts faster. Similar results were obtained with the ligand (–)-sparteine (**4**) in which case asymmetric substitution occurred by a dynamic thermodynamic resolution with the minor diastereomeric complex reacting faster.

By employing the diastereomer **8** of the chiral ligand **7**,^[15] the opposite major enantiomer of the 2-substituted pyrrolidine was formed (Scheme 4). It is possible, therefore, to prepare highly enantioenriched (*R*)- and (*S*)-2-substituted pyrrolidines, by starting from racemic organolithium species and using a dynamic resolution at ambient temperature with control of the absolute configuration by choice of the chiral ligand.



Scheme 4. a) *n*BuLi (1.2 equiv), hexane/Et₂O (4:1), 22°C, 1 h; b) chiral ligand **8** (1.5 equiv, pretreated with *n*BuLi), 30 min; c) -10°C , PhNCO. Product (*S*)-**3f**, yield 74%, e.r. 96:4.

Experimental Section

General procedure: The racemic stannane **1**, R = *i*Bu,^[13] (0.3 g, 0.72 mmol) in hexane/Et₂O (0.8 mL, 4:1) was treated with *n*BuLi (0.35 mL, 0.86 mmol, 2.5 M in hexanes) at room temperature. After 1 h, the deprotonated ligand **7** (prepared by adding *n*BuLi (0.52 mL, 1.3 mmol) to **7** (0.21 g, 1.3 mmol) in Et₂O (0.8 mL) at -30°C , then warming to room temperature) was added. After 30 min at room temperature, the mixture was cooled to -10°C and the electrophile PhNCO (0.33 mL, 3.0 mmol) was added. After 1 h, citric acid (30 mL, 10% aqueous solution) was added and the aqueous layer was extracted with Et₂O (30 mL), basified with NaHCO₃ (30 mL, saturated solution) and extracted with Et₂O (30 mL). This latter organic layer was dried (Na₂SO₄), evaporated, and the residue was purified by column chromatography on silica, eluting with light petroleum (b.p. 40–60°C)/EtOAc (4:1) to give the pyrrolidine **3f** (109 mg, 61%), $[\alpha]_{\text{D}}^{25} = +154.8$ (*c* = 0.78, CHCl₃), e.r. 97:3 determined by chiral HPLC (Chiracel AD column, hexane/EtOH 90:10, flow rate 1.0 mL min^{–1}, detection at 235 nm, retention times: 6.7 and 10.4 min).

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Water-Insoluble Lanthanum Oxychloride-Based Solid Electrolytes with Ultra-High Chloride Ion Conductivity**

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The chloride ion is well known as one of several migrating anion species in the solid electrolyte field. However, the chloride-ion conductors reported so far are all based on chlorides that are soluble in hot water or water at room temperature. This can be a critical disadvantage for the practical applications of various functional materials. In order to overcome this problem, it is essential to fabricate Cl^- ion-conducting solid electrolytes that are water-insoluble. Since the desired end material is a Cl^- ion-conductor, the solids should contain Cl^- anions. We have previously reported the Ca-doped lanthanum oxychloride solid-solution electrolyte,^[1] which has the unique characteristic of being water-insoluble. However, the Cl^- ion conductivity at 700°C was $2.8 \times 10^{-5} \text{ Scm}^{-1}$, which is still two orders of magnitude lower than conventional Cl^- ion conductors such as PbCl_2 ,^[2] BaCl_2 ,^[3] SrCl_2 ,^[4] and CsPbCl_3 .^[5]

This report centers on how the properties of this promising material were improved through a ball milling process. Ball milling resulted in a fine, homogeneous mixture of the starting materials, namely LaOCl and CaCO_3 , which in turn enabled the fabrication of high-density pellets.

Figure 1 shows the powder X-ray diffraction (XRD) results for $\text{La}_{1-x}\text{Ca}_x\text{OCl}_{1-x}$ ($x = 0.05\text{--}0.4$) solid solutions, along with the data for pure LaOCl . It is expected that LaOCl would form a solid solution with CaCO_3 with up to 20 mol % CaCO_3 . Since the radii of La^{3+} ions and Ca^{2+} ions are so similar (0.130^[6] and 0.126 nm,^[6] respectively), it is not possible to verify the formation of the solid solution based on changes of lattice parameter. A mixed phase consisting of Ca-doped LaOCl solid solution and CaO was obtained by mixing in CaCO_3 at a proportion of above 20 mol %. This clearly indicates that the solubility limit of Ca in LaOCl is around 20 mol %.

Figure 2 presents the electrical conductivity of $\text{La}_{1-x}\text{Ca}_x\text{OCl}_{1-x}$ at 800°C as a function of x . At a dopant level of 5 mol % Ca, a sharp enhancement in conductivity of over three orders of magnitude is observed. The Cl^- vacancies formed by substitution of La^{3+} ions by Ca^{2+} ions greatly facilitates Cl^- anion conduction in the LaOCl framework. The

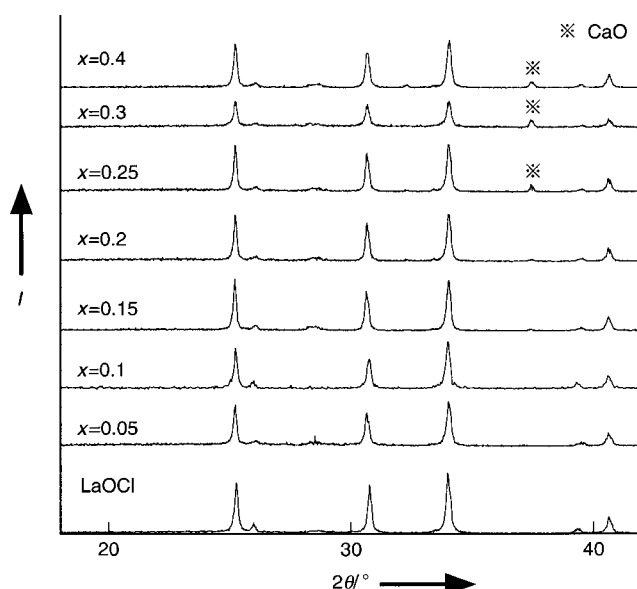


Figure 1. X-ray powder diffraction results for $\text{La}_{1-x}\text{Ca}_x\text{OCl}_{1-x}$ ($x = 0.05\text{--}0.4$) solid solutions, along with the data for pure LaOCl .

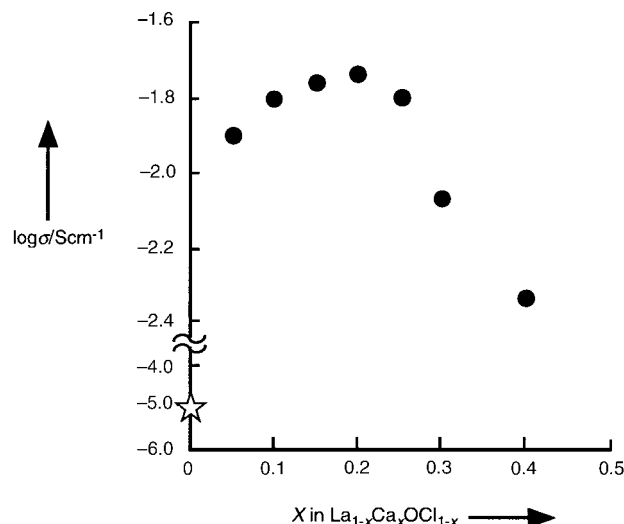


Figure 2. Electrical conductivity at 800°C as a function of x in $\text{La}_{1-x}\text{Ca}_x\text{OCl}_{1-x}$. The conductivity of pure LaOCl is also plotted (★).

conductivity gradually increases with increasing Ca content in the $\text{La}_{1-x}\text{Ca}_x\text{OCl}_{1-x}$ solid solution, with the highest ($1.9 \times 10^{-2} \text{ Scm}^{-1}$) observed for $\text{La}_{0.8}\text{Ca}_{0.2}\text{OCl}_{0.8}$, which corresponds to $x = 0.2$. A further increase of the Ca content results in a rapid decrease in conductivity, which results from the formation of the secondary CaO phase. These results corroborate that LaOCl forms a $\text{La}_{1-x}\text{Ca}_x\text{OCl}_{1-x}$ solid solution with up to 20 mol % Ca doping.

Figure 3 displays the conductivity of $\text{La}_{0.8}\text{Ca}_{0.2}\text{OCl}_{0.8}$, which exhibits the highest Cl^- ion conductivity in the $\text{La}_{1-x}\text{Ca}_x\text{OCl}_{1-x}$ series, as a function of temperature. This is presented with data for pure LaOCl , the previously reported 1.6 mol % Ca-doped LaOCl solid solution,^[1] and two typical Cl^- conductors, namely PbCl_2 and CsPbCl_3 , which both exhibit a reasonably high Cl^- ion conductivity. The conductivity of the $\text{La}_{0.8}\text{Ca}_{0.2}\text{OCl}_{0.8}$ solid solution, with an activation

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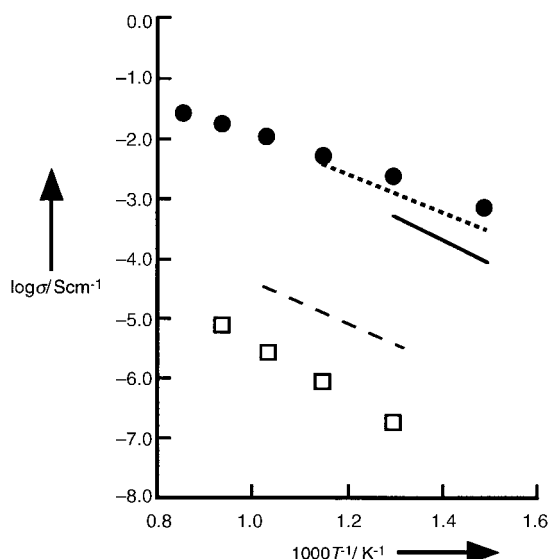


Figure 3. A plot of the conductivity of the $\text{La}_{0.8}\text{Ca}_{0.2}\text{OCl}_{0.8}$ solid solution (●) as a function of temperature. Also shown are the data for pure LaOCl (□), the $\text{La}_{0.984}\text{Ca}_{0.016}\text{OCl}_{0.984}$ solid solution (---),^[1] and the conventional Cl^- ion conductors PbCl_2 (—) and CsPbCl_3 (···)^[5] which exhibit a high Cl^- ion conductivity.

energy of 51.5 kJ mol^{-1} , is more than two orders of magnitude higher than that of the 1.6 mol % Ca-doped LaOCl solid solution. The conductivity of the former also exceeds that of conventional Cl^- ion conductors. Unlike chlorides, such as PbCl_2 and CsPbCl_3 , which are all soluble in hot water and cannot be used for high-temperature applications because of their low melting points (501 and 604°C for PbCl_2 and CsPbCl_3 , respectively)^[5] and their low stability in water vapor-containing environments, the present $\text{La}_{1-x}\text{Ca}_x\text{OCl}_{1-x}$ solid solutions are insoluble in water, and are thermally stable at temperatures as high as 1000°C . These unique characteristics enable the application of these solid electrolytes as functional devices under a variety of atmospheric and thermal conditions.

To identify the conducting species in $\text{La}_{0.8}\text{Ca}_{0.2}\text{OCl}_{0.8}$, polarization measurements were carried out at 700°C in oxygen (10^5 Pa), helium (4 Pa), and 1 vol % chlorine (in nitrogen) atmospheres. The results are shown in Figure 4; σ_{dc} and σ_{ac} denote the DC and AC conductivity, respectively. In both oxygen and helium atmospheres, a considerably high degree of polarization was observed, while no polarization

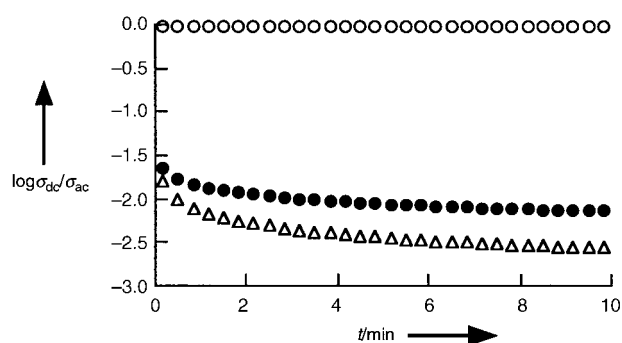


Figure 4. Polarization measurements for the $\text{La}_{0.8}\text{Ca}_{0.2}\text{OCl}_{0.8}$ solid solution in O_2 (●), He (△), and 1 vol % Cl_2 in N_2 (○) at 700°C .

was observed in 1 vol % chlorine at all. This indicates that Cl^- anions formed from the chlorine atmosphere at the cathode migrate through the $\text{La}_{0.8}\text{Ca}_{0.2}\text{OCl}_{0.8}$ solid solution and reach the anodic surface to be released as chlorine gas. The results suggest that the predominant migrating species is the Cl^- anion. Based on the polarization behavior in oxygen and helium, the Cl^- anion transference number was estimated to be higher than 0.98.

Table 1 displays the relative density and Vickers hardness of the $\text{La}_{0.8}\text{Ca}_{0.2}\text{OCl}_{0.8}$ solid solution, as well as the data for pure LaOCl , $\text{La}_{0.984}\text{Ca}_{0.016}\text{OCl}_{0.984}$,^[1] and $\text{La}_{0.8}\text{Ca}_{0.2}\text{OCl}_{0.8}$ proc-

Table 1. The relative density and the Vickers hardness of the $\text{La}_{0.8}\text{Ca}_{0.2}\text{OCl}_{0.8}$ solid solution, compared with the data for pure LaOCl , $\text{La}_{0.984}\text{Ca}_{0.016}\text{OCl}_{0.984}$,^[1] and unmilled $\text{La}_{0.8}\text{Ca}_{0.2}\text{OCl}_{0.8}$.

Solid electrolyte	Relative density [%]	Vickers hardness
$\text{La}_{0.8}\text{Ca}_{0.2}\text{OCl}_{0.8}$ (ball milled)	95.9	115
pure LaOCl	92.9	33
$\text{La}_{0.984}\text{Ca}_{0.016}\text{OCl}_{0.984}$	91.3	42
$\text{La}_{0.8}\text{Ca}_{0.2}\text{OCl}_{0.8}$ (unmilled)	93.3	30

essed without ball milling. As a consequence of the ball milling step utilized in the present study, the relative density was increased to 95.9 %, compared with 92.9, 91.3, and 93.3 % for pure LaOCl , $\text{La}_{0.984}\text{Ca}_{0.016}\text{OCl}_{0.984}$, and the unmilled $\text{La}_{0.8}\text{Ca}_{0.2}\text{OCl}_{0.8}$ solid solution, respectively. Consequently, the Vickers hardness of the ball-milled material was 115, compared with 33, 42, and 30 for the other materials. The improved relative density and mechanical strength would be a distinct advantage for practical applications.

In conclusion, a wide range of Ca-doped LaOCl solid solutions were prepared by ball milling, which enhanced the Cl^- ion conductivity by more than three orders of magnitude in comparison with that of pure LaOCl . The Ca-doped LaOCl solid-solution electrolyte has the unique feature of being insoluble in water, in addition to possessing a higher relative density and hardness, while being thermally stable at temperatures as high as 1000°C . This novel Cl^- ion conducting solid series is expected to enable the fabrication of an array of new functional materials.

Experimental Section

La_2O_3 was dissolved in hydrochloric acid (3N). LaOCl was prepared by evaporating away the water from this solution and heating in air at 700°C for 12 h. The appropriate amount of LaOCl and CaCO_3 was ball milled (Fritsch Pulverisette 7) for 12 h. The pulverized mixture was pelletized and heated at 1000°C for 12 h to form the $\text{La}_{1-x}\text{Ca}_x\text{OCl}_{1-x}$ solid solution. The RuO_2 pellet that served as the electrode was obtained by heating pelletized RuO_2 at 700°C for 6 h in air.

The formation of the solid solution electrolyte was confirmed by powder XRD analysis (M18XHF, Mac Science). The data were collected by a step-scanning method in the 2θ range of 10 – 70° with a step width of 0.02° using $\text{Cu K}\alpha$ radiation. The Ca ratio in the solid-solution electrolyte was determined by inductively coupled plasma (ICP) analysis (Shimadzu ICPS-1000IV). The AC conductivity measurements were carried out using two platinum electrodes as ion-blocking electrodes by a complex impedance method in the frequency range from 5 Hz to 13 MHz (Precision LCR meter 4192A, Hewlett Packard) between 400°C and 900°C in air. AC conductivity was found to be independent of the atmosphere used during

the measurements. The polarization measurements were conducted by applying a constant current (1 μ A) between the two RuO₂ electrodes. The voltage was measured as a function of time at 700 °C. RuO₂ electrodes were utilized when the atmosphere contained Cl₂ because this would react with Pt electrodes. DC conductivity determination was based on the voltage, applied current, RuO₂ electrode surface area, and pellet thickness. Details of similar experiments are described elsewhere.^[7]

The relative density and the Vickers hardness of the pellets were measured by a Micromeritics (AccuPyc 1330) porosimeter and a Shimadzu Micro Hardness Tester (HNV-2).

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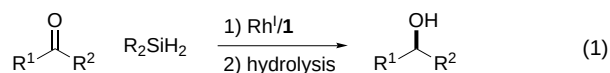
Application of a New Family of P,N Ligands to the Highly Enantioselective Hydrosilylation of Aryl Alkyl and Dialkyl Ketones**

Beata Tao and Gregory C. Fu*

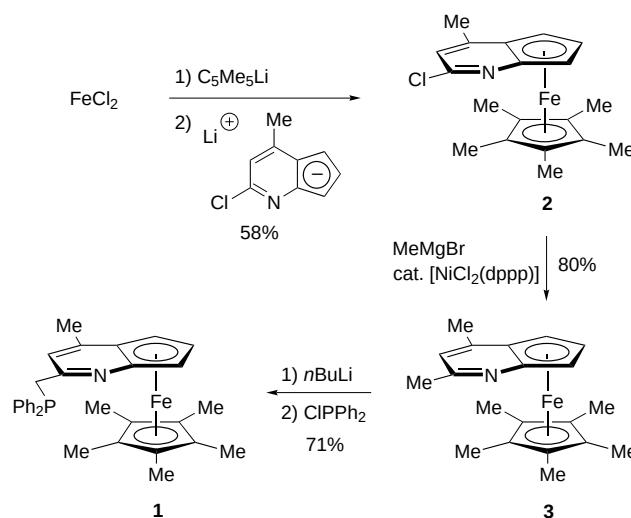
Due in large part to the utility of enantiomerically enriched alcohols and their selectively O-protected derivatives, considerable energy has been devoted to the search for efficient catalysts for the asymmetric hydrosilylation of ketones.^[1] Very good enantioselectivities have been obtained for many aryl alkyl ketones, but for dialkyl ketones they are generally more modest. Seminal discoveries have resulted from these efforts, including the development of pybox, the first highly effective bis(oxazoline)-based ligand.^[2,3]

During the past few years, we have been pursuing the design and development of new chiral ligands that are based on "planar-chiral" heterocycles,^[4] and for several metal-catalyzed processes we have demonstrated that this family of ligands can provide enantioselectivity superior to the best methods that had previously been reported.^[5] Here we describe the synthesis of a new planar-chiral P,N ligand, and we establish its exceptional efficiency in rhodium-catalyzed

asymmetric hydrosilylations of aryl alkyl ketones and dialkyl ketones [Eq. (1)].



The synthesis of planar-chiral ligand **1** is illustrated in Scheme 1.^[6] Treatment of FeCl₂ with C₅Me₅Li and then 2-chloro-4-methyl-7H-cyclopenta[b]pyridinyl lithium affords ferrocene derivative **2**.^[7] Kumada coupling of **2** with MeMgBr furnishes **3**, which is lithiated and then quenched with ClPPh₂ to provide ligand **1**, the enantiomers of which are readily resolved by chiral HPLC. We have determined the absolute configuration of (–)-**1** by X-ray crystallography.



Scheme 1. Synthesis of planar-chiral P,N ligand **1** (only (+)-**1** is depicted). dppp = 1,3-bis(diphenylphosphanyl)propane.

For an initial investigation of the utility of ligand **1**, we chose to focus on the rhodium-catalyzed asymmetric hydrosilylation of ketones. Specifically, we examined the reduction of acetophenone, and we discovered that the level of enantioselectivity is highly dependent on the choice of silane (Table 1). Thus, monoalkyl- and monoaryl silanes (entries 1 and 2), as well as dialkyl silanes (entry 3), furnish disappoint-

Table 1. Hydrosilylation of acetophenone catalyzed by Rh^I/(-)-**1**: enantioselectivity as a function of the silane.

$\text{Ph-C(=O)Me} + \text{silane} \xrightarrow[\text{THF, RT}]{2.5\% \{[\text{RhCl}(\text{cod})_2]\}, 6.0\% (-)\text{-}\mathbf{1}} \text{Ph-CH(OH)Me}$		
Entry	Silane	ee [%] ^[a]
1	<i>n</i> -octylSiH ₃	3
2	PhSiH ₃	8
3	Et ₂ SiH ₂	1
4	PhMeSiH ₂	66
5	Ph ₂ SiH ₂	80
6	<i>o</i> -TolPhSiH ₂ ^[b]	95
7	<i>o</i> -Tol ₂ SiH ₂ ^[b]	92
8	MesPhSiH ₂ ^[c]	98
9	Mes ₂ SiH ₂ ^[c]	(no reaction)

[a] Average of two runs. [b] Tol = tolyl. [c] Mes = Mesityl.

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

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- [9] Notes: a) Comparable enantioselectivity is observed in THF, Et_2O , toluene, and CCl_4 ; b) a small enhancement in enantioselectivity is obtained at lower temperature; c) the stereoselectivity does not appear to be dependent on the concentration.
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Design Optimization of 1,3-Diphospha-2,4-diboretane Diradicals**

Mark Seierstad, Christopher R. Kinsinger, and Christopher J. Cramer*

Diradicals may be defined as molecules having an even number of electrons and a narrow separation between their highest occupied and lowest unoccupied molecular orbitals (HOMO and LUMO, respectively).^[1–4] Degeneracy of these orbitals is also a possibility. Diradicals share a number of characteristic features associated with having frontier MO energies that are similar. They tend, for instance, to exhibit relatively small energy splittings between their lowest energy singlet and triplet states (ΔE_{S-T}) and between their lowest energy and first excited singlet states, where the latter splitting is associated with a long-wavelength absorption in the ultraviolet/visible (UV/Vis) spectrum of the lower energy state.

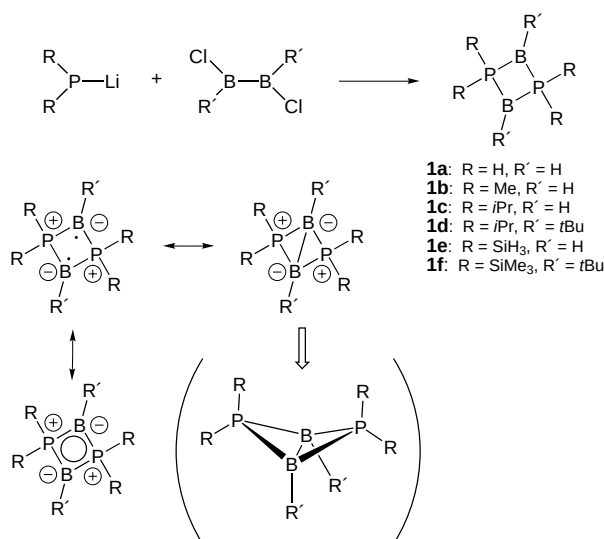
A large number of organic diradicals are known, although they are almost exclusively characterized as reactive intermediates. Typical single-center diradicals include carbenes,^[5–9] nitrenes,^[5,10–13] and nitrenium ions,^[14–16] and well known multicenter diradicals include didehydroarenes^[5,17–20] (e.g., benzyne) and non-Kekulé hydrocarbons like trimethylene-methane^[21–24] and tetramethyleneethane.^[21,25–27] An example of a diradical system that has been known since the pioneering work of Huckel in the 1930s is a high-symmetry “antiaromatic” cycloarene having $4n$ electrons and $4n$ ring atoms. All-carbon examples such as cyclobutadiene and cyclooctatetraene, however, are well known to lift the degeneracy of their frontier orbitals by distorting from D_{nh} structures to geometries belonging to lower symmetry point groups (although this by no means precludes their possible continuing description as diradicals).^[1,28,29] A key to success, then, in the design of any diradical, is to engineer the molecular and electronic structure in such a way that the frontier orbital separation remains as small as possible.^[30–32]

Recently, Scheschkewitz et al.^[33] reported that the reaction of lithium diisopropylphosphide with 1,2-di-*tert*-butyl-1,2-dichlorodiborane provided an isolable 1,3-diphospha-2,4-diboretane product **1d** (Scheme 1) having a long-wavelength UV absorption (446 nm) consistent with it having substantial diradical character, in spite of its thermal stability. Such character is easily inferred from consideration of the simplest resonance structure that may be drawn for **1d**, which places positive charges on the P atoms and a negative charge and one formally unpaired electron on each of the B atoms (Scheme 1).

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Scheme 1. Synthesis and resonance structures of 1,3-diphospha-2,4-diboretanes **1a–f**.

However, other resonance structures, also illustrated in Scheme 1, might also be reasonably expected to contribute strongly to the overall character of **1**. Clearly, if σ bonding between the B atoms can be achieved, the resulting diphosphadiborabicyclo[1.1.0]butane structure would not be expected to deviate much from normal closed-shell character. However, the ring puckering required in such a bicyclo structure is strongly disfavored when the ring is substituted with large substituents, and an X-ray crystal structure analysis of **1d** indicates the four-membered ring to be perfectly planar. Another alternative, however, is that mixing of the out-of-plane boron p orbitals with appropriate σ_{PR} and σ_{PR}^* orbitals may create the equivalent of an aromatic π system, and that spin-pairing in such delocalized hybrid orbitals will contribute to closed-shell character. This orbital picture is illustrated in Figure 1 where, in D_{2h} symmetry, the 1,3-diphospha-2,4-diborete ring contributes four electrons and four π orbitals and the P substituents contribute two electrons and two symmetry-adapted orbitals of π -like symmetry (two other symmetry-adapted combinations carrying the remaining two substituent electrons are not shown as they belong to a -type irreducible representations that do not mix with the π system). Note that the HOMO is dominated by a cross-ring B–B π bonding interaction, while the LUMO, which by symmetry cannot mix with the σ_{PR} and σ_{PR}^* combination orbitals, is B–B π^* antibonding.

This frontier orbital picture receives support from calculations reported by Scheschkewitz et al.,^[33] who reported a HOMO for **1d** from density functional theory (DFT) that was in perfect agreement with that illustrated in Figure 1. These same calculations predicted $\Delta E_{\text{S–T}}$ for **1a** to be $-17.2 \text{ kcal mol}^{-1}$. This value is fairly close to the known S–T splitting of *m*-benzynes,^[34] suggesting that the appellation diradical may be as warranted for **1d** as it is for the *meta* arylene.

With Figure 1 as a guide, however, one may ask how one might engineer still more diradical character into the 1,3-diphospha-2,4-diboretane framework, to optimize its utility as a component in molecular electronic or magnetic devices, for

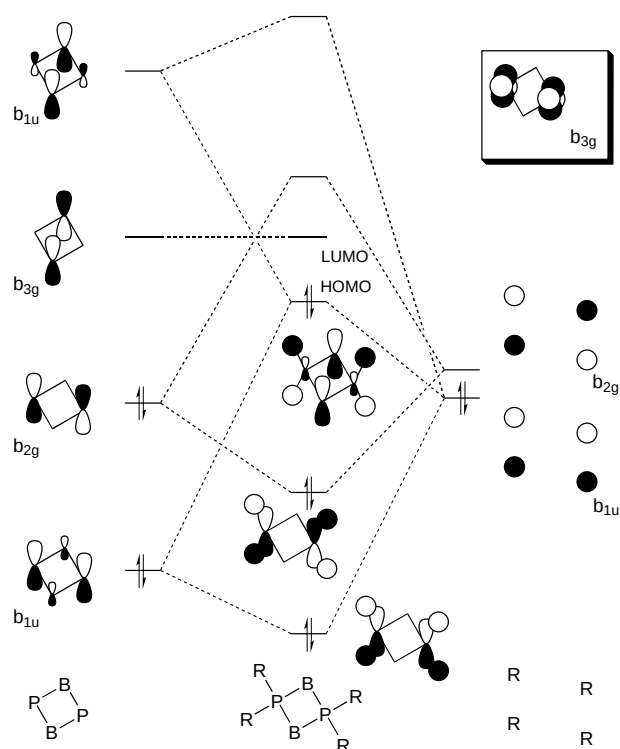


Figure 1. MO diagram of the mixing of diphosphadiborete π orbitals with symmetry-adapted substituent orbitals on P (e.g., 1s orbitals for R = H or sp^3 orbitals for R = alkyl or silyl). Inset at upper right is a b_{3g} combination of d orbitals that could hybridize with and lower the energy of the LUMO if P were to be replaced by an early transition metal.

instance. Clearly, accomplishing this goal requires that either the HOMO energy be raised relative to the LUMO or that the LUMO energy be lowered relative to the HOMO. With respect to the latter option, Figure 1 shows as an inset an orbital of appropriate symmetry to mix with the LUMO and reduce the frontier gap were the phosphorus atoms to be replaced by early transition metals so that the necessary empty d orbitals would be available for hybridization. While this option would appear to merit future consideration, we focus our attention here on what would appear to be a simpler endeavor from a synthetic perspective, namely raising the HOMO energy by employing phosphorus substituents having more electropositive character than alkyl groups; the most obvious alternative is a silyl group.

To predict whether such an approach has merit, we have carried out calculations at several levels of electronic structure theory for **1a–f** (Table 1).^[35] In addition to $\Delta E_{\text{S–T}}$, we evaluate as a diagnostic HOMO and LUMO occupation numbers from two-electron-in-two-orbital generalized valence bond (GVB(2,2)) calculations^[36]—perfect diradicals are characterized by occupation numbers of 1.0 in each orbital, while perfectly closed-shell systems have HOMO and LUMO occupation numbers of 2.0 and 0.0, respectively.^[2] Molecular geometries for all species were optimized at the DFT level using the B3LYP functional^[37,38] and the 6-31G* basis set.^[39] Energetic and geometric results with this relatively small basis set were found to be very close to those from calculations employing the much larger 6-311 + G(d,p) basis set for **1a**, **1b**, and **1e**, validating the use of the more efficient

Table 1. Computed properties of ground-state singlet diphosphadiboretanes **1** at DFT-optimized planar geometries.

Compound ^[a]	rPB [Å]	ΔE_{S-T} ^[b] [kcal mol ⁻¹]	HOMO occ. no. ^[c]	LUMO occ. no. ^[c]
1a	1.888	-18.7 (-20.0) [-19.8] ^[d]	1.79	0.21
1b	1.887	-20.1 (-22.0)	1.79	0.21
1c	1.892	-20.7	1.80	0.20
1d	1.907	-23.4	1.81	0.19
1e	1.905	-5.8 (-5.1)	1.61	0.39
1f	1.932	-8.7	1.70	0.30

[a] Based on analytic frequency analysis, **1d** and **1f** are true minima; all other compounds are transition-state structures for inversion of puckered minima. [b] Computed as 0 K enthalpy at the B3LYP/6-31G(d) and CASPT2/GVB(2,2)/6-31G(d)//B3LYP/6-31G(d) levels (the latter in parentheses, where computed). [c] From GVB(2,2)/6-31G(d) wave functions. [d] From calculations at the CCSD(T)/6-311 + G(d,p)//B3LYP/6-311 + G(d,p) level.

level for the larger structures. As for the functional, we note that time-dependent B3LYP/6-311 + G(d,p) calculations for **1b** predict a UV/Vis absorption of 451 nm, in excellent agreement with experiment for **1d**, and moreover that ΔE_{S-T} values from all DFT calculations are in excellent agreement with predictions from multireference second-order perturbation theory (CASPT2) using as reference either the GVB(2,2) wave functions or multiconfiguration wave functions spanning the full (6,6) active space illustrated in Figure 1, as well as CCSD(T)/6-311 + G(d,p) calculations for **1a** (Table 1).

As expected, replacement of alkyl groups on P with silyl groups substantially increases the diradical character of **1** by raising the energy of the hybrid HOMO relative to the LUMO. The predicted ΔE_{S-T} value of -8.7 for **1f** is closer to that of *p*-benzyne than *m*-benzyne,^[34,40] the former being an extremely reactive diradical. Its orbital occupation numbers of 1.70 and 0.30, on the other hand, are less close than the values of 1.23 and 0.77 for *p*-benzyne;^[34,40] nevertheless, the **1f** values represent a substantial increase in diradical character compared to **1d**. In addition, time-dependent B3LYP/6-311 + G(d,p) calculations for **1e** predict a UV/Vis absorption of 704 nm, that is, at much longer wavelength than measured for **1d**. As a final point of interest, we note that the ring geometry changes substantially upon silyl substitution; in particular, the P-B bonds lengthen. This derives from two phenomena. As the HOMO is net P-B bonding while the LUMO is not, enhanced occupation of the latter at the expense of the former increases P-B distances. As well, however, P devotes more s character to its bonds with Si than to those with C, thus placing more p character in its bonds to B, and this too extends P-B bond lengths.^[41] Interestingly, it also reduces B-P-B bond angles,^[41] so that the B-B distances are actually shorter in **1e** and **1f** than in any of the other compounds considered (by from 0.01 to 0.05 Å). This offers the mildly amusing paradox of increased diradical character for the species with minimum separation between the centers formally assigned as carrying the unpaired spins in the simple resonance picture of Scheme 1.

Realization of the synthesis of **1f** from the appropriate lithium bis(trimethylsilyl)phosphide would be expected to be straightforward (at least to a blithe theorist). Irrespective of that point, the design principles implicit in Figure 1 should

prove useful in future synthetic efforts founded on this exciting heterocyclic system and its analogues.

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Naphtho[1,8-*b,c*]phosphete and 1,2-Diphosphaacenaphthene from the Reaction of 1,8-Dilithionaphthalene with RPhCl_2 **

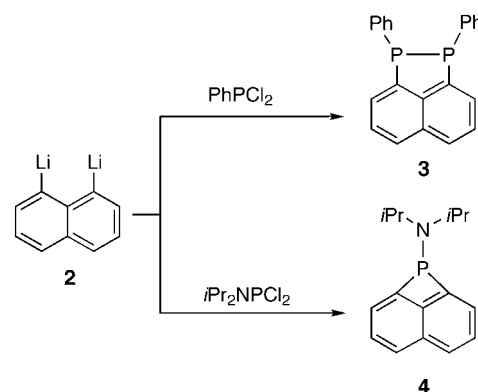
Tsutomu Mizuta,* Tooru Nakazono, and Katsuhiko Miyoshi*

Single-atom *peri*-bridged naphthalenes **1** have a highly strained and potentially useful four-membered ring which



readily undergoes a ring-enlargement reaction. The first example of **1** was reported for E = SO₂ in 1965,^[1] and since then, analogues bridged by elements of Group 13 (BR, BR₂⁻),^[2] Group 14 (CR₂, SiR₂, and GeR₂),^[3] and Group 16 (S, SO, and SO₂)^[4] have been reported. However, to our knowledge, no Group 15 analogues have been prepared and fully characterized to date.^[5] On the other hand, strained phosphorus heterocycles have attracted considerable interest owing not only to their unusual structures and reactivities, but also to their utility as a ligand towards a variety of transition-metal fragments.^[6] Herein we report the preparation and molecular structure of a phosphorus analogue of **1**.

1,8-Dilithionaphthalene (**2**), which is readily obtained by lithiation of 1,8-dibromonaphthalene (method A)^[7a] or of commercially available 1-bromonaphthalene, (method B),^[7b] is a convenient starting material for the preparation of **1**. The reaction of **2** with PhPCl₂ in hexane did not give the desired single-atom-bridged species (**1**, E = PPh), but instead yielded the diphosphorus-bridged species **3** as the major product (Scheme 1). The structure of **3** was determined by X-ray analysis (Figure 1).^[8] This compound is the first example of a $\sigma^3\text{P}-\sigma^3\text{P}$ -bridged naphthalene species which has a lone pair on each phosphorus atom, though two $\sigma^4\text{P}^+-\sigma^3\text{P}$ -bridged phosphonium analogues were reported recently.^[9] Although the reaction mechanism leading to **3** is not clearly understood,^[10] the presence of a P–P bond in **3** suggests that a reduction of the phosphorus centers takes place during the reaction. Thus, $i\text{Pr}_2\text{NPCl}_2$, which has an electron-donating R₂N group, was employed in place of PhPCl₂. The reaction of **2** with $i\text{Pr}_2\text{NPCl}_2$ gave the expected product **4**. The yield of **4** was improved to 75% when **2** was prepared by method A. An X-ray structure of **4** (Figure 2) indicates that bond angles are considerably distorted from standard values for tricoordinate phosphorus



Scheme 1. Reaction of **2** with RPhCl_2 .

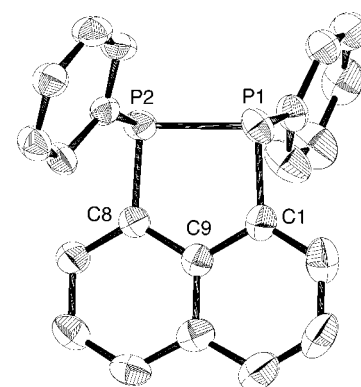


Figure 1. ORTEP drawing of **3** (thermal ellipsoids set at 50 % probability), selected bond lengths [Å] and bond angles [°]: P1–P2 2.230(1), P1–C1 1.832(4), P2–C8 1.832(4); P2–P1–C1 93.2(1), P1–P2–C8 93.4(1), P1–C1–C9 116.9(3), P2–C8–C9 116.7(3), C1–C9–C8 119.3(3).

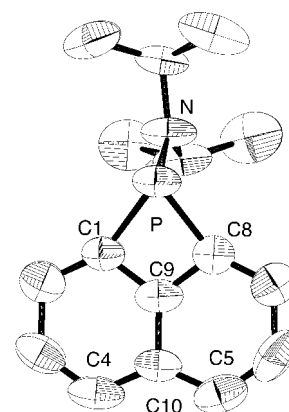


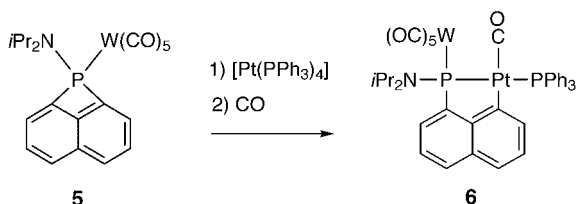
Figure 2. ORTEP drawing of **4** (thermal ellipsoids set at 50 % probability), selected bond lengths [Å] and bond angles [°]: P–N 1.654(5), P–C1 1.885(7), P–C8 1.885(7); C1–P–C8 73.1(3), P–C1–C9 89.7(4), P–C8–C9 90.4(5), C1–C9–C8 106.1(6), C4–C10–C5 131.5(8).

and sp² carbon atoms.^[11] The distortions observed in **4** are in line with those reported, and those predicted by theoretical calculations.^[12]

The reactivity of **4** was examined. Compound **4** coordinated to a [W(CO)₅] fragment to form [W(CO)₅(**4**)] (**5**), which was in turn treated with [Pt(PPh₃)₄] and then with CO gas to give **6** (Scheme 2). The isolated product **6** has a structure in which a [Pt(CO)(PPh₃)] fragment has been inserted into the strained

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Scheme 2. Insertion of the platinum fragment into a P–C bond.

P–C bond of the four-membered ring to give a 1-platina-2-phosphaacenaphthene framework.

Experimental Section^[13]

3: PhPCl_2 (6.5 mL, 48 mmol) was added at -30°C to a suspension of **2** in hexane (60 mL) which was prepared from 1-bromonaphthalene (5 mL, 36 mmol).^[7b] After vigorous stirring at -30°C for 1 h and then at 0°C for 3 h, the products were collected by filtration. The products were suspended in hexane: CH_2Cl_2 and loaded onto an Al_2O_3 column and a yellow band was collected by using CH_2Cl_2 :hexane (1:1) as the eluent. After removal of the solvents, recrystallization from diethyl ether gave a white powder, 4.88 g (59% based on PhPCl_2). ^1H NMR (300.4 MHz, CDCl_3 , TMS): δ = 7.18 (m, 10H; Ph), 7.60 (m, 2H; 3,6-naph), 7.82 (m, 2H; 1,7-naph), 7.93 ppm (d, J = 8.1 Hz 2H; 4,5-naph); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.45 MHz, CDCl_3 , TMS): δ = 127.4, 128.0, 128.5, 132.1, 132.2, 133.6, 138.4, 141.8, 142.0 ppm; $^{31}\text{P}\{^1\text{H}\}$ NMR (121.45 MHz, CDCl_3 , H_3PO_4): δ = -8.0 ppm.

4: A diethyl ether solution of **2**, prepared from 1,8-dibromonaphthalene (250 mg, 0.874 mmol),^[7a] was added to a solution of $i\text{Pr}_2\text{NPCl}_2$ (0.20 mL, 1.05 mmol) in diethyl ether (3 mL) at 0°C . The mixture was stirred overnight, then LiCl was removed by filtration. After evaporation of the solvents, the residue was loaded onto an Al_2O_3 column. A light yellow band was eluted with hexane, and collected. After removal of the solvents 169 mg of **4** (75%) was obtained as a white powder. ^1H NMR (300.4 MHz, CDCl_3 , TMS): δ = 1.18 (d, $^3J(\text{H,H})$ = 6.6 Hz, 12H; CHMe_2), 3.29 (m, 2H; CHMe_2), 7.42 (d, $^3J(\text{H,H})$ = 6.6 Hz, 2H; naph), 7.52 (m, 2H, naph), 7.70 ppm (d, $^3J(\text{H,H})$ = 8.2 Hz, 2H; naph); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.45 MHz, CDCl_3 , TMS): δ = 23.8, 47.6, 122.5, 123.8, 127.5, 129.4, 147.2 ppm; $^{31}\text{P}\{^1\text{H}\}$ NMR (121.45 MHz, CDCl_3 , H_3PO_4): δ = -8.4 ppm.

6: **5** (764 mg, 1.31 mmol), which was prepared from the reaction of **4** and $[\text{W}(\text{CO})_5(\text{thf})]$, was treated with $[\text{Pt}(\text{PPh}_3)_4]$ (1635 mg, 1.31 mmol) in toluene (90 mL) at 45°C for 3 h, and the mixture was then purged with CO gas for 10 min. The resulting solution was heated at 90°C for 2 h, followed by removal of the toluene under reduced pressure. The residue was loaded onto an Al_2O_3 column, and a yellow band was collected by elution with CH_2Cl_2 :hexane (1:4). After removal of the solvents 1252 mg (89%) of **6** was obtained. ^1H NMR (300.4 MHz, CDCl_3 , TMS): δ = 1.20 (d, $^3J(\text{H,H})$ = 6.6 Hz, 6H; CHMe_2), 1.35 (d, $^3J(\text{H,H})$ = 6.8 Hz, 6H; CHMe_2), 4.25 (m, 2H; CHMe_2), 6.77 (m, 1H), 7.30–7.60 (m, 13H), 7.73 (m, 6H), 7.87 ppm (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125.4 MHz, CDCl_3 , TMS): δ = 181.2 (PtCO), 198.3 (*cis* WCO), 201.7 ppm (*trans* WCO); $^{31}\text{P}\{^1\text{H}\}$ NMR (121.45 MHz, CDCl_3 , H_3PO_4): δ = 22.3 (d, $^2J(\text{P,P})$ = 225 Hz, $^1J(\text{P,Pt})$ = 1736 Hz; PPh_3), 75.2 ppm (d, $^2J(\text{P,P})$ = 225 Hz, $^1J(\text{P,Pt})$ = 1706 Hz, $^1J(\text{P,W})$ = 227 Hz).

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- [14] CCDC-188236 (**3**) and CCDC-188237 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Butane-2,3-diacetals of Glyceraldehyde: A Stable Alternative to Glyceraldehyde Acetonide**

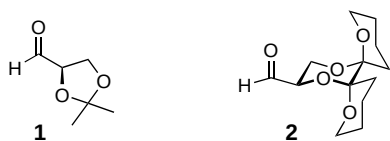
Patrick Michel and Steven V. Ley*

D-Glyceraldehyde acetonide **1** has been used extensively as a three-carbon building block for organic synthesis.^[1] However, it must always be freshly prepared owing to its propensity to polymerize, racemize, and form hydrates.^[2] This can result in severe problems, particularly on scale-up. Thus, a readily available, stable alternative that is accessible in both

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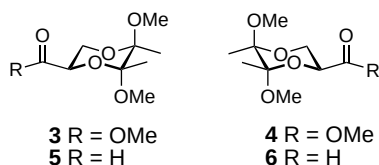
[**] We thank the BBSRC (to P.M.) and the Novartis Research Fellowship (to S.V.L.) for financial support.

enantiomeric series has the potential to be a powerful building block for synthesis. Here we describe a possible solution to this long-standing problem.

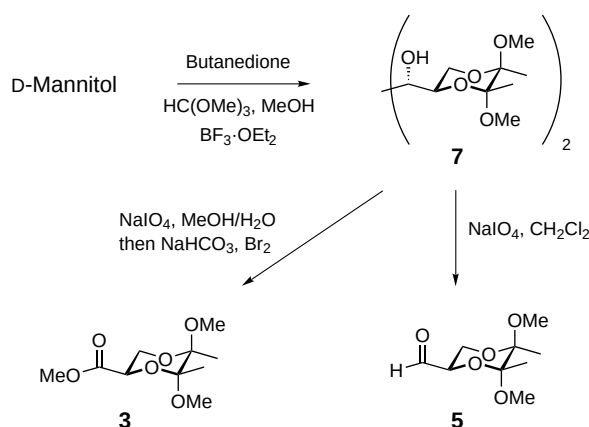


Some time ago we reported the preparation and utility of a dispiroketal-protected glyceraldehyde derivative **2**.^[3] This possessed considerable advantages over acetonide **1** in regard to both stability and reactivity, presumably due to the enhanced crystallinity of these dispiroketals and the favored placement of the aldehyde unit in a more stable equatorial environment. Although this was a step forward, the considerable increase in molecular weight and also difficulties in large-scale preparation meant that it failed to be adopted as a general replacement for **1**. We have continued to seek alternatives and have chosen to focus on the use of butane-2,3-diacetals^[4] as these are easily prepared from cheap starting materials, leading to a range of building blocks for synthesis.^[5]

Initially we investigated an approach that would produce both enantiomeric series of esters **3** and **4** and glyceraldehydes **5** and **6**.



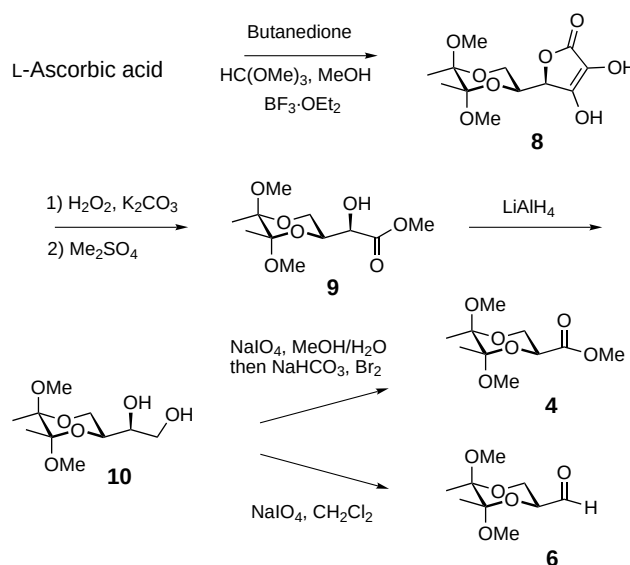
As planned, D-mannitol reacts with butane-2,3-dione in the presence of trimethyl orthoformate and boron trifluoride etherate^[4d] in methanol to give the diol **7** as the major product which could be isolated in a pure form by recrystallization from hexane (Scheme 1). Alternatively, oxidative cleavage of the crude diol **7** with sodium periodate in methanol, followed by bromine oxidation of the methyl hemiacetal^[6] gave the ester **3**^[7] as a colorless oil in 45 % yield over the two steps. The aldehyde **5** (white solid at -20°C) on the other hand, could be



Scheme 1. Reaction of D-mannitol with butane-2,3-dione to give the ester **3** and the aldehyde **5**.

isolated in 40 % overall yield by oxidative cleavage with sodium periodate in dichloromethane. These reactions were all carried out on scales in excess of 50 g, in which the only purification is a single distillation under vacuum at the final stage.

For the other enantiomeric series, we started from L-ascorbic acid as the source of chirality (Scheme 2). Protection with butane-2,3-dione gave the corresponding butane-2,3-



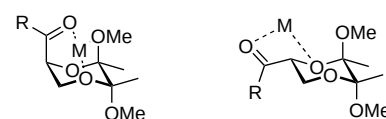
Scheme 2. Reaction of L-ascorbic acid with butane-2,3-dione to give the ester **4** and the aldehyde **6**.

diacetal **8** in 72 % yield, which was readily converted to the ester **9** by oxidative cleavage with hydrogen peroxide followed by methylation with dimethyl sulfate.^[8] Reduction to the diol **10** with LiAlH_4 followed by oxidation with periodate under the previously described conditions furnished either **4** or **6** in 52 % or 35 % overall yield, respectively, from **8**. Once again, the only purification is a single distillation at the final stage.

Although the esters **3** and **4** and the aldehydes **5** and **6** are stable and can be stored readily at -20°C for long periods of time (at least 6 months), the aldehydes decompose slowly at room temperature. Nevertheless they are considerably more stable than **1** and are significantly more convenient for use in synthesis programs.

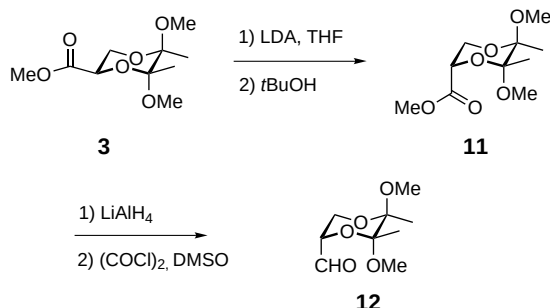
Preliminary studies concerned with the addition of organo-magnesium reagents to aldehyde **5** indicated that the *syn/anti* selectivity of addition is similar to that observed with dispiroketalaldehyde **2**.^[3] It was reasoned that an aldehyde in an axial position could potentially give even higher selectivities by improved chelation control (Scheme 3).

Thus, we decided to investigate an inversion protocol to obtain an aldehyde in an axial position. Treatment of ester **3**



Scheme 3.

with lithium diisopropylamide (LDA) at -78°C followed by protic workup with *t*BuOH at low temperature and subsequent quenching with aqueous ammonium chloride afforded mainly the inverted ester **11** (Scheme 4).^[7] Recrystallization from hexane gave only one product as a highly crystalline and stable material (53 % yield) whose structure was confirmed by X-ray crystallography.^[9] Reduction with LiAlH_4 in THF and

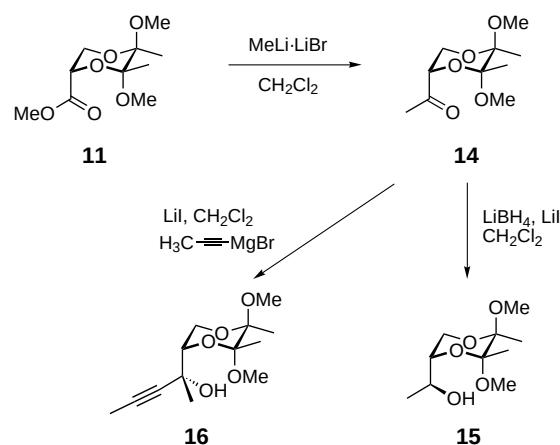


Scheme 4. Conversion of **3** to give the axial aldehyde **12**.

oxidation with oxalyl chloride and DMSO gave the axial aldehyde **12**^[7] (83 % overall yield on a 20 g scale) as a white crystalline solid whose structure was again confirmed by X-ray crystallography.^[9] This material is stable and storable for long periods of time (at least 3 months at room temperature or greater than 9 months at -20°C) and can be used without complications over several months.

The potential of **12** as a new chiral building block is illustrated by the stereofacially selective addition of Grignard reagents via β -chelation control (Scheme 3). Addition of a 1.5M Grignard reagent in dichloromethane to a solution of **12** in toluene at -95°C gave the corresponding secondary alcohols in good yield and excellent diastereoselectivity (Table 1). The stereochemical outcome of addition was confirmed by X-ray crystallography of the 4-nitrobenzoyl ester derivatives^[9] (Table 1, entries 1, 2, and 3). It was observed that several of these derivatives adopted a boat conformation whilst maintaining both methoxy groups in pseudo-axial positions.

To access the other configuration of the newly formed stereogenic center in the Grignard addition reactions, we also prepared the methyl ketone derivative **14** (Scheme 5) by addition of MeLi at -78°C to the ester **11** in dichloromethane (79 % yield; this compound could also be obtained via a



Scheme 5. Synthesis of the methyl ketone derivative **14** and its conversion to **15** and **16**.

Weinreb amide). This ketone **14** reacted with lithium borohydride in dichloromethane containing some lithium iodide at -78°C to give **15** (80 % yield, $>15:1$ stereoselectivity). If **14** was pretreated with lithium iodide in dichloromethane at -78°C and then propynyl magnesium bromide added, alcohol **16** was obtained in $>15:1$ stereoselectivity. A single recrystallization from hexane afforded alcohol **16** as a single diastereoisomer (90 % yield), the structure of which was confirmed by X-ray crystallography^[9] (Scheme 5).

In summary, we have described the large-scale preparation of both enantiomers of new butanediactal-protected glycer-aldehyde and glyceric acid derivatives. These new building blocks should find application in a range of synthetic programs.

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Table 1. Additions of Grignard reagent to **12**.

Entry	RMgX	Yield [%]	d.r.
1	CH_3MgCl	81	25:1
2	$\text{H}-\text{C}\equiv\text{C}-\text{MgBr}$	95	15:1
3	$\text{H}_3\text{C}-\text{C}\equiv\text{C}-\text{MgBr}$	93	15:1
4	$\text{CH}_3\text{CH}=\text{CH}-\text{MgBr}$	88	15:1
5	$\text{CH}_3\text{C}(\text{CH}_3)=\text{CH}-\text{MgBr}$	80	15:1

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17.4 ppm; b) **11**: m.p. 77 °C; $[\alpha]_{25}^{D} = -157.6$ ($c = 1.02$ in CHCl_3); ^1H NMR (400 MHz, CDCl_3): $\delta = 4.12\text{--}4.08$ (m, 2 H; CH, CHH), 3.94 (dd, $J = 12.0$, 5.0 Hz, 1 H; CHH), 3.76 (s, 3 H; CO_2CH_3), 3.28 (s, 3 H; OCH_3), 3.26 (s, 3 H; OCH_3), 1.32 (s, 3 H; CCH_3), 1.27 ppm (s, 3 H; CCH_3); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 171.0$, 99.6, 98.7, 68.1, 57.7, 51.9, 50.0, 48.2, 17.9, 17.7 ppm; c) **12**: m.p. 77 °C; $[\alpha]_{25}^{D} = -266.5$ ($c = 1.6$ in CHCl_3); ^1H NMR (400 MHz, CDCl_3): $\delta = 9.73$ (s, 1 H; CHO), 4.07 (d, $J = 11.6$ Hz, 1 H; CHH), 3.91–3.86 (m, 1 H; CHH), 3.77 (d, $J = 4.4$ Hz, 1 H; CH), 3.38 (s, 3 H; OCH_3), 3.28 (s, 3 H; OCH_3), 1.37 (s, 3 H; CCH_3), 1.24 ppm (s, 3 H; $\text{C(CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 201.2$, 99.4, 98.5, 74.6, 55.6, 50.3, 48.2, 17.8, 17.7 ppm.

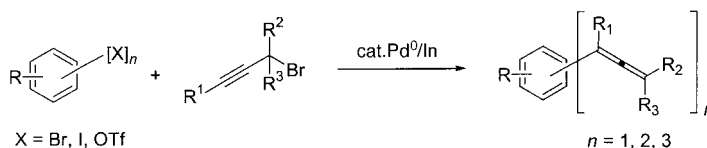
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Highly Efficient Catalytic Synthesis of Substituted Allenes Using Indium**

Kooyeon Lee, Dong Seomoon, and Phil Ho Lee*

Since allenes are versatile building blocks both for organic synthesis^[1] and in transition-metal-promoted carbon–carbon bond-forming reactions,^[2] development of practical methods for their preparation is of great interest. Allene moieties can be prepared by alkylation of allenylmethyl halides with an appropriate carbanionic species,^[1e] by $\text{S}_{\text{N}}2'$ -type selective displacement of propargyl alcohol derivatives with organo-copper reagents,^[1e,3] and by intramolecular regio- and stereo-selective reduction of alkynes.^[4] The synthesis of allenes by metal-catalyzed cross-coupling reactions is an alternative method;^[5] however, some disadvantages are the inconvenient preparation of the reagents, limited substrate scope, and incompatibility of sensitive groups to the reaction conditions.^[6] Recently, several reports have described the synthesis of allenes with transition metal complexes.^[5] Despite this recent progress a method for the highly efficient and catalytic synthesis of substituted allenes is still needed. We have realized this goal (Scheme 1) as part of our continuing studies directed toward the development of efficient indium-mediated reactions.^{[7], [8]}

The catalytic activity of several palladium complexes was initially examined in the reaction of 1-iodonaphthalene with allenylindium. The best results were obtained with 4 mol %

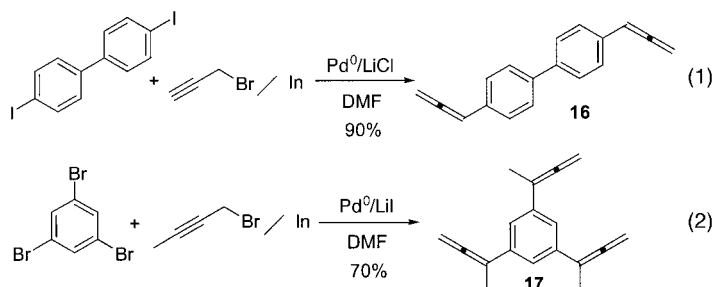


Scheme 1. Palladium-catalyzed cross-coupling reaction mediated by indium. Tf = trifluoromethanesulfonyl.

$[\text{Pd}(\text{PPh}_3)_4]$ in the presence of 3 equivalents of LiI in DMF at 100 °C under a nitrogen atmosphere (see Experimental Section), and 1-allenylnaphthalene was produced in quantitative yield (98 %) with complete regioselectivity (Table 1, entry 1). The allenylindium reagent generated in situ from the reaction of 1 equivalent of indium with 1.5 equivalents of propargyl bromide gave the best results as a coupling partner.^[9]

To demonstrate the efficiency and scope of the present method, we applied this catalytic system to a variety of propargyl halides and organic electrophiles. For the propargyl halides as coupling partners, the presence of various alkyl substituents at the α and γ positions had little effect on either the reaction rate or the product yield (Table 1). Under the optimized conditions, treatment of iodobenzene with 3-bromo-1-phenyl-1-butyne and indium gave selectively trisubstituted allene **2** in 80 % yield (entry 2). Varying the electron demand of the substituents on the arene did not diminish the efficiency and selectivity (entries 3, 7–9). It is noteworthy that protection of an oxo group and a hydroxy group on substrates is not necessary, as demonstrated by the reactions of 4-iodoacetophenone (entry 5) and 3-iodophenol (entry 6), respectively. Hetero substituents turned out to be compatible with the reaction conditions (entry 10). The method worked equally well with vinyl halides (entries 11 and 12) and imidoil bromide (entry 13). Treatment of iodophenylacetylene with allenylindium produced 3-methyl-1-phenyl-3,4-pentadien-1-yne (**14**) in 91 % yield (entry 14). In the case of vinyl triflate, the desired product **15** was obtained in 90 % yield (entry 15). Surprisingly, no propargylic cross-coupling product is formed in any reactions.

We then applied the present method to polyhalogenated aromatic compounds to obtain polyallenyl-substituted arenes, which can be used effectively in material and polymer sciences. Reaction of 4,4'-diiodobiphenyl with two equivalents of allenylindium produced 4,4'-diallenylbiphenyl **16** in 90 % yield [Eq. (1)]. We were pleased to observe that treatment of

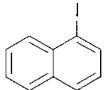
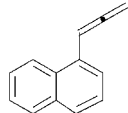
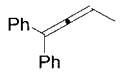
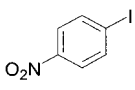
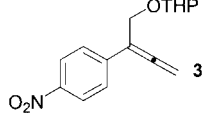
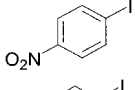
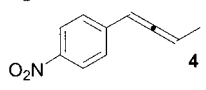
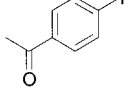
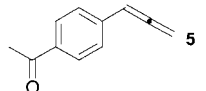
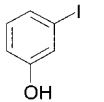
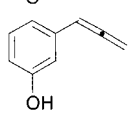
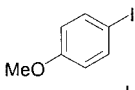
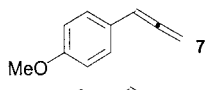
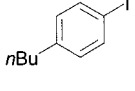
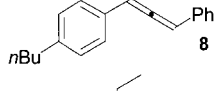
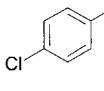
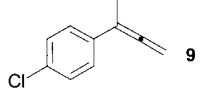
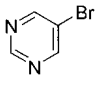
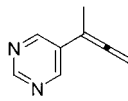
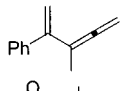
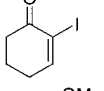
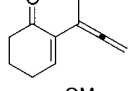
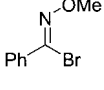
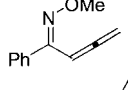
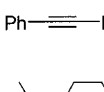
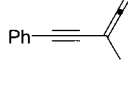
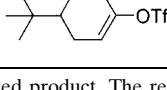
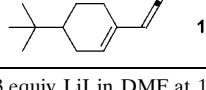


1,3,5-tribromobenzene with 1-bromo-2-butyne and indium selectively gave 1,3,5-tri(1'-methylallenyl)benzene (**17**) in 70 % yield [Eq. (2)]. On the basis of these results, unsym-

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Table 1. Palladium-catalyzed cross-coupling reactions of in-situ-generated allenylindium reagents with organic acceptors.

Entry	Acceptor	R ¹	R ²	R ³	Product	Yield [%] ^[a]
1		H	H	H	 1	98 97 ^[b] 22 ^[c] (58) ^[d] 97 ^[e] 84 ^[f]
2		Ph	Me	H	 2	80
3		THPOCH ₂ ^[g]	H	H	 3	91
4		H	H	Me	 4	90
5		H	H	H	 5	87 ^[b]
6		H	H	H	 6	90 ^[b]
7		H	H	H	 7	91 ^[b] 66 ^[f]
8		H	H	Ph	 8	90
9		Et	H	H	 9	96
10		Me	H	H	 10	92
11		Me	H	H	 11	91
12		Me	H	H	 12	90
13		H	H	H	 13	86 ^[b]
14		Me	H	H	 14	91
15		H	H	H	 15	90 ^[b]

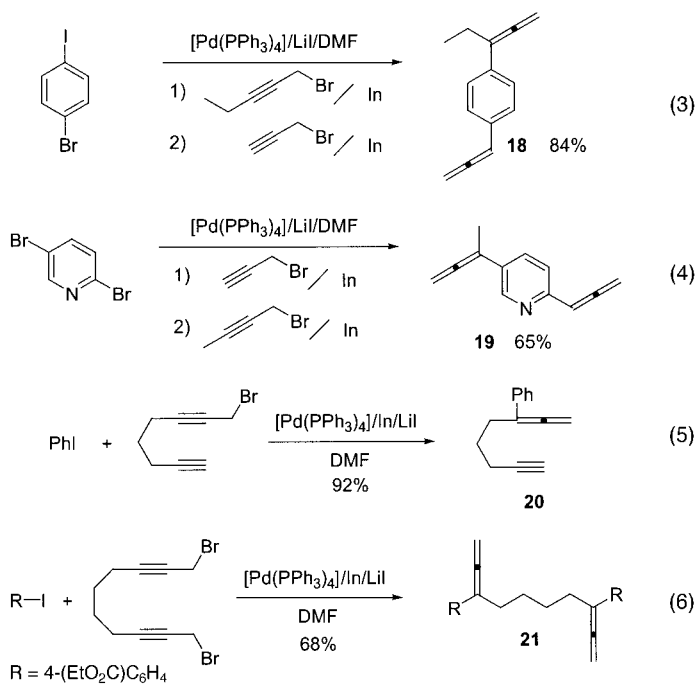
[a] Yield of isolated product. The reaction was performed in the presence of 4 mol % [Pd(PPh₃)₄] and 3 equiv LiI in DMF at 100 °C; allenylindium was obtained from the reaction of 1 equiv indium with 1.5 equiv propargyl bromide unless otherwise noted. [b] 3 Equiv LiCl was used. [c] 1 Equiv LiCl was used. [d] Yield of recovered 1-iodonaphthalene. [e] LiBr was used. [f] THF was used as a solvent. [g] THP = tetrahydropyranyl.

metrical bis(allenes) **18** and **19** were prepared chemoselectively and regioselectively in one pot from 4-bromiodobenzene and 2,5-dibromopyridine in good yields [Eqs. (3) and (4)].

Iodobenzene was treated with 1-bromo-2,7-octadiyne and indium to produce allenyne **20** in 92% yield, which is a useful compound in palladium-catalyzed carbocyclization

[Eq. (5)].^[2p] Interestingly, the double cross-coupling reaction of two equivalents of ethyl 4-iodobenzoate with one equivalent of 1,10-dibromo-2,8-decadiyne in the presence of indium yielded bis(allene) **21** in 68% yield [Eq. (6)].^[2o]

In conclusion, we have demonstrated for the first time that allenylindium reagents generated in situ from the reaction of



indium with propargyl bromides can be employed as effective cross-coupling partners in palladium-catalyzed cross-coupling reactions with a variety of organic electrophiles to produce substituted allenes, polyallenes, and unsymmetrical bis(allenes) in excellent yields with complete regioselectivity and chemoselectivity.

Experimental Section

Typical experimental procedure: 1-Iodonaphthalene (127.0 mg, 0.5 mmol) was added at room temperature under a nitrogen atmosphere to a suspension of $[Pd(PPh_3)_4]$ (23.1 mg, 4 mol %) and lithium iodide (200.8 mg, 1.5 mmol) in DMF (1 mL). After 15 min the allenylindium reagent, which was generated from propargyl bromide (89.2 mg, 0.75 mmol) and indium (57.0 mg, 0.5 mmol) in DMF (1 mL), was added, and the mixture was stirred at 100 °C for 1 h. The reaction mixture was quenched with saturated aqueous NaHCO₃. The aqueous layer was extracted with diethyl ether (3 × 20 mL), and the combined organic solvents were washed with water and brine, dried with MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with *n*-hexane to give 1-allenylnaphthalene (81.3 mg, 98 %).

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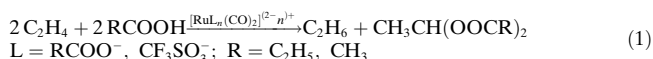
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Ethane and Ethylidene Dicarboxylates from the Ruthenium(II)-Catalyzed “Disproportionative Addition” of Carboxylic Acids to Ethene**

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Ethene is of paramount importance in chemistry and the addition reactions to the simplest olefin are paradigmatic. It is known that the acid-catalyzed addition of carboxylic acids yields esters.^[1] Herein we report a Ru^{II}-catalyzed “disproportionative addition” (that is, addition to give both oxidized and reduced products simultaneously) of carboxylic acids to give ethane and ethylidene dicarboxylate [Eq. (1)].



This novel reaction is carried out in anhydrous carboxylic acids. A number of ruthenium complexes can be employed as precursors, provided they generate [RuL_n(CO)₂]^{(2−n)+} (L = RC(O)O[−], CF₃SO₃[−]) intermediates. For instance, the triflate salt of the Ru^{II}–ethyl complex [Ru₂(C₂H₅)₂(CO)₄(H₂O)₄]²⁺ (**1**)^[2] is a suitable precursor for the reaction described in Equation (1), performed in propionic acid containing 10% of propionic anhydride. In that reaction medium, ethane and ethylidene dipropionate are formed in equimolar amounts with a turnover frequency (TOF) of 3 h^{−1} at 130° (P_{ethene} = 25 atm; [Ru] = 0.05 M), with the TOF remaining almost unchanged after 10 h. With regard to the activation of precursor **1**, it had already been shown that, in solution, the dinuclear complex is converted into the mononuclear [RuL(C₂H₅)(CO)₂(H₂O)₂] (**2**, L = propionato or triflate)^[2]. At 90°C under an inert atmosphere, complex **2** (0.1 M in propionic acid/anhydride) is dehydrated by the anhydride while, on acidolysis, quantitative ethane formation occurs. The IR absorptions of **1** in propionic acid/anhydride at 2049(s) and 1970(vs) cm^{−1} are shifted to 2090(s) and 2024(vs) cm^{−1}, which are attributable to *cis*-[RuL_n(CO)₂]^{(2−n)+} (L = RC(O)O[−] or CF₃SO₃[−]) species. When ethene (P_{ethene} = 25 atm, T = 90°C) is added, a reaction occurs that leaves the *cis*-(CO)₂Ru group intact and gives rise to new absorptions at 2059(s), 1984(vs), and 1600(s) cm^{−1}. To elucidate this reaction, the propionic acid/anhydride solvent was removed under vacuum and the residue extracted with toluene. Upon addition of hexane, crystalline [{Ru(CF₃SO₃)(CHCH₃-OC(O)C₂H₅)(CO)₂}] (**3**) was isolated in 37% yield. The molecular structure of **3** is shown in Figure 1; two bridging

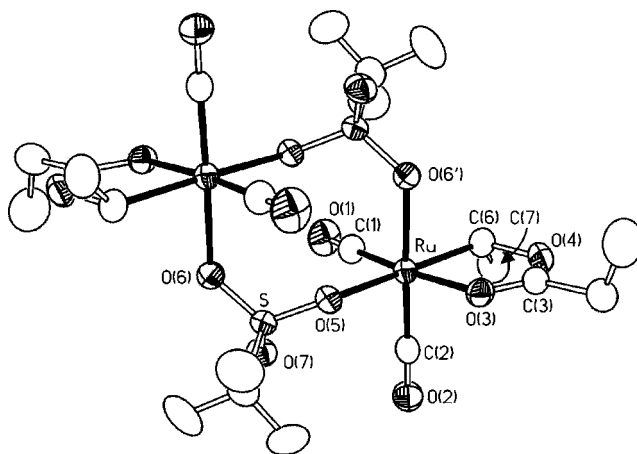


Figure 1. The molecular structure of [Ru(OSO₂CF₃)(CH(OCOC₂H₅)CH₃)(CO)₂]₂ (**3**); ellipsoids are at 30% probability. Selected bond lengths [Å] and angles [°]: Ru–C(1) 1.870(5), Ru–C(2) 1.842(5), Ru–C(6) 2.050(5), Ru–O(3) 2.091(3), Ru–O(6') 2.171(3), Ru–O(5) 2.293(3); C(2)–Ru–C(1) 87.6(2), C(2)–Ru–C(6) 93.1(2), C(1)–Ru–C(6) 93.2(2), C(2)–Ru–O(3) 93.4(2), C(1)–Ru–O(3) 173.0(2), C(6)–Ru–O(3) 79.8(2), C(2)–Ru–O(6') 176.6(2), C(1)–Ru–O(6') 95.7(2), C(6)–Ru–O(6') 86.6(2), O(3)–Ru–O(6') 83.3(1), C(2)–Ru–O(5) 93.7(2), C(1)–Ru–O(5) 99.0(2), C(6)–Ru–O(5) 166.2(2), O(3)–Ru–O(5) 87.8(1), O(6')–Ru–O(5) 85.8(1), C(3)–O(3)–Ru 112.4(3), O(3)–C(3)–O(4) 122.5(4), C(3)–O(4)–C(6) 117.8(4), O(4)–C(6)–Ru 107.2(3). Symmetry operation for primed atoms: −x, −y + 1, −z.

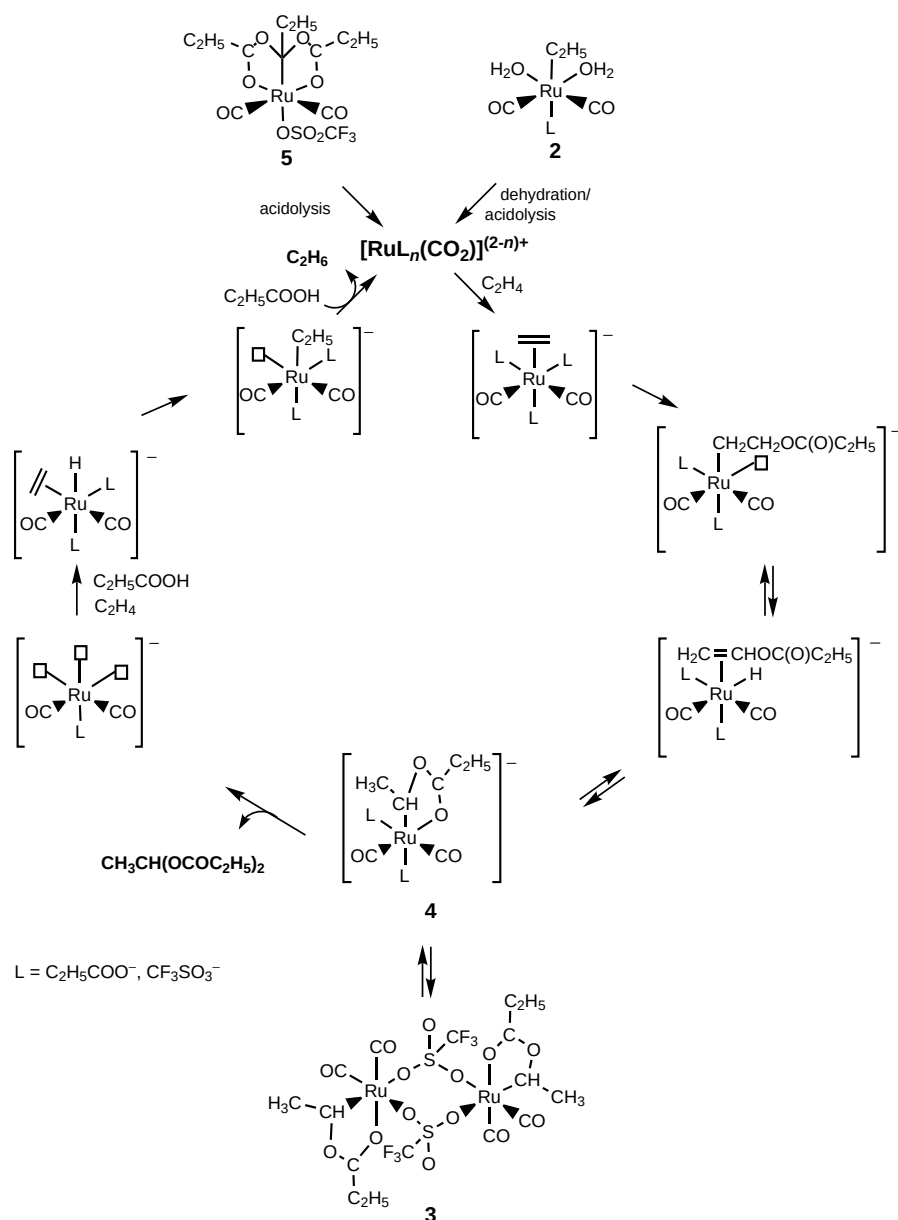
triflate ligands bind two *cis*-dicarbonyl–Ru^{II} units. The coordination sphere of each ruthenium is approximately octahedral being completed by the CHCH₃(OC(O)C₂H₅) group, which acts as a bidentate ligand through the ester oxygen atom. The IR spectrum of **3** in the solid state displays stretching frequencies of the terminal *cis*-CO groups at 2064(vs) and 1994(vs) cm^{−1}, and that of the coordinated ester carbonyl at 1633(s) cm^{−1}. In propionic acid/anhydride solution, **3** shows absorptions at 2059(s), 1984(vs), and 1600(s) cm^{−1}, identical to the frequencies reported above. This suggests that **3**, which is dinuclear in the solid state, exists as a mononuclear Ru^{II} complex in solution. This is particularly noteworthy as complexes containing bridging triflates are rare^[3] and only documented in the solid state.

The ¹H NMR spectrum of **3** in [D₄]acetic acid shows three main quartet resonances between δ = 6.1 and 6.5 ppm, attributed to the methine hydrogen atom of the alkyl ligand. These resonances, however, are affected by the addition of either the triflate or propionate salts of cesium, which are able to shift coordination equilibria in solution. For example, the addition of C₂H₅COOCs to a solution of **3** (0.2 M, molar ratio C₂H₅COOCs:Ru = 2) in [D₄]acetic acid yields a ¹H NMR spectrum that shows only a single quartet at δ = 6.16 ppm, which originates from the propionato complex. Based on the structure of **3** in the solid state, and from its spectroscopic properties, we conclude that precursor **1** at 90°C under ethene (25 atm) in propionic acid/anhydride is converted into the mononuclear ethylidene carboxylate dicarbonyl Ru^{II} complex **4** (Scheme 1), which is involved in coordination equilibria with triflate or propionato ligands.

As specified before, such a conversion is a consequence of the dehydration and subsequent acidolysis of **2**, which leads to the formation of a [RuL_n(CO)₂]^{(2−n)+} (L = RC(O)O[−] or

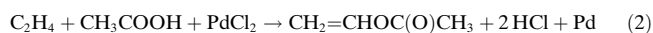
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Scheme 1. Mechanism for the Ru^{II} -catalyzed disproportionative addition of carboxylic acids to ethene. The activation of precursors **2** and **5** is also displayed.

CF_3SO_3^-) species, followed by ethene coordination, nucleophilic attack by the propionato moiety, and rearrangement of the alkyl complex by β -activation. In complex **4**, β -activation is exemplified by the fact that deuterium atoms are incorporated at both positions of the $\text{CH}-\text{CH}_3$ fragment when dissolved in $\text{C}_2\text{H}_5\text{COOD}$ at 90°C . Such behavior can be compared to that of Pd^{II} -coordinated ethene, which also undergoes nucleophilic attack by acetate groups. In this case, β -activation results in the release of a proton from the hydridopalladium moiety, and the decomposition to vinyl acetate and palladium metal [Eq. (2)].^[4]



By increasing the temperature of the above-mentioned solution to 140°C , the stepwise formation of **4** from **1** has been

followed; the Ru^{II} -catalyzed formation of equimolar amounts of ethane and ethylidene dipropionate occurs, as shown in Equation (1). IR spectroscopy shows that **4** is the only detectable species during catalysis; separate experiments confirm that **4** catalyzes the reaction with no induction period and remains unchanged. We conclude that **4** is an intermediate and that the reductive elimination of ethylidene dipropionate from **4** is the slow step of the catalytic cycle. Experiments in $\text{C}_2\text{H}_5\text{COOD}$ confirm the intermediary role of complex **4**. The ^2H NMR spectrum of the ethylidene dipropionate formed in the deuterated solvent shows deuterium incorporation in the organic product. On these grounds, the above reported H/D scrambling of **4** in $\text{C}_2\text{H}_5\text{COOD}$ appears to be related to the H/D scrambling observed in the 1,1'-diester product of the catalytic reaction. Finally, the formation of ethane in the catalytic cycle can be rationalized on the basis of an oxidative addition of propionic acid to the Ru^0 complex, formed by reductive elimination from **4**, followed by ethene insertion into the resulting hydride (Scheme 1) and acidolysis of the ethyl complex.

It is noteworthy that the catalytic reaction described in Equation (1) can be extended to other carboxylic acids. For instance, equimolar amounts of ethane and ethylidene diacetate are formed when employing **1** as a precursor in acetic acid/anhydride, with a similar TOF to that which was recorded for the above-reported propionic acid/anhydride

case. In addition, the intermediate that accumulates during the catalysis in acetic acid appears to have a similar nature to that of **4**, with C_2H_5 groups being substituted with CH_3 groups. Moreover, different precursors can be employed for the reaction described in Equation (1). For instance, the recently characterized $[\text{Ru}(\text{CF}_3\text{SO}_3)\{\text{CC}_2\text{H}_5(\text{OC}(\text{O})\text{C}_2\text{H}_5)_2\}(\text{CO})_2]$ (**5**)^[5] has been converted to complex **4** under the conditions of the catalytic reaction. The tridentate $\text{CC}_2\text{H}_5(\text{OC}(\text{O})\text{C}_2\text{H}_5)_2$ ligand of **5** is entirely dissociated, thus yielding the $[\text{RuL}_n(\text{CO})_2]^{(2-n)+}$ ($\text{L} = \text{RC}(\text{O})\text{O}^-, \text{CF}_3\text{SO}_3^-$) active species which initiate the cycle described in Scheme 1.

In conclusion, the carboxylic acid-induced disproportionation of ethene has been demonstrated. The reaction is industrially relevant since the dissociation of carboxylic acids from 1,1'-diester products is well known and constitutes a synthetic method for vinyl esters other than acetates.^[6]

Experimental Section

Complexes **1** and **5** were prepared according to literature procedures[2,5]. Catalytic runs were performed as described in reference [2]. GC analyses of ethane/ethene mixtures were performed with a 2-m Carboxen-1004 micropacked column. Ethylidene dipropionate analyses were performed with a 2-m Silicone column. $\text{C}_2\text{H}_5\text{COOD}/(\text{C}_2\text{H}_5\text{CO})_2\text{O}$ mixtures were prepared by adding D_2O to propionic anhydride and refluxing the solution for a short time. A sample of partially deuterated ethylidene dipropionate, as formed in the catalytic reaction in $\text{C}_2\text{H}_5\text{COOD}/(\text{C}_2\text{H}_5\text{CO})_2\text{O}$, was obtained by neutralization at pH 8 with NaHCO_3 , extraction with Et_2O , solvent evaporation, and distillation of the residue under vacuum: ^2H NMR (300 MHz, THF): $\delta = 6.7$ (br), 1.4 ppm (br).

3: Complex **5** (1.60 g, 3.25 mmol) was dissolved in $\text{C}_2\text{H}_5\text{COOH}/(\text{C}_2\text{H}_5\text{CO})_2\text{O}$ (50 mL, 10% anhydride) and stirred under ethene (25 atm) at 130°C. After 2 h, the gases were discharged and solvents removed by distillation (55°C, 0.1 mmHg). The oily residue was treated first with toluene (10 mL) and then with hexane (200 mL). The first aliquot of precipitate was discarded by filtration and crystals of **3** (0.47 g, 0.6 mmol, 37% yield) were obtained by cooling the mother liquor at -20°C. IR (nujol mull): $\tilde{\nu}_{\text{CO}} = 2064$ (vs), 1994(vs), 1633(s) cm^{-1} . IR ($\text{C}_2\text{H}_5\text{COOH}/(\text{C}_2\text{H}_5\text{CO})_2\text{O}$ solution): $\tilde{\nu}_{\text{CO}} = 2059$ (s), 1984(vs), 1600(s) cm^{-1} . ^1H NMR (CD_3COOD): $\delta = 6.41$ (q), 6.35 (q), 6.16 ppm (q); $\delta = 6.16$ ppm (1H, q) upon addition of $\text{C}_2\text{H}_5\text{COOCs}$ (0.8M). ^1H NMR ($[\text{D}_8]\text{THF}$): $\delta = 6.45$ (1H, q), 2.64 (2H, q), 1.81 (3H, d), 1.20 ppm (3H, t).

Complex **3** (0.1M in $\text{C}_2\text{H}_5\text{COOD}$) was maintained at 90°C for 3 h. Aliquots of 1 mL, taken at 30 min intervals, were evaporated to dryness and examined by ^1H NMR spectroscopy in $[\text{D}_8]\text{THF}$. The spectra showed the gradual decrease of both the quartet ($\delta = 6.45$ ppm) and doublet ($\delta = 1.81$ ppm) signals of **3**.

Single-crystal X-ray diffraction was carried out with a Bruker P4 diffractometer using MoK_α graphite-monochromated radiation ($\lambda = 0.71073 \text{ \AA}$), the sample being sealed in a glass capillary under an argon atmosphere. The crystal used for the measurement was a rather large colorless prism with approximate dimensions $0.50 \times 0.34 \times 0.21 \text{ mm}^3$. Cell parameters were calculated on the setting angles of 40 strong reflections with $5.0^\circ \leq \theta \leq 12.6^\circ$. Crystal data: $\text{C}_{16}\text{H}_{18}\text{F}_6\text{O}_{14}\text{Ru}_2\text{S}_2$, $M_r = 814.56$, $T = 293(2) \text{ K}$, monoclinic, space group $P2_1/n$ (No. 14), $a = 11.298(1)$, $b = 10.525(1)$, $c = 12.788(1) \text{ \AA}$, $\beta = 112.26(1)^\circ$, $V = 1407.3(2) \text{ \AA}^3$, $Z = 2$, $\rho_{\text{calc}} = 1.922 \text{ g cm}^{-3}$, $\mu(\text{MoK}_\alpha) = 1.322 \text{ mm}^{-1}$, $F(000) = 800$. The intensities of 3238 reflections with $2.0^\circ \leq \theta \leq 25^\circ$ were collected. After merging the equivalent reflections and after corrections for Lorentz, polarization, and absorption effects with an empirical method,^[7a] an internal R value of 0.0131 was obtained.

The structure was solved by standard direct and Fourier methods and refined by full-matrix least-squares procedures. The hydrogen atoms were placed in calculated positions and allowed to ride on the connected carbon atoms. In the final refinement cycle anisotropic thermal parameters were used for all heavy atoms, giving a conventional R factor (F_o) of 0.0347, calculated for 181 parameters on 2100 observed reflections [$I > 2\sigma(I)$], and a wR_2 value of 0.0436 for all 2489 data. The residual peaks in the final difference Fourier map range between 0.80 and $-0.72 \text{ e \AA}^{-3}$. The calculations were carried out using SHELX97^[7b] contained in the WINGX^[7c] suite.

CCDC-191095 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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Selective Measurements of a Nitroxide–Nitroxide Separation of 5 nm and a Nitroxide–Copper Separation of 2.5 nm in a Terpyridine-Based Copper(II) Complex by Pulse EPR Spectroscopy**

Evelyn Narr, Adelheid Godt, and Gunnar Jeschke*

Coordination by transition metals is one of the main design principles of supramolecular chemistry.^[1] The structures of such supramolecular assemblies are often elucidated by NMR spectroscopy and X-ray diffraction analysis. The latter method fails for the structural determination of noncrystalline assemblies. For paramagnetic transition metals, structural determination is further complicated by the failure of NMR methods from fast paramagnetic relaxation. In particular, the characterization of long-range arrangements over several nanometers has proved to be a significant barrier towards the further development of supramolecular structural design. On the other hand, it has been shown in the past few years that modern pulse EPR techniques^[2] are capable of measuring separations up to at least 5 nm between organic radicals in disordered systems with high precision.^[3] The application of such techniques to transition metals with considerable anisotropy of the g and/or hyperfine tensors, such as Cu^{II} , Co^{II} , V^{IV} , Mo^{V} , or Fe^{III} is more complicated, since only a small fraction of the EPR spectrum of these species can be excited by the pulses. Indeed, attempts to measure $\text{Mo}^{\text{V}}\cdots\text{Fe}^{\text{III}}$ separations in the $\text{Mo}^{\text{V}}/\text{Fe}^{\text{III}}$ state of sulfite oxidase did not result in appreciable dipolar modulations^[4] and, except for a preliminary conference report on the measurement of a $\text{Cu}\cdots\text{Cu}$ separation in azurin,^[5] no applications to transition metals have been reported to date. An estimate of the separation of a transition metal and a nitroxide spin label can also be obtained from relaxation measurements. However, this approach is restricted to separations shorter than 3 nm and to systems where the

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

longitudinal relaxation of the transition metal ion is much faster than that of the nitroxide spin label.^[6] Herein we show that the separation of a Cu^{II} ion and a nitroxide group can be measured using the double electron electron resonance (DEER) experiment with pump excitation, both in the nitroxide and the copper spectrum. The latter result indicates that measurement of the separation of two copper centers will also be feasible. Furthermore, we demonstrate that in a spin system consisting of two nitroxide radicals and a Cu^{II} ion, the nitroxide–nitroxide and nitroxide–copper separations can be independently determined by appropriate spectral selection. Such experiments are of interest not only for artificial supramolecular assemblies but also for biological macromolecules such as metalloproteins, where nitroxide spin labels can be attached by site-directed spin labeling,^[7] and for membrane proteins, where artificial metal ion binding sites can be designed.^[8]

To verify the reliability of our approach to measuring copper–nitroxide separations, we have designed a model system, copper complex **1**, with well-defined, predictable separations between the paramagnetic sites (Figure 1). The ligand **2** consists of a terpyridine unit^[9] to guarantee a well-defined coordination geometry for the Cu^{II} center, a phenylene-ethynylene-based rigid spacer, and 1-oxyl-2,2,5,5-tetramethylpyrroline-3-yl as the nitroxide label, attached through an ester moiety. The latter choice was made based on our previous experience with shape-persistent biradicals^[3c,10] to ensure low exchange coupling and restricted conformational flexibility.

To predict the separations between the paramagnetic centers we overlaid a force-field structure (MMFF94) of ligand **2** and a density functional theory (DFT) structure of the bis(4'-ethynyl-2,2':6',2''-terpyridine)copper(II) complex. In the force-field simulation we replaced the N–O group by a keto group to avoid difficulties with force-field parametrization^[11] and assumed that the center of spin density corresponds to the center of the C=O bond. For the theoretical separation between this center and the N_{tpy}' atom, we find a value of 2.26 nm. Based on an earlier comparison of such a force-field computation with DFT computations for a nitroxide biradical,^[12] we estimate that this value may be too large by approximately 0.04 nm. The DFT computation predicts a N_{tpy}–Cu bond length of 0.204 nm, which compares to 0.197–0.201 nm observed in the X-ray crystal structures of several related copper complexes with terpyridine and a 4'-substituted terpyridine group.^[13] Furthermore, the N'–Cu and C≡C bonds have been found to be colinear. Hence, we expect a

copper–nitroxide separation of 2.43 nm and a nitroxide–nitroxide separation of approximately 4.86 nm (Figure 1).

The EPR spectra of the copper ion and the nitroxide moieties (Figure 2) overlap only moderately, so that the two different paramagnetic species can be excited selectively by microwave pulses with a length of 32 ns (excitation bandwidth

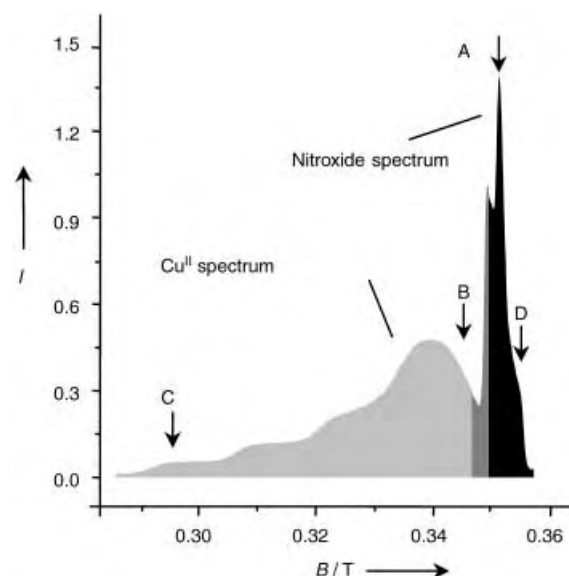


Figure 2. Excitation positions within the echo-detected EPR absorption spectra of the copper ion and the nitroxide radical.

of approximately 30 MHz or 1 mT). The maximum depth of the dipolar oscillations corresponding to the nitroxide–copper separation is obtained by applying the pump pulse at the maximum of the nitroxide spectrum (pump field A) and the observer pulses at a frequency that is larger by 200 or 1465 MHz and, thus, well outside the nitroxide spectrum (observer fields B and C, respectively).

Although we expected a significant extent of orientation selection in the copper spectrum, we obtained satisfying fits for the DEER time-domain data with our fit program^[12] that neglects such orientation selection (Figure 3a, b). This is because the data is dominated by the singularity of the Pake pattern which results from orientations that are perpendicular to the spin–spin vector. Such orientations contribute at both observer fields B and C, which indicates that the spin–spin vector is perpendicular to the g_z principal axis ($g_z = 2.258$) of the Cu^{II} g tensor. Accordingly, the outer shoulders of the dipolar spectra that correspond to orientations along the spin–spin vector can only be observed at position B (Figure 4,

arrows), that is, along the g_x or g_y axes. The relative enhancement of the narrow singularity at observer position B also gives rise to slow modulations in the time-domain data that are not fitted by the expressions neglecting orientation selection (Figure 3b). The separation values obtained from the preliminary fits (Table 1) are in good agreement with those expected theoretically.^[14]

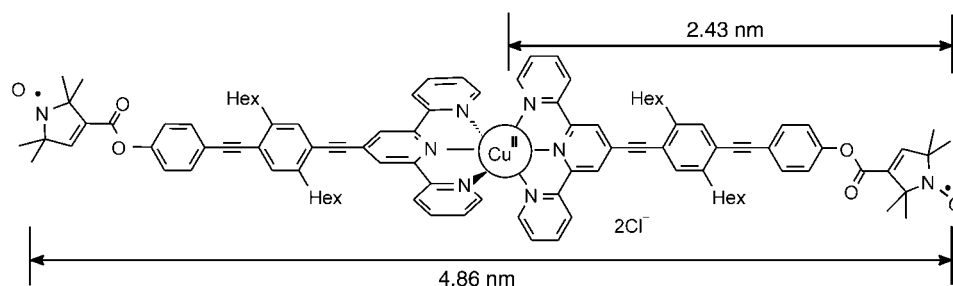


Figure 1. Rigid, doubly labeled copper(II) complex **1** with the calculated copper–nitroxide and nitroxide–nitroxide separations. The copper(II) center is hexacoordinated by two spin-labeled terpyridyl ligands **2**.

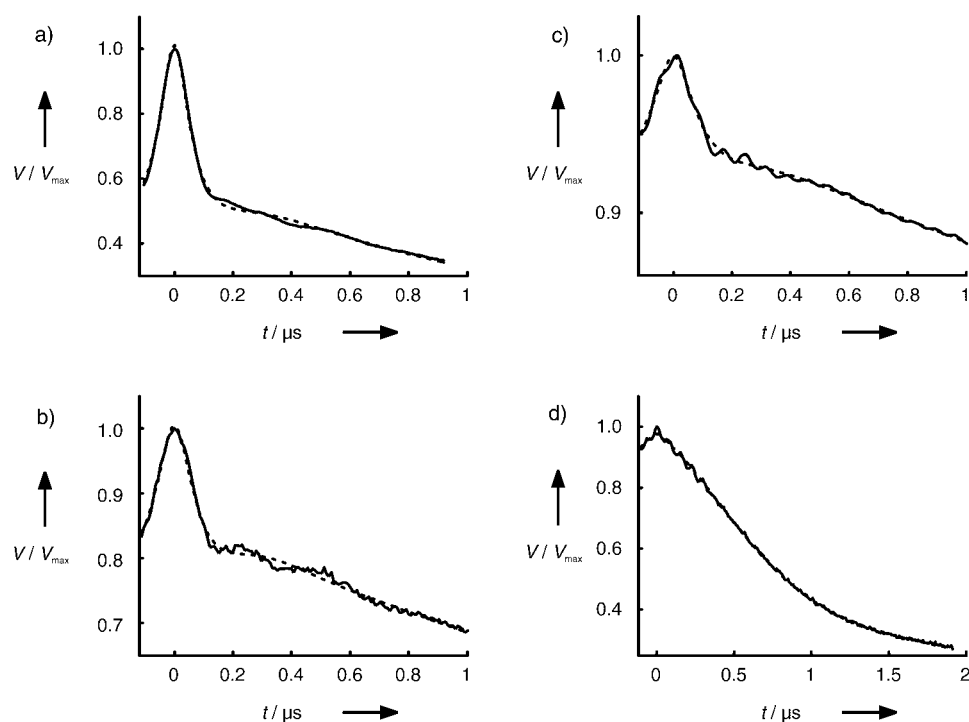


Figure 3. DEER time-domain data for several choices of pump and observer field (compare Figure 2). The dashed lines represent fits based on equation 13 in Ref. [12], with $G(r)$ given by a single Gaussian peak. Measurement times are given in parentheses. a) Pump A, observer B, separation 2.43 nm (1.5 h); b) Pump A, observer C, separation 2.46 nm (12 h); c) Pump B, observer A, separation 2.38 nm (12 h); d) Pump A, observer D, separation 5.20 nm (3.5 h).

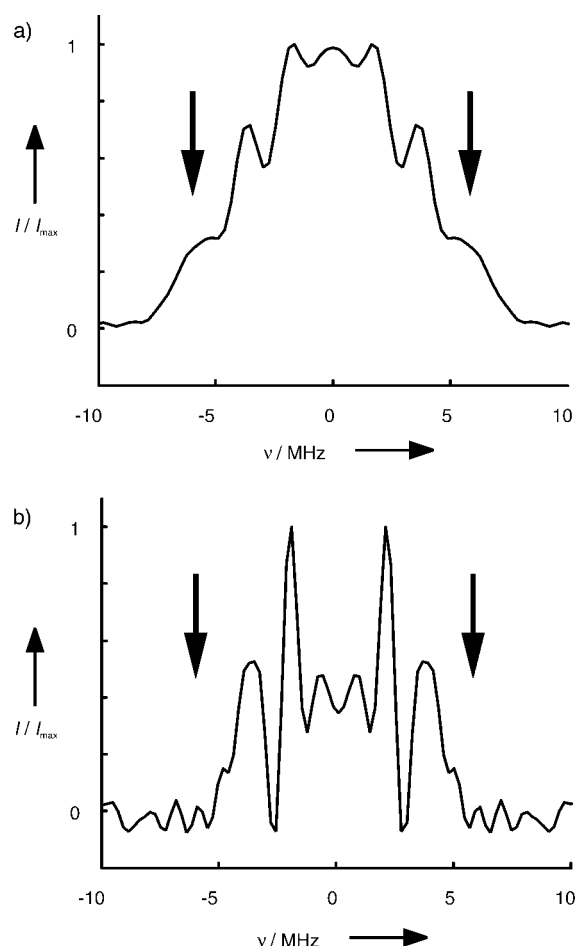


Figure 4. The effect of orientation selection on the dipolar spectra obtained by Fourier transformation of baseline-corrected DEER time-domain data. Arrows mark the dipolar frequency corresponding to the direction of the copper-nitroxide vector. a) Pump A, observer B. b) Pump A, observer C.

Table 1. Comparison of experimental and theoretical copper-nitroxide and nitroxide-nitroxide separations.

Pump field	Observer field	r_{exp} [nm]	r_{th} [nm]
A	B	2.43	Cu-NO: 2.43
A	C	2.46	Cu-NO: 2.43
B	A	2.38	Cu-NO: 2.43
A	D	5.20	NO-NO: 4.86

For the inverse experiment with the pump field B in the copper spectrum and the observer field A in the nitroxide spectrum, we obtained a much lower modulation depth (Figure 3c), which is expected as the fraction of pumped spins is smaller. In addition, nuclear modulations resulting from nearby protons are more prominent. Nevertheless, we again obtained a satisfying fit and a separation that is close to the expected value (Table 1). These results indicate that the DEER experiment can also be performed for pairs of paramagnetic centers which both feature considerable anisotropy of the g and/or hyperfine tensors. A control experiment with both the pump and observer field in the copper spectrum yielded a purely exponential decay that corresponds to the homogeneous distribution of the complexes (1 mmol L^{-1}) in the glassy frozen solution (data not shown).

By choosing both the pump field (A) and the observer field (D) within the nitroxide spectrum, we selectively observed dipolar modulation from the nitroxide-nitroxide pair, superimposed again by initial weak proton modulation (Figure 3d). In this case, the agreement between the predicted separation (4.83 nm) and the observed separation (5.20 nm) is not as good as for the nitroxide-copper separation. This is because a maximum dipolar evolution time of only $2 \mu\text{s}$ could be achieved, which is too short for the precise measurement of such long separations. Nevertheless, the precision is sufficient

to confirm the expected linear structure of the complex. Such selective measurements of intergroup separations of several nanometers should thus open up a new route for the structural determination of noncrystalline supramolecular assemblies.

Experimental Section

Synthesis and full characterization of ligand **2** is described in the Supporting Information.

EPR measurements: Four-pulse DEER time-domain signals were obtained with the sequence $(\pi/2)_{\nu_1}-\tau_1-(\pi)_{\nu_1}-t-(\pi)_{\nu_2}-\tau_1+\tau_2-t-(\pi)_{\nu_1}-\tau_2$ -echo at a temperature of 15 K on a Bruker E 580 X-Band spectrometer. A Bruker Flexline split-ring resonator ER 4118X-MS3 was used with over-coupling to $Q \approx 100$. Pump pulses were generated by feeding the output of an HP8350B sweep oscillator to one microwave-pulse-forming unit of the spectrometer. All pulse lengths were 32 ns, the dwell time was 8 ns, and the fixed interpulse delays were $\tau_1 = 400$ ns and $\tau_2 = 1200$ ns (Figure 3 a–c) or $\tau_2 = 2000$ ns (Figure 3 d). Details are discussed in the Supporting Information.

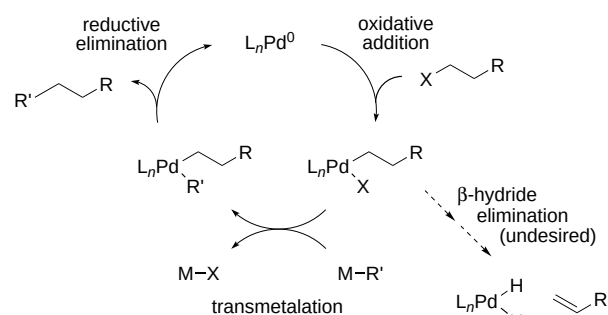
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Suzuki Cross-Couplings of Alkyl Tosylates that Possess β Hydrogen Atoms: Synthetic and Mechanistic Studies**

Matthew R. Netherton and Gregory C. Fu*

During the past few decades, remarkable progress has been reported in the development of mild and efficient nickel- and palladium-catalyzed protocols for carbon–carbon bond-forming reactions of electrophiles that contain $C(sp^2)$ -X bonds (e.g., aryl and vinyl halides and sulfonates).^[1] In contrast, general methods to cross-couple unactivated electrophiles that contain $C(sp^3)$ -X bonds, especially when β hydrogen atoms are present in the molecule, are scarce, presumably because of slow oxidative addition and/or facile β -hydride elimination (Scheme 1).^[2] In the case of alkyl halides, some advances have been described, specifically, examples of Suzuki cross-couplings of alkyl iodides, bromides, and chlorides,^[3] Negishi reactions of alkyl iodides and bromides,^[4] and Kumada couplings of alkyl bromides and a chloride.^[5]



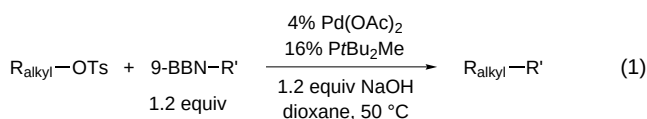
Scheme 1. Generalized mechanism for palladium-catalyzed cross-coupling reactions.

In contrast, to the best of our knowledge, at the time that we initiated our program in this area, there were no reports of palladium- or nickel-catalyzed cross-couplings of alkyl sulfonates. In the interim, however, Kambe and co-workers have described nickel-catalyzed Kumada couplings of two unfunctionalized alkyl tosylates.^[5] In this communication, we establish that Pd/*PtBu*₂Me can achieve Suzuki reactions of a range of functionalized alkyl sulfonates [Eq. (1); 9-BBN = 9-borabicyclo[3.3.1]nonane], and we report preliminary mechanistic studies of this new catalyst system.

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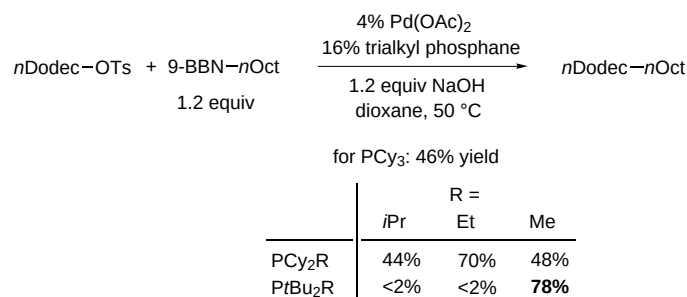
[**] We thank Johnson Matthey Inc. for supplying palladium compounds. Support has been provided by the National Institutes of Health (National Institute of General Medical Sciences, R01-GM62871), the Natural Sciences and Engineering Research Council of Canada (postdoctoral fellowship to M.R.N.), and Novartis.

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In our initial investigation of Suzuki couplings of alkyl sulfonates, we attempted to employ the catalysts that we had developed for reactions of alkyl bromides ($\text{Pd}(\text{OAc})_2/\text{PCy}_3/\text{K}_3\text{PO}_4\cdot\text{H}_2\text{O}/\text{THF}$; Cy = cyclohexyl) and alkyl chlorides ($[\text{Pd}_2(\text{dba})_3]/\text{PCy}_3/\text{CsOH}\cdot\text{H}_2\text{O}/\text{dioxane}$; dba = *trans,trans*-di-benzylidene acetone). Unfortunately, for the cross-coupling of *n*Dodec-OTs with 9-BBN-*n*Oct, these catalyst systems provide essentially none of the hoped-for eicosane (< 15 %).

After a considerable number of optimization experiments, we determined that $\text{Pd}(\text{OAc})_2/\text{PR}_3/\text{NaOH}/\text{dioxane}$ can furnish an appreciable quantity of the desired product. As illustrated in Scheme 2, this Suzuki reaction is remarkably sensitive to the structure of the trialkyl phosphane. Although PCy_3 and PCy_2iPr afford only modest yields of eicosane (ca.



Scheme 2. Effect of the structure of the trialkyl phosphane on the yield of the Suzuki cross-coupling of an alkyl tosylate.

45 %), a slight decrease in the steric demand of *one* of the alkyl groups leads to a significantly more efficient reaction (70 % yield for PCy_2Et); interestingly, a further decrease in size results in a loss in yield (48 % for PCy_2Me). For di-*tert*-butyl-substituted trialkyl phosphanes, essentially none of the desired cross-coupling product is formed if the third substituent is either isopropyl or ethyl (< 2 %), but a good yield is obtained if it is methyl (78 %).^[6]

Although we have not yet determined the origin of this striking dependence of reactivity on phosphane structure, we were pleased to discover that PtBu_2Me ,^[7] which is commercially available, is an effective ligand for a range of palladium-catalyzed Suzuki cross-couplings of alkyl tosylates that bear β hydrogen atoms (Table 1).^[8] The process tolerates a number of functional groups, including acetals and silyl ethers (entry 2), alkyl ethers (entry 3), esters (entry 4), tertiary amides (entry 5), ketones (entry 6), nitriles and olefins (entry 7), and tertiary alcohols (entry 8). Not only organoboron reagents that contain 9-BBN-C(sp³) bonds, but also those with 9-BBN-C(sp²) bonds can be employed (entry 8), and a double Suzuki coupling of a bis(tosylate) can be achieved (entry 9).^[9,10]

Although we routinely conduct these cross-couplings at 50 °C, they can in fact be accomplished at room temperature, at the expense of a long reaction time (for the coupling

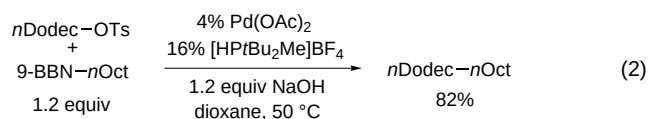
Table 1. Examples of $\text{Pd}/\text{PtBu}_2\text{Me}$ -catalyzed Suzuki cross-couplings of alkyl tosylates [see Eq. (1)].

Entry	$\text{R}_{\text{alkyl}}-\text{OTs}$	9-BBN-R'	Yield [%] ^[a]
1	<i>n</i> Dodec-OTs	9-BBN- <i>n</i> Oct	80
2		9-BBN-(CH ₂) ₁₁ OTES ^[b]	67
3		9-BBN-(CH ₂) ₅ OBn	61 ^[c]
4		9-BBN-(CH ₂) ₅ OBn	60
5		9-BBN- <i>n</i> Oct	76
6		9-BBN-(CH ₂) ₁₁ OTES ^[b]	55
7	NC(CH ₂) ₈ -OTs	9-BBN-	64
8		9-BBN-	63
9 ^[d]	TsO-(CH ₂) ₁₂ -OTs	9-BBN- <i>n</i> Oct	73

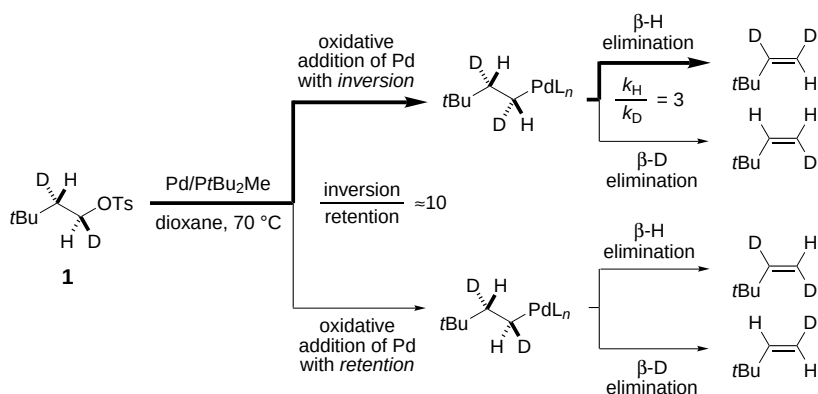
[a] Yield of isolated product, average of two runs. [b] TES = triethylsilyl. [c] Isolated as 8-cyclopentyl-octan-1-ol (after hydrogenolysis). [d] 2.4 equiv of 9-BBN-R', 8 % $\text{Pd}(\text{OAc})_2$, 32 % PtBu_2Me , and 2.4 equiv of NaOH were used.

illustrated in entry 1 of Table 1: 70 % yield after 7 days). This ability to couple an alkyl tosylate under mild conditions is noteworthy in view of the fact that aryl tosylates are generally not suitable substrates for palladium-catalyzed cross-couplings.^[1]

We have recently described the use of phosphonium salts as air-stable substitutes for air-sensitive trialkyl phosphanes,^[11] and we have demonstrated the interchangeability of these reagents for $\text{Pd}/\text{PtBu}_2\text{Me}$ -catalyzed Suzuki reactions of alkyl tosylates [Eq. (2) vs. entry 1 of Table 1].^[12]



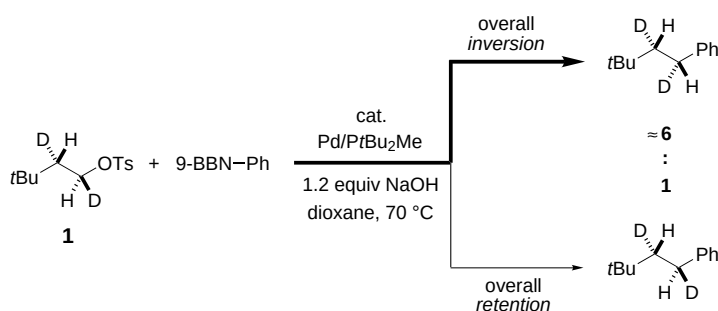
We have begun to pursue mechanistic work on our $\text{Pd}/\text{PtBu}_2\text{Me}$ -based catalyst for cross-coupling alkyl tosylates and have focused on the stereochemistry of oxidative addition (i.e., inversion vs. retention).^[13,14] As far as we are aware, this issue has not been addressed for any of the methods that have been described for coupling unactivated electrophiles that contain C(sp³)-X bonds.^[3-5] To gain insight into this stereochemical question, we treated diastereomerically pure tosylate **1**^[15] with $\text{Pd}/\text{PtBu}_2\text{Me}$, in the absence of an organoboron and NaOH, and examined the olefins that resulted from oxidative addition and then β -hydride elimination (Scheme 3).^[16] On the basis of ¹H NMR analysis, we determined that oxidative addition occurs primarily with inversion



Scheme 3. Determination of the stereochemistry of oxidative addition of an alkyl tosylate to Pd/PrBu₂Me.

of configuration (and that β -hydride elimination proceeds with 3:1 selectivity for H in preference to D).^[17]

In a second investigation, we explored the stereochemical course of a Pd/PrBu₂Me-catalyzed cross-coupling of tosylate **1** with an organoborane (Scheme 4). ¹H NMR analysis of the coupled product revealed that the Suzuki reaction occurs principally with inversion (ca. 6:1) at carbon.^[17] Taken together, the studies outlined in Schemes 3 and 4 are consistent with predominant inversion of configuration during oxidative addition of the tosylate, along with (well-precedented) retention of configuration during reductive elimination.^[14]



Scheme 4. Examination of the stereochemistry of a Pd/PrBu₂Me-catalyzed Suzuki cross-coupling of an alkyl tosylate.

In summary, we have developed the first palladium- or nickel-catalyzed cross-coupling process that is effective for functionalized alkyl tosylates, specifically, a mild, Pd/PrBu₂Me-based method for achieving Suzuki reactions. We have determined that, in contrast to couplings of alkyl bromides and chlorides, PrBu₂Me (rather than PCy₃) is the ligand of choice for Suzuki reactions of tosylates. In initial mechanistic studies, we have established that alkyl tosylates oxidatively add to the catalyst with predominant inversion of configuration at carbon. Ongoing work is focused on expanding the scope of palladium-catalyzed cross-couplings of alkyl electrophiles (e.g., Stille reactions) and on enhancing our understanding of the origin of the exceptional reactivity of our catalyst system.

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- [9] Under the conditions described in Table 1, we have examined the Suzuki cross-coupling of 9-BBN-*n*Oct with two other alkyl sulfonates. For *n*Dodec-OMs, the desired product was generated in 51% yield; for *n*Dodec-OSO₂CH₂CF₃, no coupling was observed.
- [10] We do not intend to suggest that achieving Suzuki cross-couplings of alkyl tosylates is now a solved problem. Although we believe that this Pd/PrBu₂Me-based catalyst system represents significant progress, important challenges remain, including the coupling of more hindered reaction partners, as well as the coupling of boronic acids, neither of which proceed in appreciable yield under the conditions described in Table 1.
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- [16] We have also isolated and characterized the palladium-containing product of the reaction, [Pd(PrBu₂Me)₂H(OTs)].
- [17] We have confirmed these results by investigating the corresponding reaction of the diastereomer of tosylate **1**.

Cell-Free Biosynthesis of Fluoroacetate and 4-Fluorothreonine in *Streptomyces cattleya***

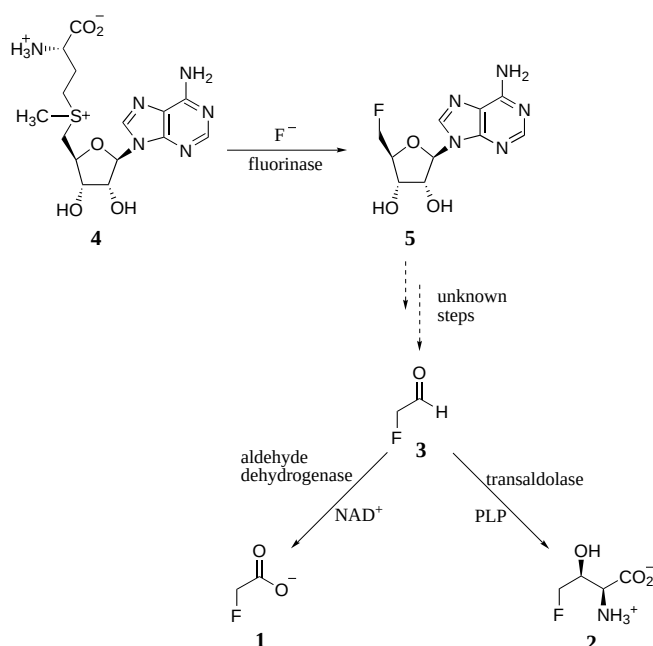
Christoph Schaffrath, Steven L. Cobb, and David O'Hagan*

Fluoroacetate **1** and 4-fluorothreonine **2** (Scheme 1) are secondary metabolites of the Actinomycete bacterium *Streptomyces cattleya*. These metabolites merit biosynthetic attention as they are among the very rare group of naturally occurring fluorine-containing compounds. It is perhaps surprising that Nature has hardly evolved the biochemistry of organofluorine metabolites, particularly as fluorine substitution can confer very particular properties such as toxicity, polarity, etc. to organic compounds. Accordingly, there are a huge number and range of commercially generated fluorinated compounds, but of course all of these are of anthropogenic origin. In this context, enzymatic syntheses of organofluorine compounds is interesting, not only at a mechanistic level but also since the prospects of biotransformation routes to this class of compound are attractive.

Fluoroacetate **1** is the most widely distributed fluorometabolite and is found as a toxin in a range of tropical and subtropical plants.^[1] The identification of fluoroacetate **1** and also 4-fluorothreonine **2** from the bacterium *S. cattleya*^[2,3] provided a more convenient investigative system than plants and could potentially provide further insight into fluorometabolite biosynthesis. We have recently identified the enzyme in *S. cattleya* that is responsible for C–F-bond formation.^[4] This fluorination enzyme, the first of its class, mediates a reaction between an inorganic fluoride ion and (*S*)-adenosyl-L-methionine (SAM; **4**) to generate 5'-fluoro-5'-deoxyadenosine (**5**) (5'-FDA; Scheme 1). Also fluoroacetaldehyde (**3**) has been established as a late and common intermediate^[5] in the formation of both fluoroacetate (**1**) and 4-fluorothreonine (**2**; Scheme 1) and each of the enzymes that converts **3** into **1** (an aldehyde dehydrogenase)^[6] and **3** into **2** (a PLP transaldolase)^[7] have been isolated and purified.

We report herein the cell-free biosynthesis of **1** from inorganic fluoride. The cell-free system has also been used to confirm 5'-FDA and fluoroacetaldehyde as genuine intermediates on the biosynthetic pathway to **1** and **2**.

The biotransformation of fluoride ions (10 mM) into fluoroacetate was carried out in an NMR tube with cell-free extracts of *S. cattleya*, supplemented with **4** (0.4 mM). The progress of the biosynthesis was monitored in real time by recording ¹⁹F NMR spectra at one-hour intervals over 17 h at 25 °C. No such reactions took place without added cell-free extract. Over the course of the experiment, signals for three



Scheme 1. Enzymatic formation of 5'-FDA (**5**) from SAM (**4**) leading to the formation of fluoroacetaldehyde (**3**), the common precursor for fluoroacetate (**1**) and 4-fluorothreonine (**2**).

organofluorine species are apparent (Figure 1). The peak at –215 ppm is assigned to fluoroacetate **3**. The presence of fluoroacetate in the final mixture was confirmed independently by derivatization and GC/MS analysis.^[8] The remaining two ¹⁹F NMR signals A (δ = –229.4 ppm) and B (δ = –229.7 ppm) have identical multiplicities (doublets of quartets, J = 47 Hz and J = 29 Hz), which indicates that they have similar fluorine environments.

It is clear that the cell-free extract contains all the enzymes in an active form, required to convert fluoride into **1**. The biosynthesis is efficient with fluoroacetate, emerging after 1 h.

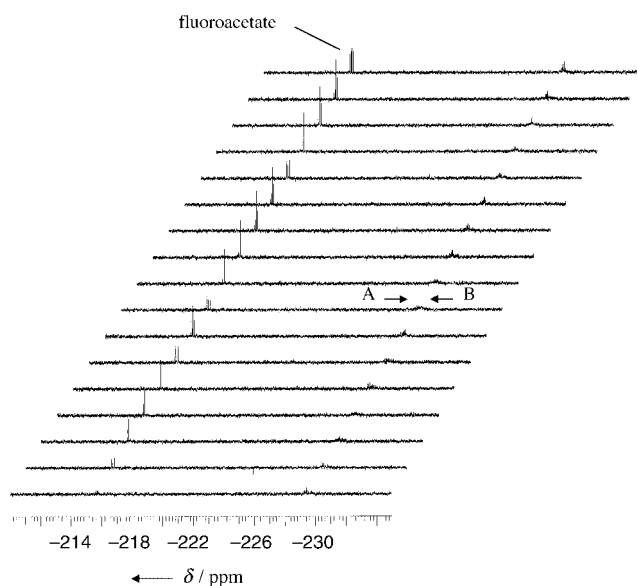


Figure 1. ¹⁹F NMR spectra (recorded every hour) of fluorine-containing products generated in the *S. cattleya* cell-free extract when incubated with SAM (0.4 mM) and fluoride ion (10 mM).

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[**] This work was supported by the Engineering and Physical Science Research Council (SC) and the University of St. Andrews (CS)

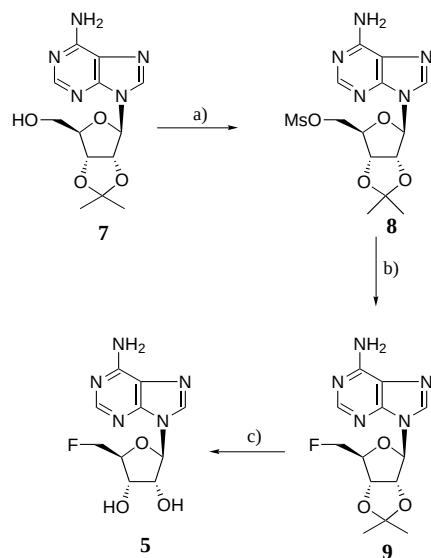
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The last step in fluoroacetate biosynthesis involves the action of an NAD⁺-dependent aldehyde dehydrogenase, an enzyme that is inhibited by iodoacetamide.^[6] When the cell-free experiments were carried out under a similar set of conditions but with added iodoacetamide (10 mM), fluoroacetate **1** no longer accumulated, which is consistent with the inhibition of the aldehyde dehydrogenase. The compounds that give rise to signals A and B accumulated as before, and signal A completely disappeared after 20 h, whereas signal B remained. The compound that gives rise to signal B was isolated by preparative HPLC and was analyzed both by ¹H and ¹⁹F NMR spectroscopy as well as by MALDI-TOF mass spectrometry and GC-MS, after derivatization by *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA). Based on these studies, signal B was assigned to 5'-fluoro-5'-deoxyinosine (**6**; 5'-FDI). 5'-FDI is presumably derived from a hydrolytic reaction of 5'-FDA (the product of the fluorination reaction) mediated by an adenosine deaminase.^[9] The compound that gives rise to signal A could not be identified.

To confirm the role of 5'-FDA (**5**) as an intermediate in the biosynthetic pathway to fluoroacetate, it was necessary to prepare a sample of 5'-FDA for biotransformation studies. Accordingly, **5** was prepared in a three-step route starting from **7**. Mesylation^[10] of the protected adenosine to generate **8** followed by treatment with tetrabutylammonium fluoride (TBAF) allowed fluorination at the 5' position to give **9**. Deprotection under mild acidic conditions then gave the required 5'-FDA (**5**) as shown in Scheme 2.

The cell-free extract preparation of *S. cattleya* was then incubated with synthetic **5** (10 mM) and the *in vitro* biotransformation was monitored in real time by recording ¹⁹F NMR spectra at one-hour intervals over 20 h at 25 °C (Figure 2).

The resultant ¹⁹F NMR spectra shown in Figure 2 clearly indicates a number of organofluorine compounds derived from **5**. Fluoroacetate **1** (which gives rise to a triplet at $\delta = -215.8$ ppm) is obvious as before. Furthermore, the high-



Scheme 2. Reagents and conditions: a) MsCl, pyridine, 25 °C, 20 h, 73%; b) TBAF (2.5 equiv), MeCN, reflux, 24 h, 46%; c) dilute H₂SO₄, 25 °C, 4 h, 70%.

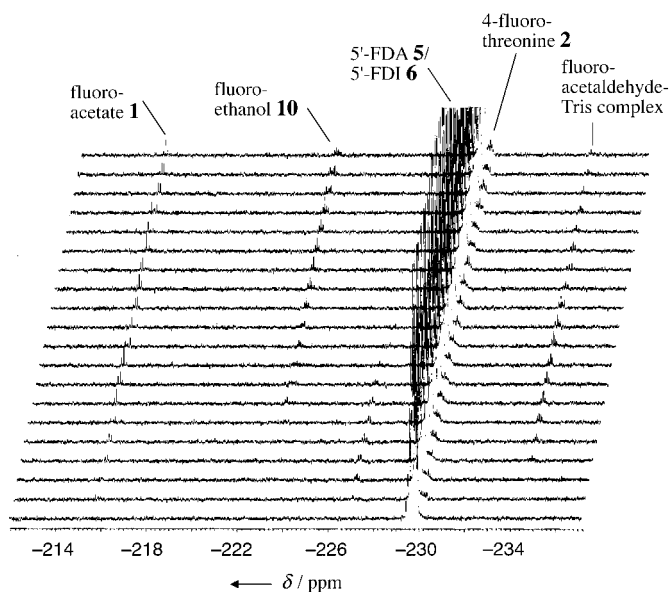


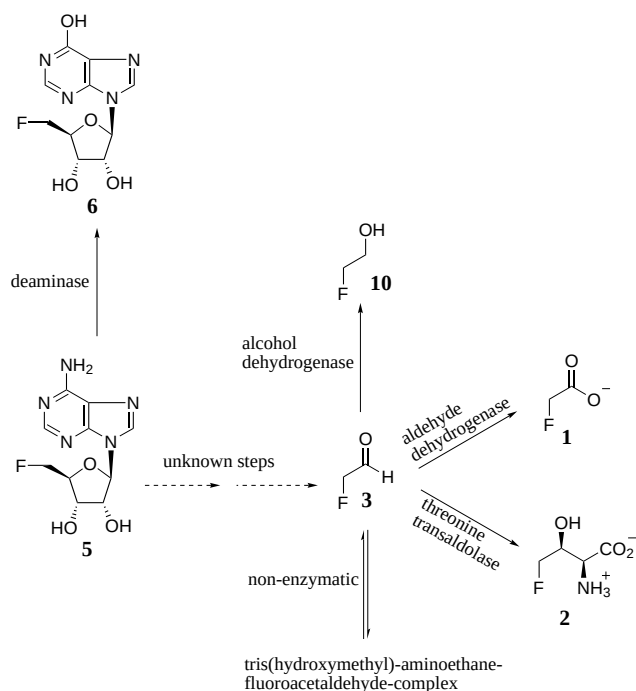
Figure 2. ¹⁹F NMR spectra (recorded every hour) of fluorine-containing products generated in the *S. cattleya* cell-free extract when incubated with 5'-FDA (10 mM).

intensity signals between $\delta = -229$ ppm and -230 ppm correspond to added 5'-FDA **5** and its rapid conversion into 5'-FDI (**6**) by the action of an adenosine deaminase. Notably, 4-fluorothreonine (**2**) ($\delta = -230.1$ ppm) is evident, which indicates that all the activities and cofactors are present in the cell-free extract for its biosynthesis from 5'-FDA **5**. The presence of 4-fluorothreonine in the extract was independently confirmed by GC-MS analysis.^[8] Perhaps the most surprising observation in this experiment is the presence of 2-fluoroethanol (**10**) ($\delta = -223$ ppm). The signal at $\delta = -234.3$ ppm in the ¹⁹F NMR spectrum was assigned to a complex between **3** and tris(hydroxymethyl)aminoethane (**11**), a constituent of Tris buffer. Although the structure of this complex is ambiguous at present, control reactions with synthetic fluoroacetaldehyde at various pH values and with different buffers have confirmed that this ¹⁹F NMR signal is identical to that observed when only fluoroacetaldehyde is dissolved in Tris buffer. In the cell-free extract, a complex between **3** and **11** accumulates and then disappears, thus indicating a reversible reaction, which presumably generates an imine or a cyclic aminal. Concomitantly, the concentration of fluoroethanol **10** steadily increases. It was previously established that fluoroethanol is not involved in the biosynthesis of the organofluorine compounds in *S. cattleya*.^[11] It appears therefore that under these conditions **3** is generated from **5** and that there is an adventitious and irreversible bioconversion (alcohol dehydrogenase) of **3** into **10**, which shifts the equilibrium from the aldehyde-Tris complex to **10**.

There is another signal in the ¹⁹F NMR spectrum at $\delta = -227$ ppm, which appears before the signal for **3** and accumulates for a short period (between 2–10 h), before disappearing. This unknown and transient compound may be an intermediate between 5'-FDA (**5**) and **3**.

In conclusion, we have described a successful bioconversion of fluoride ion and SAM (**4**) in a cell-free extract of *S. cattleya* to generate fluoroacetate **1**, which indicates that all the

enzymatic activities are present within the extract to mediate the entire biosynthesis. Incubation of a synthetic sample of 5'-FDA (5), the initial product of enzymatic fluorination, with the cell-free extract resulted in the accumulation of 3 (and 10), thus confirming the role of 5 as a biosynthetic intermediate of 1 and 2. An overview of this biotransformation is shown in Scheme 3. The accumulation of 3 in this case appears to have promoted the biosynthesis of 2 as well as 1. A transient signal ($\delta = -227$ ppm) was also observed in the ^{19}F NMR spectrum in this experiment, which is presumably a metabolic intermediate between 5 and 3. This compound has not yet been identified.



Scheme 3. Schematic representation of the bioconversions observed after incubating 5'-FDA with the *S. cattleya* cell-free extract.

Experimental Section

Streptomyces cattleya NRRL 8057 was grown in 500-mL flasks in a medium of the composition previously described.^[3] After 6 days of incubation, the cells were harvested and washed with Tris buffer (50 mM, pH 7.8) and resuspended in the same buffer (0.1 g wet-cell weight mL⁻¹). Ultrasonication and centrifugation gave a supernatant that was used directly as the cell-free extract. Biotransformations were initiated by supplementation of SAM (0.4 mM) and NaF (10 mM) or by the addition of 5'-FDA (10 mM) to the cell-free extract, and the reactions were incubated at 28 °C for up to 20 h. For real-time analysis by ^{19}F NMR spectroscopy, the sample was prepared in the same manner but D₂O was added (100 μL). ^{19}F NMR spectra were recorded on a Varian Inova 500-MHz NMR spectrometer.

GC-MS analyses were performed on an Agilent 6890 gas chromatograph connected to an Agilent 5973 mass-selective detector. The methods used for analysis were similar to those previously described.^[8] Fluoroacetate was analyzed by GC-MS in the scan mode after preparation of its *p*-phenylphenacyl derivative.^[8] MS (EI⁺): m/z (%): 272 (9.5), 182 (13.7), 181 (100), 152 (65.9). 4-Fluorothreonine (2) was analyzed as its per(trimethylsilyl)-derivative (obtained by treatment with MSTFA) by GC-MS operated in the scan mode. MS (EI⁺): m/z (%): 236 (53.4), 218 (100), 147 (15.6), 128 (14.2), 100 (11.2).

9: White powder; m.p. 159–160 °C; ^1H NMR (300 MHz, CDCl_3 , 25 °C): δ = 1.40 (s, 3H; CH_3), 1.64 (s, 3H; CH_3), 4.52 (dm, 1H; 4'-H), 4.62 (ddd, J = 46.7, 14.5, 10.4 Hz, 1H; 5'-H_a/5'-H_b), 4.63 (ddd, J = 46.7, 13.5, 10.4 Hz, 1H; 5'-H_a/5'-H_b), 5.10 (dd, $J(3'\text{H},2'\text{H})$ = 6.3 Hz, $J(3'\text{H},4'\text{H})$ = 3.8 Hz, 1H; 3'-H), 5.37 (dm, $J(2'\text{H},3'\text{H})$ = 6.3 Hz, 1H; 2'-H), 5.68 (br s, 2H; NH_2), 6.19 (d, $J(1'\text{H},2'\text{H})$ = 1.93 Hz, 1H; 1'-H), 7.93 (s, 1H; 2-H/8-H), 8.36 ppm (s, 1H; 2-H/8-H); ^{13}C NMR (75 MHz, CDCl_3 , 25 °C): δ = 25.7 (CH_3), 27.5 (CH_3), 81.1 (d, $J(\text{C}3',\text{F})$ = 6.8 Hz; $\text{C}3'$), 83.3 (d, $J(\text{C}5',\text{F})$ = 171.8 Hz; $\text{C}5'$), 84.9 ($\text{C}2'$), 85.9 (d, $J(\text{C}4',\text{F})$ = 19.5 Hz; $\text{C}4'$), 91.3 ($\text{C}1'$), 115.0, 120.5, 139.7 ($\text{C}2/\text{C}8$), 149.8, 153.7 ($\text{C}2/\text{C}8$), 156.0 ppm; ^{19}F NMR (282.2 MHz, CDCl_3 , 25 °C): δ = -228.86 ppm (dt, $J(\text{F},4'\text{H})$ = 23.6 Hz, $J(\text{F},5'\text{H})$ = 46.7 Hz); MS (CI, CH_4): m/z (%): 310 (100) [$M^+ + \text{H}$], 290 (10) [$-\text{HF}$], 251 (8), 207 (5), 175 (7), 75 (40); HRMS (CI): calcd for $\text{C}_{13}\text{H}_{17}\text{FN}_5\text{O}_3$ [$M + \text{H}^+$]: 310.1315, found: 310.1321.

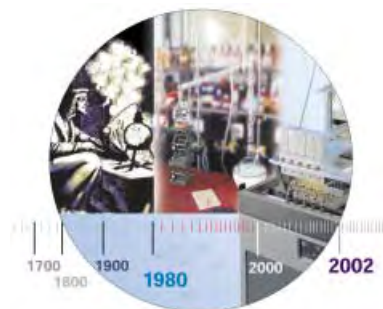
5: White powder, m.p. 203–204 °C [lit.^[12] 205–206 °C]; ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$, 25 °C): δ = 4.11 (dm, $J(\text{F},4'\text{H})$ = 23.8, 1H; 4'-H), 4.26 (m, 1H; 3'-H), 4.60 (m, 1H; 2'-H), 4.64 (dm, $J(\text{F},5'\text{CH}_2)$ = 47.8, 2H; CH_2), 5.46 (br s, 1H; OH), 5.65 (br s, 1H; OH), 5.94 (d, $J(1'\text{H},2'\text{H})$ = 4.86 Hz, 1H; 1'-H), 7.33 (br s, 2H; NH_2), 8.16 (s, 1H; 2-H/8-H), 8.27 ppm (s, 1H; 2-H/8-H); ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$, 25 °C): δ = 69.7 (d, $J(\text{C}3',\text{F})$ = 6.0 Hz), 73.4 ($\text{C}2'$), 82.6 (d, $J(\text{C}4',\text{F})$ = 18.0 Hz), 83.3 (d, $J(\text{C}5',\text{F})$ = 171.8 Hz), 88.0 ($\text{C}1'$), 119.4, 139.7, ($\text{C}2/\text{C}8$), 149.7, 153.1 ($\text{C}2/\text{C}8$), 156.4 ppm; ^{19}F NMR (282.2 MHz, $[\text{D}_6]\text{DMSO}$, 25 °C): δ = -230.0 ppm (dt, $J(\text{F},4'\text{H})$ = 23.8 Hz, $J(\text{F},5'\text{H})$ = 47.8 Hz); MS (ES): m/z (%): 269.98 (100) [M^+].

Received: August 5, 2002 [Z19887]

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COVER PICTURE

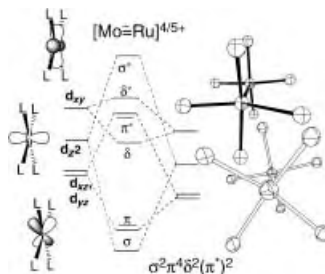
The cover picture shows the progress made in the development of separation techniques over the centuries. The retort and the distillation apparatus symbolize the repertoire of purification methods, which expanded only slightly from the foundations of chemistry to the 1980s. The automated synthesizer symbolizes the increasing demand for the automation of multiparallel techniques, which require simple work-up protocols. Thus, a large variety of specialized separation techniques has been developed. Today the spectrum contains, in addition to classical aqueous work-up, the use of ionic, perfluorinated, or supercritical liquids as well as the application of polymer- and dendrimer-supported separation strategies. An overview of the recent developments and applications of modern separation methods can be found in the Review by W. Bannwarth, R. Haag, et al. on p. 3964 ff.



REVIEWS

Contents

More bonds than metals: The “abnormally” high energies of heterodinuclear bonds in hydrogen halides lead to the concept of electronegativity. Multiple bonds between different transition-metal atoms have not yet given rise to a basic chemical concept but they possess the potential to help elucidate the fundamental properties of interactions between d elements. The picture shows the MO diagram of metal–metal bonding in the Mo–Ru core. Unique to bimetallic complexes of transition metals, the MoRu^{5+} core, when stabilized by porphyrin ligands, exists in the solid state as an equimolar mixture of an eclipsed and a staggered conformer.



J. P. Collman,*
R. Boulatov 3948–3962

Heterodinuclear Transition-Metal
Complexes with Multiple Metal–Metal
Bonds

Keywords: bond theory • cluster
compounds • electronic structure •
metal–metal interactions • transition
metals

Angew. Chem. 2002, 114, 4120–4134

There is no one best method! Rather the best separation strategy for an organic synthesis must be determined on a case by case basis. Herein the advantages and disadvantages of the current important processes—including the application of ionic liquids, supercritical solvents, fluoros systems, and polymer-protected precursors—in regard to their parallelization and automation are described and compared.



Angew. Chem. **2002**, *114*, 4136–4173

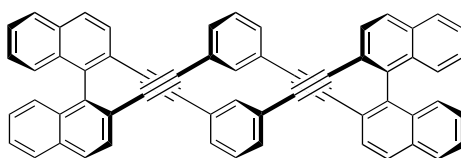
C. C. Tzschucke, C. Markert,
W. Bannwarth,* S. Roller, A. Hebel,
R. Haag* 3964–4001

Modern Separation Techniques for the
Efficient Workup in Organic Synthesis

Keywords: biphasic catalysis •
combinatorial chemistry • parallel
synthesis • polymeric supports •
separation techniques

HIGHLIGHTS

A bumper crop of “polyunsaturated” cyclophanes has recently been harvested as a result of methodological advances, which have once again fertilized the field of cyclophane chemistry. Features of these designed molecules include structural novelty, strain and its consequences, unusual electronic effects, exploitable physical properties, and stereochemistry. Otera’s “enantiopure double-helical alkynyl cyclophanes” (example shown in picture) are perhaps the pick of the crop.



G. J. Bodwell,* T. Satou 4003–4006

“Polyunsaturated” Cyclophanes

Keywords: alkynes • arenes • cross-
coupling • cyclophanes • strained
molecules

Angew. Chem. **2002**, *114*, 4175–4178

VIPs

The following communications are “Very Important Papers” in the opinion of two referees. They will be published shortly (those marked with a diamond will be published in the next issue). Short summaries of these articles can be found on the *Angewandte Chemie* homepage at the address <http://www.angewandte.org>

Pd^{II}-Catalyzed Cyclization of Alkynes with Aldehydes, Ketones, or Nitriles Initiated by the Acetoxypalladation of Alkynes

L. Zhao, X. Lu*



Isoprenoid Biosynthesis through the Methylerythritol Phosphate Pathway: The (*E*)-4-Hydroxy-3-methylbut-2-enyl Diphosphate Synthase (GcpE) is a [4Fe–4S] Protein

M. Seemann, B. T. S. Bui,
M. Wolff, D. Tritsch, N. Campos,
A. Boronat, A. Marquet,
M. Rohmer*



Experimental Observation and Confirmation of Icosahedral W@Au₁₂ and Mo@Au₁₂ Molecules

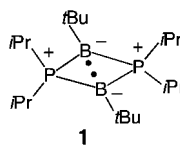
X. Li, B. Kiran, J. Li, H.-J. Zhai,
L.-S. Wang*

Tuning the Regioselectivity in the Palladium(II)-Catalyzed Isomerization of Alkylidenecyclopropyl Ketones: A Dramatic Salt Effect

S. Ma*, J. Zhang

Make or break: Stable biradicaloid main group element compounds could provide deep insight into fundamental processes of bond making and bond breaking. Whereas for a long time such compounds were only known as highly reactive intermediates or postulated as transition states, recently through the isolation of the stable crystalline 1,3-diphospha-2,4-diborabicyclo[1.1.0]butane (**1**) a decisive step has been taken towards achieving a better understanding of the steps involved in making and breaking bonds.

Angew. Chem. **2002**, *114*, 4178–4184



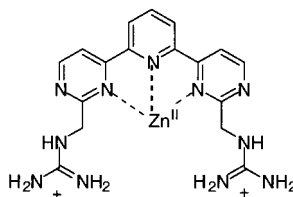
H. Grützmacher,* F. Breher 4006–4011

Odd-Electron Bonds and Biradicals in Main Group Element Chemistry

Keywords: biradicals • bond stretch isomers • main group elements • phosphorus • radicals

COMMUNICATIONS

Cooperation is the key! Multifunctional catalysis with cooperativity approaching that found for enzymes is reported in the hydrolysis of RNA using a synthetic catalyst that includes one zinc atom and two guanidinium groups (see picture).



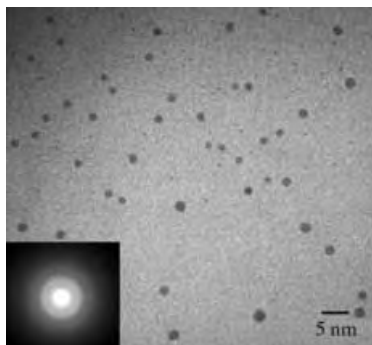
H. Aït-Haddou, J. Sumaoka, S. L. Wiskur, J. F. Folmer-Andersen, E. V. Anslyn* 4014–4016

Remarkable Cooperativity between a Zn^{II} Ion and Guanidinium/Ammonium Groups in the Hydrolysis of RNA

Keywords: bioinorganic chemistry • enzyme catalysis • hydrolysis • RNA • zinc

Angew. Chem. **2002**, *114*, 4185–4188

Graphite nanoparticles, with diameters as small as 2 nm (see picture) can be fabricated by the carbonization of polypyrrole nanoparticles of similar dimensions, which have been prepared by a low-temperature polymerization technique in which a micellar microemulsion acts as a “nanoreactor”. The graphite nanoparticles exhibit excellent transparent conductive performance in a polycarbonate medium, and may be envisaged as a substitute for carbon nanotubes.



J. Jang,* J. H. Oh, G. D. Stucky 4016–4019

Fabrication of Ultrafine Conducting Polymer and Graphite Nanoparticles

Keywords: conducting materials • graphite • micelles • nanostructures • polymers

Angew. Chem. **2002**, *114*, 4188–4191

Nanoporous shell or sphere-in-sphere structures have been constructed by consecutive alternating adsorption of polyelectrolytes and SiO_2 on melamine formaldehyde particles, followed by removal of the cores with HCl and SiO_2 with HF. The shells have been distinguished by confocal laser scanning microscopy imaging (see picture) by partially labeling the inner shell with fluorescein (yellow emission) and the outer sphere with rhodamine B (red emission).



Z. Dai, L. Dähne,* H. Möhwald, B. Tiersch 4019–4022

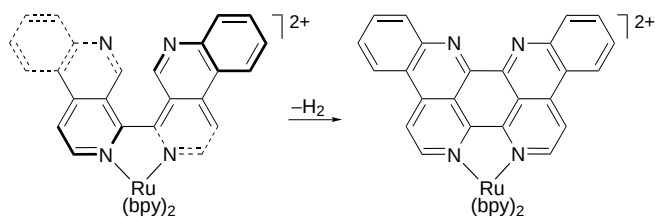
Novel Capsules with High Stability and Controlled Permeability by Hierarchic Templating

Keywords: capsules • nanostructures • permeability • polyelectrolytes • self-assembly

Angew. Chem. **2002**, *114*, 4191–4194



The fabrication of Ru^{II}–polypyridyl complexes with “large-surface” ligands can be achieved by utilizing metal coordination to facilitate a dehydrogenation reaction (see scheme). This modular methodology efficiently yields biologically active eilatin-containing complexes, as well as Ru^{II} complexes of previously unknown ligands.



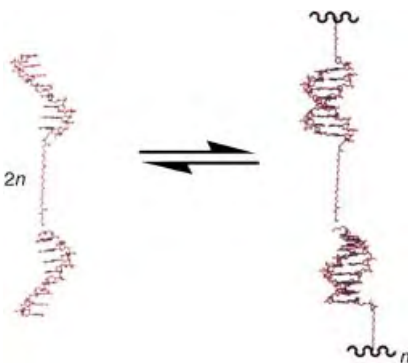
Angew. Chem. **2002**, *114*, 4194–4198

E. C. Glazer, Y. Tor* 4022–4026

Ru^{II} Complexes of “Large-Surface” Ligands

Keywords: bridging ligands • dehydrogenation • ligand design • N ligands • ruthenium

Fundamental studies of reversible polymerizations can be achieved with intrinsically modular oligonucleotide-based monomers (OMs) comprised of oligonucleotide sequences that are covalently linked directly or through a synthetic spacer. The thermodynamics and kinetics of association are determined by the variable OM base system. The number of reversible interactions and the conformational flexibility along the polymer backbone are dependent on the spacer.



Angew. Chem. **2002**, *114*, 4198–4200

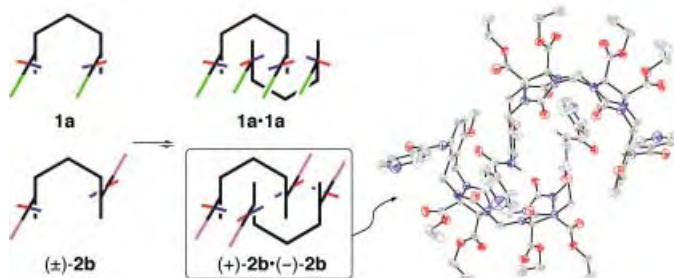
E. A. Fogleman, W. C. Yount, J. Xu, S. L. Craig* 4026–4028

Modular, Well-Behaved Reversible Polymers from DNA-Based Monomers

Keywords: DNA structures • polymers • self-assembly • supramolecular chemistry



Clip Art: Achiral (**1a**) and chiral ((±)-**2b**) molecular clips undergo diastereoselective H-bond-mediated self-assembly, both in solution and the solid state, to yield homodimer **1a**·**1a** and the heterochiral aggregate (+)-**2b**·(–)-**2b**. Mixtures of the achiral and chiral clips do not yield heterodimers, but rather undergo an efficient self-sorting process.



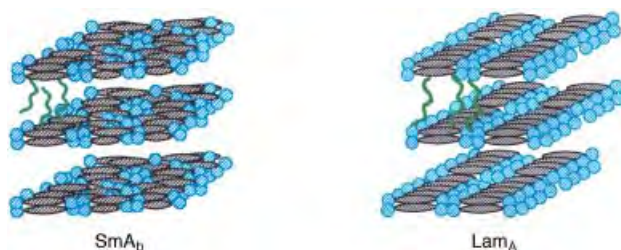
Angew. Chem. **2002**, *114*, 4200–4203

A. Wu, A. Chakraborty, J. C. Fetting, R. A. Flowers II,* L. Isaacs* 4028–4031

Molecular Clips that Undergo Heterochiral Aggregation and Self-Sorting

Keywords: chirality • hydrogen bonds • pi interactions • self-assembly

Competition between microsegregation and rigidity in bolaamphiphilic biphenyl derivatives bearing lateral semiperfluorinated alkyl chains leads to the formation of novel smectic liquid-crystalline phases, designated SmA_b and Lam_A , in which the rigid rodlike segments are organized parallel to the planes of the layers.



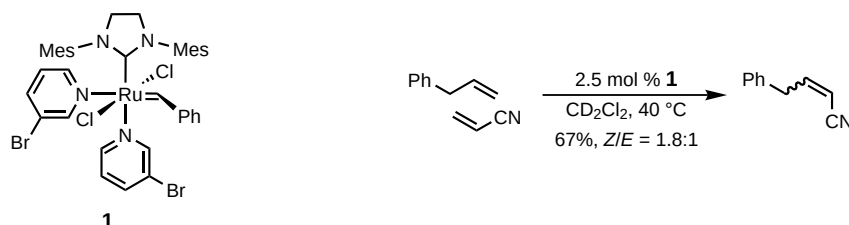
Angew. Chem. **2002**, *114*, 4203–4207

X. H. Cheng, M. K. Das, S. Diele,
C. Tschierske* 4031–4035

Novel Liquid-Crystalline Phases with
Layerlike Organization

Keywords: amphiphiles • hydrogen
bonds • liquid crystals • mesophases •
microsegregation

 **The highest initiation rate** of any reported ruthenium-based catalyst was found for the new olefin-metathesis catalyst $[(\text{H}_2\text{IMes})(3\text{-Br-py})_2(\text{Cl})_2\text{Ru}=\text{CHPh}]$ (**1**), which was synthesized in one step from commercially available reagents. Complex **1** is highly efficient for the cross metathesis of acrylonitrile, which is generally a poor substrate for metathesis reactions (e.g., see scheme). Mes = 2,4,6-trimethylphenyl.



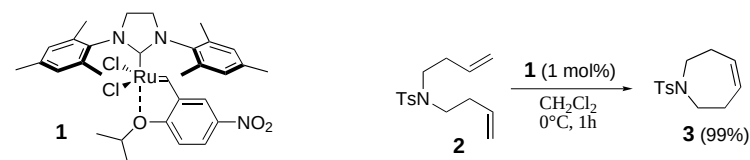
Angew. Chem. **2002**, *114*, 4207–4209

J. A. Love, J. P. Morgan, T. M. Trnka,
R. H. Grubbs* 4035–4037

A Practical and Highly Active
Ruthenium-Based Catalyst that Effects
the Cross Metathesis of Acrylonitrile

Keywords: homogeneous catalysis •
metathesis • N ligands • ruthenium

A simple three-step synthesis leads to the formation of the active complex **1**, which operates under very mild conditions (even at 0 °C!) and can be successfully applied in various types of olefin metathesis (ring-closing metathesis, cross metathesis, enyne metathesis), for example, in the cyclization of **2** to form **3**.



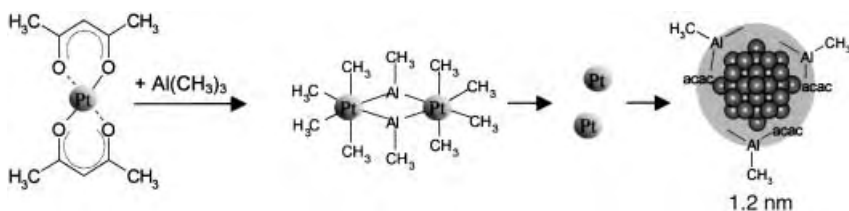
Angew. Chem. **2002**, *114*, 4210–4212

K. Grela,* S. Harutyunyan,
A. Michrowska 4038–4040

A Highly Efficient Ruthenium Catalyst
for Metathesis Reactions

Keywords: alkenes • homogeneous
catalysis • metathesis • ruthenium

An organometallic compound is the key intermediate during the formation of colloidal Pt particles from $[\text{Pt}(\text{acac})_2]$ and $\text{Al}(\text{CH}_3)_3$. Additional studies confirm the formation of stable Pt colloids with an average diameter of 1.2 nm, which are stabilized by organoaluminum components (see scheme). Without the stabilizer a Pt nanopowder with a particle size of 1.4 nm is isolated.



Angew. Chem. **2002**, *114*, 4213–4216

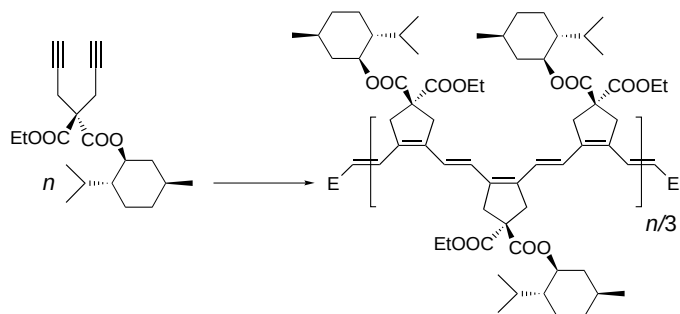
K. Angermund, M. Bühl, E. Dinjus,
U. Endruschat, F. Gassner,
H.-G. Haubold, J. Hormes, G. Köhl,
F. T. Mauschick, H. Modrow, R. Mörtel,
R. Mynott,* B. Tesche, T. Vad,
N. Waldöfner,
H. Bönemann* 4041–4044

Nanosopic Pt Colloids in the
“Embryonic State”

Keywords: colloids • nanostructures •
nucleation • platinum

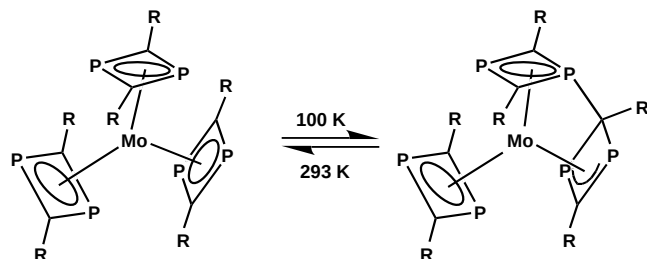


Taking the sting out of controlling rings: Highly regular, alternating *cis-trans*-polyenes solely containing five-membered rings have been prepared by living alkyne cyclopolymerization of 1,6-heptadiynes using fine-tuned Schrock initiators (see scheme). The resulting polyenes possess interesting physical properties that are different from those of existing poly(heptadiyne) systems.



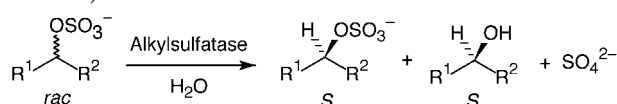
Angew. Chem. **2002**, *114*, 4226–4230

Bicycles made in crystals: The phosphorus atoms of the π ligand 1,3-diphosphate turn out to be ambiphilic centers with pronounced intramolecular reactivity. This property results in a temperature-dependent bond formation in [(2,4-di-*i*Bu-1,3-diphosphate)₃Mo], which is found to be a topotactic reaction in the single crystal (see scheme). This new reactivity principle can be used to explain a series of complex interligand bond-formation reactions of phosphorus heterocycles.



Angew. Chem. **2002**, *114*, 4221–4226

The biocatalytic hydrolysis of ($\pm$)-*sec*-alkyl sulfate esters with an alkylsulfatase from *Rhodococcus ruber* DSM 44541 proceeded with high enantioselectivity (up to 99% *ee*) and with absolute stereoselectivity through inversion of configuration. Thus, a *rac* substrate was converted into homochiral *S*-configured products (see scheme).

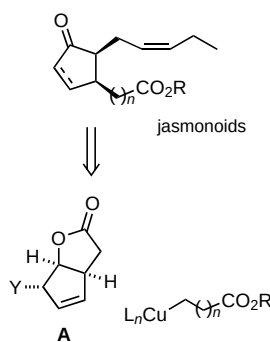


Angew. Chem. **2002**, *114*, 4230–4231



An important class of phytohormones are jasmonoids. A variety of jasmonoids in the natural *cis* configuration are now accessible by a general strategy. Key building blocks are enantiomerically pure lactones of type **A** with a leaving group **Y** which can be prepared by a catalytic asymmetric synthesis. Reaction with zinc cyanocuprates affords products with the requisite *cis* configuration that can be transformed into the target compounds in a few steps.

Angew. Chem. **2002**, *114*, 4231–4234



U. Anders, O. Nuyken,*
M. R. Buchmeiser,*
K. Wurst 4044–4047

Stereoselective Cyclopolymerization of 1,6-Heptadiynes: Access to Alternating *cis-trans*-1,2-(Cyclopent-1-enylene)vinylenes by Fine-Tuning of Molybdenum Imidoalkylidenes

Keywords: alkynes • carbene ligands • metathesis • molybdenum • polymerizations

C. Topf, T. Clark,* F. W. Heinemann, M. Hennemann, S. Kummer, H. Pritzkow, U. Zenneck* 4047–4052

Ambiphilicity: A Characteristic Reactivity Principle of π -Bound Phosphorus Heterocycles

Keywords: DFT calculations • molybdenum • P ligands • phosphorus heterocycles • π interactions • solid-state reactions

M. Pogorevc, W. Kroutil, S. R. Wallner, K. Faber* 4052–4054

Enantioselective Stereoinversion in the Kinetic Resolution of *rac-sec*-Alkyl Sulfate Esters by Hydrolysis with an Alkylsulfatase from *Rhodococcus ruber* DSM 44541 Furnishes Homochiral Products

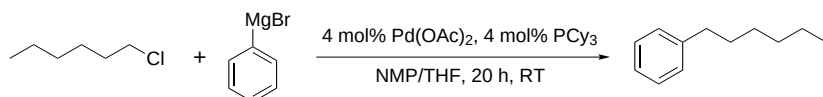
Keywords: alkylsulfatase • biotransformations • configuration inversion • hydrolysis • sulfate ester

M. Ernst, G. Helmchen* 4054–4056

A New Synthesis Route to Enantiomerically Pure Jasmonoids

Keywords: asymmetric catalysis • asymmetric synthesis • copper • jasmonoids • natural products

Chloroalkanes refined: A simple catalyst system renders the palladium-catalyzed coupling reaction of functionalized alkyl chlorides and Grignard reagents at room temperature (see example in scheme; PCy₃ = tricyclohexylphosphane, NMP = *N*-methylpyrrolidinone).



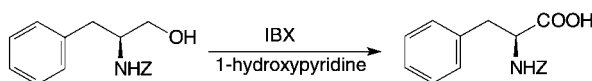
Angew. Chem. **2002**, *114*, 4218–4221

A. C. Frisch, N. Shaikh, A. Zapf,
M. Beller * 4056–4059

Palladium-Catalyzed Coupling of Alkyl
Chlorides and Grignard Reagents

Keywords: alkyl halides • cross-coupling •
Grignard reaction • Kumada coupling •
palladium

Under mild conditions and without the use of toxic metals, the oxidation of primary alcohols and aldehydes to the corresponding carboxylic acids with 1-hydroxy-1,2-benziodoxole-3(*1H*)-one-1-oxide (IBX) proceeds in the presence of 1-hydroxypyridine or *N*-hydroxysuccinimide (see scheme). The reaction tolerates a wide variety of functional groups.



Angew. Chem. **2002**, *114*, 4216–4218

R. Mazitschek, M. Mülbauer,
A. Giannis * 4059–4061

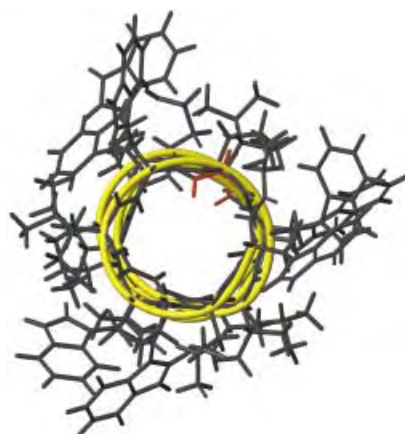
IBX-Mediated Oxidation of Primary
Alcohols and Aldehydes To Form
Carboxylic Acids

Keywords: alcohols • aldehydes •
carboxylic acids • IBX • oxidation



Variable ion channels: A 22mer peptide derived from the D,L-peptide gramicidin A changes from an inactive to a highly ion-channel-active conformation (see picture). The helical structure of the active and inactive conformations was characterized by NMR spectroscopy and circular dichroism; conductance measurements led to the conclusion that there are two symmetrical binding sites for the Cs atom in the active form.

Angew. Chem. **2002**, *114*, 4234–4238



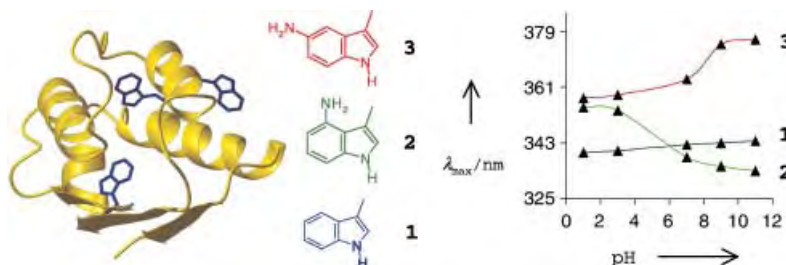
H.-D. Arndt, D. Bockelmann, A. Knoll,
S. Lamberth, C. Griesinger,*
U. Koert * 4062–4065

Cation Control in Functional Helical
Programming: Structures of a D,L-Peptide
Ion Channel

Keywords: circular dichroism •
conformational analysis • ion channels •
NMR spectroscopy • peptides



Functional protein design: Replacement of the tryptophan indole moiety in proteins with aminoindoles converts pH-insensitive into pH-sensitive fluorescent proteins (see picture). Such global substitution of residues in target proteins by noncanonical amino acids with defined spectral properties offers a unique approach for the design of protein-based molecular sensors.



Angew. Chem. **2002**, *114*, 4238–4242

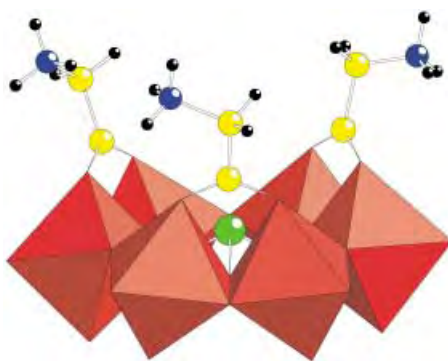
N. Budisa,* M. Rubini, J. H. Bae,
E. Weyher, W. Wenger, R. Golbik,
R. Huber, L. Moroder 4066–4069

Global Replacement of Tryptophan with
Aminotryptophans Generates Non-
Invasive Protein-Based Optical pH
Sensors

Keywords: amino acids • biosensors •
gene expression • protein engineering •
tryptophan



Taming the uncontrollable: The novel heteropolymolybdates, such as the $[\text{Se}^{\text{IV}}\text{Mo}_6\text{O}_{21}(\text{O}_2\text{CCH}_2\text{NH}_3)_3]^{2-}$ ion shown, functionalized by amino acids, can be derivatized at two different positions in a controlled manner. In addition, further functionalization of the clusters through the amino groups is possible, thus the 18 new compounds are ideal candidates for pharmaceutical applications.



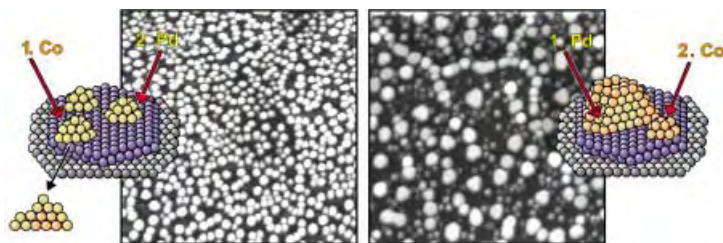
U. Kortz,* M. G. Savelieff, F. Y. A. Ghali,
L. M. Khalil, S. A. Maalouf,
D. I. Sinno 4070–4073

Heteropolymolybdates of As^{III} , Sb^{III} , Bi^{III} ,
 Se^{IV} , and Te^{IV} Functionalized by Amino
Acids

Keywords: amino acids • chirality •
cluster compounds • molybdenum •
polyoxometalates • structure elucidation

Angew. Chem. **2002**, *114*, 4246–4249

Building catalyst models for complex catalytic systems is still a challenging task. In the case of supported bimetallic catalysts, such models can be obtained by taking advantage of nucleation and growth processes during the metal vapor deposition of two metals onto a suitable support (see picture). In this way, the origin of the sometimes surprisingly large changes observed in the adsorption and reaction properties of these systems in comparison to the pure metals can be studied in detail.



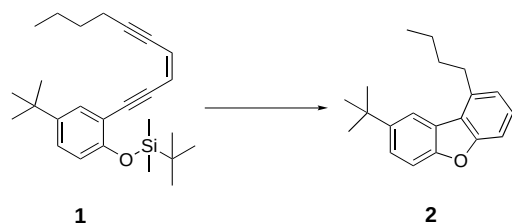
M. Heemeier, A. F. Carlsson,
M. Naschitzki, M. Schmal, M. Bäumer,*
H.-J. Freund 4073–4076

Preparation and Characterization of a
Model Bimetallic Catalyst: Co–Pd
Nanoparticles Supported on Al_2O_3

Keywords: adsorption • bimetallic
particles • desorption • heterogeneous
catalysis • scanning probe microscopy

Angew. Chem. **2002**, *114*, 4242–4245

An anionic cycloaromatization reaction provides an efficient method for the synthesis of the dibenzofurans **2** by treatment of the *tert*-butyldimethylsilyl ethers **1** with sodium methoxide or potassium carbonate in methanol at reflux for 16 h, and gives 50–94% yields of **2**.



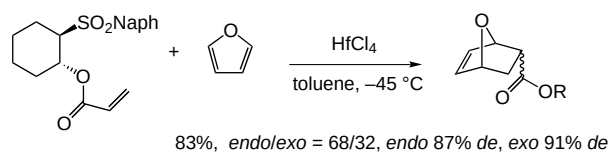
M.-J. Wu,* C.-Y. Lee,
C.-F. Lin 4077–4079

A Route to 5-Substituted Dibenzofurans
by Anionic Cycloaromatization of 2-
(6-Substituted 3-Hexene-1,5-diynyl)phenyl
tert-Butyldimethyl Ethers and Related
Molecules

Keywords: cyclization • enediyne •
fused-ring systems • heterocycles

Angew. Chem. **2002**, *114*, 4251–4253

High yields and high *endo* selectivity of the cycloadducts formed from the Diels–Alder reaction of furan or substituted furans occurs with an HfCl_4 catalyst (see scheme). The use of the catalyst allows reactions to be performed at low temperature under kinetic control, as shown for the highly diastereoselective Diels–Alder reaction of a chiral acrylate.



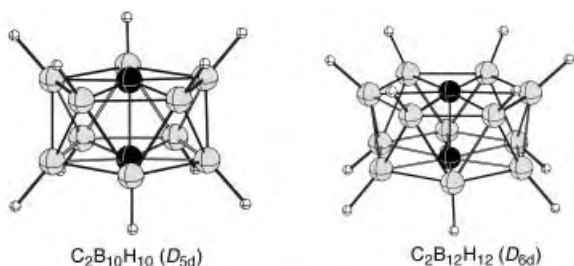
Y. Hayashi,* M. Nakamura, S. Nakao,
T. Inoue, M. Shoji 4079–4082

The HfCl_4 -Mediated Diels–Alder
Reaction of Furan

Keywords: asymmetric synthesis •
cycloaddition • furanes • hafnium •
pericyclic reaction

Angew. Chem. **2002**, *114*, 4253–4256

Wheel-shaped molecules, exemplified by $C_2B_{10}H_{10}$ (D_{5d}) and $C_2B_{12}H_{12}$ (D_{6d}) (see picture), are predicted by DFT computations to be stable minima. The “axles” of these “wheels” are comprised of conjoined, nearly planar, penta- or hexacoordinate carbon atoms, or their isoelectronic B^- , Al^- , Si , and Ge counterparts.



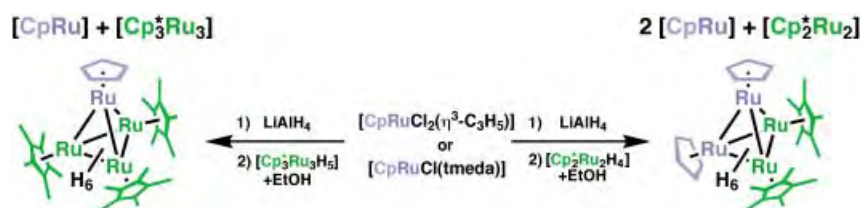
Angew. Chem. **2002**, *114*, 4256–4259

Z.-X. Wang,
P. von R. Schleyer* 4082–4085

Planar Hypercoordinate Carbons Joined:
Wheel-Shaped Molecules with C–C Axles

Keywords: boranes • density functional calculations • hypercoordinate carbon • nanostructures

A series of tetranuclear ruthenium hexahydride clusters containing several different combinations of Cp (C_5H_5) and Cp* (C_5Me_5) ligands, was systematically synthesized from the reaction of $[CpRuCl_2(\eta^3-C_3H_5)]$ or $[CpRuCl(tmeda)]$ (tmeda = tetramethylethylenediamine) with $LiAlH_4$ followed by treatment with trinuclear, dinuclear, or mononuclear Cp*Ru complexes in the presence of ethanol.



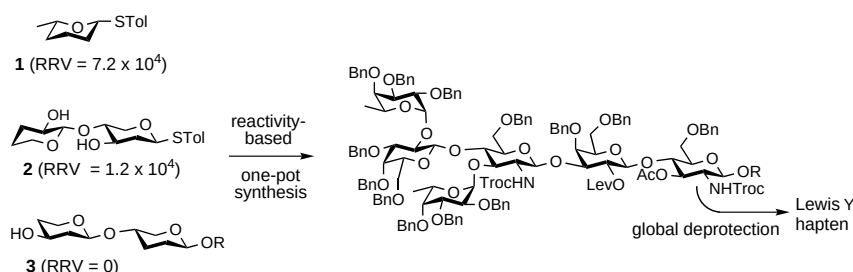
Angew. Chem. **2002**, *114*, 4259–4261

Y. Ohki, N. Uehara,
H. Suzuki* 4085–4087

Rational Synthesis of Tetranuclear
Ruthenium Polyhydride Clusters and
Their Mixed-Ligand Analogues

Keywords: cyclopentadienyl ligands • hydride ligands • ruthenium • structure elucidation • tetranuclear complexes

The stereospecific synthesis of a tumor-related carbohydrate antigenic hapten, Lewis Y, from three basic building units **1–3** has been achieved by a reactivity-based one-pot strategy. RRV = relative reactivity value.



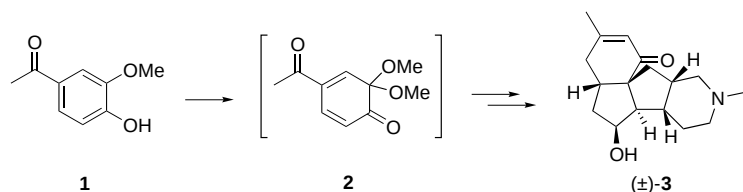
Angew. Chem. **2002**, *114*, 4261–4264

K.-K. T. Mong, C.-H. Wong* 4087–4090

Reactivity-Based One-Pot Synthesis of a
Lewis Y Carbohydrate Hapten:
A Colon–Rectal Cancer Antigen
Determinant

Keywords: antigens • antitumor agents • glycosylation • oligosaccharides • reactivity-based synthesis

The power of the masked *o*-benzoquinone Diels–Alder protocol is shown in a total synthesis of magellanine ($(\pm)$ -**3**). The highly compact molecular architecture of **3** was constructed from acetovanillone (**1**) via a masked *o*-benzoquinone **2** in an overall yield of 12% over 16 steps (or 9% over 14 steps).



Angew. Chem. **2002**, *114*, 4264–4267

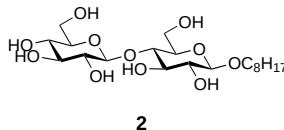
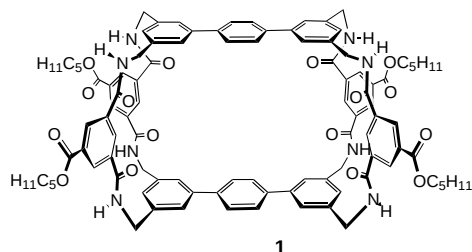
C.-F. Yen, C.-C. Liao* 4090–4093

Concise and Efficient Total Synthesis of
Lycopodium Alkaloid Magellanine

Keywords: cycloaddition • natural products • rearrangement • total synthesis



Selective oligosaccharide recognition remains a challenge for supramolecular chemistry. Tricyclic receptor **1** was designed to bind the all-equatorial β -cellobiosyl unit in **2**. Remarkably, it succeeds while showing no detectable affinity for five other mono- and disaccharide substrates.



Angew. Chem. **2002**, *114*, 4267–4270

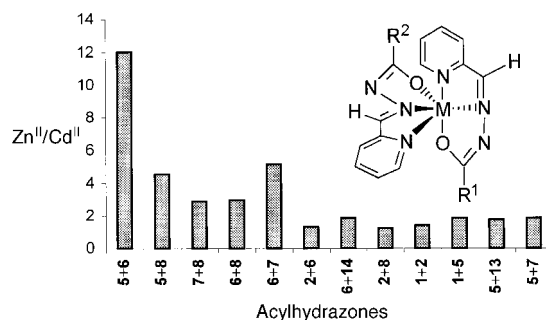
G. Lecollinet, A. P. Dominey, T. Velasco, A. P. Davis* 4093–4096

Highly Selective Disaccharide Recognition by a Tricyclic Octamide Cage

Keywords: carbohydrates • molecular recognition • oligosaccharides • stereoselectivity • supramolecular chemistry



The dynamic nature of metal–ligand interactions facilitates the formation of metal ion acylhydrazone complex libraries. From these libraries, metal ion complexes with two different types of ligands (**1**–**14**; $R^1 \neq R^2$) are shown to have superior extraction properties. Mixed–ligand combinations enhance the selectivity of extraction of Zn^{II} over Cd^{II} (see figure).



Angew. Chem. **2002**, *114*, 4270–4272

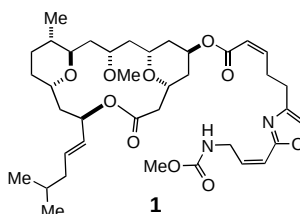
S. Choudhary, J. R. Morrow* 4096–4098

Dynamic Acylhydrazone Metal Ion Complex Libraries: A Mixed–Ligand Approach to Increased Selectivity in Extraction

Keywords: cadmium • combinatorial chemistry • coordination modes • N ligands • separation processes • zinc



A compound that could never be isolated again despite intensive efforts after it was first found in the sponge *Leucascandra caveolata* in 1996 is leucascandrolide A (**1**). An enantioselective, convergent total synthesis of this polyoxygenated marine macrolide proceeds in 23 steps and 2% overall yield. The strategy relies on the application of modern asymmetric reactions for enantio- and diastereoselective transformations.



Angew. Chem. **2002**, *114*, 4272–4275

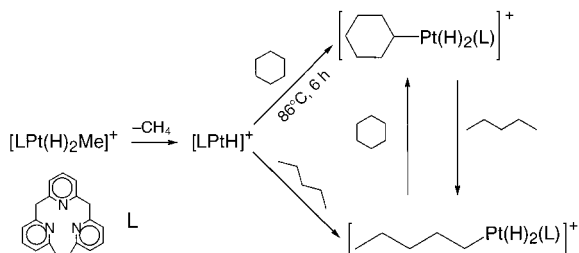
A. Fettes, E. M. Carreira* 4098–4101

Total Synthesis of Leucascandrolide A

Keywords: aldol reaction • alkynes • asymmetric synthesis • natural products • total synthesis

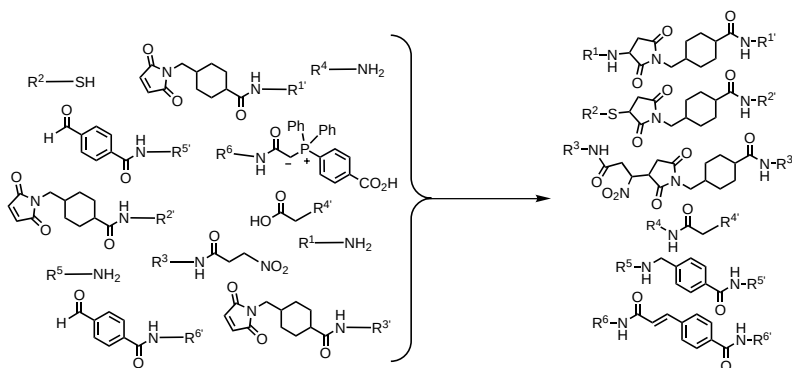


Reversible alkane oxidative addition occurs to transient $[\text{LPtH}]^+$ ($\text{L} = [2.1.1]-(2,6)\text{-pyridinophane}$; see scheme), which is generated at 86°C from $[\text{LPtMe}(\text{H})_2]^+$ in 1:1 hydrocarbon/ CD_2Cl_2 mixtures. DFT calculations reveal why $[\text{LPtMe}(\text{H})_2]^+$ eliminates methane, not dihydrogen, and why, in contrast to $[\text{LPtMe}_2\text{H}]^+$, no alkane dehydrogenation occurs.



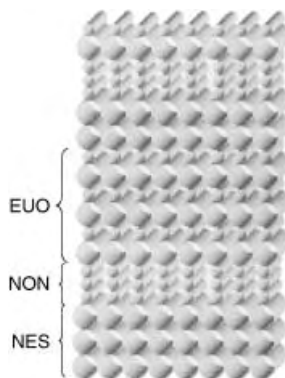
Angew. Chem. **2002**, *114*, 4276–4278

Diversification without spatial separation can be achieved using DNA-templated synthesis. Twelve reactants with functional groups of similar reactivity linked to different DNA sequences (R , R') were subjected to several different reaction types within the same solution and only six sequence-programmed products out of the more than 28 possibilities were formed (see scheme).



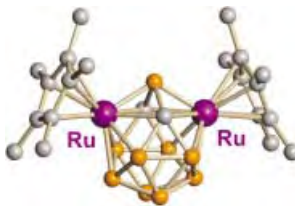
Angew. Chem. **2002**, *114*, 4278–4282

An intergrowth of three structurally related zeolites with the NON, EUO, and NES framework topologies forms the basis of a structural model for ERS-10 zeolite. The picture shows a roll stacking model of ERS-10; large cylinders: 10-ring channels, small cylinders: 6-ring channels.



Angew. Chem. **2002**, *114*, 4283–4286

Polyhedral expansion of stable 12-vertex *closo*-ruthenacarborane $[(\eta\text{-C}_5\text{Me}_5)\text{Ru}(\text{C}_2\text{B}_9\text{H}_{11})]^-$ by direct insertion of $[(\eta\text{-C}_5\text{R}_5)\text{Ru}]^+$ fragments takes place under very mild conditions (-78°C). The resulting 13-vertex diruthenacarboranes (see picture) are very stable although they have two electrons less than required by Wade's rules.



Angew. Chem. **2002**, *114*, 4286–4288

A. N. Vedernikov,*
K. G. Caulton * 4102–4104

Control of $\text{H-C}(\text{sp}^3)$ Bond Cleavage
Stoichiometry: Clean Reversible Alkyl
Ligand Exchange with Alkane in
 $[\text{LPt}(\text{Alk})(\text{H})_2]^+$ ($\text{L} = [2.1.1]-(2,6)\text{-Pyridinophane}$)

Keywords: alkanes • C-H activation •
hydride ligands • platinum • structure-
activity relationships

C. T. Calderone, J. W. Puckett,
Z. J. Gartner, D. R. Liu * 4104–4108

Directing Otherwise Incompatible
Reactions in a Single Solution by Using
DNA-Templated Organic Synthesis

Keywords: combinatorial chemistry •
diversification • oligonucleotides •
synthetic methods • template synthesis

S. Zanardi,* G. Cruciani, L. C. Carluccio,
G. Bellussi, C. Perego,
R. Millini * 4109–4112

Framework Topology of ERS-10 Zeolite

Keywords: structure elucidation • X-ray
diffraction • zeolites

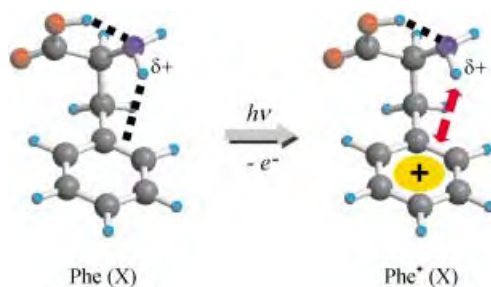
A. R. Kudinov,* D. S. Perekalin,
S. S. Rynin, K. A. Lyssenko,
G. V. Grintselev-Knyazev,
P. V. Petrovskii 4112–4114

Direct Electrophilic Insertion into a
Twelve-Vertex Metallocarborane

Keywords: boron • cluster compounds •
metallocarboranes • ruthenium

As much as 8 kcal mol^{-1} separates the ionization energies of the lowest energy conformers of L-phenylalanine. This conformation-dependent energy difference, by far the largest reported to date for any molecule, is associated with the drastic change in hydrogen bonding upon ionization (see picture).

Angew. Chem. **2002**, *114*, 4288–4291



K. T. Lee, J. Sung, K. J. Lee, Y. D. Park, S. K. Kim * 4114–4117

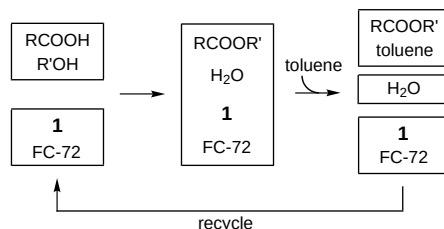
Conformation-Dependent Ionization Energies of L-Phenylalanine

Keywords: amino acids • conformation analysis • hydrogen bonds • ionization potentials



A perfectly selective esterification that discriminates between primary and sterically hindered or aromatic carboxylic acids occurs in the presence of the fluoroalkyldistannoxane $[\{\text{Cl}(\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2)_2\text{SnOSn}(\text{CH}_2\text{CH}_2\text{C}_6\text{F}_{13})_2\text{Cl}\}_2]$ (**1**). The reaction gives 100 % yield with a strict 1:1 ratio of the carboxylic acid and alcohol reactants, and the catalyst can be recycled without any loss of activity.

Angew. Chem. **2002**, *114*, 4291–4293

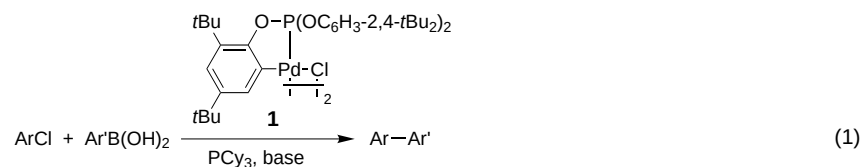


J. Xiang, A. Orita, J. Otera * 4117–4119

Fluorous Biphasic Esterification Directed towards Ultimate Atom Efficiency

Keywords: alcohols • biphasic catalysis • carboxylic acids • esters • tin

The most active catalyst yet reported for the Suzuki coupling of activated aryl chlorides, even for electronically deactivated substrates, is generated by addition of tricyclohexylphosphane to the otherwise inactive orthopalladated complex **1** [Eq. (1); for example, $\text{Ar} = \text{C}_6\text{H}_4\text{-4-OMe}$, $\text{Ar}^1 = \text{Ph}$].



Angew. Chem. **2002**, *114*, 4294–4296

R. B. Bedford,* C. S. J. Cazin, S. L. Hazelwood (née Welch) 4120–4122

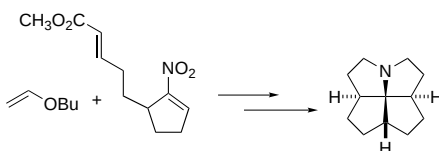
Simple Mixed Tricyclohexylphosphane–Triarylphosphite Complexes as Extremely High-Activity Catalysts for the Suzuki Coupling of Aryl Chlorides

Keywords: C–C coupling • homogeneous catalysis • palladium • Suzuki reaction



To provide an opportunity for X-ray analysis of an unsubstituted fenestrane, one of the ring-fusion carbon atoms was replaced with a nitrogen atom to facilitate salt formation; the key strategic step to the first 1-aza-fenestrane (see scheme) involves the tandem $[4+2]/[3+2]$ cycloaddition of a nitrocyclopentene with butyl vinyl ether. The adduct with borane provided crystals suitable for X-ray analysis, which revealed the planar deformation of the central carbon atom to be modest (116.1 and 116.6°).

Angew. Chem. **2002**, *114*, 4296–4299

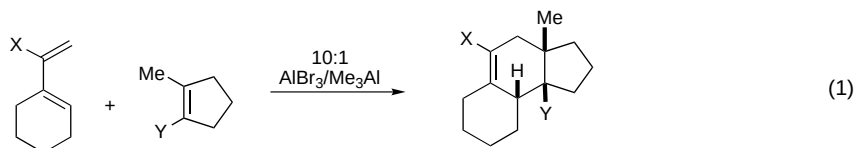


S. E. Denmark,* L. A. Kramps, J. I. Montgomery 4122–4125

Synthesis of *cis,cis,cis,cis*-[5.5.5.5]-1-Aza-fenestrane

Keywords: anti-van't Hoff/Le Bel compounds • cycloaddition • fenestrane • nitroalkene • polycycles

The right mix! A 10:1 mixture of AlBr_3 and AlMe_3 promotes the Diels–Alder reaction of hindered dienophiles. For example, the Diels–Alder reaction of an acetyldiene with a *tert*-butyldimethylsilyl (TBS) enol ether gave mainly the *exo* cycloadduct in 77% yield [Eq. (1); $\text{X} = \text{COMe}$, $\text{Y} = \text{OTBS}$]. Oxidation, hydrolysis, reduction, and desilylation of this cycloadduct afforded a BCD ring analogue of ouabain.



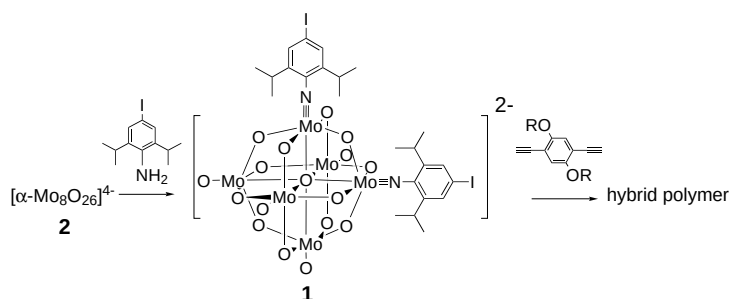
Angew. Chem. **2002**, *114*, 4299–4302

M. E. Jung,* P. Davidov 4125–4128

Efficient Synthesis of a Tricyclic BCD Analogue of Ouabain: Lewis Acid Catalyzed Diels–Alder Reactions of Sterically Hindered Systems

Keywords: cycloaddition • diastereoselectivity • Diels–Alder reaction • Lewis acids • synthetic methods

Molybdenum blocks in organic polymers: Bifunctionalized hexamolybdate anions (such as **1**) can be selectively synthesized in high yields by using the octamolybdate anion **2** as the starting material. The ion **1** can then be used in the synthesis of the first main-chain-polyoxometalate-containing hybrid polymer.



Angew. Chem. **2002**, *114*, 4303–4306

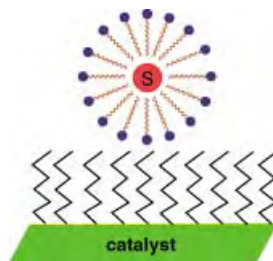
L. Xu, M. Lu, B. Xu, Y. Wei, Z. Peng,* D. R. Powell 4129–4132

Towards Main-Chain-Polyoxometalate-Containing Hybrid Polymers: A Highly Efficient Approach to Bifunctionalized Organoimido Derivatives of Hexamolybdates

Keywords: molybdenum • organic–inorganic hybrid composites • polymers • polyoxometalates

 **No organic solvents** are required using this novel concept for the heterogenization of (catalytic) reactions. The method relies on a multiphase transport process, namely on the transport of emulsified hydrophobic substrates to a hydrophobically derivatized sol-gel entrapped catalyst (see figure; S = substrate), and the transport of the resulting emulsified product from the catalyst-entrapping environment back into the aqueous bulk.

Angew. Chem. **2002**, *114*, 4306–4308

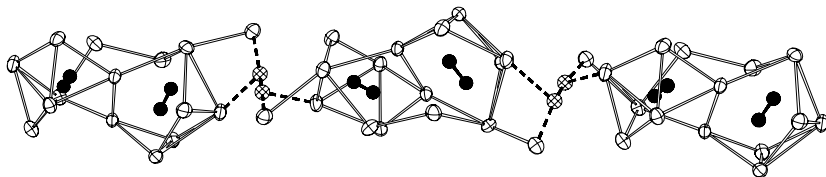


R. Abu-Reziq, D. Avnir,* J. Blum* 4132–4134

A Three-Phase Emulsion/Solid-Heterogenization Method for Transport and Catalysis

Keywords: green chemistry • micelles • phase-transfer catalysis • sol-gel processes • water chemistry

 **The largest known silver(I) cluster with encapsulated acetylide ions**, $(\text{Et}_4\text{N})_6[\{(\text{Ag}_2\text{C}_2)_2(\text{AgCF}_3\text{CO}_2)_8(\text{CF}_3\text{CO}_2)_3(\text{H}_2\text{O})_2\}_2]$, and an infinite anionic silver(I) column with co-intercalation of cyanide and acetylide ions, $(\text{Et}_4\text{N})_3[(\text{Ag}_2\text{C}_2)_2(\text{AgCN})(\text{AgCF}_3\text{CO}_2)_{11}(\text{CF}_3\text{CO}_2)_3(\text{H}_2\text{O})_6]$ (see picture; black dumbbells C_2^{2-} , cross-hatched dumbbells CN^-), have been synthesized and subsequently characterized by X-ray single-crystal structure analysis.



Angew. Chem. **2002**, *114*, 4309–4311

Q.-M. Wang, T. C. W. Mak* 4135–4137

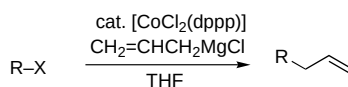
Facile Construction of Anionic Silver(I) Aggregates with Embedded Acetylide and Cyanide Ions

Keywords: aggregation • carbides • clusters • cyanides • silver



Facile construction of quaternary carbon centers:

The cobalt-catalyzed coupling reaction of not only primary and secondary but also tertiary alkyl halides with allylic Grignard reagents proceeds smoothly (see scheme; dppp = 1,3-bis(diphenylphosphanyl)propane; R = primary, secondary, or tertiary alkyl group). A radical mechanism is proposed for the oxidative addition of alkyl halides to cobalt.



Angew. Chem. **2002**, *114*, 4311–4313

T. Tsuji, H. Yorimitsu,
K. Oshima * 4137–4139

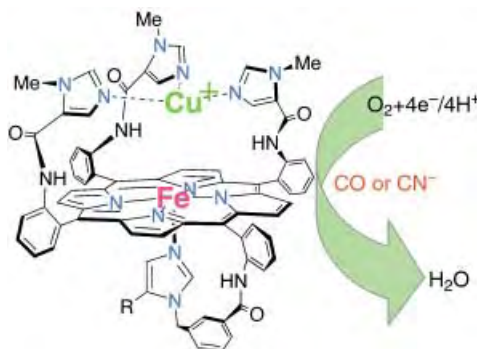
Cobalt-Catalyzed Coupling Reaction of Alkyl Halides with Allylic Grignard Reagents

Keywords: allylation • C–C coupling • cobalt • cross-coupling • radical reactions



Iron loses its inhibitions!

Comparative voltammetry of close functional heme/Cu_B analogues (see picture) in the FeCu and Cu-free forms revealed a Cu-induced destabilization of CO and CN[−] ion binding to the Fe center. During steady-state reduction of O₂ under physiologically relevant conditions, an up to fivefold higher concentration of CN[−] ion is required to inhibit the same fraction of the FeCu catalyst as of the Cu-free analogues.



Angew. Chem. **2002**, *114*, 4313–4316

J. P. Collman,* R. Boulatov,
I. M. Shiryayeva,
C. J. Sunderland 4139–4142

Distal Cu Ion Protects Synthetic Heme/Cu Analogues of Cytochrome Oxidase against Inhibition by CO and Cyanide

Keywords: bioinorganic chemistry • electrochemistry • inhibitors • iron • oxidoreductases • porphyrinoids



Supporting information on the WWW
(see article for access details).

* Author to whom correspondence should be addressed



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Clifford Mead,
Thomas Hager

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Handbook of Combinatorial Chemistry

Kyriacos C. Nicolaou,
R. Hanks, W. Hartwig

R. Breinbauer, E. Gonthier,
H. Waldmann 4145

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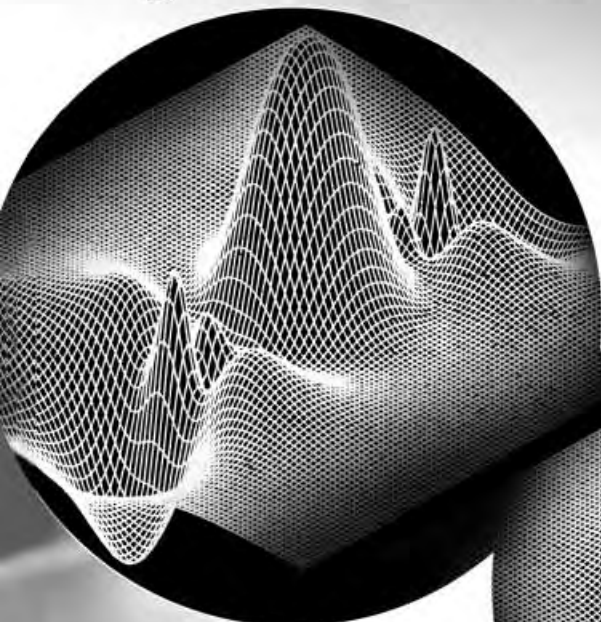
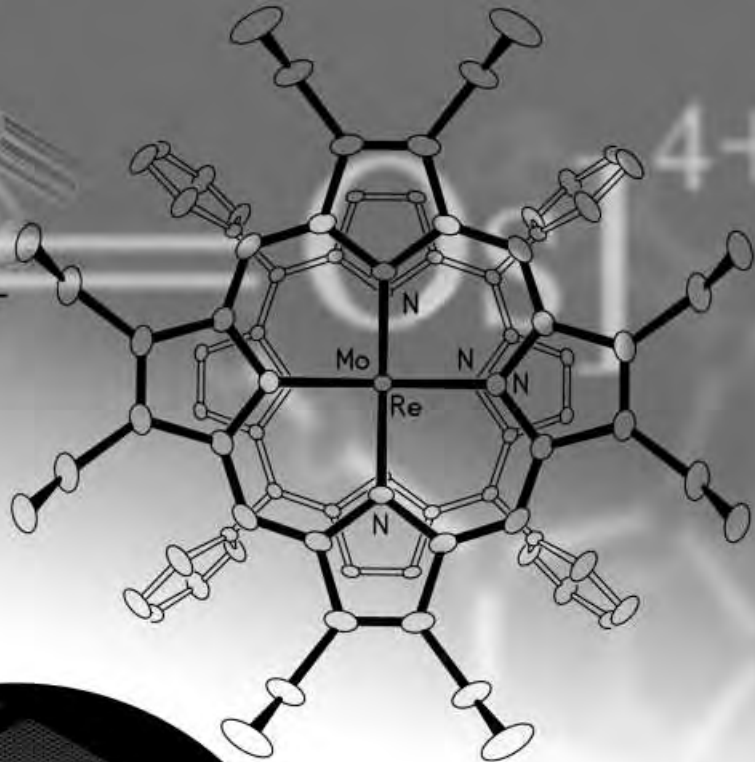
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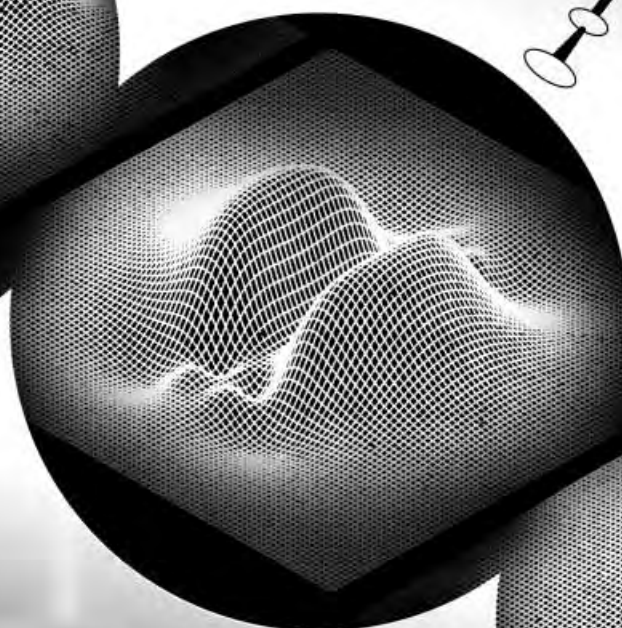
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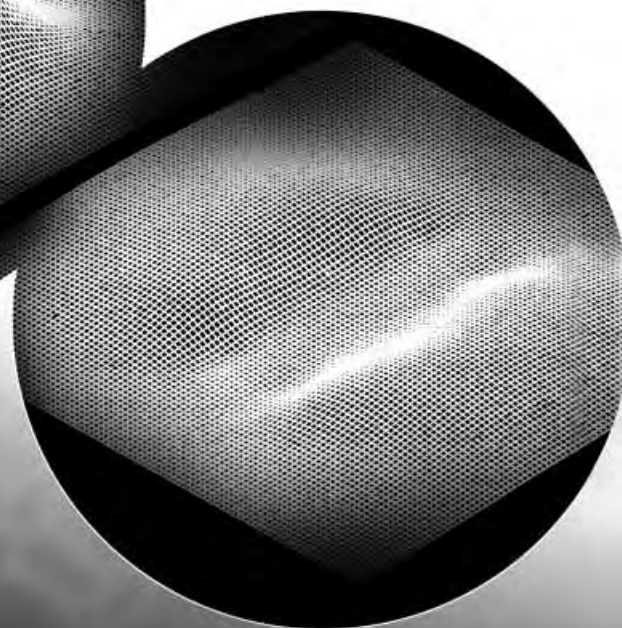
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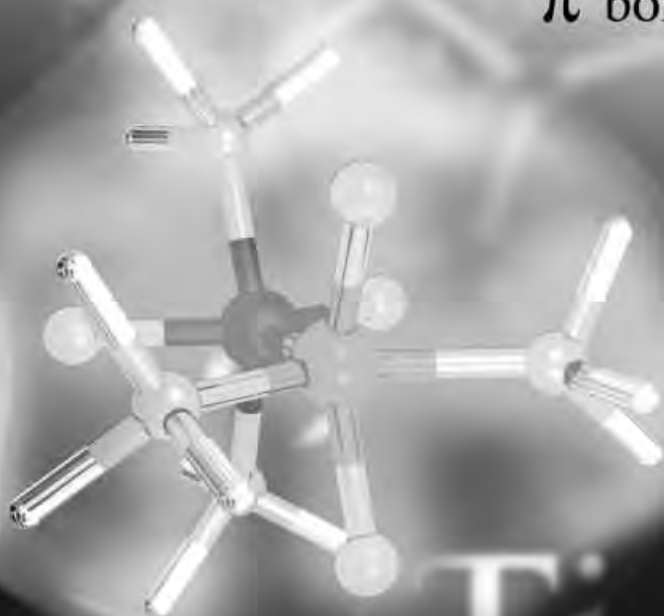
σ bond



π bond



δ bond



Heterodinuclear Transition-Metal Complexes with Multiple Metal–Metal Bonds

James P. Collman* and Roman Boulatov

Interactions between a pair of transition-metals can range from weak anti-ferromagnetic coupling to bonds of the highest multiplicity known in chemistry, for example, quadruple in isolatable compounds. Tremendous effort has been invested in studying homodinuclear transition-metal–metal bonds. In contrast, relatively little attention has been devoted to heterodinuclear analogues, as it is substantially more challenging to prepare and handle such entities. Yet, in this largely unexplored area of transition-metal

chemistry, novel chemical interactions with unprecedented reactivities are likely to be found. Heterodinuclear analogues of diatomic transition-metal dimers being yet inaccessible, dinuclear complexes with Werner-type ligands provide examples of high-multiplicity bonds between different d elements in their least-perturbed form. Such compounds provide an opportunity to probe fundamental issues of chemical bonding between transition-metals, by revealing how and to what extent such bonds are affected by

differences in the two metals. Complexes wherein electronically unsaturated heterodinuclear cores are stabilized by π -acidic ligands (such as CO) hold the potential of new chemical reactions (including catalytic) that capitalize on the synergetic effect of two transition-metal centers.

Keywords: bond theory • cluster compounds • electronic structure • metal–metal interactions • transition-metals

1. Introduction

It seems probable that no multiple bonds between two different transition-metals existed in nature (or, at least on this planet) until chemists attempted to synthesize them. This situation illustrates the progress made over the past 50 years in the area of di- and polynuclear transition-metal complexes. Species which we now know have homonuclear multiple metal–metal bonds were prepared as early as the 19th Century (e.g. $[\text{Cr}_2(\mu\text{-O}_2\text{CMe})_4(\text{H}_2\text{O})_2]$ ^[1]) but it was not until 1956 when Figgis and Martin suggested that the diamagnetism of chromium acetate is a result of what they thought was a weak (5 kcal mol^{−1}) quadruple bond between the Cr atoms.^[2] This appears to be the first explicit mentioning of a multiple metal–metal bond in the literature. In 1964 Cotton proposed that the $[\text{Re}_2\text{Cl}_8]^{2-}$ ion contains an extremely strong Re⁴–Re bond (the δ component alone was estimated at 60 kcal mol^{−1}).^[3, 4] Since then, numerous dinuclear compounds

have been synthesized wherein bonds between two identical transition-metal atoms have some multiple character.^[5–9] Tremendous effort has been invested in studying such species experimentally as well as theoretically.^[10–14]

In contrast, relatively little attention has been devoted to mixed-metal dinuclear transition-metal complexes, such work being hampered by synthetic challenges. Yet it is this largely unexplored area of transition-metal chemistry where novel chemical interactions, which may have unprecedented properties and unusual reactivities, are likely to be found.

Although diatomic transition-metal dimers can be prepared in the gas phase,^[15] isolatable dinuclear cores must be stabilized by auxiliary ligands. Two distinct classes of unsaturated dinuclear compounds are known, those with and without π -acidic ligands. In complexes with only Werner-type ligands (e.g. those with weak or no π -acidity), a subset of metal d orbitals interacts weakly with ligand orbitals so that, in the first approximation, the metal–metal bonding can be considered as isolated from metal–ligand interactions. In contrast, π -acidic ligands (e.g. CO) significantly affect the metal–metal interaction by extensive mixing between metal and ligand orbitals of π symmetry.^[16, 17] While compounds of these two classes differ in the nature of metal–metal bonding, they manifest related structural (e.g. short metal–metal separations) and reactivity patterns.

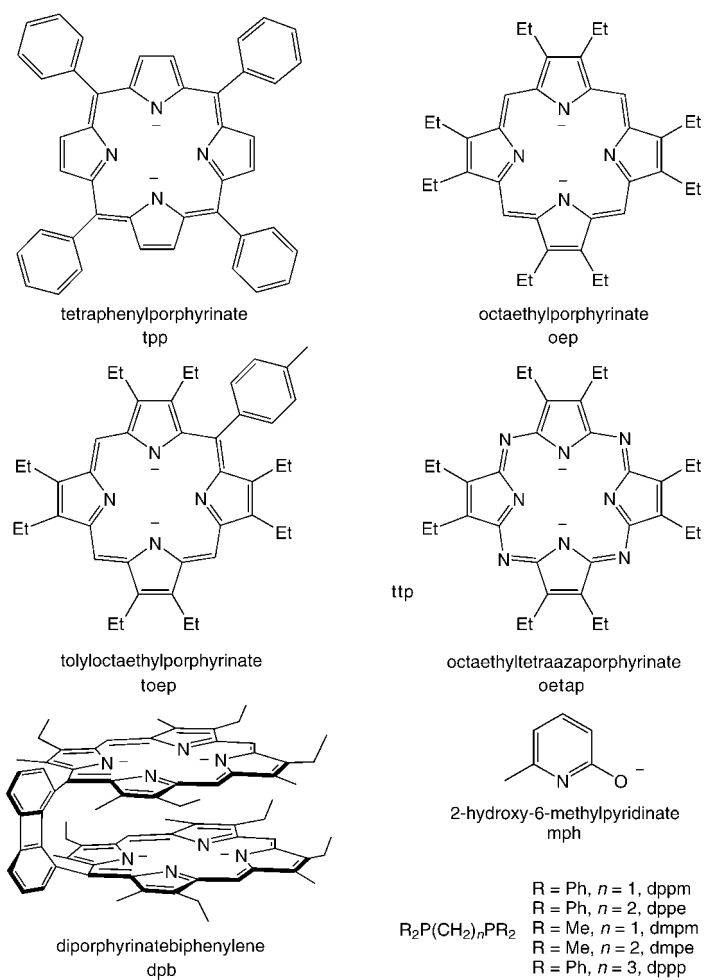
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2. Heterodinuclear Complexes Without π -Acidic Ligands.

2.1. Molecular Structure and Metal–Metal Bonding.

All reported complexes of this class are listed in Table 1 (see also Scheme 1).^[18–41] The compounds are stable at room temperature under anaerobic and anhydrous conditions, and most of them have been characterized crystallographically. The four major metal-donor-atom geometries observed in homodinuclear complexes^[10] are also represented in heterodinuclear compounds (Scheme 2), although only one example of the face-sharing bi-octahedral (FSBO) and $(ML_3)_2$ stereochemical types are known. Edge-sharing bi-octahedral (ESBO) and FSBO complexes contain two and three donor atoms, respectively, that coordinate to both metal centers. Dinuclear complexes of the $(ML_3)_2$ and $(ML_4)_2$ structural types comprise two flattened trigonal- (ML_3) or square-pyramidal (ML_4) units, connected face-to-face by a metal–metal bond and, in some cases, by the backbone(s) of bridging ligands. High metal–metal bond multiplicities result in intermetal distances that are 0.2–0.9 Å shorter than single bonds between the same metal ions in a comparable coordination environment.

Useful qualitative description of metal–metal bonding in most heterodinuclear transition-metal complexes is given by simple molecular orbital (MO) diagrams derived for the highest symmetry accessible within the corresponding structural type (Figure 1). In an ESBO complex each ML_4 fragment has three metal-localized orbitals (derived from the nonbonding t_{2g} set in the O_h symmetry), the positive overlap of which generates the σ , π , and δ MOs of the M_2^{x+} core. Because of the relatively long intermetal separations, the δ overlap is particularly weak and is effectively nonbonding (nb), so that the maximum formal metal–metal bond order in an ESBO complex is two. Among the MOs of the M_2^{x+} core only the δ orbital is of the right symmetry to interact with orbitals of the bridging ligands; these π -donor interactions



Scheme 1. Structures of some Werner-type ligands used to stabilize transition-metal heterodinuclear cores.

destabilize the δ MO and often invert the δ/δ^* order ($\delta^* < \delta$).^[42, 43] Small HOMO/LUMO gaps ($\approx 1000\text{ cm}^{-1}$) and the $^1A_1$ ground state ($\sigma^2\pi^2(\delta/\delta^*)^2$) observed in the ESBO heterodi-

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J. P. Collman

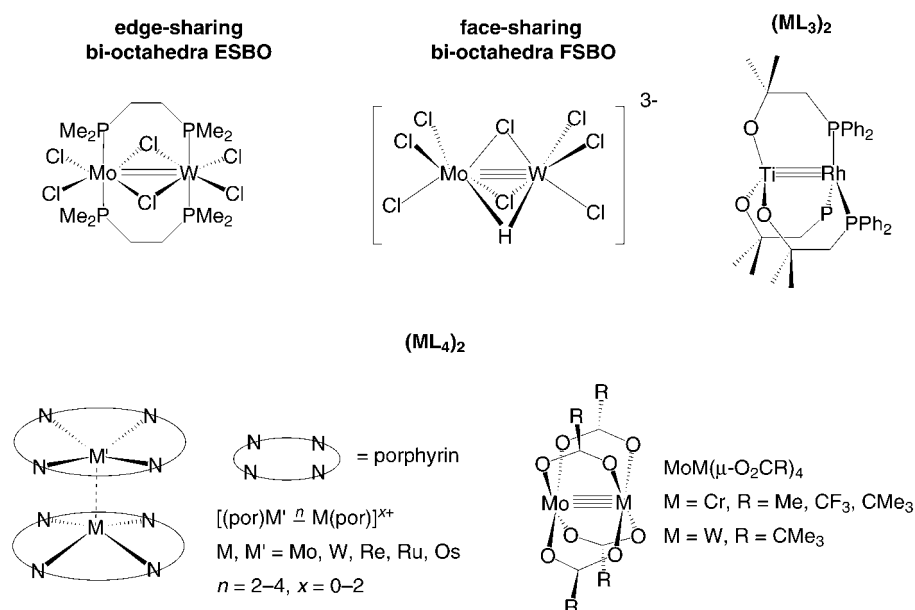


R. Boulatov

Table 1. Heterodinuclear cores stabilized by Werner-type ligands arranged by structural type.^[a]

Heterodinuclear core	Ground-state configuration ^[b]	Examples ^[c]	M–M' separation [Å]		Synthesis ^[d]
			M–M'	Single bond ^[e]	
ESBO Mo≡W ⁶⁺	$\sigma^2\pi^2(\delta^{nb})^2$	5 isomers of [MoWCl ₄ (μ-Cl) ₂ (PP) ₂] (PP = dppe, dppm) ^[18, 19] [MoWCl ₄ (μ-Cl)(μ-H)(μ-dppm)] ^[20]	2.682(1)–2.7320(6) 2.4932(6)	2.92 2.92	reaction 6
FSBO Mo≡W ⁶⁺	$\sigma^2\delta^4$	[MoWCl ₆ (μ-Cl) ₂ (μ-H)] ^{3–} ^[21, 22]	2.445(3)	2.92	reaction 7
(ML ₃) ₂ Ti≡Rh ³⁺	see text	[Ti(μ:η ¹ ,η ¹ -OCMe ₂ CH ₂ PPh ₂) ₃ Rh] ^[23]	2.2142(11)	2.92	reaction 3
(ML ₄) ₂ Ru=Os ⁴⁺	$\sigma^2\pi^4(\delta^{nb})^4\pi^{*2}$	[(oep)OsRu(oetap)] ^[24] [RuOs(dpb)] ^[25]			reaction 1
Mo ⁿ Ru ⁵⁺ $n \geq 2.5$	$\sigma^2\pi^4(\delta^{nb})^2(\delta^{nb}/\pi^*)^1$ [f]	[(oep)MoRu(tpp)] ⁺ ^[26] [g]	2.181(2)	2.88	reaction 1
Mo ⁿ Os ⁵⁺ $n \geq 2.5$	$\sigma^2\pi^4(\delta^{nb})^2(\delta^{nb}/\pi^*)^1$ [f]	[(oep)MoOs(tpp)] ⁺ ^[27]	2.238(3)	2.96	reaction 1
M ⁿ M ⁴⁺ M = Mo, W; M' = Ru, Os, $n > 2$	$\sigma^2\pi^4(\delta/\delta^{nb})^2\pi^{*2}$ (MoRu)	[(oep)MM'(tpp)] ^[26, 27]			reaction 1
Mo ^{3.5} W ⁵⁺	$\sigma^2\pi^4\delta^1$	[MoW(μ-O ₂ CCMe ₃) ₄] ^[21]	2.194(2)	2.92	
Mo ^{3.5} Ru ⁵⁺	$\sigma^2\pi^4\delta^2(\delta^*/\pi^*)^1$ [f]	[(tpp)MoRu(oep)] ⁺ ^[26] [g]	2.211(2)	2.88	reaction 1
W ^{3.5} Ru ⁵⁺	$\sigma^2\pi^4\delta^2(\delta^*/\pi^*)^1$ [f]	[(oep)WRu(tpp)] ⁺ ^[27]	2.297(2)	2.90	reaction 1
Cr ⁴ Mo ⁴⁺	$\sigma^2\pi^4\delta^2$	[CrMo(μ-O ₂ CMe) ₄] ^[28] [CrMo(μ-L) ₄] (L = O ₂ CCF ₃ ; ^[28] O ₂ CCMe ₃ ; ^[29] mph ^[30])	2.050(1)	no data	reaction 4
Mo ⁴ W ⁴⁺	$\sigma^2\pi^4\delta^2$	[MoW(μ-mph) ₄] ^[31] [MoW(μ-O ₂ CCMe ₃) ₄] ^[32] [P ₂ Cl ₂ MoWCl ₂ P ₂] (P, P' = PMe ₂ Ph, PMePh ₂ , PMe ₃) ^[33, 34] [MoWBr ₄ P ₄] (P = PMe ₂ Ph, PMePh ₂) ^[35]	2.091(1) 2.080(1) 2.207(1)–2.2092(7)	2.92 2.92 2.92	ligand exchange reaction 5 reaction 5 reaction 2
		[MoWX ₄ (μ-PP) ₂] (X = Cl, Br; PP = dppm, dppe, dmpe, dmpm) ^[35, 36] [(por)MoW(por)] (por = toep, oep) ^[37] [(tpp)MoRe(oep)] ⁺ ^[38]	2.2110(7)–2.243(1) 2.2350(12)	2.92 2.98	ligand exchange reaction 5 reaction 1

[a] See Scheme 1 for chemical structures of oep, oetap, tpp, toep, dpb, mph, and molecular formulas of bidentate phosphanes. Multiple bonds between two different transition-metal atoms may be present in several other dinuclear complexes; there is either insufficient evidence to ascertain whether the bond is multiple, or the compounds were not adequately characterized. A mixture of diamagnetic [(PMe₃)₃Cl_nMo(μ-Cl)(μ-S)WCl_m(PMe₃)₂] ($n = 1, m = 2; n = 2, m = 1$) was prepared from [S=WCl₂(PMe₃)₃] and [MoCl₂(PMe₃)₃];^[39] these complexes may have the ESBO geometry and one Mo=W bond. Formation of [Mo≡W(NMe₂)₆] (as a mixture with the homodimers) in a reaction between LiNMe₂ and a solid with an empirical composition MoW₂Cl₁₂ was claimed based on mass-spectrometric evidence.^[40] Finally, an ESBO ion, [CrMoCl₃]^{3–}, possibly with a formal Cr=Mo bond ($\sigma^2\delta^4$), may form in a reaction between [MoCl₆]^{2–}, CrCl₂, and Cl[–] ions.^[41] [b] See Figure 1. The δ^{nb} notation designates weakly or non-interacting metal-based orbitals of δ symmetry. [c] See Scheme 2. [d] See Scheme 3. [e] The M–M' separation averaged over all structures deposited in Cambridge Crystallographic Structural Database (CCSD) as of October 2001 and designated as having a single M–M' bond. [f] The nature of the SOMO is presently unknown.^[26, 27] [g] Both the eclipsed and staggered conformers are present in the solid state (Figure 2).^[27]



Scheme 2. Structures of select heterodinuclear transition-metal complexes (structural type listed in bold).

nuclear complexes,^[18, 19] are consistent with this qualitative picture and indicate that the weak room-temperature paramagnetism of these compounds arises from thermally populated ($\delta\delta^*$) excited states.

The magnetic properties of the only reported FSBO heterodinuclear ion, [MoWCl₆(μ-Cl)₂(μ-H)]^{3–}, have not been studied. Based on the MO diagram in Figure 1, this (d–d)⁶ complex should have a $\sigma^2\delta^4$ ground state and a triple Mo–W bond. This MO diagram is likely to be applicable to the MoW⁶⁺ core as it correctly describes the ground-state configurations of all W₂⁶⁺ and most Mo₂⁶⁺ congeners.^[13, 44]

The (ML₄)₂ geometry is the only common structural type in which a quadruple bond is possible. The overlap of effectively nonbonding, with

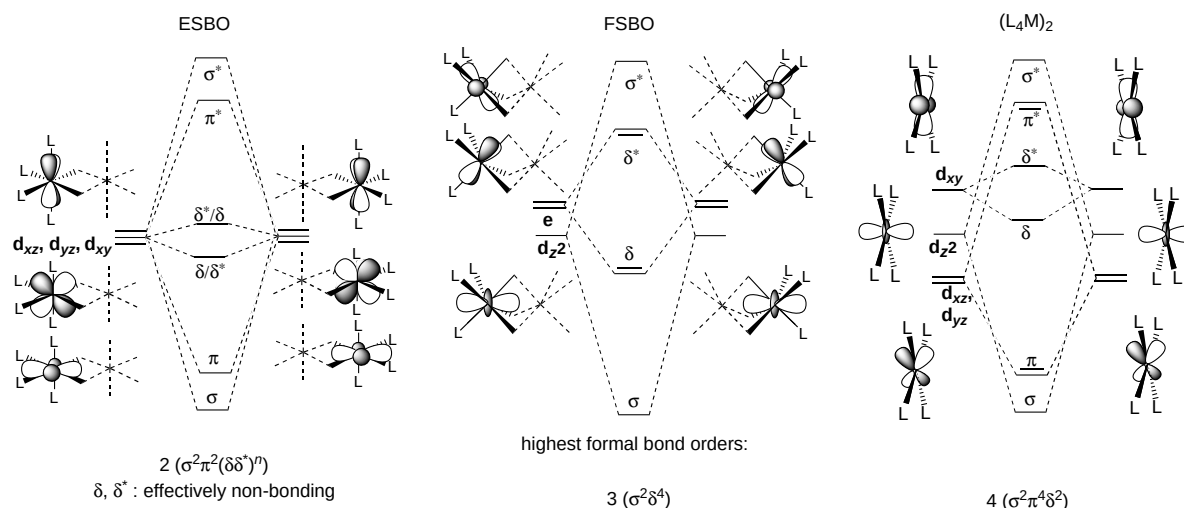


Figure 1. Qualitative MO diagrams of the metal–metal bonding between transition metal atoms in three major structural types of dinuclear complexes without π -acidic ligands. In the ESBO the d_{xz} and d_{yz} orbitals are rotated 45° around the axial L–M–L axis relative to their orientation in a t_{2g} set in O_h symmetry. In the FSBO the e set is comprised of a pair of strongly mixed d_{xz}/d_{yz} and $d_{xy}/d_{x^2-y^2}$ orbitals.^[10]

respect to the metal–ligand interactions, d_{xy} , d_{xz} , d_{yz} and d_{z^2} orbitals of the ML_4 fragments generates the σ , two π , and a δ MOs of the metal–metal core. The δ overlap, which depends on the L–M–M–L dihedral (torsion) angle (χ) as $\cos 2\chi$, is maximum in the eclipsed conformation ($\chi = 0^\circ$) and is annihilated if the L_4M moieties are staggered ($\chi = 45^\circ$). The diamagnetism and the eclipsed solid-state conformation of all known $(d-d)^8$ heterodinuclear complexes suggest a $\sigma^2\pi^4\delta^2$ ground state and quadruple M–M' bonds. The electronic stabilization from maximal δ overlap over rides increased nonbonding repulsions in the sterically least-favorable eclipsed conformation of $(L_4M)_2$ -type heterodinuclear complexes without bridging ligands: $(d-d)^8$ $[MoWX_4P_4]$ (X = Cl, Br, P = phosphane)^[33–35] and $[(tpp)MoRe(oep)]^+$,^[38] and $(d-d)^9$ $[(oep)WRu(tpp)]^+$.^[27] In contrast, the $(d-d)^9$ $MoRu^{5+}$ derivative exists in the solid state as an equimolar mixture of an eclipsed and a staggered conformer (Figure 2).^[27] Such a situation is unprecedented among homodinuclear compounds and may arise from the electronic stabilization engendered by the δ bond being comparable to the difference in noncovalent ligand–ligand interactions between the two conformers.

The MO diagram in Figure 1 predicts a diamagnetic $\sigma^2\pi^4(\delta^{nb})^4$ ground-state configuration for a $(d-d)^{10}$ complexes, as is indeed observed for homodinuclear $[(por)_2Re_2]$ ^[45] and $[(por)_2M'_2]^{2+}$ ($M' = Ru, Os$; $por = oep, tpp$).^[46] However, isoelectronic structurally analogous heterodinuclear complexes, $[MM'(por)_2]$ ($M = Mo, W$; $M' = Ru, Os$; $por = oep, tpp$), have a triplet $^3A_2$ ground state, consistent with the $\sigma^2\pi^4\delta^2\pi^{*2}$ electronic configuration (in the absence of a crystal structure it is unknown if the δ orbital is bonding).^[26, 27] The origin of the inversion ($\pi^* < \delta^*$) in heterodinuclear $(d-d)^{10}$ cores is not yet known. Whereas the $\delta^* \approx \pi^*$ or $\pi^* < \delta^*$ ordering in most homodinuclear $Ru_2^{4/5+}$ and $Os_2^{4/5+}$ complexes is caused by π -donor interactions between the δ^* orbitals and orbitals of bridging ligands,^[10, 47] the stereoelectronic properties of the porphyrin do not allow such orbital interactions. Because the $[MM'(por)_2]$ species have a rare among dinuclear transition-metal complexes π^{*2} HOMO,^[44] they may be

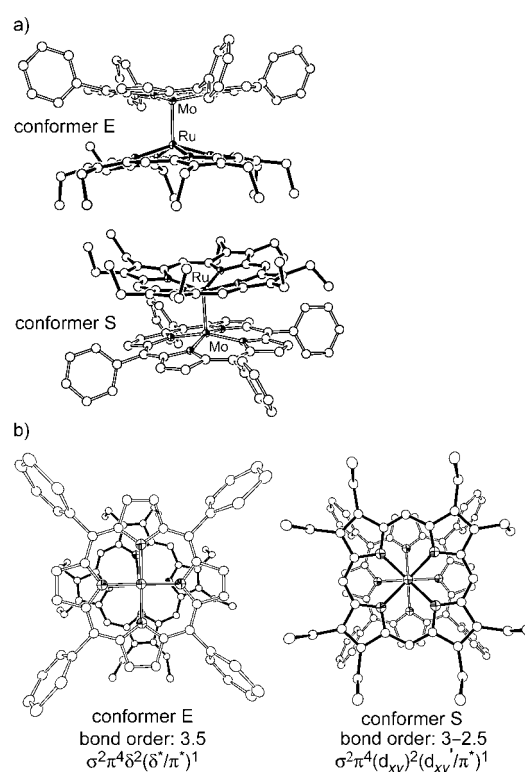


Figure 2. ORTEP drawings of $(d-d)^9$ $[oep]MoRu(tpp)^+$ (tpp is drawn with open bonds, oep with bold bonds). a) half the unit cell containing one molecule of an eclipsed (E) and a staggered (S) conformer; b) view along the Mo–Ru vector for each conformer; the perspective is exaggerated to show better the relative arrangement of the macrocycles. Unlabeled spheres with shaded octants represent the N atoms; counterions, solvent molecules, and hydrogen atoms are omitted; thermal ellipsoids are for 50% (a) or 25% (b) probability.

interesting objects to study the electron correlation effects in bimetallic derivatives of heavy transition elements.

A triple Ti–Rh bond in $[Ti(\mu-OCMe_2CH_2PPh_2)_3Rh]$ was suggested to arise from one $Ti(d_{\sigma})$ – $Rh(d_{\sigma})$ and two dative $Rh(d_{\pi}) \rightarrow Ti(d/p_{\pi})$ interactions.^[23] The generic MO diagram

for $(ML_3)_2$ -type complexes predicts a single $(\sigma^2\pi^4\pi^{*4})$ bond, but it is probably a less adequate depiction of this polar “early–late” Ti–Rh bond.^[14, 48] Notably, no multiple homo-nuclear Ti–Ti and Rh–Rh bonds are yet known.

The one-electron orbital description of the metal–metal bond, discussed above, is useful in categorizing dinuclear transition-metal complexes and qualitatively rationalizing many of their properties. However, any *quantitative* treatments of a metal–metal bond must incorporate extensive configuration interactions as the separations of the energies of the MOs comprising such bonds are comparable to the energy of interactions among many electrons confined to a dimetallic core.^[10, 44, 49] This importance of excited states (Table 2) is seen, for example, in that, in contrast to early main-group elements,^[50] a multiplicity of a transition-metal–metal bond derived from computational studies is always substantially lower than that obtained from simple MO arguments (formal bond order, FBO) and may differ significantly among isoelectronic structurally analogous dinuclear complexes.

Very few computational studies of heterodinuclear metal–metal bonds have been reported, apparently because of the difficulty in dealing with the intrinsic dissymmetry of such entities.^[51] Cr–Mo bonding in the most studied heterodinuclear complex, $[CrMo(\mu-O_2CH)_4]$, was found to be more similar to that in the Mo_2^{4+} rather than Cr_2^{4+} analogues (Table 2).^[51–54] Qualitatively, the difference was ascribed to higher covalency of the Cr–Mo bond resulting from the improved overlap of the 3d orbitals with more polarizable and diffuse 4d orbitals of the Mo.^[51] The slight polarity of the δ -Cr⁴⁺–Mo^{δ+} bond was ascribed^[51, 52] to different radial distributions of 3d and 4d orbitals.

Stranger et al. have carried out broken-symmetry DFT calculations on series of $(d-d)^6$ FSBO $[MM'Cl_9]^{3-}$ and ESBO $[MM'Cl_6(\mu-PH_2CH_2PH_2)]$ complexes ($M, M' = Cr, Mo, W$).^[43, 55] Among heterodinuclear compounds of these types only $[MoWCl_6(PP)_2]$ ($PP = dmpm, dpmp, dppe$) have been reported.^[19] In a notable contrast to the tetracarboxylates, weak antiferromagnetic coupling was found for both the Cr_2^{6+} and the hypothetical $CrMo^{6+}$ cores as opposed to strong Mo–Mo bonds in the Mo_2^{6+} congeners.

2.2. Synthesis

The most versatile synthesis of heterodinuclear cores is high-vacuum solid-state pyrolysis of mononuclear metalloporphyrins stabilized by thermally labile axial ligands (Scheme 3, Reaction 1). The loss of these ligands at 180–220 °C generates four-coordinate metalloporphyrin fragments that recom-

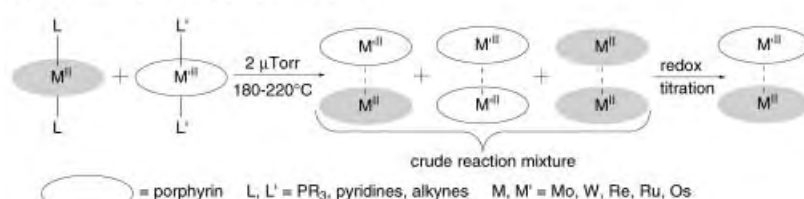
Table 2. Computed orbital population of quadruple M–M' bonds in $[MM'(\mu-O_2CH)_4]$ ($M, M' = Cr, Mo$).^[a]

Core	σ	π	δ	δ^*	π^*	σ^*	Net bond order
Cr ₂	1.48	2.59	1.09	0.91	1.41	0.52	1.16
CrMo	1.78	3.39	1.41	0.59	0.61	0.22	2.58
Mo ₂	1.89	3.69	1.65	0.35	0.31	0.11	3.23

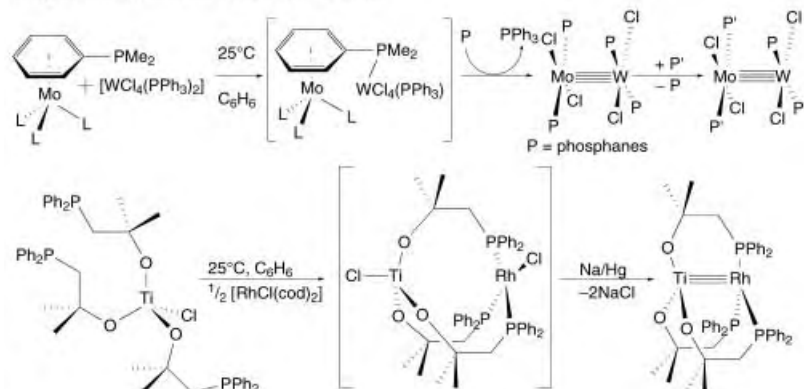
[a] Adapted from ref. [51].

bine randomly to yield a mixture of homo- and heterodinuclear bisporphyrin compounds. The latter are isolated by cycles of selective oxidation and reduction based on different redox potentials of homo- and heterodimers and different solubilities of neutral and cationic metalloporphyrins in nonpolar solvents (“redox titration”).^[46]

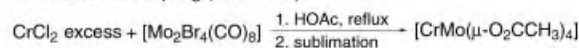
High-vacuum solid-state pyrolysis (reaction 1):



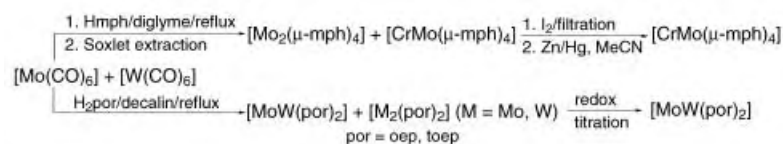
Bridge-assisted dimerization (reactions 2, 3):



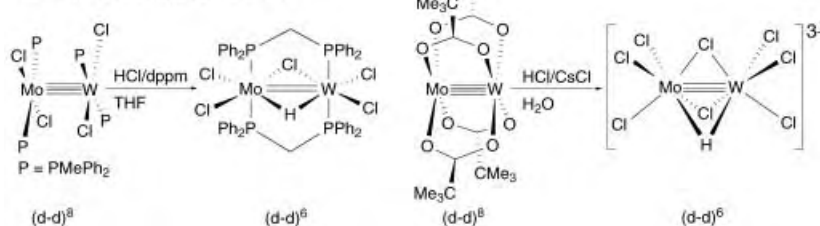
Non-oxidative coupling (reaction 4):



Oxidative coupling (reaction 5):



Oxidative addition (reactions 6, 7):



Scheme 3. Representative syntheses of heterodinuclear transition-metal complexes.

The success of this synthetic strategy is based in large part on the unique attributes of the porphyrin as an auxiliary ligand to stabilize dinuclear metal cores. First, pyrolysis is applicable to a wide range of 4d and 5d metals^[56] as suitable mononuclear metalloporphyrin precursors are known for almost every transition element. Second, the yields of heterodimers can be optimized in a rational way, by selecting mononuclear precursors of similar thermal stabilities. The latter are adjusted by the appropriate choice of the porphyrin and axial ligands. For example, less σ -basic porphyrins tend to give more thermally stable derivatives with identical combinations of metals and axial ligands, whereas alkylphosphanes are lost several times faster than pyridines or acetylenes are. Third, because a porphyrin can not be displaced from most metal ions, scrambling of porphyrin ligands does not complicate syntheses of heteroleptic heterodinuclear derivatives. The latter are better suited for crystallographic studies as they are free of the solid-state disorder in which both crystallographic sites have fractional occupancy by both metals. Fourth, the combined magnetic anisotropy of the two macrocycles in a bismetalloporphyrin produces a characteristic ^1H NMR spectrum resonance pattern, which is sufficient to establish formation of the dinuclear derivative without crystallographic characterization. In addition, series of metal–metal bonded bisporphyrins with identical metal-donor-atom geometries but containing various spectroscopic markers and/or of varying stereoelectronic characteristics are accessible by using porphyrins with appropriate peripheral substituents. Fifth, pyrolysis is readily applicable to 2nd and 3rd row transition-metal complexes of porphyrin-like ligands, such as tetraazaporphyrins, phthalocyanines, and corroles. Because electronic properties of these macrocycles differ from those of the porphyrin, they may stabilize metal cores, which are otherwise inaccessible.

Heterodinuclear complexes of non-porphyrin ligands have been prepared by a variety of less general routes. Clever methods have been used to synthesize unbridged MoW^{4+} ^[57] and bridged TiRh^{3+} ^[23] cores. Formation of the metal–metal bond is facilitated and the selectivity of dimerization is significantly improved by preordinating metal fragments with a suitable bridging ligand (Reactions 2 and 3, Scheme 3).^[58] Neither method has yet been extended to other multiply bonded heterodinuclear cores.^[57, 59] A reaction between $[\text{Mo}_2\text{Br}_4(\text{CO})_8]$ and CrCl_2 in refluxing acetic acid yields $[\text{MoCr}(\mu\text{-OCCH}_3)_4]$ in a good yield (Scheme 3, Reaction 4).^[29] $[\text{MoW}(\mu\text{-L})_4]$ ($\text{L} = \text{O}_2\text{CCMe}_3$ ^[32] or mph ^[31]) and $[\text{MoW}(\text{por})_2]$ ($\text{por} = \text{toep}$, oep)^[37] have been prepared by oxidative coupling of $[\text{Mo}(\text{CO})_6]$ and $[\text{W}(\text{CO})_6]$ in the presence of the corresponding ligand (Scheme 3, Reaction 5).

A variety of other MoW^{4+} derivatives have been obtained by ligand substitution in $[\text{MoW}(\mu\text{-O}_2\text{CCMe}_3)_4]$ ^[60] or in $[\text{MoWCl}_4(\text{PMe}_3)_4]$,^[34–36, 61] but this approach does not yield novel heterodinuclear cores. However, oxidative addition of HCl ^[20, 21] or two Cl atoms (from CH_2Cl_2 or PhICl_2 ^[19]) to such complexes generates doubly and triply bonded MoW^{6+} cores (Scheme 3, Reactions 6–7).

2.3. Physicochemical Properties

With the exception of the force constants of metal–metal bonds $\kappa(\text{MM}')$, in bismetalloporphyrins, physicochemical data are limited to Group 6 derivatives (Table 3).^[10, 19, 21, 34–37, 57, 60–67] In most cases, the properties of the congeners show monotonic and expected trends.

Out of 17 crystallographically characterized heterodinuclear cores, there is one example each of a MM' bond being shorter (in $[\text{MoW}(\mu\text{-O}_2\text{CCMe}_3)_4]$) or longer (in the $[\text{MoW}(\mu\text{-Cl})_2(\mu\text{-H})\text{Cl}_6]^{3-}$ ion) than either homonuclear analogue (entries 3 and 6, respectively).^[10, 57, 62, 68–70] Bond-length trends in similar compounds of the 2nd and 3rd row transition metals have been ascribed to the relative importance of bond lengthening, as a result of core–core repulsions (which accounts for longer W–W bonds relative to Mo–Mo ones), and bond shortening as a result of relativistic phenomena (e.g. shorter W–L than Mo–L bonds).^[10] A nonlinear trend in metal–metal separations may result if the relative contributions of these effects are significantly different for a heterodinuclear core than for the homonuclear congeners. However, the metal–metal separations may also be substantially affected by the stereoelectronic requirements of relatively rigid bridging-ligand sets.

For a number of heterodinuclear complexes, metal–metal vibration frequencies, $\nu(\text{MM}')$, identified by resonance Raman spectroscopy, have been used to calculate $\kappa(\text{MM}')$ within the diatomic-oscillator approximation. However, opinions differ^[10, 71] as to whether comparisons of such diatomic force constants among homologous complexes of different metals provide meaningful information on the relative strengths of metal–metal bonds.

In contrast to light main-group elements, where $\text{C}=\text{O}$ and $\text{N}=\text{O}$ bonds are substantially stronger than the homonuclear analogues, such as $\text{C}=\text{C}$, $\text{O}=\text{O}$, and $\text{N}=\text{N}$, $\text{O}=\text{O}$, no unambiguous examples of a similar effect are known for metal–metal bonds between transition-metal atoms. Although $\kappa(\text{MoW})$ in $[\text{MoWCl}_4(\text{PMe}_3)_4]$ was found to be larger than those in the homodinuclear analogues (Table 3, entry 9), it is unclear if this small difference is meaningful within the diatomic-oscillator approximation. While force constants in the $[\text{MM}'(\mu\text{-mph})_4]$ series ($\text{M}, \text{M}' = \text{Cr}, \text{Mo}, \text{W}$) increase monotonically from Cr_2 to MoW , the very low value of $\kappa(\text{W}_2)$ appears to be either underestimated or represent unusually large ligand perturbation (entry 8).

With the exception of the recently reported $\kappa(\text{Mo}_2)$, $\kappa(\text{MoW})$, and $\kappa(\text{W}_2)$ values that change monotonically (entry 10)^[72–74] but might be systematically underestimated,^[72] a decrease in the force constants of both homo- and heteronuclear 4d–4d and 5d–5d bonds with the number of d electrons is described by the same linear function in all known metalloporphyrins (Figure 3). Remarkably, force constants of isoelectronic homo- and heteronuclear 4d–4d or 5d–5d bonds of different charge ($\kappa(\text{WOs}^{4+}) \approx \kappa(\text{Os}_2^{6+})$) or electronic configuration ($\kappa(\text{Ru}_2^{6+}, \sigma^2\pi^4(\delta^{\text{nb}})^4) \approx \kappa(\text{MoRu}^{4+}, \sigma^2\pi^4\delta^2\pi^{*2})$) are very similar. Force constants of 4d–5d bonds are intermediate between those of the isoelectronic 4d–4d and 5d–5d analogues.

Table 3. Physicochemical properties of hetero- and homodimers of Group 6 elements.^[a]

parameter	entry	FBO ^[a]	auxiliary ligands	Cr ₂	CrMo	Mo ₂	MoW	W ₂
bond length [Å]	1	4	Cl ₄ P ₄ ^[b]			2.14(2)	2.21(2)	2.28(2)
	2	4	(μ-O ₂ CMe) ₄ ^[62]	1.966(14)	2.050(1)	2.0934(8)		
	3	4	(μ-O ₂ CCMe ₃) ₄			2.088(1) ^[10]	2.080(1) ^[32]	2.194(10) ^[c]
	4	4	(μ-mph) ₄ ^[57]			2.065(1)	2.091(1)	2.161(1)
	5	3.5	varies ^[d]			2.164(2)	2.194(2)	2.312
	6	3	(μ-Cl) ₂ (μ-H)Cl ₆ ^{3−[e]}			2.372(11)	2.445(3) ^[21]	< 2.421(17)
	7	2	(μ-Cl) ₂ Cl ₄ (PP) ₂ ^[f]			2.76(2)	2.71(3)	2.68(1)
force constants, κ(M [±] M'), mdyne [Å] ^[g]	8	4	(μ-mph) ₄	4.73	5.04	5.10	5.47	4.71
	9	4	Cl ₄ (PR ₃) ₄ ^[60]			3.54 (R = Me)	3.84 (R = Me)	3.65 (R = Bu)
	10	4	(oep) ₂ ^[37, 72]			2.72	2.89	4.08
³¹ P NMR chemical shifts, δ [ppm]	11	4	Cl ₄ (PMe ₃) ₄			−8.3	−27.9 (Mo); 11.2 (W)	−7.3
	12	2	Cl ₄ (μ-Cl) ₂ (PP) ₂ ^[f]			≈10	≈−130 (Mo), ≈130 (W)	≈−10
diamagnetic anisotropy [Å ³] ^[h]	13	4	Cl ₄ (PP) ₂			−4.45 × 10 ^{−3}	−5.1 × 10 ^{−3}	−5.7 × 10 ^{−3}
¹ (δ ²) → ¹ (δδ*) [nm] ^[i]	14	4	Cl ₄ (PMe ₃) ₄			582	635	657
rotation barrier [kcal mol ^{−1}] ^[37]	15	4	(toep) ₂			10.8(1)	10.6(1)	12.9(1)
E _{1/2} ^{ox} (MM ^{4+/5+}) [V] ^[57]	16	4	(μ-mph) ₄	1.01	0.35	0.20	−0.16	−0.35
				(irrever.)				
E _{1/2} ^{ox} (MM ^{4+/3+}) [V] ^[57]	17	4	Cl ₄ (PR ₃) ₄			0.64 (R = Me)	0.42 (R = Me)	0.04 (R = Bu)
	18	4	Cl ₄ (PR ₃) ₄			−1.92 (R = Me)	−1.86 (R = Me)	−2.16 (R = Bu)
IP _δ [eV] ^[57]	19	4	(μ-mph) ₄	6.8	6.0	5.89	5.60	5.3
	20	4	Cl ₄ (PMe ₃) ₄			6.44	6.11	5.81
	21	4	(μ-O ₂ CCMe ₃) ₄			6.75	6.34	5.93
M [±] M bond strength [kcal mol ^{−1}] ^[10]	22	4	(μ-O ₂ CMe) ₄	≈45	≈55	≈75		

[a] Entries in bold indicate a non-monotonic trend. See Scheme 1 for structures of oep, toep, mph, and formulas of the bidentate phosphane ligands, electrochemical data versus the saturated calomel electrode (SCE); FBO = formal bond order. [b] The average of six, nine, and five homologues, respectively, containing both monodentate and bridging phosphane ligands.^[34–36, 61] [c] The W₂ homologue is not characterized; the value is the average W–W separation in five tetracarboxylate dimers. [d] [Mo₂(μ-SO₄)₄(H₂O)₂]^{3−},^[63] [MoW(μ-O₂CCMe₃)₄]^[21] [W₂Br₂(μ-O₂CCMe₃)₃(thf)₂].^[64] [e] For Mo₂⁶⁺, the average of four compounds; the W₂ congener has not been studied crystallographically; the value is the average W–W separation in two [W₂(μ-Cl)₃Cl₆]^{3−} ions,^[65, 66] which is likely to be longer than the W–W bond in [W₂(μ-Cl)₂(μ-H)Cl₆]^{3−} based on comparison of the corresponding Mo₂ derivatives. [f] The average M–M' separation in three derivatives (PP = dppe, dppm, dmpm).^[19] [g] See Figure 3 for metal–metal force constants in bismetalloporphyrins. [h] The average value of two ([Mo₂X₄(μ-dmpm)₄], X = Br, I),^[36] five ([MoWCl₄(μ-PP)₄], PP = dppe, dppm, dmpm, dmpe (two isomers)),^[61] and three ([W₂X₂(μ-dppm)₂], X = Cl, Br; and [W₂Cl₄(μ-dppe)₂])^[35] homologues, respectively. [i] See ref. [35] for more examples.

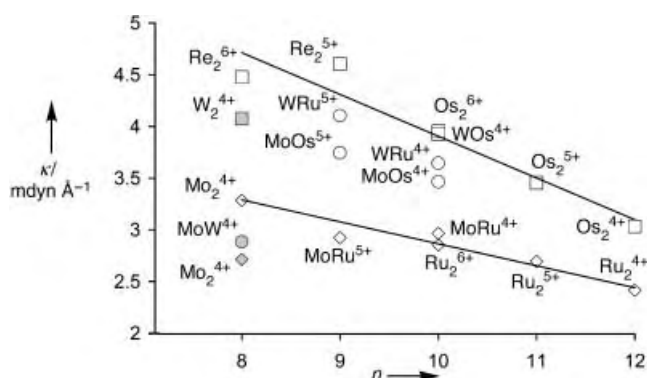


Figure 3. Correlation between the number of d electrons (*n*), and the force constant κ , of a 4d–4d ($\diamond$), 5d–5d ($\square$), or 4d–5d ($\circ$) metal–metal bonds in porphyrin-stabilized bimetallic cores. Solid lines are linear least-squares fits of the data for “same-series” bonds. The gray data points represent force constants that may be systematically underestimated.^[72]

The substantially different ³¹P NMR spectroscopy chemical shifts in [MoWCl₄(PMe₃)₄] and [MoWCl₄(μ-Cl)₂(PP)₄] relative to those in the homonuclear congeners (Table 3, entries 11, 12) is qualitatively consistent with the partial ionic character of the ¹(δ²) ground state,^[75] which results in a polar δ–Mo–W^{δ+} bond in a non-centersymmetric Mo–W core. Interestingly, although magnetic anisotropies of N=O and C=O bonds are substantially higher than those of the C=C bonds, anisotropies of the quadruple bonds (Table 3, entry 13), albeit the largest known, increase monotonically from Mo₂ to W₂.^[35]

The complex δ manifold of a (d–d)⁸ metal–metal bond (Figure 4) has been remarkably well studied in the Mo₂⁴⁺ core.^[12, 75, 76] In contrast, only the ¹(δ²)–¹(δδ*) gap (determined from UV/Vis spectra of [MoWCl₄(PR₃)₄] compounds,^[35] Table 3, entry 14) and the low limit on the ¹(δ²)–¹(d_{xy}d_{xy}) energy difference (δ barrier^[77, 78]) are known for a heteronuclear bond. The δ barrier and the (partially off-

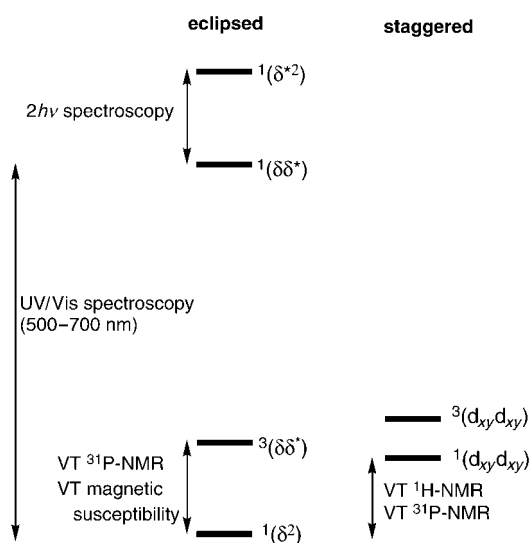


Figure 4. A qualitative diagram of the δ manifold of a (d–d)⁸ bimetallic core; the ionic states in the staggered conformer are not shown. Experimental methods used to study particular transitions are listed.

setting) difference in noncovalent ligand–ligand interactions in the eclipsed and staggered conformations of an unbridged (ML₄)₂ complex are mostly responsible for the barrier of rotation around a quadruple bond. The latter was measured in [MoW(toep)₂] by variable-temperature (VT) ¹H NMR spectroscopy. The ¹H NMR spectrum of a metal–metal-bonded bisporphyrin, wherein at least one of the macrocycles is of lower than fourfold symmetry and carries a group with sufficient magnetic anisotropy to affect the ¹H chemical shifts of the second porphyrin, is temperature-dependent (Figure 5).^[79] A standard dynamic NMR spectroscopic analysis yields the rotation barrier; its average value for several [Mo₂(por)₂] dimers (10.2(5) kcal mol^{−1})^[46, 79] is remarkably close to the δ barrier of the Mo⁴–Mo bond derived from magnetic studies (10.3(5) kcal mol^{−1}).^[78] However, the rotation barriers in the [MM'(toep)₂] series (M, M' = Mo, W) are so similar (Table 3, entry 15) that any trends in the δ barrier may be obscured by decreasing noncovalent interactions from the Mo₂⁴⁺ to W₂⁴⁺ derivatives.

The techniques that have been used to estimate the ¹(δ^2)–³($\delta\delta^*$) and ¹($\delta\delta^*$)–¹(δ^2) separations (Figure 4) in Mo₂⁴⁺ derivatives should be applicable to heterodinuclear cores, but this has not been done to date. The diradical ¹(δ^2)–³($\delta\delta^*$) gap (and the δ barrier) was estimated from VT ³¹P NMR spectroscopic studies of a series of [Mo₂X₄(PP)₂] dimers (X = Cl, Br, I), wherein the bridging phosphane ligands, PP, induce a torsion angle, χ , which varies from 0° in [Mo₂Cl₄(dmpm)₂] to

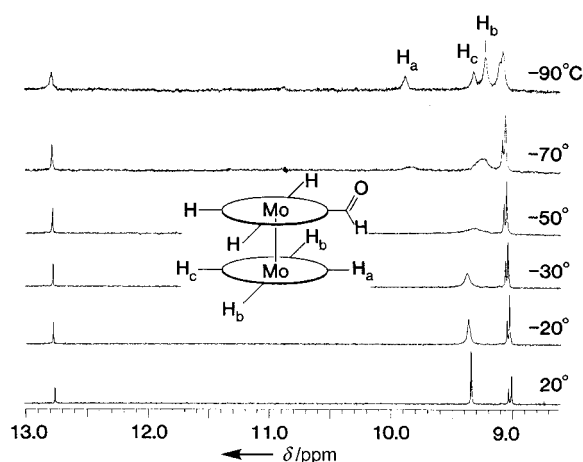


Figure 5. Variable temperature ¹H NMR spectra (300 MHz) of [(oep)-Mo⁴-Mo(oep-CHO)]. Adapted from ref. [79]; (Copyright: The National Academy of Sciences, USA).

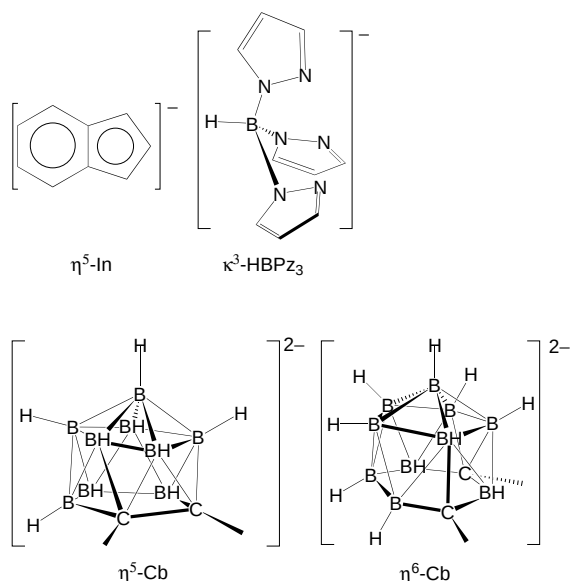
69° in [Mo₂Cl₄(dppp)₂] (Scheme 1).^[77, 78] As χ approaches 45°, the ¹(δ^2)–³($\delta\delta^*$) separation decreases so that temperature-dependent ¹(δ^2)–³($\delta\delta^*$) spin equilibrium induces paramagnetic shifts in ³¹P NMR resonance signals. The ¹(δ^2)–³($\delta\delta^*$) gap is estimated for each χ value by applying a standard contact-shift model. Extrapolation of these data to χ = 0° and χ = 45° yields ¹(δ^2)–³($\delta\delta^*$) and ¹($d_{xy}d_{xy}$)–³($d_{xy}d_{xy}$) separations, respectively. The difference between these two values ap-

Table 4. Representative examples of heterodinuclear transition-metal cores stabilized by π -acidic ligands.

Heterodinuclear core	<i>n</i> (Ve) ^[a]	Example ^[b]	M–M' separation [Å] ^[c]		
			listed example	saturated analogue	single bond
ZrRh	30	[Cp*Zr(μ-OCH ₂ Ph ₂ P) ₂ RhMe ₂] ^[86]	2.444(1)		3.08
CrMn	30	[C ₆ Me ₆ Cr(μ-CO) ₃ MnCP*] ^[87]			
MoW	32	[Cp(PMe ₃)Mo(μ-CR)W(CO) ₂ (η ⁶ -Cb)], ^[88] [(CO)(η ⁵ -In)Mo(μ-L)W(CO) ₂ Cb] (L = PPh ₂ , ^[89] CR ^[90])	2.702(1)	2.708(1), 2.657(2)	2.92
MoRu	32	[Cp(CO)Mo(μ-Cl)(μ-CO)Ru(CO)(PPh ₃) ₂] ^[91]			
MoCo , ^[d] WCo	32	[(η ⁶ -Cb)(CO) ₂ M(μ-CR)Co(η ⁴ -C ₄ Me ₄)] ^[92]	2.540(1)		2.73
WCo	30	[(η ⁴ -C ₄ Me ₄)Co(μ-CO) ₃ WCP] ^[93]	2.356		2.71
	32	[Cp(O=)W(μ-R≡COMe)(μ-PPh ₂)Co(CO)(PPh ₃ H)], [Cp(OH)W(μ-CR)(μ-PPh ₂)Co(CO) ₂ (PPh ₃ H)], [CpW(μ-CR)(μ-PPh ₂)Co(CO) ₂] ^[96]	2.612(1)	2.758(1) ^[95]	2.90
MoRh , WRh ^[d,e]	30	[Cp(CO)M(μ-CO) ₂ Rh(PPh ₃) ₂] ^[94]	2.588(1)	2.9212(7)	2.84
WFe ^[e]	32	[(CO) ₃ Fe(μ-L)W(CO) ₂ L'] (L' = Cp, L = C(CO)(SiPh ₃), ^[97] CR; L' = pz ₃ BH, L = PPh ₂ , CR) [(CO) ₂ Fe(μ-CR)(μ-CO)(μ-dmpm)W(pz ₃ BH)] ^[95, 98]	2.516(1)–2.658(2)		2.79
WRu ^[e,f]	30	[(η ⁵ -EtMe ₄ C ₅)W(μ-CO) ₃ RuCP*] ^[99]	2.410(1)		2.90
WRh	30	[CpLW(μ-CO) ₂ Rh(PPh ₃) ₂] (L = CO, C ₂ H ₄) ^[98]	2.587(1)		2.82
	32	[(η ⁵ -Cb)(CO)W(μ-CO)(μ-CR)Rh(PPh ₃) ₂] ^[100]	2.681(1), 2.662(2)	2.796(1) ^[101]	2.82
WIr ^[e]	32	[(η ⁵ -Cb)(CO) ₂ W(μ-CR)IrP ₂] (P = monodentate phosphane) ^[102]	2.590(1)	2.876(1) ^[103]	2.83
WPt ^[e]	28	[(η ⁵ -CbR)W(μ-CO) ₂ Pt(PEt ₃) ₂] ^[102]	2.602(1)	2.843(2)	2.78
	30	[Cp(C ₂ H ₄)W(μ-CO) ₂ Pt(PEt ₃) ₂] ⁺ ^[104]	2.602(1)	2.795(1)	
MnFe	30	[(η ⁴ -C ₄ Me ₄)Fe(μ-CO) ₃ MnCP*] ^[87]			
MnRh	30	[PPh ₃ (CO) ₂ Mn(μ-CO) ₂ Rh(PPh ₃) ₂] ^[94]			
FeCo, FeRh, FeIr	32	[(η ⁶ -C ₆ H ₆)Fe(μ-CO) ₂ MCp*] ^[105]			
ReRh, ReIr ^[d]	32	[(PCy ₂) ₂ Re(μ-PCy ₂) ₂ ML ₂] (L = ½ 1,5-cod, PMe ₃) ^[106]	2.6573(5)		2.92
ReRh	30	[CpHRe(μ-CO) ₂ Rh(PPh ₃) ₂] ^[106]	ca. 2.54		2.90
CoRh	32	[Cp*Co(μ-CO)(μ-L)RhCP*] (L = CO, CH ₂) ^[107]	2.4040(5)		2.60
CoIr	32	[LCo(μ-CO) ₂ IrL'] (L, L' = Cp, Cp*) ^[108]	2.45(2)	2.624(1)	2.66
RhIr	32	[Cp*Rh(μ-CO) ₂ IrCP*] ^[108]			

[a] The number of valence electrons in the M–M' core; *n* = 34 corresponds to an electronically saturated dinuclear organometallic complex with a single M–M' bond if both metal centers satisfy the 18-electron rule. [b] Cp = C₅H₅[−]; Cp' = C₅H₄Me[−]; Cp* = C₅Me₅[−]; R = −C₆H₄(*p*-Me); see Scheme 4 for chemical structures of In, HBPz₃, and Cb. [c] The “saturated analogue” is a complex derived from the corresponding unsaturated compound by ligand addition; the “average single” bond refers to the M–M' separation averaged over *all* structures designated as having a single M–M' bond in CCSD (the October 2001 release). [d] A MM' core in bold indicates the core was studied crystallographically. [e] See ref. [102] for additional examples. [f] See ref. [109] for additional examples.

proximates to the δ barrier. Notably, even at $\chi = 45^\circ$, where the $d_{xy}-d_{xy}$ overlap is annihilated, $^1(d_{xy}d_{xy})$ remains lower than $^3(d_{xy}d_{xy})$ because of configuration interactions.^[80] A series of MoW^{4+} derivatives with varying values of χ , which would be necessary to extend this method to heterodinuclear metal–metal bonds may be obtained from $[\text{MoWCl}_4(\text{PMe}_3)_4]$ by



Scheme 4. Select polyhapto (polydentate) ligands used to stabilize unsaturated heterodinuclear cores in organometallic complexes.

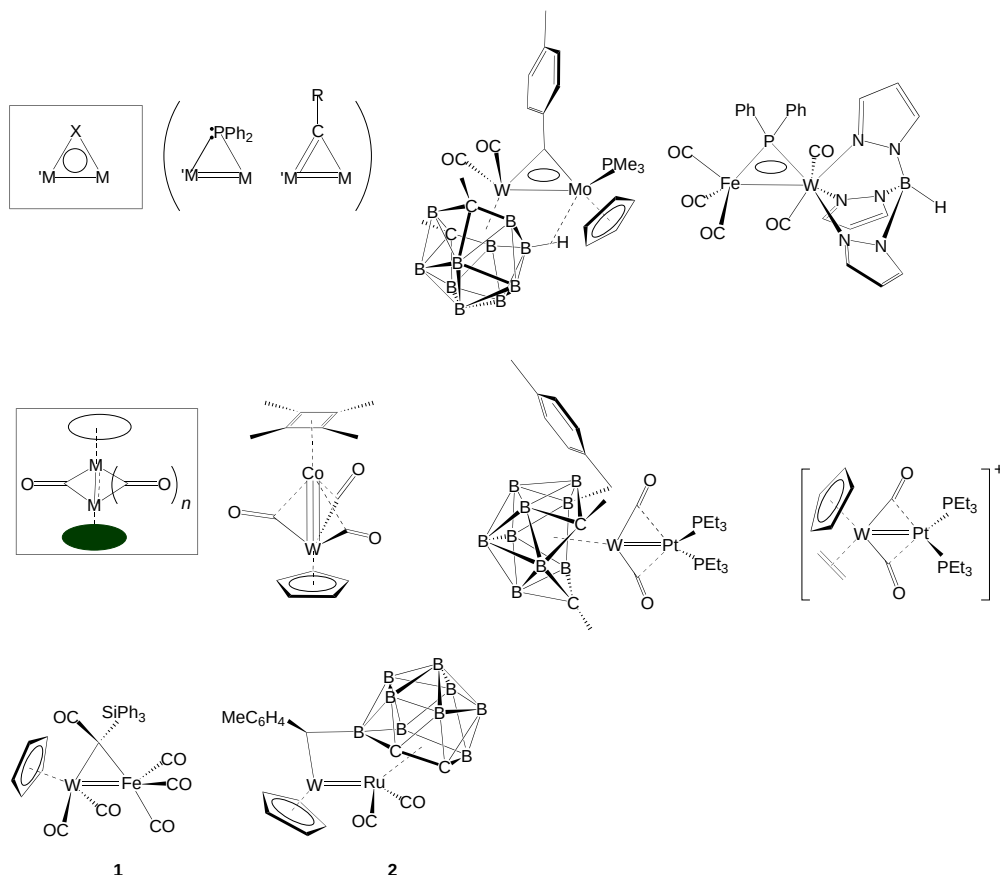
using the well-developed phosphane-substitution method.^[35, 36]

The ionic ($^1(\delta^{*2})$, $^1(\delta\delta^{*})$) states of the Mo_2^{4+} core have been studied by two photon spectroscopy (Figure 4).^[76] Induced fluorescence from the $^1(\delta\delta^{*})$ state is observed upon two-photon $^1(\delta^2 \rightarrow \delta^{*2})$ excitation followed by rapid nonradiative decay to the $^1(\delta\delta^{*})$ state. The $^1(\delta\delta^{*})-^1(\delta^{*2})$ gap (4800 cm^{-1}), estimated from the difference in the $^1(\delta^2 \rightarrow \delta\delta^{*})$ and $^1(\delta^2 \rightarrow \delta^{*2})$ transition maxima, is comparable to the $^1(\delta^2)-^3(\delta\delta^{*})$ gap (4840 cm^{-1}) measured by VT ^{31}P NMR spectroscopy.

Finally, the difference between the energies of the electron in a singly occupied δ and δ^{*} orbitals (ΔW), which is indicative of the strength of the δ interaction, is given by the $^2(\delta \rightarrow \delta^{*})$ transition frequency in optical absorption spectra of $(d-d)^{7/9}$ dinuclear compounds. The latter should be easily accessible by one-electron oxidation or reduction of corresponding quadruple-bonded heterodinuclear complexes. Unfortunately, optical methods are not easily applicable to metalloporphyrins, as their absorption spectra are dominated by the porphyrin chromophore.

2.4. Reactivity

Reactivity of heterodinuclear complexes has been little studied, and again most available data are on Group 6 metals. The susceptibility of MoW^{4+} and MoCr^{4+} cores toward



Scheme 5. Structures of representative unsaturated heterodinuclear organometallic compounds arranged by structural type. In carboranes only those B-bound H atoms that participate in agostic interactions are shown.

oxidative and nucleophilic additions appears intermediate between that of the more robust Mo_2^{4+} and more reactive Cr_2^{4+} and W_2^{4+} congeners. For example, unlike W_2^{4+} cores, the Mo_2^{4+} , and MoW^{4+} analogues are not oxidized by acetic acid. On the other hand, the $\text{Cr}^{\text{IV}}\text{--Mo}$ bond is readily cleaved by Cl^- ions^[81] and acetonitrile^[28] (in acidic media), to yield mononuclear Cr species and Mo_2 dimers. Likewise, $[\text{MWCl}_4\text{P}_4]$ but not the Mo_2 analogue, is oxidized by CH_2Cl_2 (to $[\text{MWCl}_6\text{P}_4]$, $\text{M}=\text{Mo}$ or W ; $\text{P}=\text{mono-}$ or $\text{bidentate phosphanes}$)^[19] and oxidative addition of HCl to the MoW^{4+} and W_2^{4+} cores occurs at significantly milder conditions than to the Mo_2^{4+} core.^[20, 82]

In $[\text{CrMo}(\mu\text{-O}_2\text{CMe})_4]$ the modest affinity of the Cr^{II} center to axial ligation contrasts dramatically with that of $[\text{Cr}_2(\mu\text{-O}_2\text{CMe})_4]$, which can not be isolated in the condensed phase without axial ligands or without strong intermolecular association through carbonyl oxygen atoms.^[10] Higher covalency of the Mo--Cr bond (Section 2.1.) was suggested^[51] to account for this difference. In $[\text{MoWCl}_4(\text{PMePh}_2)_4]$ Mo-bound phosphanes are more labile, as could be expected, thereby allowing synthesis of a heteroleptic heterodinuclear complex, $[(\text{PMe}_3)_2\text{Cl}_2\text{--MoWCl}_2\text{PMePh}_2)_2]$.^[34] Finally, dimerization of MoW^{4+} moieties yields approximately equimolar amounts of both isomers of a rectangular Mo_2W_2 core, which suggests the absence of preference for formation of homo- over heterometallic bonds.^[83]

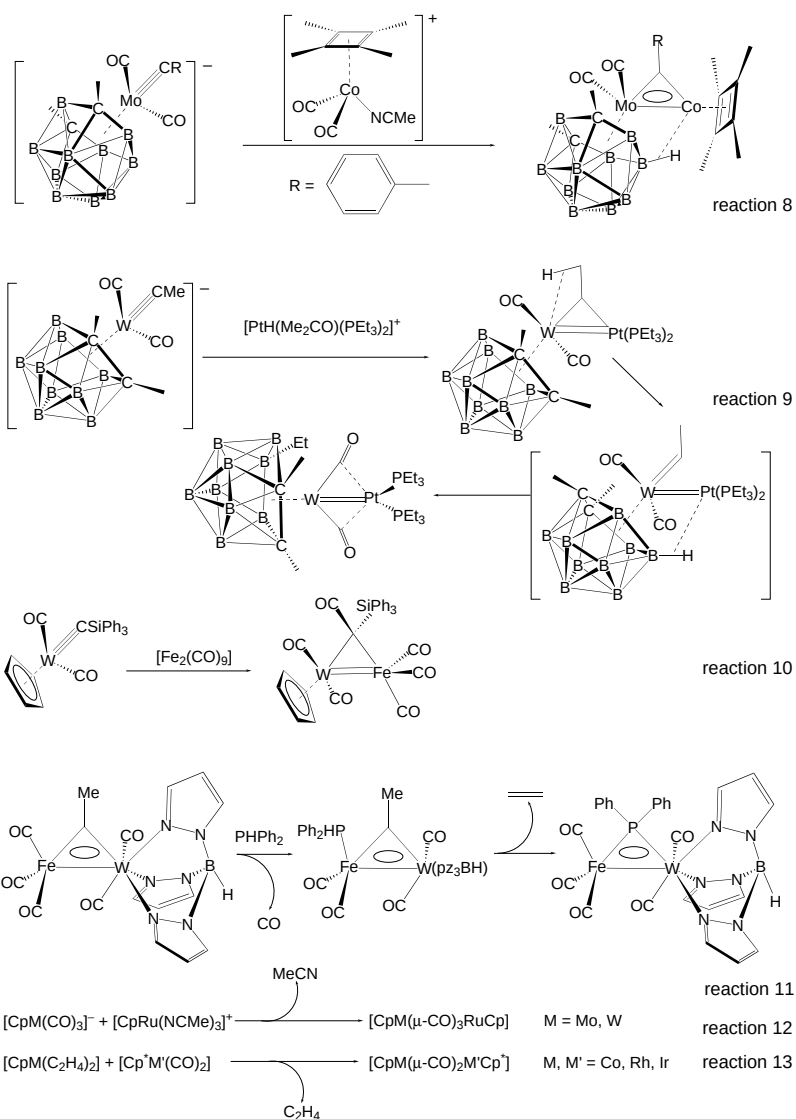
3. Electronically Unsaturated Heterodinuclear Organometallic Species

In a dimetallic core stabilized by π -acidic ligands (e.g. CO), the metal–metal bonding, which is significantly affected by extensive π -acceptor–ligand–metal interactions,^[16] does not necessarily lead to concentration of the electron density in the immediate space between two metal centers. These interactions do not necessarily lead to concentration of the electron density in the immediate space between two metal atoms. Identification of specific metal–metal MOs is often not possible or productive and assignment of a metal–metal bond order often relies on the assumption that at least one metal center should satisfy the 18-electron rule. The situation is even more ambiguous if the 18-electron configuration is not obligatory for either metal (e.g. those in Groups 4, 5, 8, and 9). While it is debatable if the metal–metal interactions in unsaturated dinuclear organometallic compounds (i.e. those with 32 or fewer valence electrons) should be viewed as multiple metal–metal bonds,^[16, 84] such complexes manifest structures and reactivities which are related to those of dinuclear complexes with Werner-type ligands.

A recent explosion of interest in heterodinuclear organometallic compounds^[14, 85] is motivated in large part by the promises of substrate

activation by the bimetallic species, particularly by reactions based on the dissymmetry of a heterodinuclear core. Although most such complexes are electronically saturated, unsaturated heteronuclear organometallic species are particularly attractive as their greater reactivity is not dependent on ligand or dimer dissociation to create reaction sites in the coordination spheres of the metal center(s). Such complexes have also been studied as precursors for mixed-metal clusters^[85] and models of materials with strong metal–support interactions (SMSI).

Unsaturated heterodinuclear organometallic complexes are significantly more numerous than their counterparts without π -acidic ligands and such complexes are known for most transition metals (Table 4).^[86–109] Although their coordination spheres may be made up of a variety of donor molecules, most contain at least one polyhapto (or chelating) ligand (Scheme 4). These ligands sterically disfavor a nucleophilic attack on, or oligomerization of, unsaturated metal cores thereby stabilizing the complexes.^[110]



Scheme 6. Representative syntheses of unsaturated organometallic heterodinuclear complexes. In carboranes, only those B-bound H atoms that participate in agostic interactions are shown.

The dominant structural motifs (boxed structures, Scheme 5) are based on 1) a trinuclear core resulting from a metal–metal bond bridged by either an alkylidyne or a phosphide group and 2) on the $[\text{Cp}_2\text{M}_2(\text{CO})_x]$ ($\text{Cp} = \text{C}_5\text{H}_5^-$) structure,^[16] although heterodimers often contain a single Cp-related ligand. Other structures are less common (compounds **1** and **2**, Scheme 5).

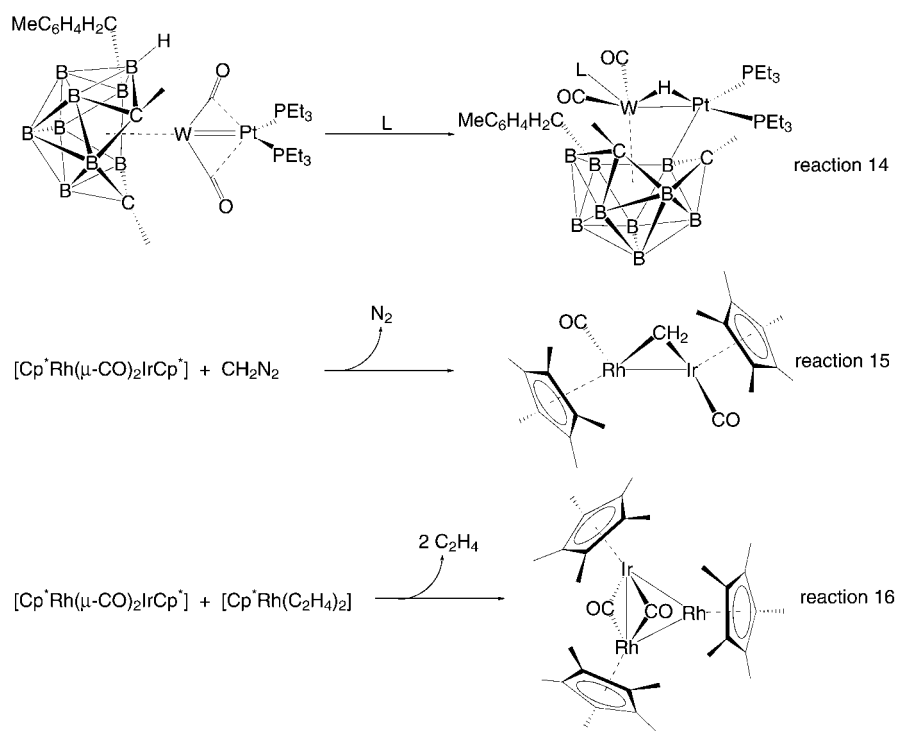
The dimetallocyclopropene-type complexes, the synthesis and chemistry of which has been developed by F. G. A. Stone and co-workers,^[102] have been obtained by addition of a metal alkylidyne to a mononuclear complex with labile ligand(s), occasionally followed by other transformations (Scheme 6, Reactions 8–10). Some μ -alkylidyne complexes can be converted into μ -phosphide analogues (Reaction 11). Syntheses of other heterodimers include reactions between $[\text{LM}(\text{CO})_x]^-$ ions (L is a ligand in Scheme 4) and labile cationic complexes and recombination of unsaturated mononuclear fragments generated in situ (Reactions 12 and 13, respectively).

The intermetal distances in unsaturated organometallic compounds are significantly shorter than those in structurally related saturated MM' cores (Table 4). Although the latter often contain an additional ligand, which increases unfavorable noncovalent interactions around the metal, the observed metal–metal-bond elongation is significantly greater than could be expected from the more congested arrangement alone. This effect indicates that electronic saturation leads to the population of MOs with $\text{M}-\text{M}'$ antibonding character.^[16]

The reactivity of unsaturated heterodinuclear organometallic compounds (Scheme 7) is often consistent with the presence of multiply bonded MM' cores. This reactivity includes inertness to substrates that react readily with mononuclear metal centers with half the valence electrons of the dinuclear core. For example, neither 30-electron $[\text{CpHRe}(\mu\text{-CO})_2\text{Rh}(\text{PPh}_3)_2]$ nor 32-electron $[\text{Cp}(\text{CO})_2\text{Mo}(\mu\text{-CO})(\mu\text{-Cl})\text{Ru}(\text{CO})(\text{PPh}_3)_2]$ reacts with H_2 ,^[91, 106] even though H_2 readily adds to mononuclear 16-electron Rh and Ru centers. In contrast, in certain carborane-stabilized complexes coordination of an exogenous ligand to one metal center induces intramolecular B–H activation at the other metal center (Reaction 14, Scheme 7). In addition, ligands, such as SO_2 , CH_2 (from CH_2N_2), and metal fragments isolobal with CH_2 (e.g. RhCp^* ; $\text{Cp}^* = \text{C}_5\text{Me}_5^-$) add readily across MM' bonds (Reactions 15 and 16).

4. Summary and Outlook

Stabilization of heterodimetallic cores by Werner-type ligands yields complexes wherein the ligands do not signifi-



Scheme 7. Representative reactions of unsaturated heterodinuclear organometallic complexes. In the carborane only the B–H unit that adds to Pt is shown.

cantly perturb the metal–metal bonding. These complexes provide an opportunity to probe fundamental issues of bonding between transition metals and to discover new types of chemical bonds. An intriguing issue is the origin of the “inverted” ground-state configuration of Group 6 and 8 metal–metal cores (e.g. $\sigma^2\pi^4\delta^2\pi^{*2}$ in MoRu^{4+} compared to $\sigma^2\pi^4(\delta^{\text{nb}})^4$ in the isoelectronic isostructural Ru_2^{6+} derivatives). More systematic studies of the δ MOs in MoW^{4+} cores, accessible with existing synthetic and physical techniques, may reveal interesting differences with the well-studied Mo_2^{4+} δ manifold. However, the lack of preparative methodologies remains the major impediment to systematic studies of multiple bonds between different transition-metal ions. Only solid-state high-vacuum pyrolysis of metalloporphyrins is applicable to a broad range of transition metals. In contrast, with the exception of $[\text{Ti}(\mu\text{-OCMe}_2\text{CH}_2\text{PPh}_2)_3\text{Rh}]$, no heterodinuclear species in non-porphyrin environments are known outside Group 6.

Metal–metal bonding in unsaturated dinuclear organometallic species is significantly attenuated by π -acceptor-ligand–metal interactions. These complexes are relatively easily accessible and include pairs of almost every transition-metal atom, thereby comprising a pool of compounds which can be searched for novel reactivities. Such complexes have a potential use as catalysts wherein one metal center serves as a reservoir of reducing equivalents for multielectron processes, such as small molecule activation.^[111] A number of processes, if performed by a mononuclear catalyst, would require unreasonably large changes in its oxidation state and thus are unlikely to be catalytic. Unsaturated heterodimetallic compounds may also be synthetically advantageous precursors to higher-nuclearity mixed-metal clusters.

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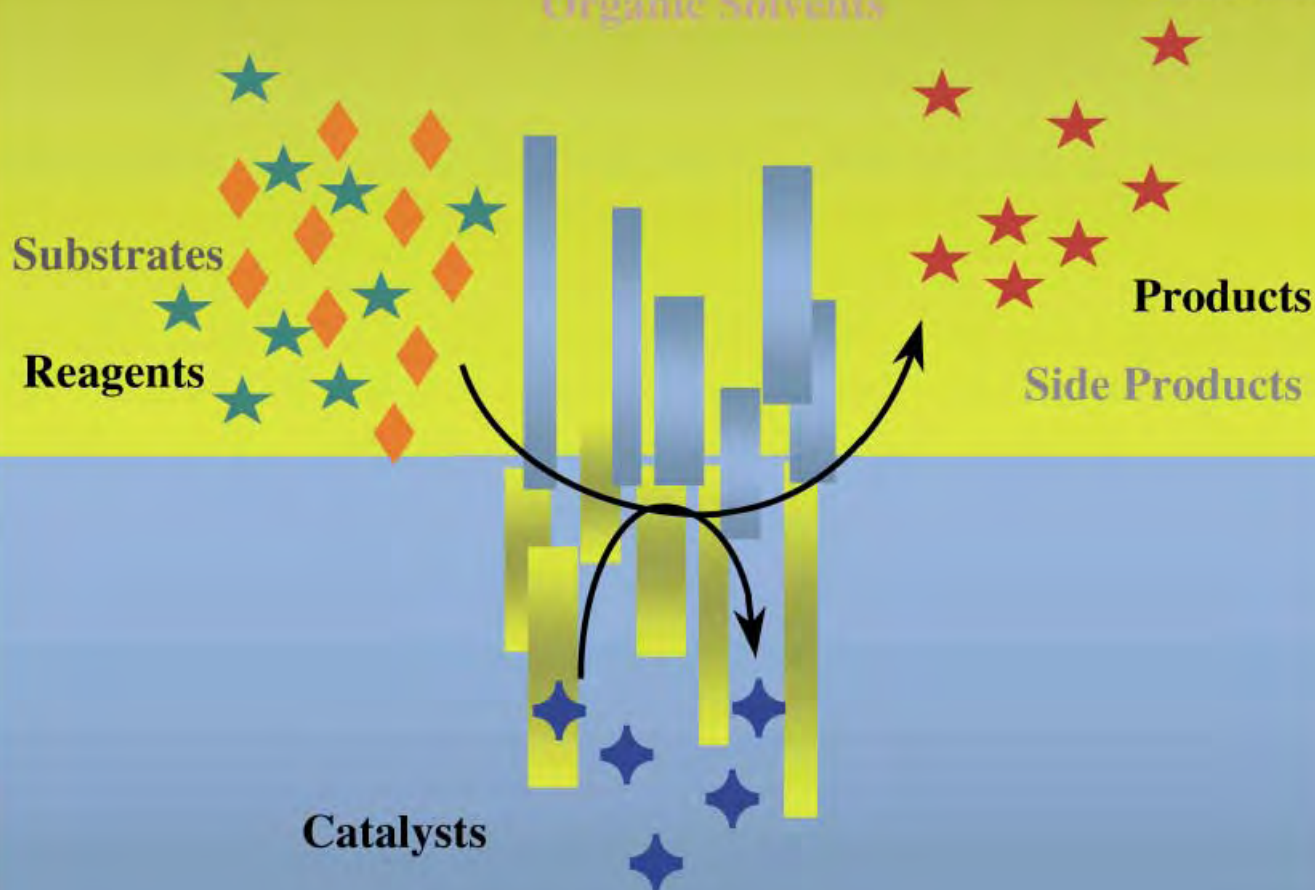
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Modern Separation Techniques for the Efficient Workup in Organic Synthesis

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The shift of paradigm in combinatorial chemistry, from large compound libraries (of mixtures) on a small scale towards defined compound libraries where each compound is prepared in an individual well, has stimulated the search for alternative separation approaches. The key to a rapid and efficient synthesis is not only the parallel arrangement of reactions, but simple work-up procedures so as to circumvent time-consuming and laborious purification steps. During the initial development stages of combinatorial synthesis it was believed that rational synthesis of individual compounds could only be achieved by solid-phase strategies. However, there are a number of problems in solid-phase chemistry: most notably there is the need for a suitable linker unit, the limitation of the reaction conditions to certain solvents and reagents, and the heterogeneous reaction conditions.

Further disadvantages are: the moderate loading capacities of the polymeric support and the limited stability of the solid support. In the last few years several new separation techniques have been developed. Depending on the chemical problem or the class of compounds to be prepared, one can choose from a whole array of different approaches. Most of these modern separation approaches rely on solution-phase chemistry, even though some of them use solid-phase resins as tools (for example, as scavengers). Several of these separation techniques are based on liquid–liquid phase separation, including ionic liquids, fluorous phases, and supercritical solvents. Besides being benign with respect to their environmental aspects, they also show a number of advantages with respect to the work-up procedures of organic reactions as well as simplicity in the isolation of products. Another

set of separation strategies involves polymeric supports (for example, as scavengers or for cyclative cleavage), either as solid phases or as soluble polymeric supports. In contrast to solid-phase resins, soluble polymeric supports allow reactions to be performed under homogeneous conditions, which can be an important factor in catalysis. At the same time, a whole set of techniques has been developed for the separation of these soluble polymeric supports from small target molecules. Finally, miscellaneous separation techniques, such as phase-switchable tags for precipitation by chemical modification or magnetic beads, can accelerate the separation of compounds in a parallel format.

Keywords: biphasic catalysis • combinatorial chemistry • parallel synthesis • polymeric supports • separation techniques

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1. Introduction

Combinatorial synthesis^[1, 2] is regarded as one of the key disciplines for providing the constant supply of chemical compounds that may be monitored for their biological activity on the vastly increasing number of biological targets. Together with high-throughput screening formats and efficient data management this will undoubtedly lead to an acceleration in the process of drug discovery. The initial focus in combinatorial chemistry was on the rapid synthesis of highly complex mixtures comprising minute amounts of individual compounds. This strategy became prominent because of the ingenious split-and-combine approach and tagging strategies

to simplify deconvolution once activity on a biological target had been observed. Although this strategy offers a minimum synthetic effort per prepared compound it has been largely substituted by the preparation of individual compounds in amounts of 1–50 mg by the use of parallel synthesis. One reason for this shift of paradigm was the tedious deconvolution process after screening, which resulted quite often in false

positives. The individually pure compounds prepared by parallel synthesis can be characterized and stored in easily accessible repositories which contain sets of highly diverse compounds. As a consequence of the high purity of the compounds the screening data are reliable.

During the initial development stages of combinatorial synthesis—possibly biased by the straightforward solid-phase

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From left to right: C. Markert, S. Roller, W. Bannwarth, R. Haag, A. Hebel, C. C. Tzschucke

Willi Bannwarth was born in 1947 in Bad Säckingen and started his career as a laboratory technician and chemical engineer. Afterwards he studied chemistry at the Universität Münster, where he wrote his Diploma thesis on anionic cycloadditions while working with Prof. T. Kauffmann. After his doctoral studies on the synthesis of pteridine nucleotides with Prof. W. Pfeleiderer, Konstanz, he was a postdoctoral fellow with Sir A. Battersby in Cambridge (UK). From 1979 until 1996 he worked at Roche Basel (Switzerland). In 1992 he finished his Habilitation in organic chemistry at the Universität Konstanz. From 1996 until 1999 he worked at Byk Gulden Pharmaceuticals in Konstanz, where he established a “new technologies” section. Since 1999 he has been professor for organic chemistry at the Universität Freiburg. His research interests are bioorganic and combinatorial chemistry.

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synthesis of oligonucleotides and peptides—it was believed that rational synthesis of individual compounds could only be achieved by solid-phase strategies. The main advantage of solid-phase synthesis is that larger excesses of reagents may be applied, thereby driving the reactions to completion. Moreover, the excesses of reagents can be removed after the reaction by simple filtration procedures, thus avoiding time-consuming purification steps. Besides the need for two additional steps involved in chemistry on solid supports, namely the attachment of the starting material and the release of the product, there are a number of difficulties involved in solid-phase chemistry. Most notably there is the need for a suitable linker unit, the limitation of the reaction conditions to certain solvents and reagents, the heterogeneous reaction conditions, the moderate loading capacities (typically $<1.5 \text{ mmol g}^{-1}$), the stability of the solid support, the cumbersome monitoring of the reaction, and the identification of the compounds attached to the solid support. A number of alternative solution approaches and the use of solid-phase-bound reagents and scavengers have emerged because of these difficulties.

The key to a rapid and efficient synthesis is not only the parallel arrangement of reactions, but easy to perform work-up procedures that will circumvent time-consuming and laborious purification steps so that they can be carried out in a parallel fashion. There is no general principle for achieving this goal, but during the last few years several new techniques have been developed. Depending on the chemical problem or the class of compounds to be prepared, one can choose from a whole array of different approaches. In this review we have summarized and compared the latest (since ca. 1999) achievements in this area since the previous review by Curran in 1998.^[3] We have also focused on separation techniques which are simple enough that the work-up can be performed in a parallel format and might be suitable for process automation.

2. Liquid–Liquid-Phase Separation

The majority of chemical reactions are carried out in an organic solvent. These solvents can have detrimental effects on the environment and human health as a result of inflammability, volatility, and toxicity. Hence, tremendous efforts have been made during the last decade to replace hazardous organic solvents by alternative reaction media. These encompass water, supercritical media (especially supercritical CO_2), perfluorinated solvents, and ionic liquids. Besides being benign with respect to their environmental aspects, they also show a number of advantages with respect to work-up procedures used in organic reactions as well as simplicity of product isolation.

Ionic liquids and perfluorinated solvents are not miscible with a number of organic solvents. Such combinations can be

used to provide biphasic systems for catalysis. In such systems the transition-metal catalyst resides in the second phase (ionic liquid or fluoruous phase) whereas the products and starting materials are dissolved in the organic phase. The reactions are carried out under vigorous stirring and/or heating. After the reaction, the layers are reformed and separated by decantation and/or extraction (Figure 1). The catalyst in the ionic

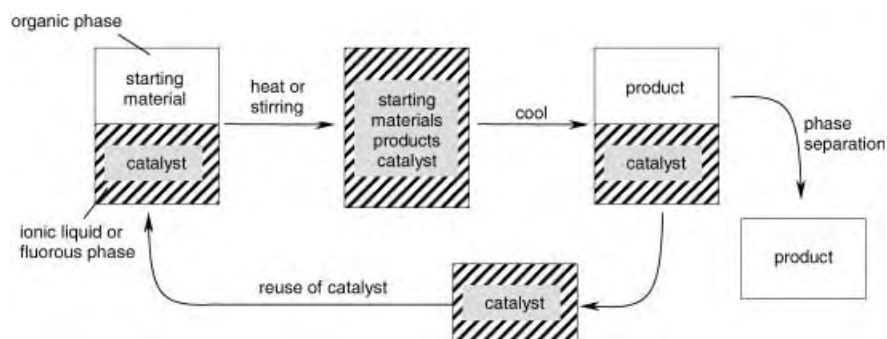


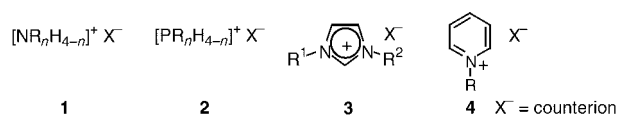
Figure 1. Principle of a simple work-up procedure when using fluoruous-phase chemistry or ionic liquids.

liquid or fluoruous phase can be reused. The only prerequisite is that the starting materials have to be at least partially soluble in the second phase to guarantee respectable reaction rates. This principle has been demonstrated for a number of catalytic processes. For many applications of reactions in ionic liquids, where the starting material and the product represent liquids themselves, there is no need to add an organic solvent to create the biphasic system. Alternatively, the reaction can be carried out in the ionic liquid and after the reaction it is extracted with an organic solvent to isolate the products. If the products are volatile enough they can be distilled directly from the ionic liquid. In both cases the catalyst remains in the ionic liquid and can be reused. Examples of parallelization and automation in the case of liquid–liquid-phase separation are rare; however, many robotic systems are now able to separate liquid phases which will enhance automation of these techniques in the future.

2.1. Ionic Liquids

Ionic liquids represent salts with a low melting point ($<100^\circ\text{C}$). Their vapor pressure is negligible below their decomposition temperatures and, thus, no ionic liquid used as a reaction media is lost by evaporation. Some of the ionic liquids show liquid behavior over a range of several hundred degrees centigrade and thus they can be employed over a wide temperature range.^[4–8]

The common classes of ionic liquids comprise: Alkyl ammonium salts (**1**), alkylphosphonium salts (**2**), N,N' -dialkyl



imidazolium salts (**3**), and *N*-alkyl pyridinium salts (**4**), of which the *N,N'*-dialkyl imidazolium salts have attracted particular attention since they are easily prepared and are liquid over a wide range of temperatures.

Ionic liquids have been used as solvents for numerous organic and inorganic reactions. The physical and chemical properties vary depending on the combination of cation and anion. Hence, their properties can be modulated and adapted to the chemical reaction for which the ionic liquid is envisaged by varying the anions and cations. Ionic liquids composed of weakly coordinating ions represent highly polar, yet non-coordinating solvents. The solvent properties are largely determined by their ability to act as a hydrogen-bond donor or acceptor and the degree of delocalization of the anionic charge. Their ability to form hydrogen bridges also has an influence on the viscosity of the ionic liquids. A low tendency to form hydrogen bridges occurs in parallel with low viscosity. Variation of the chain length of the alkyl substituents on the cation or anion allows the lipophilicity to be adjusted. Increased chain lengths lead to higher lipophilicity.

A number of ionic liquids are air and moisture stable and are relatively easy to handle. Some of them, for example, most of the imidazolium and ammonium salts, are hygroscopic and reactions involving these ionic liquids are best carried out under an inert atmosphere. The nature of the pertinent anion not only has an effect on the melting behavior (Table 1) and the handling properties, it also affects the stability as well as the acidity of the ionic liquid.

Table 1. Effect of the anion on the melting point of [EMIM]⁺X[−].^[a]

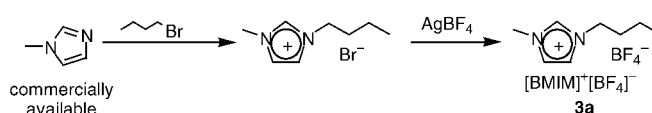
[X] [−]	M.p. [°C]
Cl [−]	87
NO ₃ [−]	55
AlCl ₄ [−]	7
BF ₄ [−]	6
CF ₃ SO ₃ [−]	−9

[a] EMIM = 1-ethyl-3-methylimidazolium.

Salts with NO₃[−], PhSO₃[−], and N(SO₂CF₃)₂[−] counterions are air and moisture stable, while AlCl₄[−] salts are hygroscopic and moisture sensitive. Salts with Al₂Cl₇[−] counterions show acidic behavior which can have a beneficial effect on activation the catalysts used in ionic liquids. Recently, it was reported that the combination of dicyanamide (dca) anions with cations of the type **1**, **3**, and **4** gave ionic liquids with low viscosity and water miscibility. Furthermore, these ionic liquids show donor characteristics as a consequence of the ligand properties of the anion.^[9]

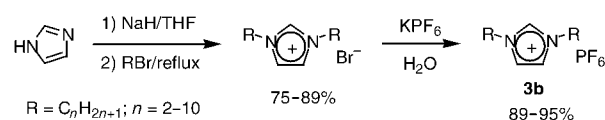
2.1.1. Synthesis of Ionic Liquids

Ionic liquids are prepared starting from the corresponding amine or phosphane in a two-step procedure. Alkylation leads to quarternization of the nitrogen or the phosphorus atom, respectively. This process is usually followed by anion metathesis with an alkali or ammonium salt of the desired anion. This principle is illustrated in Scheme 1 for the preparation of [BMIM]⁺[BF₄][−] (**3a**, BMIM = 1-*n*-butyl-3-methylimidazoli-



Scheme 1. Preparation of [BMIM]⁺[BF₄][−] (**3a**).

um).^[10, 11] Alternatively, the anion exchange can be achieved by using an ion-exchange resin. If after the alkylation step the anion is a halogenide, it can also react with a Lewis acid to create the desired anion (for example, AlCl₄[−]). It has been postulated for a long time that the unsymmetrical nature of the cation plays a major role in the low melting point of imidazolium-derived ionic liquids. Recently it was demonstrated that symmetrical imidazolium salts such as **3b** are also room-temperature ionic liquids (Scheme 2).^[12]



Scheme 2. Synthesis of the C₂-symmetrical ionic liquid **3b**.

High purity of ionic liquids is of prime importance for achieving reliable synthesis in these media. Therefore, all the steps involved in their preparation have to proceed with high efficiency, since purification after synthesis is extremely tedious. Some of the ionic liquids, especially the ones with imidazolium as the cation, are commercially available. Their price is still very high, which to a certain extent prevents their application for routine synthesis.

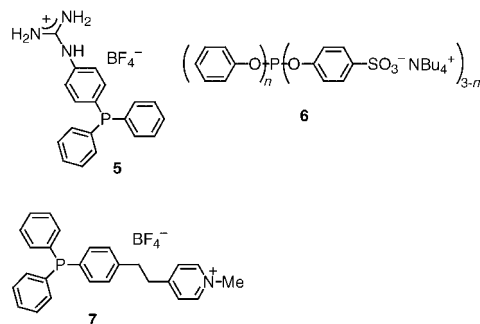
2.1.2. Work-Up and Isolation Procedures

The beneficial effects of ionic liquids in regard to environmental aspects that result from their nonvolatility has already been alluded to in Section 2.1. In addition to that, ionic liquids allow for simple work-up procedures and straightforward isolation protocols for products, particularly with respect to transition-metal catalysis.

Ionic liquids with noncoordinating anions represent highly polar organic solvents that dissolve polar transition-metal complexes without usually affecting their properties. In general, they allow immobilization of the complex in the ionic liquid without modification of the ligands. In a number of cases, ionic liquids have a beneficial effect on the catalytic reaction, which proceeds more efficiently than in organic solvents. Under these circumstances the ionic liquid acts not only as a solvent but also as a co-catalyst. The reason for this may be a better stabilization of the transition state or activation of the catalyst (as a result of the Lewis acidity of the ionic liquid)^[13] or the formation of carbene-like ligand structures.^[14]

In applications where the starting material and the product represent liquids themselves, there is no need to add an organic solvent to create the biphasic system. This was demonstrated for the hydrogenation of olefins.^[10, 15] Alternatively, the reaction can be carried out in the ionic liquid and

the product is isolated by extraction with an organic solvent. The products can be distilled directly from the ionic liquid if they are sufficiently volatile. In both cases the catalyst remains in the ionic liquid and can be reused. In some examples a small leaching of the catalyst out of the ionic liquid into the organic layer was observed. This effect can be minimized by modification of the ligands with ionic groups as shown in the P^{III} ligands **5**–**7**.^[16]



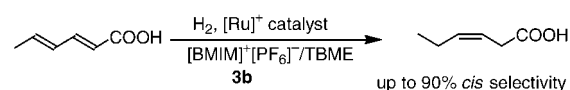
Ionic liquids as reaction media allow for parallel arrangements of reactions followed by straightforward isolation of the products and hence for the rapid synthesis of compounds. So far, this potential has not yet been exploited. This is because of the still limited number of types of reactions which have been carried out in ionic liquids and because of the relatively high costs involved.

2.1.3. Homogeneous Catalytic Reactions in Ionic Liquids

2.1.3.1. Hydrogenations

There are a number of catalysts available for homogeneous hydrogenations. In the first reported examples of homogeneous hydrogenations involving ionic liquids the starting material and the product represented highly lipophilic liquids (for example, hydrogenation of hexene or cyclohexene) in which the polar catalyst was immobilized without any modification in the ionic liquid and no additional organic solvents were necessary for the isolation of the product. The solubility of hydrogen in ionic liquids seems to be high enough to obtain respectable reaction rates.^[10, 15]

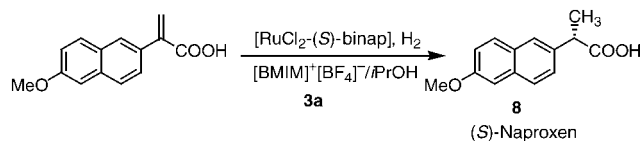
Recently, an interesting example of stereoselective hydrogenation in a biphasic system consisting of $[BMIM]^+[PF_6]^-$ /TBME was reported to give high selectivity for *cis*-3-hexanoic acid (Scheme 3).^[17]



Scheme 3. Stereoselective hydrogenation in **3b**/TBME to give *cis*-3-hexanoic acid.

Enantioselective hydrogenation in biphasic systems formed by ionic liquids and organic solvents is also possible. This was first demonstrated for the hydrogenation of acetamidocinnamic acid in a mixture of $[BMIM]^+[BF_4]^-$ /isopropanol to

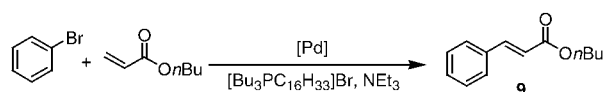
give (*S*)-phenylalanine (64 % *ee*).^[15] The same biphasic system was applied to the hydrogenation of aryl acrylic acids with a $[Ru\text{-}binap]$ catalyst as illustrated in the preparation of (*S*)-naproxen (**8**, Scheme 4).^[18] The catalyst was reused after phase separation and isolation of the product.



Scheme 4. Preparation of (*S*)-naproxen by hydrogenation in **3a**/iPrOH.

2.1.3.2. Carbon–Carbon Coupling Reactions

Pd-catalyzed carbon–carbon bond forming reactions have received considerable attention as a consequence of their enormous synthetic potential. The Heck reaction in particular has found widespread application for the synthesis of olefins by Pd-mediated vinylation of aryl halides. The reaction is best performed in polar organic solvents such as DMF or NMP. A relatively large amount of catalyst (> 1 mol %) is required for satisfactory conversions and recycling of the catalyst is hampered by decomposition. It was reported that these shortcomings could be overcome by use of an ionic liquid. The first example involved the coupling of bromobenzene with *n*-butyl acrylate to yield *trans*-cinnamic *n*-butyl ester **9** in tetraalkyl ammonium- and tetraalkyl phosphonium derived ionic liquids of type **2** (Scheme 5).^[19] The ionic liquid was reported to have a stabilizing effect on the Pd catalyst such that it could be reused for several consecutive runs.



Scheme 5. Heck reaction leading to *trans*-cinnamic *n*-butyl ester.

The same reaction was also carried out in $[BMIM]^+[PF_6]^-$ as the solvent and $Pd(OAc)_2$ or $PdCl_2$ as the catalyst with NEt_3 as the base. The products were isolated by extraction with hexane and the catalyst could be reused several times.^[20] It was also demonstrated that Pd/C and NEt_3 could also be used successfully as the reusable catalyst and base, respectively.^[21] Böhm and Herrmann have investigated the Heck reaction in ionic liquids in great detail and have shown impressively the advantages of ionic liquids over conventional solvents. A striking feature is the stabilization and the activation of the Pd catalyst: even $Pd(OAc)_2$ or $Pd(PPh_3)_4$ can be used in the absence of additional phosphines to couple chloroarenes. The products were either extracted or distilled from the ionic liquid and the catalyst was used for several consecutive runs.^[22]

Xiao and co-workers found that Heck reactions carried out in $[BMIM]^+Br^-$ proceeded more efficiently and gave a higher selectivity for the *trans* product than those carried out in $[BMIM]^+[BF_4]^-$.^[14] The in situ formation of heterocyclic carbene complexes by deprotonation of BMIM-derived ionic liquids was proposed to explain this finding (Figure 2a). Calò et al. used Pd–benzothiazole carbene complexes directly for Heck reactions in tetrabutylammonium bromide (TBAB;

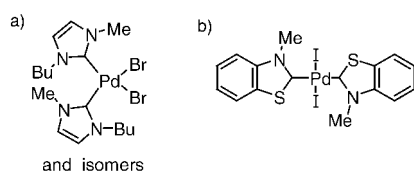
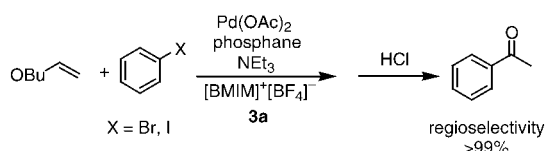


Figure 2. Pd-carbene complexes formed in situ in ionic liquids.

Figure 2b. They demonstrated that very fast and efficient couplings occurred, especially for the preparation of β,β -diaryl acrylates. Recycling of the catalyst was impaired and only three consecutive runs could be performed.^[23, 24]

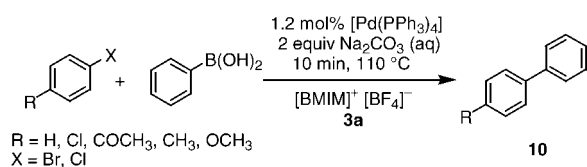
The Heck arylation of electron-rich olefins such as enol ethers leads to a mixture of regioisomers. Regioselective substitution at the olefinic carbon atom α to the oxygen atom can only be achieved when aryl halides are replaced by the corresponding triflates or when a stoichiometric amount of silver triflate or thallium acetate is added. Aryl halides can be transformed in $[\text{BMIM}]^+[\text{BF}_4]^-$ and the reaction proceeds with high efficiency and high regioselectivity (Scheme 6). The ionic



Scheme 6. Heck reaction for the regioselective formation of acetophenone.

liquid not only promotes the ionic pathway of the Heck reaction to give the α -arylated product but leads at the same time to an acceleration of the reaction.^[25] Recently, it was demonstrated that under ultrasonic irradiation the Heck reaction in ionic liquids proceeds at ambient temperature (30 °C) with reaction times of 1.5–3 h.^[26] The products were separated from the catalyst by extraction with 10% ethyl acetate in petroleum ether and purified by chromatography. The catalyst could be reused at least three times.

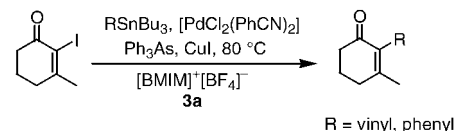
The first example of Suzuki cross-coupling reactions in $[\text{BMIM}]^+[\text{BF}_4]^-$ was reported recently (Scheme 7).^[27] Compared to standard protocols for Suzuki couplings, a significantly increased activity of the applied $[\text{Pd}(\text{PPh}_3)_4]$ complex

Scheme 7. Suzuki coupling in **3a**.

was observed during the formation of the desired biphenyl derivatives **10**. Only minimal formation of the homocoupling product could be detected, which simplified the work-up. The desired products were obtained by extraction with diethyl ether, by sublimation, or precipitation after the addition of

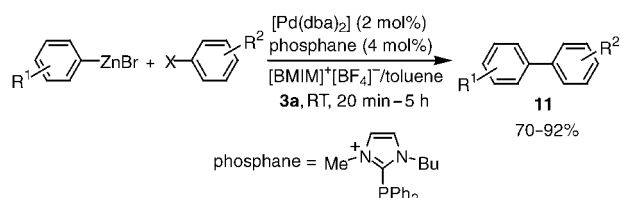
water, with no leaching of the catalyst into the product. The catalyst was recycled at least three times without loss of activity. Suzuki coupling reactions in ionic liquids could also be promoted by ultrasound irradiation to proceed at ambient temperature.^[28]

Stille couplings were also reported (Scheme 8).^[29] The products were isolated by extraction with diethyl ether and the $[\text{BMIM}]^+[\text{BF}_4]^-$ catalyst could be recycled five times with no (for Pd^{II} systems) or only a slight loss in activity (for Pd^0 systems). In addition, the ionic-liquid layer was stored for

Scheme 8. Stille coupling in **3a**.

several weeks after extraction with no special precautions to exclude air or moisture, and gave the same coupling yields as a freshly prepared catalyst solution.

The Negishi coupling of organozinc compounds and aryl iodides was demonstrated in a two-phase system composed of $[\text{BMIM}]^+[\text{BF}_4]^-$ and toluene (Scheme 9).^[30] In most cases the reaction proceeded within a few minutes at room temperature and led to the desired cross-coupling products **11**. Aryl bromides and aryl nonaflates required longer reaction times. After the reactions the ionic liquid containing the catalyst was separated from the toluene by decantation and was reused for subsequent coupling reactions. After the third cycle a significant decrease in the yield was observed.

Scheme 9. Negishi coupling in **3a**.

The homocoupling of aryl halides in $[\text{BMIM}]^+[\text{PF}_6]^-$ with $[(\text{PPh}_3)_n\text{Ni}^0]$ as the catalyst was reported recently.^[31] The desired biaryls were obtained in moderate to good yields after extraction with diethyl ether. The catalyst was recycled but in the second run a decrease in activity was already observed.

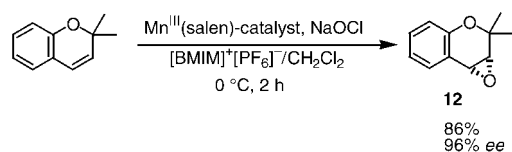
The Pd^0 -catalyzed formation of C–C bonds by allylic nucleophilic substitution with C nucleophiles (Tsuji–Trost coupling) was also performed in ionic liquids. In the reaction of malonic acid derivatives with 3-acetoxy-1,3-diphenylprop-1-ene, the anion was formed with K_2CO_3 or DBU directly in $[\text{BMIM}]^+[\text{BF}_4]^-$ and the coupling products were obtained in high yields.^[32] The recycling of the catalyst was only possible after replacement of PPh_3 by the more polar phosphane $\text{P}(m\text{-C}_6\text{H}_4\text{SO}_3\text{Na})_3$ and reactions could be performed three times. The Tsuji–Trost coupling of ethyl cinnamyl carbonate and ethyl acetoacetate was carried out in a biphasic system of $[\text{BMIM}]^+\text{Cl}^-/\text{methyl cyclohexane}$.^[33] The reaction proceeded

more efficiently than in water/organic biphasic mixtures and the coupling product was isolated in a yield of 90%. The recycling was hampered by the high solubility of the product in the ionic liquid.

In summary, it can be stated that ionic liquids are ideal media to perform Pd-mediated C–C couplings. In most cases the catalyst can be fixed in the ionic liquid without modification of the ligands. The work-up is easily performed and the products can be separated from the catalyst in the ionic liquid by using lipophilic solvents such as diethyl ether. Both the catalyst and the ionic liquid can be recycled. Ionic liquids can stabilize the Pd catalyst and cause activation, and even unreactive aryl halides can be used. They also allow for the application of “cheap” Pd compounds, such as PdCl₂, and the expensive Cs₂CO₃ can often be replaced by less expensive bases.

2.1.3.3. Oxidations

Although a number of ionic liquids are fairly stable towards oxidation, there have been only a very limited number of reports on oxidations in biphasic systems involving ionic liquids. One example is the stereoselective epoxidation using Jacobsen's chiral [Mn^{III}(salen)] complex in a mixture of [BMIM]⁺[PF₆][−] and CH₂Cl₂ in a ratio of 1:4 (Scheme 10).^[34] A considerable activation of the catalyst by the ionic liquid was



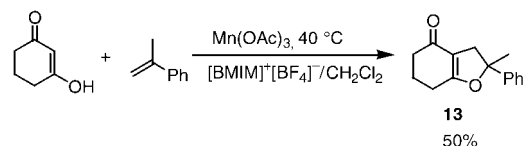
Scheme 10. Stereoselective epoxidation by using the chiral Jacobsen [Mn^{III}(salen)] complex.

reported. The catalyst was recycled five times and a only small decrease in yield and in *ee* values of **12** was observed. Another epoxidation of alkenes and allyl alcohols in [EMIM]⁺[BF₄][−] using methyl trioxorhenium (MTO) and urea/H₂O₂ was reported recently.^[35] Excellent conversions and selectivities were obtained for a number of substrates. The reaction was performed in a homogeneous fashion since MTO as well as urea/H₂O₂ are completely soluble in [EMIM]⁺[BF₄][−]. The oxidation solution was anhydrous, and opening of the epoxides to form the diols did not occur. Since MTO as well as the ionic liquid are not soluble in diethyl ether, the remaining reactants and products were isolated by extraction with diethyl ether after the reaction.

Oxidations of aromatic aldehydes to the corresponding carboxylic acids were carried out in [BMIM]⁺[PF₆][−] with oxygen at atmospheric pressure and [Ni(acac)₂] (acac = acetyl acetonate) as the catalyst.^[36] The yields were lower than the ones obtained for the same type of oxidations carried out in perfluorinated solvents with perfluoroalkyl-tagged acac ligands of Ni²⁺ complexes.^[37] The ionic liquid [BMIM]⁺[BF₄][−] was used in the oxidation of codeine methyl ether to thebaine with MnO₂.^[38] The yield was rather low when the oxidation

was carried out directly in the ionic liquid with sonication. Performing the oxidation in THF under sonication followed by selective extraction of MnO₂ and other inorganic by-products enabled thebaine to be isolated in high yield.

Carbonyl compounds such as β-diketones or β-ketoesters can be oxidized with Mn(OAc)₃ to form radicals which can then undergo carbon–carbon bond-forming reactions. The reaction has to be carried out under harsh conditions which limits its scope of application severely. It was demonstrated that performing the reactions in [BMIM]⁺[BF₄][−]/CH₂Cl₂ yielded the desired products **13** in respectable yields (Scheme 11).^[39] At the end of the reaction the Mn(OAc)₂ was recovered by precipitation and after filtration it was re-



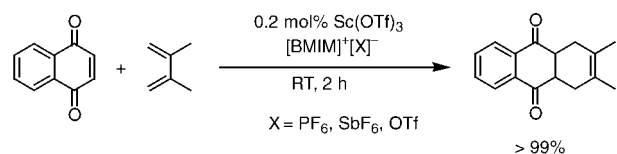
Scheme 11. Mn(OAc)₃ oxidations leading to C–C bond formations.

oxidized by KMnO₄ and reused. The ionic liquid was also recycled without detriment to the product yields.

2.1.3.4. Diels–Alder Reactions

Several authors have investigated Diels–Alder reactions in ionic liquids. The first reported example was the cycloaddition of cyclopentadiene with crotonaldehyde or methacrolein as dienophiles in dialkyl imidazolium salts as ionic liquids.^[40] The results clearly demonstrated that the ionic liquid acted as a Lewis acid which allowed the reaction to be performed at low temperature and which led to a high *endo:exo* selectivity. These results were confirmed later for the same type of diene and dienophiles.^[41–43] A recycling of the ionic liquid was demonstrated as well.

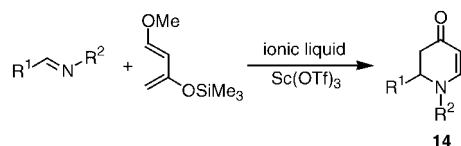
An impressive study on Diels–Alder reactions was reported recently in which a number of different dienophiles were treated with a selection of dienes in [BMIM]⁺[X][−] in the presence of 0.2 mol% Sc(OTf)₃ (an example is shown in Scheme 12).^[13] The reaction proceeded with high yields with



Scheme 12. Diels–Alder reaction in an ionic liquid catalyzed by Sc(OTf)₃.

PF₆[−], SbF₆[−], and OTf[−] counterions. The type of anion had only little effect on the catalytic activity. The *endo:exo* selectivity was generally higher than for the same reaction in CH₂Cl₂. After completion of the reaction and extraction of the product with diethyl ether, the ionic liquid phase containing the Sc(OTf)₃ was recovered. The ionic-liquid phase was reused 11 times without any loss of activity.

Recently, aza-Diels–Alder reactions for the preparation of 6-aryl-5,6-dihydro-4-pyridones (**14**) in ionic liquids were reported (Scheme 13).^[44] The imine dienophiles were pre-



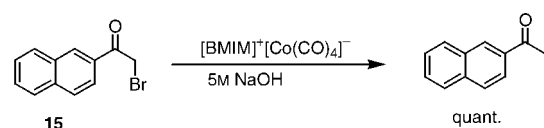
Scheme 13. Aza-Diels–Alder reaction in ionic liquids.

pared in situ from the aldehyde and the amine directly in the ionic liquid. The ionic liquid used was 8-ethyl-1,8-diazabicyclo[5.4.0]-7-undecenium trifluoromethanesulfonates. The yield could be increased significantly by the addition of $\text{Sc}(\text{OTf})_3$ in a microencapsulated form. The products were isolated by extraction with diethyl ether and the ionic liquid together with the microencapsulated Lewis acid were reused. The same high yields as observed in the first run were obtained.

2.1.3.5. Miscellaneous Reactions

In the last few years an increasing number of reports have appeared on synthetic methods which take advantage of the favorable properties of ionic liquids. Among the reported reactions are hydroformylations in $[\text{BMIM}]^+$ -derived ionic liquids in which the aldehydes are formed in remarkably high *n/iso* ratios,^[45] $[\text{Cr}(\text{salen})]$ -catalyzed ring-opening reactions of epoxides with TMSN_3 ,^[46] electrophilic nitrations of aromatic compounds,^[47] the Biginelli multicomponent reaction for the preparation of 3,4-dihydropyrimidin-2-(1*H*)-ones,^[48] and nucleophilic displacement reactions.^[49]

It was outlined in Section 2.1 that the anion of the ionic liquid may also be catalytically active, as observed for example with chloroaluminate anions which can act as Lewis acids. An interesting example in this respect is the application of $[\text{BMIM}]^+[\text{Co}(\text{CO})_4]^-$ as both solvent and reagent for the debromination of 2-bromoketones **15** (Scheme 14).^[50]

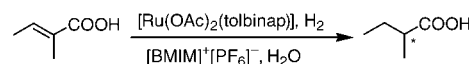


Scheme 14. Debromination of 2-bromoketones in/with $[\text{BMIM}]^+[\text{Co}(\text{CO})_4]^-$.

2.1.3.6. Combination of Ionic Liquids and Supercritical CO_2

Recently, the combination of an ionic liquid and supercritical carbon dioxide (scCO_2) has emerged as a new system for biphasic homogeneous catalysis. Supercritical CO_2 is soluble in ionic liquids and decreases their viscosity, thereby enhancing the mass transfer. On the other hand, ionic liquids are not particularly soluble in scCO_2 . Hence, nonvolatile

compounds can be extracted quantitatively out of ionic liquids by scCO_2 without any contamination. This was first demonstrated by the extraction of naphthalene from $[\text{BMIM}]^+[\text{PF}_6]^-$ by scCO_2 .^[51] Recently, the system was applied to batch-wise asymmetric hydrogenation (Scheme 15). The product was



Scheme 15. Asymmetric hydrogenation in an ionic liquid followed by extraction with scCO_2 .

extracted out of the ionic liquid by scCO_2 after the reaction and the catalyst could be reused for four further runs.^[52, 53]

Another example was reported for the batch-wise hydrogenation of CO_2 and alkenes using Wilkinson's catalyst.^[54] Hydroformylation reactions^[55] and the Ni-catalyzed hydrovinylation of styrene were reported.^[56] More recently, the ionic liquid/ scCO_2 system was extended to continuous flow processes.^[57, 58]

2.2. Perfluorinated Systems

Since the seminal work by Vogt^[59] and by Horváth and Rábai^[60] perfluorinated solvents and compounds with fluorine labels have emerged as powerful tools in synthetic organic chemistry. Not surprisingly, fluorine systems (Fluorous Biphasic System, FBS) have been the subject of several recent reviews.^[61–66]

Perfluoroalkanes and—to a certain degree—perfluorinated ethers and amines show a very low miscibility with common organic solvents. The miscibility is temperature dependent and increases with increasing temperature.^[67] This phase behavior can be employed to separate molecules with complementary solubilities in organic and fluorine solvents.^[68] Perfluorinated solvents are exceedingly hydrophobic and chemically inert. They are considered to be of low toxicity and they are thought to have no ozone-depletion potential, although they do exhibit long atmospheric lifetimes (>2000 years), which makes them potent greenhouse gases. This situation should be taken into account when using or disposing of perfluorinated solvents.^[69]

According to the alchemists rule “*similia similibus solvuntur*” the solubility of a compound in perfluorinated solvents can be enhanced by attaching long perfluoroalkyl chains (perfluoro tags) to the molecule. The assumption that a fluorine content exceeding 60% (of the molecular weight) is needed to gain differential solubility in fluorine solvents has been reiterated in the literature. This value cannot be more than a rough approximation, since solubilities and partitioning coefficients are dependent on a number of structural features.^[70–72] In general, the preferential relative solubility in the fluorine solvent is augmented as the length and number of perfluoroalkyl chains attached to it increase and the polarity of the molecule decreases. However, the absolute solubility of the compound drops as

the length of the perfluoroalkyl chains increases. On the other hand common organic compounds, even very unpolar ones such as *n*-alkanes, show very low partitioning into the fluoruous phase.

As mentioned above, the immiscibility of fluoruous and organic solvents in conjunction with the differential solubilities can be used to separate molecules with a fluoruous label from unlabeled compounds. This possibility leads to a multitude of different separation and purification strategies. The common denominator is that one specific component with a fluoruous label (for example, catalyst, reagent, by-product, product) is preferentially soluble in the fluoruous phase, while the other components of the reaction mixture (product, starting material, reagents, impurities) are soluble in the organic layer. Depending on the application and the partitioning coefficients, the separation can be performed as a conventional liquid–liquid extraction, as a continuous extraction, or as a solid-phase extraction with fluoruous reversed-phase silica gel (FRPSG).^[73]

In principle, fluoruous techniques are similar to other phase-labeling strategies, such as those based on water-soluble reagents or catalysts and solid-phase-bound reagents, catalysts, or substrates. The logic governing such separation strategies has been reviewed.^[3]

2.2.1. Perfluorinated Solvents as Reaction Media

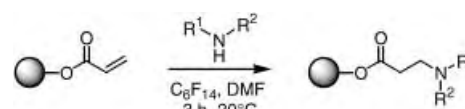
Perfluorinated solvents have found only limited use as reaction media because of their low solvating power. However, this very low miscibility with organic compounds means that products are readily isolated by simple decantation. A perfluorinated solvent can be used to azeotropically remove reaction products and thus shift the equilibrium of the reaction. This principle was demonstrated by Zhu for esterifications and transesterifications as well as for acetal and enamine formation by using a modified Dean–Stark apparatus.^[74]

Another interesting feature is the high solubility of gases in perfluorinated solvents;^[75] since large amounts of oxygen are soluble they have also been tested as blood substitutes.^[76–79] For the same reason they receive attention as reaction media for oxidations. Klement and Knochel have described the oxidation of alkyl zinc compounds to hydroperoxides with molecular oxygen in perfluorohexanes, while mixtures of hydroperoxides and the corresponding alcohols are obtained by the direct oxidation of organometallic compounds in common solvents.^[80] Trialkyl boranes have been oxidized to alcohols in a similar manner.^[81]

A fluoruous biphasic system has been used to spatially separate catalysts in a cascade of ring-closing metathesis (RCM) and a Heck reaction.^[82] The RCM was performed at room temperature with the Grubbs catalyst. Since the Grubbs catalysis is not compatible with either palladium acetate nor phosphane ligands, a perfluoro-tagged triphenylphosphane was used. At room temperature the solvent system is biphasic, and the RCM proceeds in the organic phase with the palladium complex residing in the fluoruous phase. The mixture becomes homogeneous upon heating and the Heck reaction is catalyzed by the palladium complex. Results

obtained with the fluoruous phosphane were better than those with a nontagged phosphane, but were not as good as with solid-phase-bound phosphane.

An interesting concept in solid-phase organic synthesis is the use of perfluorinated solvents to accelerate reactions with substrates bound to a polystyrene resin. As a consequence of the low solvating power of the fluoruous solvent, the reagent is confined to the resin, thus increasing the local concentration. A small amount of polar cosolvent is needed, possibly to swell the resin (Scheme 16).^[83]

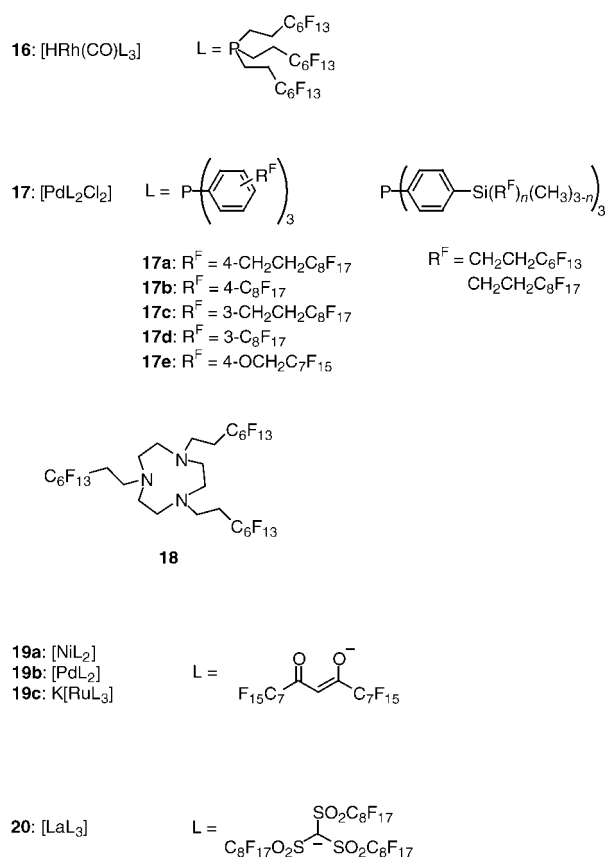


Scheme 16. Increase of the local substrate concentration within the resin by a perfluorinated solvent.

2.2.2. Perfluoro-Tagged Catalysts

The main field of application for fluoruous separation strategies is in fluoruous biphasic catalysis (FBC). The catalyst is modified with a fluoruous tag, and thus can be removed from the product by extraction with a fluoruous solvent. At the beginning of the reaction the perfluoro-tagged catalyst together with the substrate and reagents is present in a biphasic mixture of fluoruous and organic solvent. The reaction can proceed either in a heterogeneous fashion with the catalyst in the fluoruous phase and the other reactants in the organic phase, or under homogeneous conditions if the reaction temperature is high enough for the biphasic mixture to become monophasic.^[84] Upon completion of the reaction, the mixture is cooled to restore the biphasic system. Ideally, the catalyst now remains exclusively in the fluoruous layer, while all the product is dissolved in the organic phase. The phases are separated to yield products free of catalyst contaminations, and the fluoruous layer containing the catalyst, which can be reused for further reactions.

The importance of such catalyst systems lies mainly in the field of combinatorial synthesis and industrial processes. FBC represents a way to simplify work-up and purification in parallel synthesis to give easy extraction procedures, which even allow for automation. This possibility avoids difficult purification procedures such as chromatography or distillation, which would hamper parallel work-up. Thus, compound libraries can be prepared for high-throughput screening. Products without heavy-metal contaminations, which could impair biological assays, are especially important for such applications. In addition to simplified purification, the option of catalyst recycling plays an important role in industrial processes. Expensive catalysts contribute significantly to the cost of a product. Recycling of such a catalyst as well as a simplified product isolation can greatly reduce the costs of a process. To date, a growing number of catalysts has been modified with perfluoro tags (see for example, structures **16–20**).



The hydroformylation of terminal olefins was among the first reactions to be performed in FBC.^[60, 85] The hydroformylation of 1-decene catalyzed by rhodium complex **16** was studied in detail (Scheme 17). A total turnover number

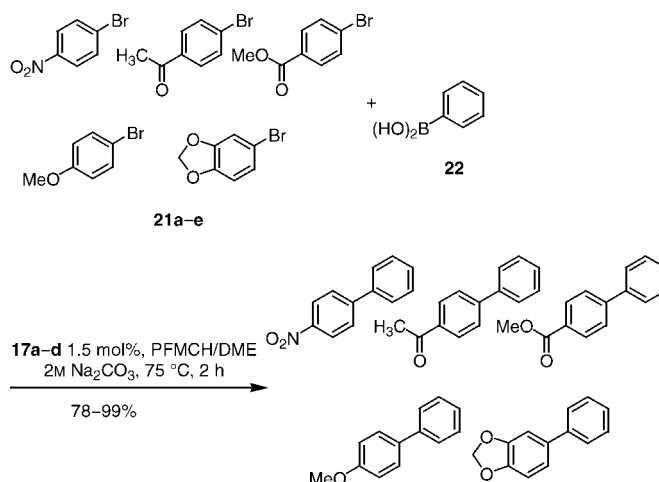


Scheme 17. Hydroformylation with an in situ generated fluororous rhodium catalyst.

exceeding 35 000 with a loss of only 1.18 ppm rhodium per mole of undecanal was achieved in nine consecutive runs using the same fluororous phase containing the catalyst. In the continuous hydroformylation of ethene the resulting propanal was distilled from the high-boiling fluororous phase. No loss of catalyst activity was detected over 60 days. Similar rhodium catalysts have been used for hydrogenations,^[86] hydroborations,^[87, 88] and hydrosilylations of olefins^[89, 90] in fluororous biphasic systems.

Hydrogenation of olefins was also achieved with dendrimer-encapsulated palladium nanoparticles that were soluble in fluororous phases.^[91] A bimetallic rhodium catalyst was used in the cyclopropanation of alkenes and recovered by fluororous extraction.^[92] The palladium-catalyzed C–C bond-forming reactions that have been performed in fluororous biphasic systems include the Heck reaction,^[93] benzannulation of conjugated enynes,^[94] palladium-catalyzed allylic substitution^[95, 96] as well as Negishi,^[97] Stille,^[98] Suzuki,^[99] and Sonogashira reactions.^[100] The Suzuki coupling of five different aryl bromides **21** with phenylboronic acid (**22**) was carried out with

four different palladium complexes (**17a–d**, Scheme 18).^[99] The fluororous phase was extracted with DME and water and the catalysts reused five times without any loss of activity. The yields of the biaryls were generally high and independent of the phosphane employed.



Scheme 18. Suzuki coupling in PFMCH/DME.

Numerous oxidation reactions have been carried out under fluororous biphasic conditions because of the good solubility of oxygen in perfluorinated solvents. Alcohols were oxidized to aldehydes or ketones with molecular oxygen by using a catalyst system of CuBr, perfluoroalkyl-tagged bipyridine, and 2,2,6,6-tetramethylpiperidine-*N*-oxide (TEMPO). Yields were high for benzylic alcohols, and in one example the catalyst was recovered and reused eight times without any significant decrease in yield.^[101] A variety of alcohols was oxidized to aldehydes or ketones with palladium(II) acetate and perfluoro-tagged pyridines as ligands.^[102] Although only a small amount of leaching of palladium was observed, the catalytic activity in consecutive runs could be retained only if a small amount of additional ligand was added before every other run.^[103]

A series of fluororous β -diketonates **19** of transition metals were prepared.^[104] Nickel complex **19a** was used in the aerobic oxidation of aldehydes to carboxylic acids^[37] as well as in combination with *i*PrCHO and oxygen for the oxidation of sulfides to sulfoxides or sulfones.^[37] This oxidation could also be catalyzed by cobalt complexes with perfluoro-tagged porphyrin or phthalocyanine ligands, but recycling of the catalyst was unsuccessful.^[105] Palladium complex **19b** was used as the catalyst for the oxidation of terminal olefins to methyl ketones with *tert*-butylhydroperoxide (TBHP) as oxidant.^[106] Oxidation of cyclohexene to cyclohexenol and cyclohexenone was achieved with a manganese complex with ligand **18** using oxygen and substoichiometric amounts of TBHP as the oxidant.^[107, 108]

Selective epoxidation reactions of internal olefins in the presence of terminal double bonds was achieved by the use of ruthenium complex **19c** and excess *i*PrCHO/oxygen.^[37] The epoxidation of olefins has also been catalyzed by perfluoro-tagged cobalt–porphyrin complexes.^[109] Asymmetric epoxidations were achieved with perfluoro-tagged

manganese–salen complexes.^[110–112] A fluoros aryl selenic acid catalyst for the epoxidation of olefins with hydrogen peroxide could be recycled ten times without loss of catalytic activity.^[113]

Friedel–Crafts acylations and other Lewis acid promoted reactions were carried out in FBS using fluoros lanthanide methides **20**. High yields were reported, and the Lewis acid was quantitatively recovered by phase separation and reused in several consecutive runs.^[114, 115]

Fluorous tin oxides have been used in transesterifications^[116] and in the monotosylation of 1,2-diols.^[117] The enantioselective addition of diethylzinc to aldehydes has been performed with different perfluoro-tagged catalysts.^[118–121]

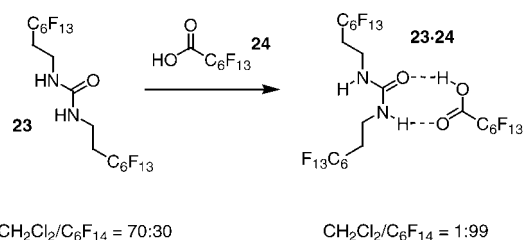
Recently, Gladysz and co-workers employed the fluoros phosphane $P(CH_2CH_2C_8F_{17})_3$ as catalyst for the addition of alcohols to the triple bond of methyl propiolate.^[122] During the reaction, the phosphane was dissolved in octane at 65 °C. Subsequently, the catalyst was precipitated at –30 °C and separated by decantation. No fluoros solvent was needed.

2.2.3. Perfluoro-Tagged Reagents

After any reaction, chemists are faced with the problem of isolating the product. This is done by exploiting more- or less-pronounced differences in the physical properties of product and impurities. Simple purification procedures are needed in combinatorial syntheses of libraries for high-throughput screening.^[123] Furthermore, the procedure should be the same for every compound of a library to allow for automation and parallel synthesis. Similar to the situation of catalysis described in Section 2.2.2, perfluoro-tagged reagents can be used to easily separate reaction by-products and excess reagents from the product. This is achieved either by extraction with a fluoros solvent or by filtration over FRPSG. The resulting solution should now contain only organic molecules while the fluoros phase retains the perfluoro-labeled reagent. Therefore, a large excess of reagent can be used to ensure complete conversion.^[124] This approach is especially attractive if reagents or by-products are toxic, expensive, or difficult to remove. The strategy is similar to the use of solid-phase-bound reagents, but since the fluoros reagents are individual soluble molecules their behavior is closer to conventional soluble compounds, and under appropriate conditions the reaction can proceed homogeneously.

The use of trialkyl tin reagents and selenium compounds has been limited by their toxicity. Fluorous tin reagents have been used in radical dehalogenations,^[125] in the allylation of aldehydes,^[126, 127] and in Stille coupling reactions.^[128] Fluorous tin azide was used in the synthesis of tetrazoles.^[124] Perfluoro-tagged aryl selenium reagents were employed in the conversion of carbonyl compounds to their α,β -unsaturated derivatives and in the reduction of dimesylates to alkenes.^[129, 130]

The partitioning coefficient of bis(perfluoroalkyl)ureas **23** between perfluorohexane and CH_2Cl_2 could be significantly increased by the addition of perfluoroalkanoic acids **24** (Scheme 19). This is thought to be the result of hydrogen bonding between the urea and the acid, which results in complex **23·24** which is less polar than the individual

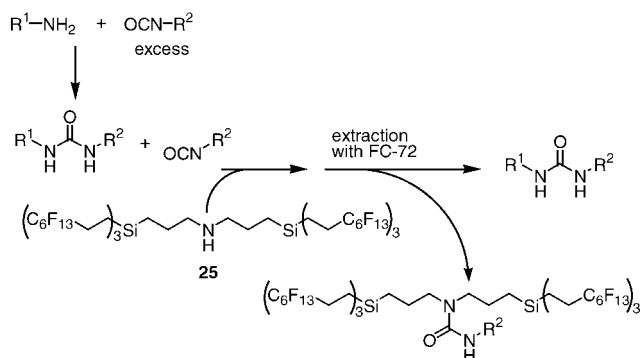


Scheme 19. The partitioning of **23** between CH_2Cl_2 and perfluorohexane is reversed upon addition of **24**.

compounds. The utility as a reagent was demonstrated by dehydration of urea to the corresponding carbodiimide and its subsequent employment as a condensation reagent for the formation of peptide and ester bonds. The urea by-product was removed by extraction with perfluoroheptanoic acid in perfluorohexane, whereas dialkyl ureas formed by conventional carbodiimide reagents are notoriously difficult to remove. The advantage of this strategy is that the reagent itself shows appreciable partitioning into the organic phase, which in turn results in respectable reaction rates. Only upon addition of the perfluoroalkanoic acid scavenger is the partitioning coefficient reversed.^[131]

The application of perfluoro-tagged triphenylphosphanes to Wittig olefinations was suggested initially by Horváth and Rábai.^[60] The realization of this idea in the synthesis of substituted ethyl cinnamates and cinnamic nitriles was recently reported.^[132] Similarly, perfluoro-tagged triphenylphosphanes, solid-phase-bound phosphane, and triphenylphosphane were compared in an aza-Wittig reaction to give 3*H*-quinazolin-4-ones.^[133]

A sulfoxide with a short fluoros tag was employed in Swern oxidations. This reagent is soluble in CH_2Cl_2 and it was removed from the crude product by continuous extraction with FC-72.^[134] A perfluoro-tagged binol derivative was employed in the enantioselective protonation of a samarium enolate. The chiral proton source was recovered and could be reused several times.^[135] Amine **25** was used to scavenge excess isocyanate from an automated synthesis of a library of ureas (Scheme 20). The product was obtained in high purity after removal of the fluoros urea by extraction with FC-72.^[136] Polymers soluble in fluoros solvents efficiently sequester iron ions from organic solvents. Analogous water-soluble polymers have been used to remove trace metals from aqueous solutions.^[137]



Scheme 20. Application of **25** as an isocyanate scavenger in the synthesis of ureas.

2.2.4. Perfluoro-Tagged Products

A fluorous label can also be attached to the substrate itself which renders the product soluble in fluorous solvents. Thus, this approach offers an opportunity for easy isolation and makes it particularly attractive for parallel synthesis of compound libraries. After extraction, only the labeled product is found in the fluorous phase, whereas all the other organic compounds remain in the organic phase. As an alternative to liquid–liquid extraction, the reaction mixture can be absorbed on FRPSG (Figure 3). The organic com-

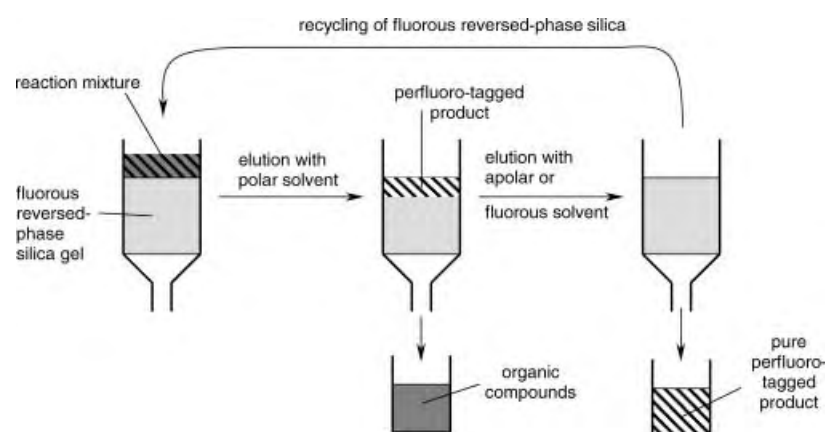


Figure 3. Separation of perfluoro-tagged compounds from organic compounds by solid-phase extraction.

pounds are eluted with a polar organic solvent (methanol/water, acetonitrile/water), while more fluorophilic solvents (diethyl ether, perfluoroalkanes) elute the perfluoro-tagged product.^[73] This strategy is conceptually similar to solid-phase synthesis, but offers distinct advantages: 1) The fluorous-tagged substances can be characterized by NMR spectroscopy, 2) reactions can be followed by thin-layer chromatography or HPLC, and 3) homogeneous reactions result in higher reaction rates.^[3, 124]

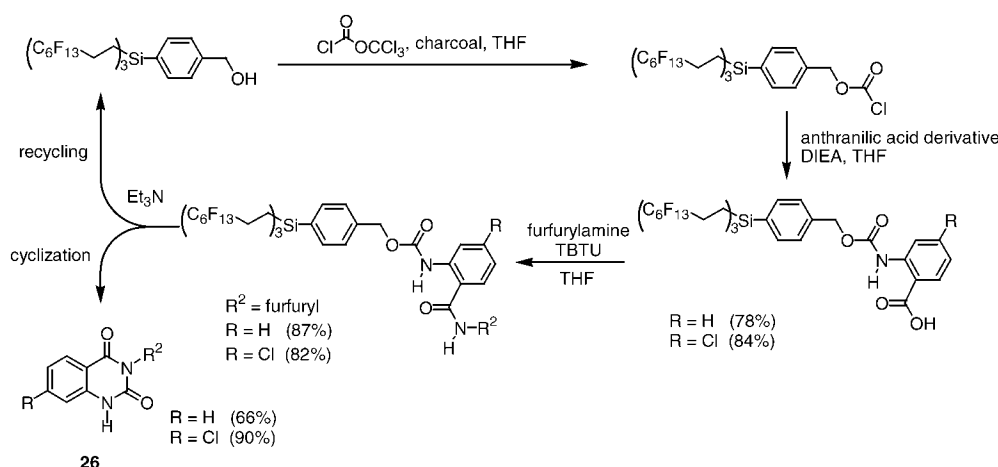
While permanent labeling is necessary for catalysts or reagents, only temporary attachment of the fluorous tag to the substrate is required here (usually through the use of a modified protecting group). A perfluoro-tagged benzyloxy-

carbonyl protecting group was successfully used in the multistep synthesis of quinazolinones (Scheme 21). The product was isolated after every step by liquid–liquid extraction with FC-72. Finally, quinazolinone **26** was removed from the fluorous label by intramolecular cyclization. Since only the desired product undergoes cyclization, all incompletely converted molecules stay attached to the fluorous label and are separated from the product by extraction.^[138] Fluorous labeling was employed by Theil and co-workers in the kinetic resolution of 1-phenylethanol. Lipase was used to catalyze the enantioselective esterification

of the racemic alcohol with a polyfluoroalkanoic acid. Extraction with FC-72 separated the enantiomerically enriched alcohol from the ester.^[139] Polyfluoroalkylsilyl groups were also employed as fluorous labels in the cycloaddition of nitriloxides to allyl silyl ether, in Ugi and Biginelli multicomponent reactions, and in the purification of Grignard products.^[124, 140]

Solid-phase extraction with FRPSG is now beginning to replace liquid–liquid extraction procedures.^[73] In a recent example amino acids protected by a fluorous Boc group were coupled with different amines by Curran and co-workers. The crude reaction mixtures were adsorbed on FRPSG. The organic reagents and by-products were eluted with methanol/water, the fluorous-tagged amides were eluted with methanol/diethyl ether. Alternatively, prepara-

tive HPLC over a fluorous reversed-phase column was used.^[141] Preparative HPLC was used to deconvolute product mixtures coded with perfluoroalkyl chains of different length. In this approach, the synthesis is conducted with a mixture of substrates, each uniquely labeled with a perfluoroalkyl group of certain length. Upon completion of the mixture synthesis, the individual products are separated by HPLC over a fluorous reverse-phase column, with the single components eluted in order of increasing length of the fluorous tag (however, other structural features of the product also influence the order of elution). The principle was demonstrated for the synthesis of mappicine analogues and for the addition products of thiolates to acrylates.^[142, 143]



Scheme 21. Use of a fluorous protecting group in the synthesis of quinazolinones.

FRPSG was used to purify perfluoralkyl allyl compounds obtained by free-radical addition of perfluoroalkyl iodides to allyl trialkyl tin.^[144] A similar synthesis of perfluoroalkyl-ethenes was reported earlier.^[145]

2.3. Supercritical Fluids

Although the discovery of the supercritical state dates back to 1822,^[146] it was not until the pioneering work of Zosel^[147] in 1978 that supercritical fluids (SCFs) found acceptance as solvents. They are now employed on an industrial scale for the extraction of hops, spices, flavors, perfumes, and for the decaffeination of coffee.^[148, 149] In the last few years SCFs have been attracting ever increasing attention since they were found to be environmentally and toxicologically benign media for chemical reactions.^[150–157] SCFs are particularly attractive in synthesis as they provide some unique properties such as high diffusion rates, enhanced heat transfer, compressibility, and the absence of gas–liquid boundaries. Their solvent properties can be easily tuned by pressure and addition of cosolvents, which provides an attractive means to influence phase behavior as well as the rate and selectivity of catalytic reactions. Product separation is fairly straightforward and essentially solvent-free products are obtained. The use of SCFs are also beneficial in different purification processes such as chromatography, crystallization, or precipitation, on both laboratory and industrial scales, thus reducing the amount of waste organic solvents significantly. However, until now extensive parallelization and automatization has been limited by the need for high-pressure equipment and by safety concerns.

2.3.1. The Concept of Supercritical Fluids

The critical point represents the highest pressure (p_C) and temperature (T_C) at which the vapor and liquid phases of a substance can exist in equilibrium. The distinction between gas and liquid disappears above the p_C and T_C values, and the supercritical fluid has physical properties which are intermediate between those of a liquid and a gas. The critical data for some SCFs are depicted in Figure 4.^[158]

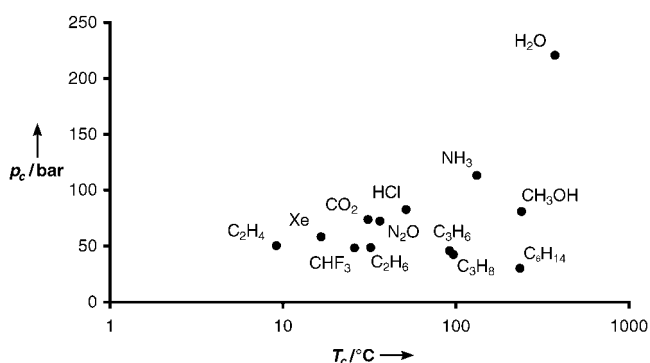


Figure 4. Critical data for some SCFs.

The properties of SCFs such as polarity, dielectric constant, viscosity, and solubility properties can vary dramatically with temperature and pressure.^[159] The dielectric constant of a solvent influences chemical reactions whenever the reactants and transition state differ in polarity. The viscosity influences reactions that are diffusion-controlled or in which cage effects are important. Thus, adjusting the temperature and pressure provides a means to control reaction rates and selectivities. Furthermore, reactions can be driven to completion by precipitation of a product, and selective precipitation can be used during reaction work-up. Another important feature of SCFs is their total miscibility with gases. This observation turns SCFs into ideal media for reactions such as hydrogenation, hydroformylation, and oxidation with oxygen, where the solubility of the gaseous reagent is traditionally rate limiting.

Among the different SCFs depicted in Figure 4, scCO₂ and scH₂O have found widest acceptance. Supercritical water forms only a few hydrogen bonds and its dielectric constant (ϵ_r) is reduced from 80 to 5.^[160] Hence, scH₂O is attractive for replacing organic solvents at temperatures above 200–350 °C, where it readily dissolves most organic compounds. However, the application of scH₂O is limited not only to reactants and products that are thermally stable, but also by its corrosive properties.

Carbon dioxide becomes supercritical at $T_C = 31.1$ °C and $p_C = 73.8$ bar, thus allowing for essentially mild SCF applications. Carbon dioxide is obtained as a by-product of fermentation and combustion processes. It is essentially nontoxic, nonflammable, nonprotic, and chemically inert to a wide range of reaction conditions.^[161] Furthermore, scCO₂ has been used as a C₁-building block.^[162, 163] Since scCO₂ is a nonpolar medium, the best solubility is observed for nonpolar solutes. The solubility of polar substances can be substantially increased by adding polar cosolvents or microemulsions.^[164] Organic fluorocarbons show a particular high solubility in scCO₂. Numerous examples are reported in which so-called perfluoro tags have been used to solubilize substrates, reagents, and catalysts.^[157, 165, 166] With scCO₂ and perfluorinated solvents both representing very nonpolar media, it is not surprising that their fields of application and research show a certain analogy. In fact, a number of the perfluoro-tagged reagents, ligands, and catalysts (see Section 2.2) have also been successfully tested in scCO₂ applications. Another synthetic SCF strategy makes use of two-phase systems, which allows for SCF transfer catalysis^[167] or catalyst immobilization.^[56] The combination of scCO₂ and ionic liquids is especially attractive (see Section 2.1.3.6).

Product isolation after a reaction in a SCF is straightforward since most SCFs, including CO₂, can be removed by simple depressurization. This is particularly useful in syntheses of thermally unstable compounds or for pharmaceutical syntheses where products have to be free of solvent residues. In analogy, high-quality crystals without any solvent molecules have been generated for X-ray diffraction studies by crystallization from a supercritical solution (CSS).^[168] In contrast to conventional batch crystallization, pressure provides a second parameter in addition to temperature to trigger nucleation and growth of crystals.

There are even more elaborate separation protocols which take advantage of the tunable solvent power of SCFs. In particular, the combination of catalysis and extraction with a supercritical solution (CESS) is a new method for the recovery of homogeneous catalysts.^[169–171] After venting the reactor the product is extracted from the residue with a SCF whose density is tuned to dissolve the product selectively. Thus, the catalyst remains in the reactor and can be reused. The consecutive use of scCO_2 and a perfluorinated solvent has been exploited in a similar strategy.^[172] Finally, the rapid expansion of supercritical solutions (RESS)^[173] and the supercritical antisolvent precipitation (SASP)^[174, 175] processes are mentioned. Both are of relevance in pharmaceutical formulation as they allow for an effective reduction in particle size combined with a narrow size distribution.

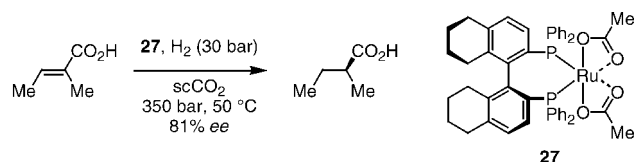
2.3.2. Synthetic Reactions in Supercritical Fluids

SCFs have received only a little attention as reaction media in synthetic organic chemistry. It is noteworthy, however, that a number of large-scale industrial syntheses are performed under supercritical conditions, with the Haber–Bosch synthesis of ammonia and the Fischer–Tropsch reaction, as well as polyethylene, polymethylmethacrylate, and polystyrene production^[176] probably being the most important ones.

2.3.2.1. Hydrogenation

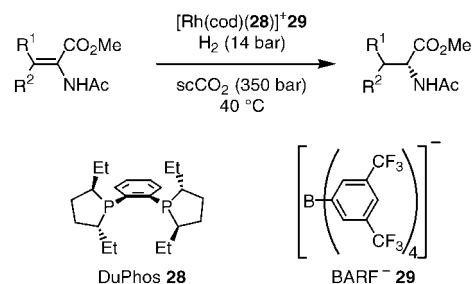
Hydrogen mass-transfer is often the rate-determining process in hydrogenation reactions. Whereas hydrogen has a rather limited solubility in most organic solvents, it is completely miscible with SCFs and turns them into ideal media for this kind of reaction. SCFs have so far been used beneficially in both homogeneous and heterogeneous hydrogenation reactions of a wide range of substrates.^[177–179] Baiker and co-workers observed no increase in the enantioselectivity of a heterogeneous asymmetric hydrogenation in supercritical ethane, but observed a rate enhancement compared to the analogous reaction in toluene.^[180, 181] The same effect was reported by Poliakov and co-workers.^[178, 179]

Noyori used Ru catalyst **27** containing a partially hydrogenated binap ligand for improved solubility in scCO_2 in homogeneous catalytic asymmetric hydrogenation reactions. The enantiomeric excess obtained was comparable to those obtained in liquid organic solvents (Scheme 22).^[182] The



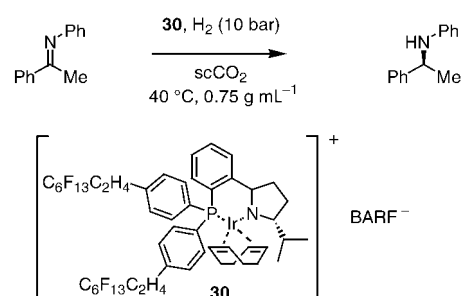
Scheme 22. Asymmetric hydrogenation using a modified Ru–binap complex.

bidendate DuPhos ligand (**28**) and the CO_2 -philic BARF[−] counterion (**29**) were used by Tumas and co-workers (Scheme 23).^[183] Asymmetric inductions obtained were comparable to those achieved in methanol or hexane. The perfluoro-tagged cationic iridium(i) complex **30** was tested as a catalyst for the enantioselective hydrogenation of

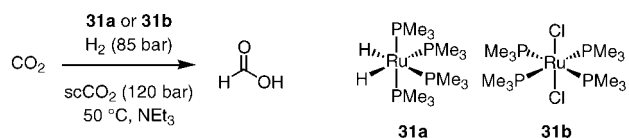


Scheme 23. Asymmetric hydrogenation using a modified Ru–DuPhos complex.

prochiral imines in scCO_2 .^[170] The highest enantioselectivities were obtained with BARF[−] as the counterion (Scheme 24). The hydrogenation of scCO_2 by soluble rhodium(ii) catalysts **31a** or **31b** to yield formic acid, which could be further converted into methyl formate or *N,N*-dimethylformamide (Scheme 25) was also reported by Noyori and co-workers.^[162, 163]



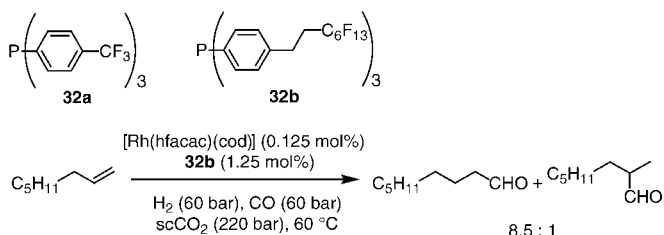
Scheme 24. Asymmetric hydrogenation of prochiral imines.



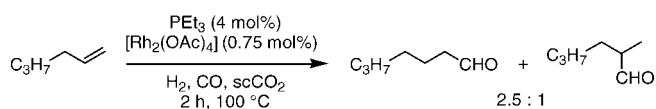
Scheme 25. Hydrogenation of carbon dioxide.

2.3.2.2. Hydroformylation

Hydroformylation of propene in scCO_2 was reported as early as 1991.^[184, 185] Fluorinated phosphane ligands **32** were used by Palo and Erkey as well as Leitner and co-workers to obtain scCO_2 -soluble rhodium(i) catalysts for hydroformylation reactions. The results obtained were comparable to those obtained in conventional systems (Scheme 26).^[186–188] Similar results were found using commercially available trialkylphosphanes, which also show reasonable solubility in scCO_2 (Scheme 27).^[189]

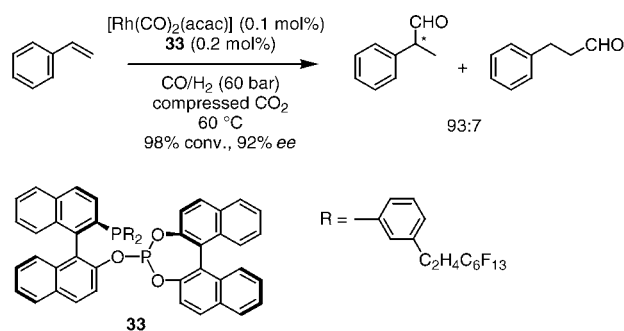


Scheme 26. Hydroformylation using **32a** and **32b**.



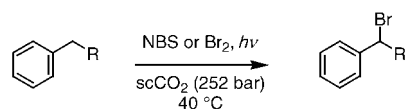
Scheme 27. Use of trialkylphosphanes in hydroformylation reactions.

Asymmetric catalytic hydroformylation using the per-fluoro-tagged (*R,S*)-binaphos ligand **33** and $[\text{Rh}(\text{CO})_2(\text{acac})]$ in dense CO_2 was addressed by Leitner and co-workers as well as by Lin and Akgerman.^[169, 190, 191] The products were isolated by using a CESS procedure. The pressure was reduced to give a liquid–gaseous two-phase system, which was consequently extracted with dense CO_2 , with the active catalyst left behind for subsequent reactions (Scheme 28).

Scheme 28. Asymmetric hydroformylation using a fluorinated binaphos ligand **33**.

2.3.2.3. Halogenation

Tanko and Blackert investigated photo-initiated bromination reactions in scCO_2 as a “green” alternative to halogenated solvents.^[161] They found selectivities almost identical to the ones observed in chlorinated solvents. Only with molecular bromine as the brominating agent did the competing electrophilic aromatic substitution occasionally produced a small amount of a side product. This problem did not occur in the Ziegler bromination with NBS (Scheme 29).

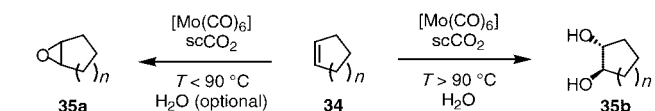
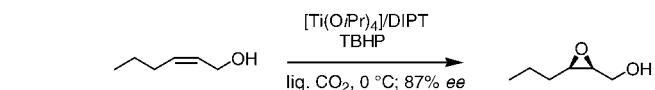
Scheme 29. Bromination in scCO_2 .

2.3.2.4. Oxidation^[192]

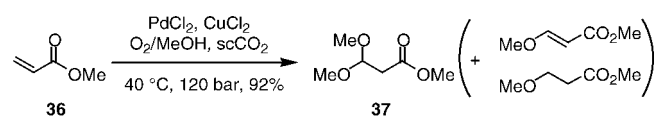
As a result of their inertness towards oxidation, scH_2O and scCO_2 are attractive media for oxidation reactions since they provide safe processes and avoid the formation of side products from solvent oxidation. Supercritical water has found its widest and most important application in the supercritical water oxidation process (SCWO) for the total aerobic oxidation of toxic wastes.^[193–196] Oxidation reactions are usually performed in scCO_2 and benefit from the expanded explosion limits which allow for higher oxidant/

substrate ratios. Even highly exothermic oxidation processes may be controlled efficiently as scCO_2 shows better heat-transport capacities than gaseous mixtures.

A number of oxidation reactions in scCO_2 have been reported in which a metal catalyst and a TBHP oxidizing agent have been used. For example, cyclic olefins **34** could be oxidized selectively to either epoxides **35a** or *trans*-1,2-diols **35b** with $[\text{Mo}(\text{CO})_6]$ as the catalyst (Scheme 30).^[197, 198] Similarly, allylic and homoallylic alcohols have been epoxidized in liquid CO_2 using $[\text{VO}(\text{O}i\text{Pr})_3]$ as the catalyst.^[198] This epoxidation reaction can also be conducted asymmetrically by employing the Sharpless procedure (Scheme 31).^[198]

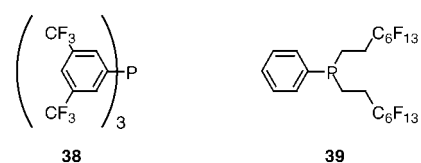
Scheme 30. Oxidation of cyclic olefins in scCO_2 .Scheme 31. Asymmetric Sharpless epoxidation in scCO_2 .

Molecular oxygen is without doubt the most attractive oxidant for selective catalytic oxidation reactions. Again, such reactions can profit from being performed in SCFs, since total miscibility with oxygen is achieved and the oxygen concentration can be easily adjusted.^[199] For example, the autoxidation of substituted phenols by Schiff base complexes in scCO_2 gave high selectivities for the corresponding quinone at a oxygen/substrate ratio of at least 200/1, which is only practical in SCFs.^[200] Scheme 32 shows an example of a palladium(II)-catalyzed oxidation of an acrylic ester **36** to dimethylacetal **37**.^[201]

Scheme 32. Pd-catalyzed oxidation of acrylic ester **36** with molecular oxygen.

2.3.2.5. C–C Coupling

Carrol and Holmes applied the perfluoro-tagged phosphane ligand **38** for solubilization of Pd complexes and successfully employed them for Heck, Suzuki, and Sonogashira couplings in scCO_2 .^[202] Ligand **39** was shown to be

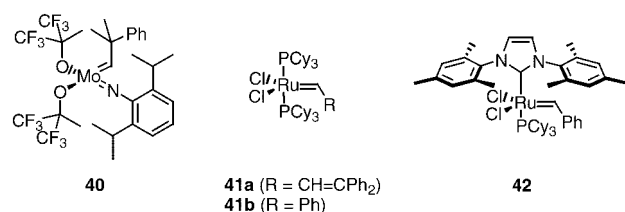


suitable for Heck and Stille couplings in scCO_2 .^[203] The two palladium complexes **17a** and **17d** were successfully tested in a Stille coupling.^[172] Product purification and catalyst recycling was achieved by extracting the residue with FC-72 after dissipation of the CO_2 . In both steps, the difference in solubility between scCO_2 and the fluorinated solvent is mediated by the perfluoro tags. The recovered catalyst was reused and showed no loss in activity.

Surprisingly, the catalyst $[\text{Pd}(\text{PPh}_3)_2]\text{Cl}_2$, which is expected not to dissolve in scCO_2 , also mediated these Stille couplings. Recently, palladium acetate in combination with the non-fluorous ligand tris(*tert*-butyl)phosphane was also reported to give good yields in Heck and Suzuki couplings conducted in scCO_2 .^[204]

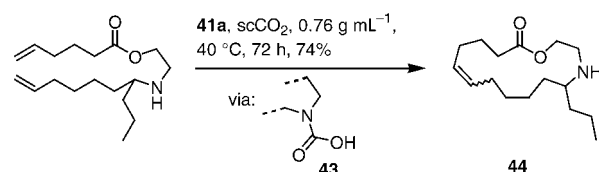
2.3.2.6. Olefin Metathesis

Fürstner, Leitner, and co-workers investigated ring-closing metathesis (RCM) reactions in dense CO_2 . A 16-membered ring could be closed in yields of over 90% at high pressures, while mainly oligomers were obtained at lower pressures.^[205, 206] This observation was explained in terms of the Ziegler–Ruggli principle, with higher pressure corresponding to a higher CO_2 density and, hence, a higher dilution. The complexes used as catalysts or catalyst precursors in scCO_2 are shown in structures **40**–**42**.^[205, 206] While complex **40** is



completely soluble in scCO_2 , carbenes **41** and **42** showed no visible solubility. Isolation of the product by this process is commonly referred to as selective supercritical fluid extraction (SFE). In principle the organic materials can be collected directly from the gas stream by using appropriate traps to leave the catalyst behind.^[147]

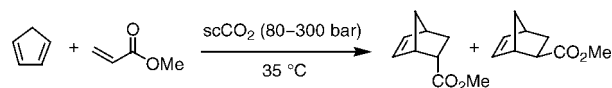
The reversible formation of a carbamic acid in scCO_2 from a secondary amine has been used successfully as a protecting strategy in the metathesis approach to the natural product epilachnen (**44**, Scheme 33).^[205] Secondary and primary amines deactivate complex **41a** and therefore requires protection. In scCO_2 , however, the amine is reversibly transformed into the corresponding carbamic acid **43** and good yields of the aza macrocycle **44** are obtained.^[205]



Scheme 33. Protecting strategy in the synthesis of epilachnen (**44**).

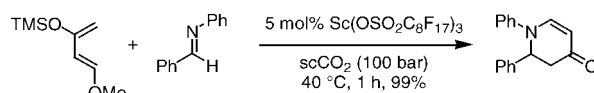
2.3.2.7. Diels–Alder Reactions

A significant increase in the rate constant of the cycloaddition of maleic anhydride and isoprene was observed near the critical pressure.^[207–209] Furthermore, Kim and Johnston found a slight pressure dependency of the *exolendo* ratio of Diels–Alder reactions in SCFs (Scheme 34).^[210] The transition states leading to the two isomeric products differ in their dipole moments. Interactions with the nonpolar solvent scCO_2 are pressure or density dependent, thus causing a difference in diastereoselectivity.



Scheme 34. Example of the pressure dependency of a Diels–Alder reaction.

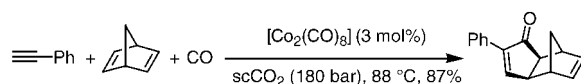
Rayner and co-workers used soluble scandium triflate for a number of Lewis acid catalyzed Diels–Alder reactions in scCO_2 and found improved diastereoselectivities compared to those obtained in conventional solvents.^[211] For the analogous aza-Diels–Alder reactions, Kobayashi and co-workers were able to show a relationship between catalyst activity and the length of the perfluoroalkyl chains (Scheme 35).^[212]



Scheme 35. Aza-Diels–Alder reaction performed in scCO_2 .

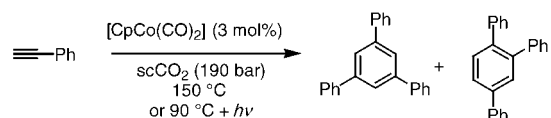
2.3.2.8. Miscellaneous Synthetic Reactions

Jeong et al. reported the synthesis of a substituted cyclopentenone by a Pauson–Khand reaction (Scheme 36).^[213] A $[\text{CpCo}(\text{CO})_2]$ -catalyzed cyclotrimerization of alkynes in



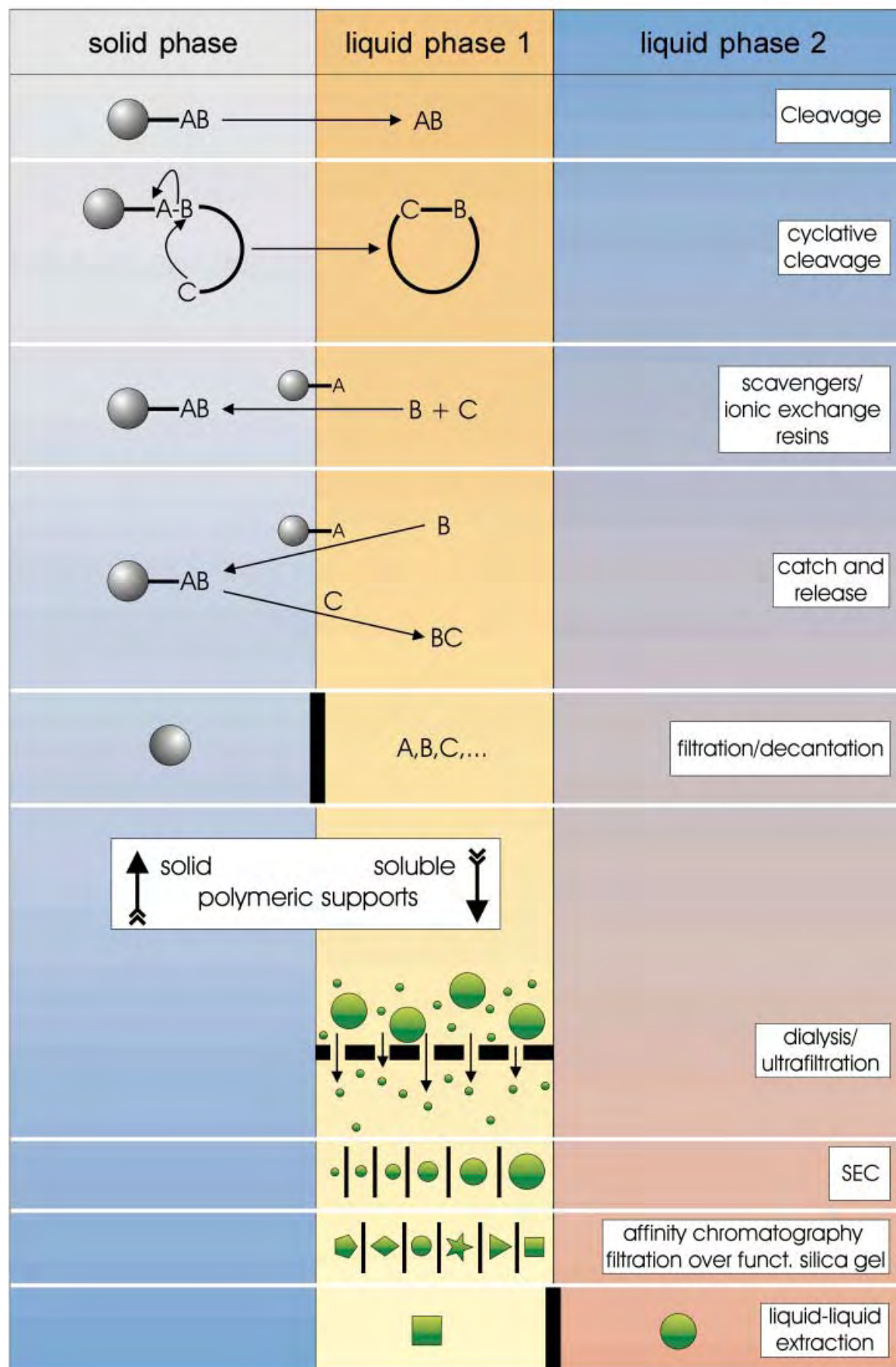
Scheme 36. Pauson–Khand reaction in scCO_2 .

scCO_2 was reported by Avilés and co-workers (Scheme 37).^[214] Tumas and co-workers applied an in situ generated rhodium catalyst with fluorinated trialkylphosphane ligands to hydroboration of alkenes.^[215] Similarly, ruthenium- and rhodiumphosphane complexes were successfully used as catalysts for the hydrosilation of olefins in dense CO_2 .^[216] The great interest in utilizing SCFs for polymerization processes has been described in a series of review articles.^[157, 217, 218]



Scheme 37. $[\text{CpCo}(\text{CO})_2]$ -catalyzed cyclotrimerization of alkynes in scCO_2 .

Polymer-based separation techniques



3. Polymer-Based Separation and Purification Techniques

Polymeric supports have been used for over 50 years to simplify and accelerate the work-up of organic reactions. Initially ion-exchange resins dominated the field, while in the last decade more specific polymeric supports and linker systems have been used. A number of different polymers, cross-linked (insoluble) and non-cross-linked (soluble), have been used for many different applications.^[219]

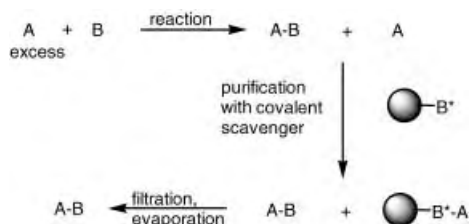
3.1. Polymer-Supported Scavenger Reagents

The ability to use multiparallel purification techniques is of great importance to solution-phase combinatorial synthesis. Polymer-supported scavenger reagents can be used since they allow for an automated purification protocol for a large number of parallel reactions.^[220–224] In general, one or more solid-supported reagents which selectively bind to impurities, either covalently or ionically, are added to a reaction mixture. The choice of scavenger depends on the nature of both the impurity as well as the desired product.

This work-up procedure has frequently been performed in a parallel format. However, most of the employed scavengers have relatively small loading capacities and hence this approach is useful only for small-scale reactions. Even though the protocol can be performed by a robotic system, the automated addition of beads is still problematic. To circumvent the handling problems associated with beads, a so-called pass-flow system has recently been developed by Kirschning et al.^[225] Here the beads are immobilized on a porous glass frit sealed in a pressure tubing. This reactor can be operated by an automated HPLC system.

3.1.1. Covalent Scavengers

The general concept of covalent scavengers is shown in Scheme 38: Reagent **A** is present in an excess to drive the reaction to completion. The resulting reaction mixture contains the product **AB** and the remaining reagent **A**. Subsequently, the polymer-supported scavenger is added, which bears a reactive functionality **B*** that is similar to compound **B**, to consume the remaining starting material **A**. The isolation of the product is achieved by filtration and

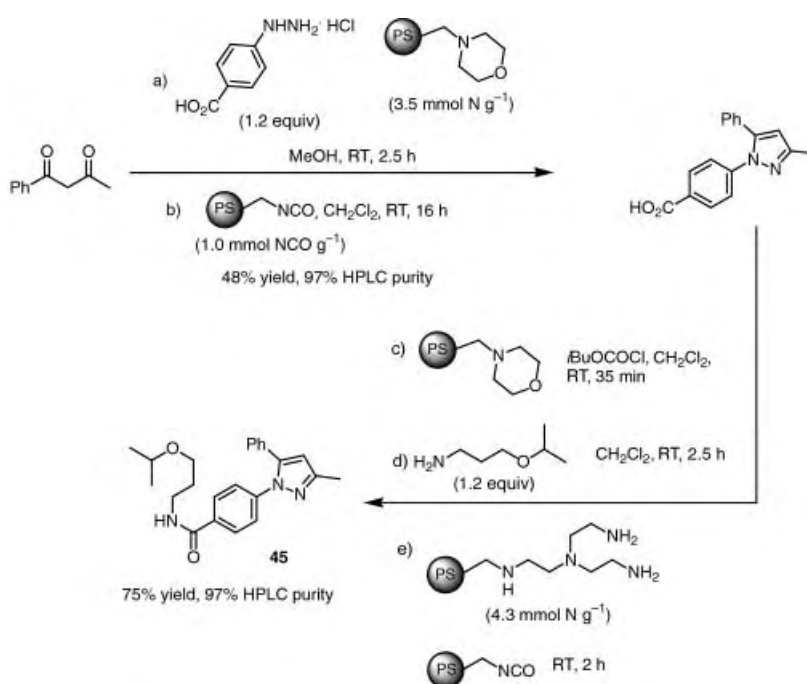


Scheme 38. Schematic representation of a reaction purification with covalent scavengers.

solvent evaporation.^[226] Covalent scavengers have been designed for the removal of electrophiles in the presence of nucleophiles and vice versa.

3.1.1.1. Removal of Electrophiles by Nucleophilic Resins

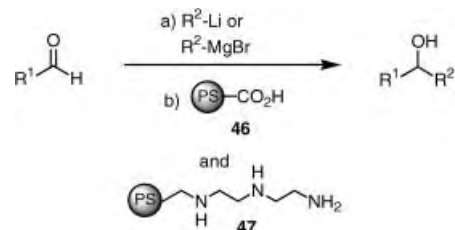
Booth and Hodges described the preparation of polystyrene-supported derivatives of tris(2-aminoethyl)amine for the scavenging of ureas, thioureas, sulfonamides, amides, and pyrazoles.^[227] The multistep synthesis of a pyrazole **45** is shown in Scheme 39. In the first reaction, a polymer-bound amine is used to remove hydrochloric acid. Excess hydrazine is scavenged by a polymer-bound isocyanate. In the subsequent step the acid is activated, again in the presence of a polymer-supported base, and coupled with an amine. After this reaction, the polymer-bound amine and isocyanate are used together to remove any residual activated acid and amine. The simultaneous use of electrophilic and nucleophilic scavengers is possible, since they cannot react with each other



Scheme 39. Synthesis of pyrazole by using polymer-supported scavengers.

because they are immobilized on different beads. These resins have also been used successfully for removing acid chlorides, sulfonyl chlorides, and isothiocyanates from solutions.^[228]

Aldehydes have been separated from alcohols through formation of an imine with a primary amine resin **47** (Scheme 40).^[229] In this reaction a carboxylic acid resin **46**

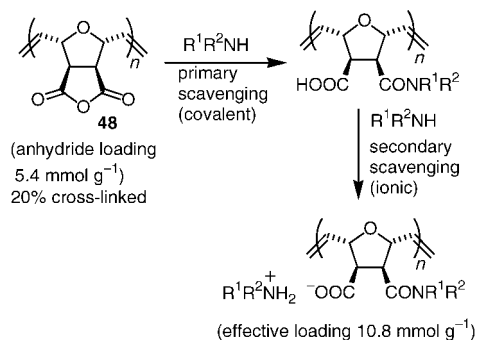


Scheme 40. Separation of aldehydes from alcohols by formation of an imine with a primary amine resin.

was used to remove any excess Grignard reagent, reprotonate the metal alkoxide, and scavenge the metal ions as salts of the resin. In another example, derivatized cellulose beads with a high loading of primary amines were used to scavenge amides and ureas.^[230] In contrast to common polystyrene materials, this support can be degraded by enzymes, which could solve disposal problems.

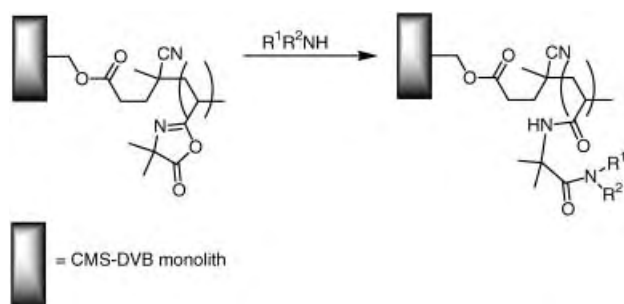
3.1.1.2. Removal of Nucleophiles by Electrophilic Resins

A number of resins have been developed for the removal of amines or hydrazines from solution (Scheme 39). A good choice are polymer-bound isocyanates^[231] since no by-products are released from the resin during the quenching reaction. Furthermore they can be used for scavenging excess primary and secondary amines during the formation of amides and sulfonamides,^[227, 232–234] as well as for the separation of secondary amines from tertiary amines and tertiary amino alcohols. Other electrophilic resins are polymer-supported aldehydes and acid chlorides.^[232] Another alternative for removing excess amines and hydrazines are the so called ROMPGEL scavengers **48**, which are high-loading supported anhydrides (Scheme 41).^[235]



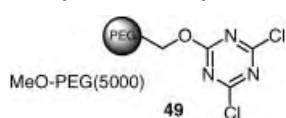
Scheme 41. Sequestration of excess amine with a ROMPGEL scavenger.

Another approach uses grafted macroporous polymer monolith disks as scavengers for amines (Scheme 42).^[236, 237] These materials consist of poly(chloromethylstyrene-*co*-di-



Scheme 42. Macroporous polymeric CMS-DVB monolith scavengers for the separation of amines.

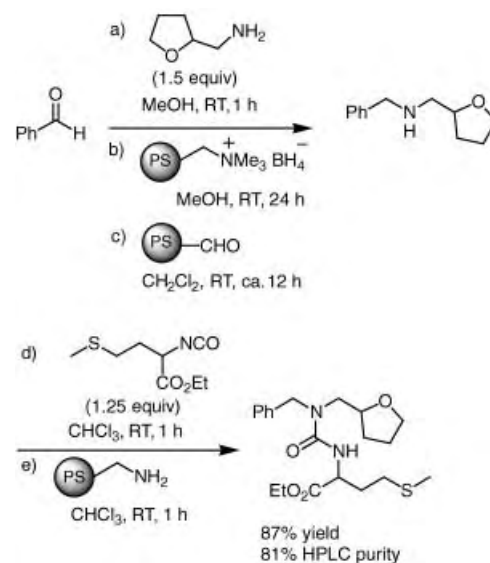
vinylbenzene) and are activated by graft polymerization of 4-vinyl-2,2-dimethylazlactone to its porous surface. Falchi and



Taddei described polyethylene glycol-dichlorotriazine (PEG-DCT, **49**) as a soluble electrophilic scavenger.^[238] It can be

obtained from reaction of trichlorotriazine with MeO-PEG-OH ($M_w = 5.000 \text{ g mol}^{-1}$) and can be used as a scavenger for primary, secondary, and tertiary alcohols, as well as for diols, polyalcohols (for example, D-mannitol), and for thiols in different kinds of reactions such as the formation of esters, silyl ethers, acetals, thioacetals, and thioglycosides. (For further properties and separation techniques for soluble polymers see Section 3.4.)

The simultaneous use of both nucleophilic and electrophilic scavengers has been reported by Kaldor, Siegel et al.^[232] for the alkylation and acylation of amines. Purification of the products was achieved through the use of immobilized amines, isocyanates, aldehydes, and acid chlorides. Although a complex distribution of products is obtained, purities up to 95% can be reached. Another example is shown in Scheme 43. In the first step the reductive amination requires

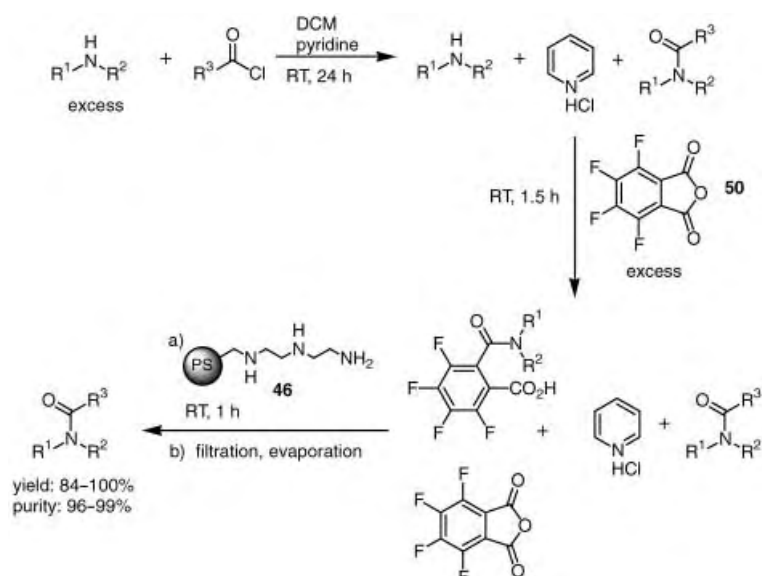


Scheme 43. Simultaneous use of electrophilic and nucleophilic scavenger resins for purification.

the use of an excess of amine to drive the imine formation to completion. Then polymer-bound borohydride is added for imine reduction and subsequently the excess of primary amine can be scavenged by a polystyrene-bound carbaldehyde. Reaction of the resulting secondary amine with excess of a functionalized isocyanate yielded the desired urea. Residual isocyanate was removed with an aminomethylated polystyrene resin.^[223]

3.1.2. Purification by Sequestration-Enabling Reagent Technique

Another form of separation using covalent scavengers is the so-called sequestration-enabling (SER) technique. For example, an excess of amine in a crude product can be derivatized to a carboxylic acid by reaction with surplus tetrafluorophthalic anhydride (**50**, Scheme 44).^[229] The polymeric amine scavenger **46** is then added. This reagent plays three different roles: eliminating the HCl formed during the first reaction step, thus allowing the pyridine to be removed by evaporation, and removing the hemitetrafluorophthalic acid and the excess

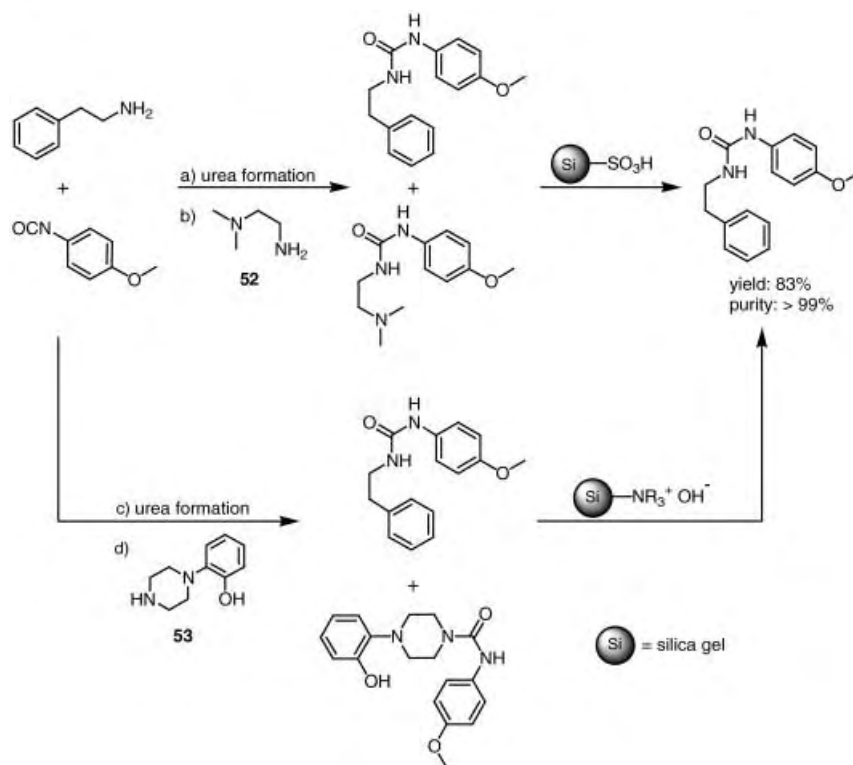


Scheme 44. Derivatization of excess amine with tetrafluorophthalic anhydride as a SER.

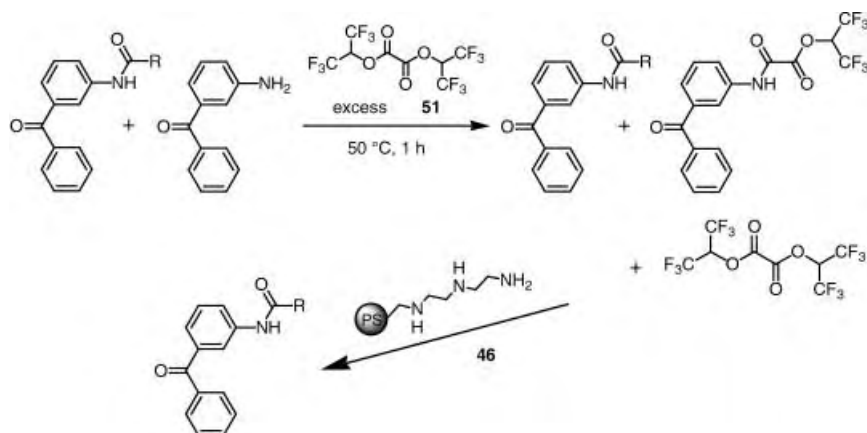
of SER reagent **50** by ionic interaction and covalent binding, respectively. This technique using electrophilic SER reagents allows for the creation of products with high purity.

A variation of the SER technique uses bis(hexafluoroisopropyl) oxalate (**51**) to form a hemiamide with an excess of amine.^[239] Subsequently, the remaining active ester functionality is covalently sequestered along with excess of **51** by treatment with the polymer-bound amine **46** (Scheme 45). These SER methods are superior to the use of polymer-supported isocyanates for the removal of anilines.

Nucleophilic SER reagents have also been described.^[229, 240, 241] Scheme 46 shows an example of amine SERs **52** and **53** to remove excess isocyanate. In the case of **52**, the resulting basic compounds can be separated by cation-exchange chromatography. Alternatively, when **53** is used as the SER, the generated phenolic component is



Scheme 46. Removal of excess isocyanate with a nucleophilic amine SER.



Scheme 45. Removal of amines with hexafluoroisopropyl oxalate (**51**) through formation of a hemiamide.

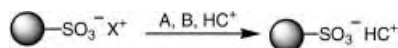
removable by anion-exchange chromatography. In general, it is often more cost-effective to perform a SER reaction so as to take advantage of a readily available and inexpensive purification resin than to spend time in developing a special scavenger resin for the same purpose.^[226] The same limitations apply for parallelization and automation of the SER technique as already mentioned for polymer-supported scavenger reagents.

3.1.3. Purification with Ion-Exchange Resins

Polystyrene-based macroporous resins functionalized with quaternized amines and sulfonates, so-called ion-exchange resins, have been known since the 1950s

and used in a wide variety of applications. Typical usages include purification of water,^[242] serum analysis,^[243] and protein purification.^[244] In addition, they can also be used as reagents and scavengers in solid-phase organic synthesis and the purification of extremely hydrophilic molecules such as peptides and amino acids which are often difficult to purify by other methods.^[245, 246] An advantage of ion-exchange chromatography over traditional methods such as HPLC or flash chromatography is that one can reliably predict the elution characteristics of a broad range of molecules solely by the presence or absence of an ionizable site in the molecule.

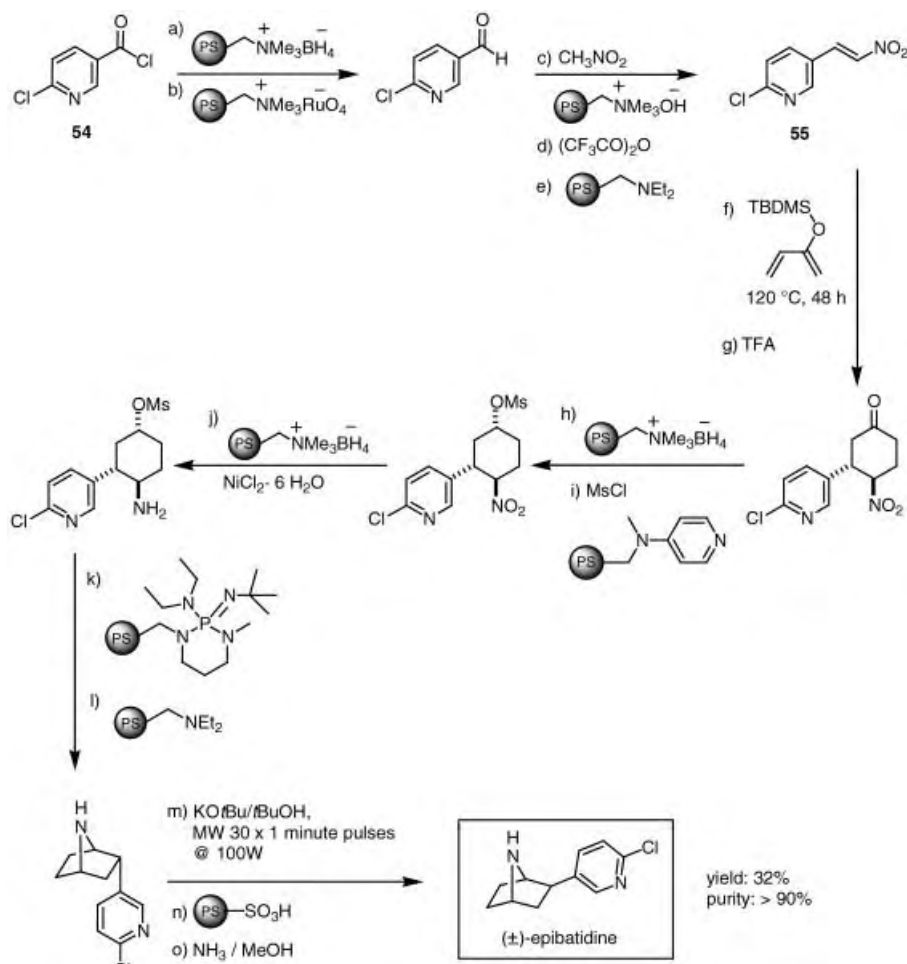
The typical way of using a strong cation ion exchange column is depicted in Scheme 47.^[240] Two neutral molecules A and B pass through a sulfonic acid based



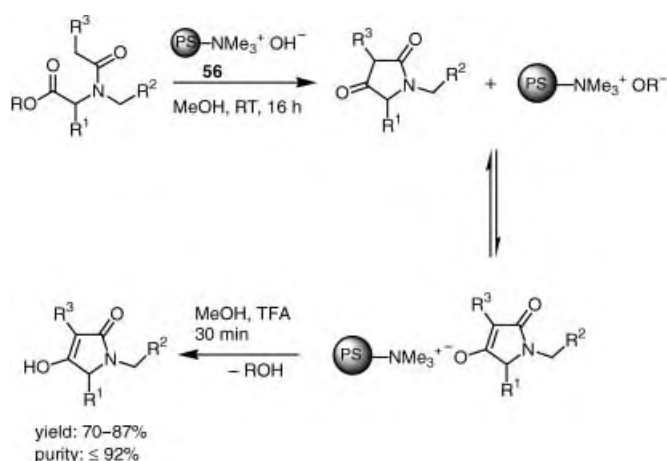
Scheme 47. Interaction with a strong cationic ion exchange resin.

cation-exchange column, while the protonated molecule C is retained. In a similar way, a cationic ion-exchange resin can be used as a scavenger for the purification of organic reactions containing, for example, amines or ammonium salts. In contrast to covalent scavenger reagents, which are mainly based on gel-type microporous PS beads with relatively moderate loading capacities (1–2 mmol g⁻¹), ion-exchange resins can have much higher loading capacities (up to 5 mmol g⁻¹). An impressive example by Ley and co-workers^[247] demonstrates the high potential of scavengers in natural product synthesis, namely, the use of cation-exchange resins as scavengers in the final purification of the multistep synthesis. Scheme 48 describes the linear ten step sequence of the potent analgesic (±)-epibatidine. This compound was accessible in an overall yield of 32% and in more than 90% purity without column chromatography. This example demonstrates once more the utility of polymer-supported reagents in combination with polymer-supported scavengers for combinatorial synthesis. For example, the conversion of the acid chloride **54** to the intermediate nitroalkene **55** (five steps!) could be performed in a one-pot procedure.

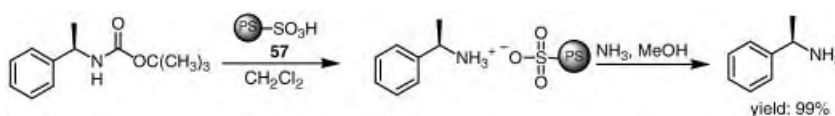
Ion-exchange resins can not only be used in purification steps but may also be included in a chemical reaction. Kulkarni and Ganesan described the application of Amberlyst A-26 (OH⁻ form, **56**) for effecting both ring closure and purification of libraries of 2,4-pyrrolidinediones (Scheme 49).^[248] Cyclization yields the desired products as their ionically bound enolates, which were cleaved by treatment with trifluoroacetic acid. Ten compounds with yields of 70–87% and good purities of up to 92% were reported. A combination of purification and deprotection of a Boc protecting group was described by Bergbreiter, Romo, and co-workers.^[249] They used an Amberlyst-15 exchange resin **57** in its SO₃⁻ form. As depicted in Scheme 50 the products were treated with an excess of resin **57** at room temperature in CH₂Cl₂. This process resulted in deprotection and allowed the free amino group to bind ionically to the polymeric support. By-products and impurities were subsequently washed off. Release of the primary amines were



Scheme 48. Synthesis of (±)-epibatidine by using supported reagents and scavengers.



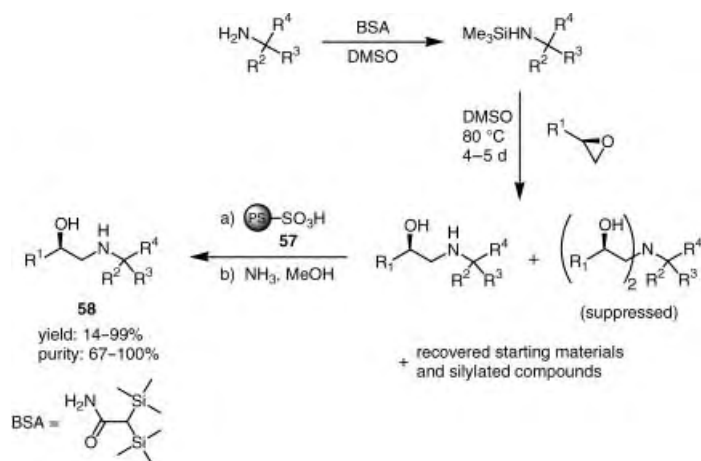
Scheme 49. Synthesis of 2,4-pyrrolidinediones using a basic ion-exchange resin.



Scheme 50. A combination of purification and deprotection with a sulfonic acid based Amberlyst-15 exchange resin.

achieved with ammonia in methanol. Ten amines were synthesized with yields of up to 99 %.

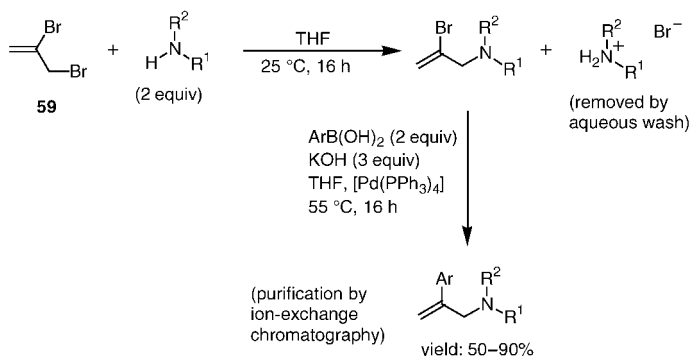
Siegel and co-workers reported the synthesis of a library of 48 β -amino alcohols **58** by using a parallel synthesis approach.^[250] In the first step the primary amine is silylated in situ with bis(trimethylsilyl)acetamide (BSA) in DMSO, before adding an epoxide to the reaction mixture (Scheme 51). Isolation of the desired ethanolamine was



Scheme 51. Synthesis of a 48 compound library of β -aminoalcohols, purified by a strong ion-exchange chromatography.

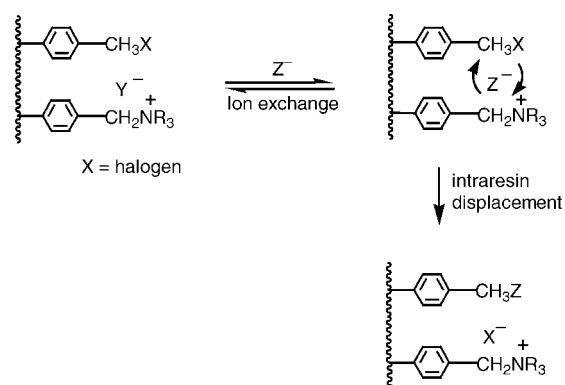
achieved using a strongly acidic ion-exchange resin **57**. The amine was retained on the column while residual epoxide, silicon by-products, and DMSO were removed by washing with methanol. Subsequently, the method was applied to an array of 8×6 reactions with yields up to 99 % and purities up to 100 %. Recently, Siegel, Organ, and co-workers described the synthesis of a 1344-member allylic amine library.^[251] First, the alkylation of an excess of secondary amine with 2,3-dibromopropene (**59**) was achieved (Scheme 52). The HBr salt of the excess amine was then removed either by filtration or aqueous extraction. A subsequent Suzuki cross-coupling reaction yielded the allylamine which was purified by ion-exchange chromatography.

Another recent application of cation-exchange resins as scavengers is the removal of boronic acids from solution.^[252] In this application the complexed boronic acid can be subsequently released by cyclative cleavage (see Section 3.2.1.2). Regen et al. reported on a chloromethylated polystyrene for



Scheme 52. Purification of a library of allylic amines by ion-exchange chromatography.

the scavenging of organic anions by covalent and ionic interactions.^[253] Scheme 53 shows how such partially quaternized anion-exchange resins can be used. The pendant



Scheme 53. General concept using partially quaternized anion-exchange resins as covalent scavengers; X = Cl, $\text{Y}^- = \text{Cl}^-$, $\text{Z}^- = \text{cholate anion}$.

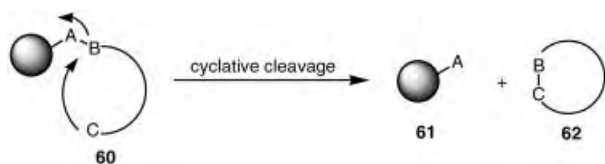
quaternary ammonium groups concentrate organic anions and therefore assist the nucleophilic displacement at the chloromethyl sites.^[254–256] The ammonium groups allow for the swelling of the resin in aqueous media and thus make the chloromethyl groups accessible. Another possible way of purification is based on polymer-supported reagents. A polystyrene resin is generally used as the support and different ligands are immobilized on it. Typical ligands include amines, pyridines, imidazoles, oximes, hydroxylamines, Schiff bases, thiols, crown ethers, and a variety of phosphorus ligands.^[257] This procedure thus allows a wide range of different metal ions to be recovered from solution.

3.2 Selective Cleavage from the Polymeric Support

An attractive feature of polymer-supported multistep organic synthesis is that the desired products can be selectively cleaved from the polymeric support. If a supported compound has not successfully passed every single step of the executed reaction sequence it will not be cleaved from the polymer support. Completion of a polymer-supported multistep synthesis with a selective cleavage reaction can yield products of high purity even if the previous transformations did not proceed quantitatively.^[3] Thus, one of the decisive disadvantages of polymer-supported chemistry, the inability to purify polymer-bound intermediates from each other, can be overcome. Selective cleavage provides final products which ideally do not require purification, thus greatly facilitating rapid synthesis^[258] and making this separation strategy ideal for parallel and automated synthesis.

3.2.1. Cyclative Cleavage

As shown in Scheme 54, cyclative cleavage is the result of an intramolecular reaction that yields a cyclized product. The polymer-bound side products are incapable of cyclizing, and thus remain attached to the polymeric support on release of the desired material.^[259] Those groups which undergo intermolecular reactions during the cleavage step also remain



Scheme 54. The principle of cyclative cleavage.

bound to the polymeric support.^[260] Cyclative cleavage often involves formation of a carbon–heteroatom bond during the cyclization step, but there are also examples of carbon–carbon bond-forming cyclizations.^[261]

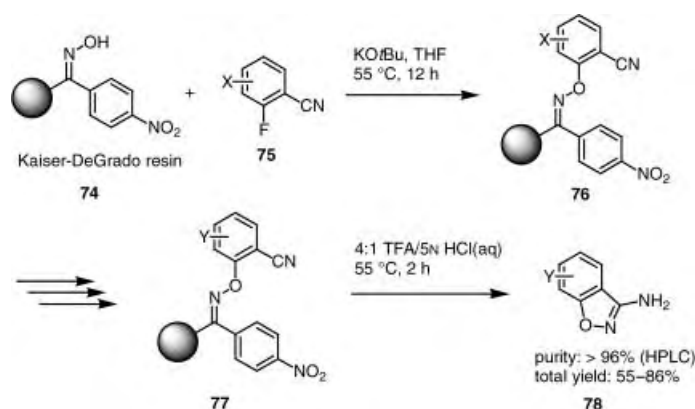
3.2.1.1. Cyclative Cleavage with Carbon–Heteroatom Bond Formation

Several polymer-supported approaches to heterocycles obtained by cyclative cleavage have been described. Examples include benzazepinones,^[262] benzodiazepinones,^[258, 263] diazepindiones,^[264–266] hydantoin,^[258, 263, 267–274] thiohydantoin,^[268] thiazolylhydantoin,^[275] benzopyrones,^[276] benzoisothiazolones,^[258] benzisoxazoles,^[277, 278] diketopiperazines,^[265, 279–281] diketomorpholines,^[280] quinazolidinones,^[282, 283] hydroxyquinolinones,^[284] pyrazolones,^[285–287] dihydropyridines,^[288] dihydropyrimidinones,^[289] pyridine-fused heterocycles,^[290] oxazines,^[291, 292] oxazolines,^[291, 292] oxazolidinones,^[293–296] phthalides,^[297] lactones,^[298–300] lactams,^[301] cyclic sulfonamides,^[302] cyclic ethers,^[303–306] cyclic imides,^[307] tetrahydro- β -carbolines,^[308, 309] 2-quinolone,^[310] coumarin,^[310] indolyl diketopiperazine alkaloids,^[311, 312] and cyclic peptides.^[313–315] Photoinduced cyclative cleavage reactions have also been reported.^[310, 316]

Diketopiperazines are quite common in nature and many natural products have been isolated with a wide range of biological activities. Szardenings et al. described two methods for the solid-phase-supported synthesis of diketopiperazines with three or four centers of diversity.^[280] Each of them includes a cyclative cleavage step. The first method (Scheme 55) starts with the esterification of a protected

amino acid **64**. Deprotection and reductive amination furnishes a secondary amine **67**, which is then acylated with a Boc-protected amino acid **68**. Successive deprotection results in the cyclization precursor **69b**. The cleavage-mediated cyclization yielded pure compounds **70** (> 90 % by LC). Potential side products, including nonalkylated **71**, nonacylated **72**, or over-alkylated **73**, remain attached to the resin and do not contaminate the library mixtures. Alternatively, these structures can also be prepared by a one-step Ugi multicomponent reaction and subsequent cyclative cleavage. Other than the building blocks, no further reagents are required, which makes this procedure especially attractive for high-throughput synthesis.

Lepore and Wiley reported on the synthesis of 3-aminobenzisoxazoles **78** (Scheme 56).^[277, 278] Several on-resin modifications such as hydrolysis and amide-bond formation, Mitsunobu reactions, nucleophilic aromatic substitutions, Suzuki reactions, Sonogashira couplings, and Horner–Wadsworth–Emmons olefinations are possible, depending on the group X. Cyclative cleavage is induced by aqueous acidic conditions.

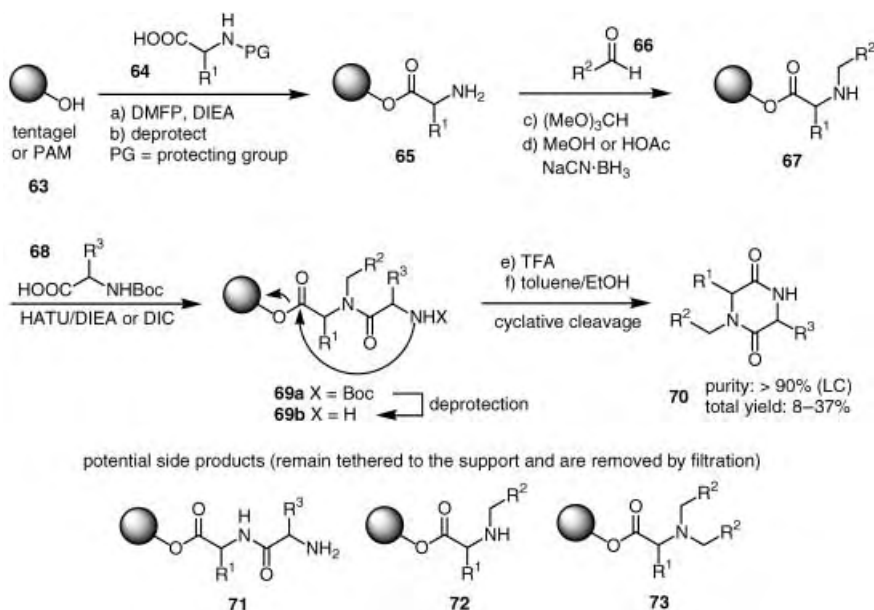


Scheme 56. Synthesis of 3-aminobenzisoxazoles.

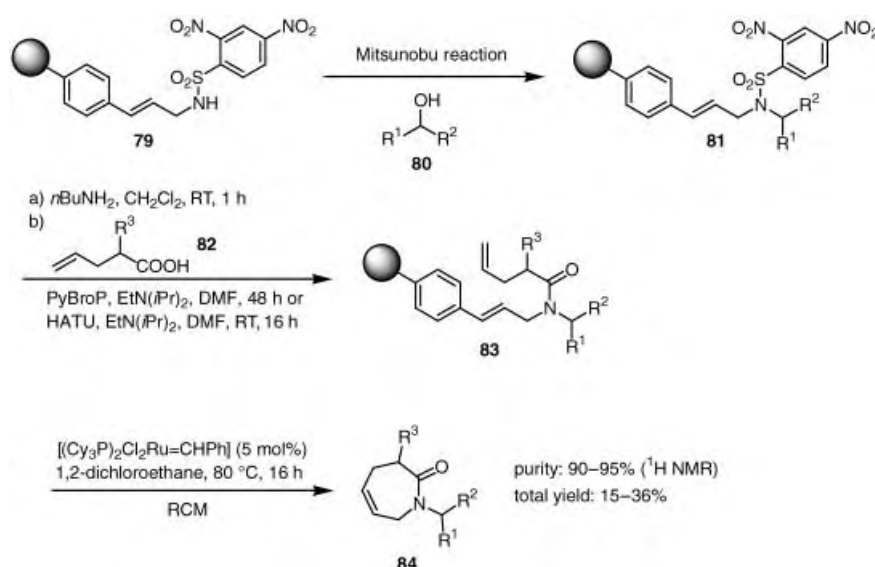
3.2.1.2. Cyclative Cleavage with Formation of a C–C Bond

Formation of a C–C bond in the cyclative cleavage step can occur in several ways. Ring-closing metathesis has been used most frequently, for example, in the synthesis of dihydropyranes,^[317] pipercolinnic acid derivatives,^[317] Freidinger lactams,^[317–320] and other N heterocycles,^[321] furans,^[322] phenols,^[323] and macrocycles.^[324–326] The advantages of this cyclization reaction are the chemical stability of an olefinic linker, the mild conditions required for cleavage, and the tolerance of the catalyst to a wide range of functional groups (for example, –COOH, –CONH–, –CHO, –CO–, –OH, –SONH–).^[261]

Piscopio et al. described the synthesis of Freidinger lactams **84** by using an initial Mitsunobu loading step to obtain an intermediate resin-bound sulfonamide **81** (Scheme 57).^[318] After cleavage of the sulfo-



Scheme 55. Preparation of diketopiperazines.



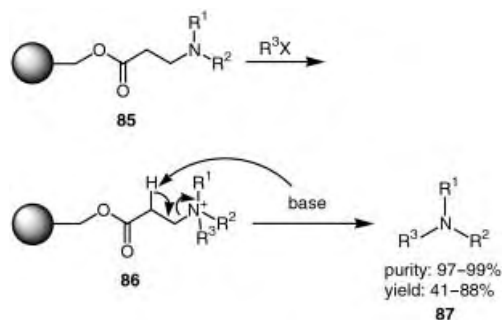
Scheme 57. Synthesis of Freidinger lactams.

namide group and acylation with an ω -unsaturated pentenoic acid derivative **82**, ring-closing metathesis with concomitant substrate cleavage provided the desired lactam **84** in high purity (90–95% by ^1H NMR spectroscopy). The ring-closing step can also include formation of a bond between the carbon atoms of a nucleophilic and an electrophilic. In this way, cyclic ketones,^[327] tetramic acid derivatives,^[328–331] indols (through the Wittig reaction),^[332] and macrocycles (through the Horner–Wadsworth–Emmons reaction) have been prepared.^[333] Ring closure by a transition-metal-mediated C–C coupling reaction has also been reported.^[334, 335]

A cyclative cleavage based on a catch-and-release strategy was recently reported by Vaultier and co-workers.^[252] In this case, a boronic acid was trapped by a cationic ion-exchange resin and subsequently released by an intramolecular Suzuki-type reaction.

3.2.2. Noncyclative Selective Cleavage

Noncyclative selective cleavage is mostly limited to selective elimination and fragmentation reactions.^[303–305, 336–339] Morphy and co-workers described the synthesis of tertiary amines **87** in which a selective β -elimination cleaving step was applied (Scheme 58).^[336] Coupling of the starting amine to an acrylate-functionalized polystyrene resin (Michael addition) and quaternization furnished the precursor for cleavage (**86**). Each step in the sequence has to proceed successfully for the

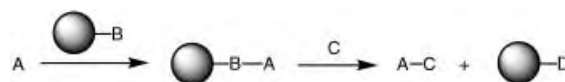


Scheme 58. Selective cleavage of a tertiary amine.

final Hofmann elimination to occur. The purity of the final product **87** was found to be similar whether or not the individual reactions were driven to completion.

3.3. Catch-and-Release

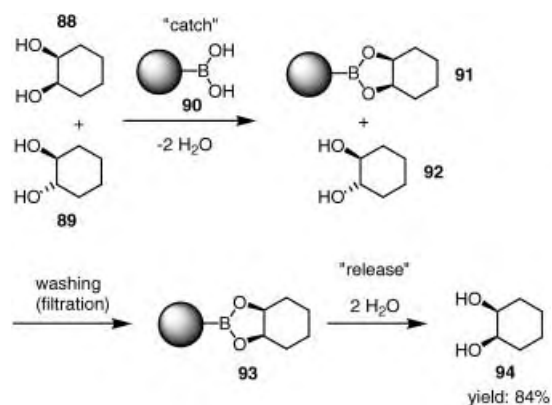
The catch-and-release strategy combines the features of both solution-phase chemistry and solid-phase chemistry. The principle of the catch-and-release strategy is shown in Scheme 59.^[340] A desired low-molecular-weight compound **A** (which was synthesized in solution) is immobilized on a functionalized polymeric support to yield an activated polymer intermediate. Soluble impurities such as by-products, excess reactants, or solvent are removed by a simple filtration/washing protocol. By using this strategy merely for purification purpose, the next step will release the desired product into a new solution environment. However, it is also possible to carry out one or several modification steps on the polymer-bound compound before performing the final release step. In the latter case, catch-and-release implies a transformation to the desired compound A–C and, as such, combines solution and solid-phase synthesis.

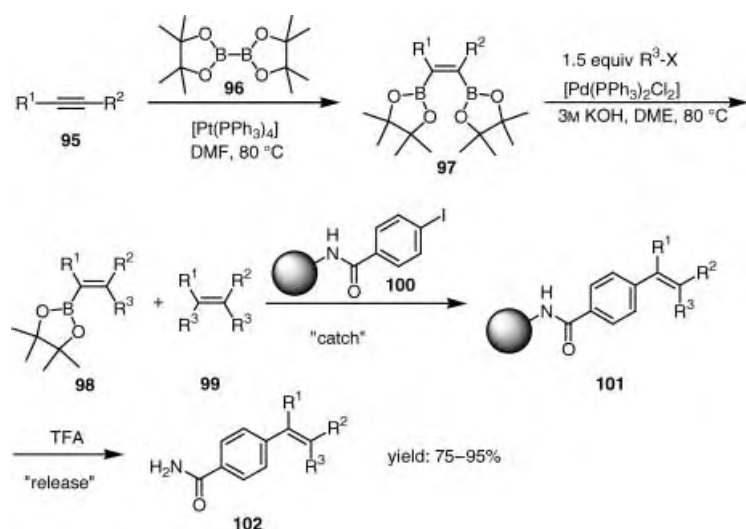


Scheme 59. The principle of the “catch-and-release” strategy.

The use of this method as a separation technique can facilitate the work-up, and is therefore particularly well-suited for multiparallel chemistry. Several applications in automated synthesis have been reported.^[341–343] Since a comprehensive overview of this technique was recently published^[340] we will describe only a few instructive applications.

An early example using “catch-and-release” as a purification strategy was reported by Seymour and Fréchet.^[344] They separated *cis*-diol **88** from *cis/trans* mixtures using polystyrene resin **90** functionalized with boronic acid groups (Scheme 60). Brown and Armstrong used the catch-and-release strategy for

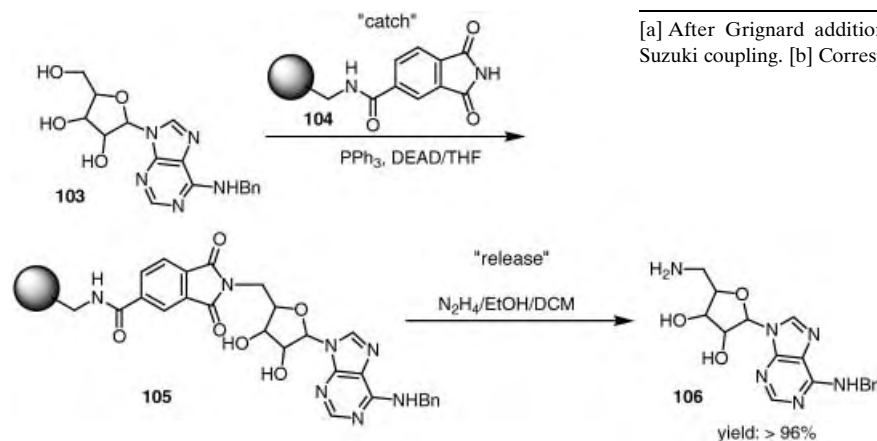
Scheme 60. Separation of *cis*-diols from a *cis/trans* mixture.



Scheme 61. Separation of Suzuki coupling products.

the separation of compounds resulting from a Suzuki coupling reaction (Scheme 61).^[345] The bis(boryl)alkene **97** is transformed with 1.5 equivalents of an organohalide to give the monoaddition product **98** along with the diaddition product **99**. The mixture is combined with a resin-bound aryl iodide **100** to initiate a second Suzuki reaction. Only the monoaddition product **98** is captured on the solid support. Several coupling products **102** were obtained in high yields (75–95%) after cleavage with TFA. This route was applied to the parallel synthesis of tamoxifen derivatives.^[346]

Aronov and Gelb described a procedure to “catch” alcohols and “release” amines (Scheme 62).^[347] The “catch” step is realized by a Mitsunobu reaction of the alcohol **103** with a phthalimide-containing resin **104**. After washing off the soluble compounds from the resin, a hydrazinolysis “release” step releases the corresponding amine **106** in high yield (>96%) and purity. This polymer-supported phthalimide could be used for the selective conversion of less sterically hindered alcohols into corresponding primary



Scheme 62. Synthesis of primary amines by the catch-and-release strategy.

amines or the generation of a resin-based combinatorial library starting with an alcohol. Combinations of both catch-and-release and cyclative cleavage have been employed to synthesize oxazolines, oxazines,^[291, 292] and benzopyrones.^[276] Table 2 gives a selection of further examples of the application of the catch-and-release strategy.

3.4. Purification and Separation with Soluble Polymeric Supports

It is generally believed that soluble polymeric supports are difficult to separate from the reaction mixture. However, this disregards their advantages (for example, homogeneous reaction conditions, standard analytical techniques, and high-loading capacities in some cases).

Table 2. Examples for the application of the catch-and-release strategy.

“Caught” compound	“Released” compound
acyl chlorides	amides ^[342] heterocyclic amides ^[387]
alcohols	alcohols (purification) ^[388] heteroatom-substituted amines, thiolates, imidazoles ^[a] ^[389] amines ^[347] oxazines, oxazolines ^[291] secondary and tertiary amines ^[391]
aldehydes	alkenes (purification), alcohols ^[392]
alkenes	benzopyrones ^[276]
alkynyl ketones	methyl esters ^[393]
9-anthrylmethyl-tagged esters	amines (purification) ^[240, 250]
amines	ureas ^[394] secondary and tertiary amines ^[391] guanidines ^[395]
β -amino alcohols	β -amino alcohols (purification) ^[396]
aryl boronic acids	macroheterocycles ^[252]
aryl carboxylic acids	aryl amines ^[397]
borylalkenes	tetrasubstituted ethylenes ^[345, 346]
carboxylic acids	<i>N</i> -hydroxysuccinimide esters ^[398]
carbonyl compounds	enones
iodoalkanes	alkanes, alkenes ^[392]
lithioaryls	arenes
ketones	1,2,3-thiadiazoles (after Stille coupling) ^[341]
phenols	aryl triflates and aryl nonaflates ^[399]
pyridines	alkylated dihydropyridones ^[400]
sulfonyl chlorides	sulfonamides ^[342]
α,β -unsaturated carbonyls	α,β -unsaturated carbonyls (purification) ^[b] ^[401]

[a] After Grignard addition, Wittig reactions, NaBH₄ reduction, reductive amination, Suzuki coupling. [b] Corresponding Diels–Alder adducts obtainable.^[390]

Several techniques for the separation of soluble polymers from low-molecular-weight compounds have been evaluated (see Table 3).^[348–351] There are various methods that separate macromolecules by size (preparative SEC, dialysis, membrane filtration and centrifugation).^[352–354] All of them are suitable for automation, however, little effort has been undertaken, compared to the progress made in solid-phase synthesis, for multiparallel automation in this area. Also, other separation techniques, such as precipitation,

Table 3. Separation techniques for soluble polymeric supports.

	Dialysis ^[a]	Ultrafiltration ^[a]	SEC ^[a]	Precipitation/filtration ^[b]	Liquid-phase separation ^[b]
M_w of polymer [g mol ⁻¹]	> 1000	> 1000	–	> 3000	–
sample volume [mL]	10–1000	1–100	< 1	1–100	10–1000
commercially available	yes	yes	yes	no	no
suitable for automation	yes	yes	yes	no	yes
suitable for high-throughput	no	yes	yes	no	yes
limitations	unsuitable for final cleavage step	–	–	unsuitable for multistep syntheses	different solubilities required

[a] Separation by differences in hydrodynamic volume; SEC = size-exclusion chromatography. [b] Separation by differences in solubility.

phase separation, and filtration through a silica cartridge have been reported. However, the application of these techniques to solution-phase synthesis depends on the physicochemical properties of each individual polymer. In addition, these techniques are sensitive to the change of functional groups on the polymeric support during the synthesis. Therefore, the use of soluble polymeric supports in combinatorial synthesis requires the careful selection of the appropriate separation technique.

3.4.1. Separation of Soluble Polymeric Supports by Size

For efficient and fast separations by size (hydrodynamic volume) homogenous polymeric supports should have medium molecular weights (5000–50 000 g mol⁻¹) and narrow molecular weight distributions (< 1.5). In addition, macromolecules with a persistent three-dimensional structure (for example, highly branched polymers) are preferable to a linear polymer structure. Purification based on size is general, since it does not rely on other physical differences between support-bound compounds, reagents, and catalysts. However, the eluent must be carefully chosen for the individual problem.

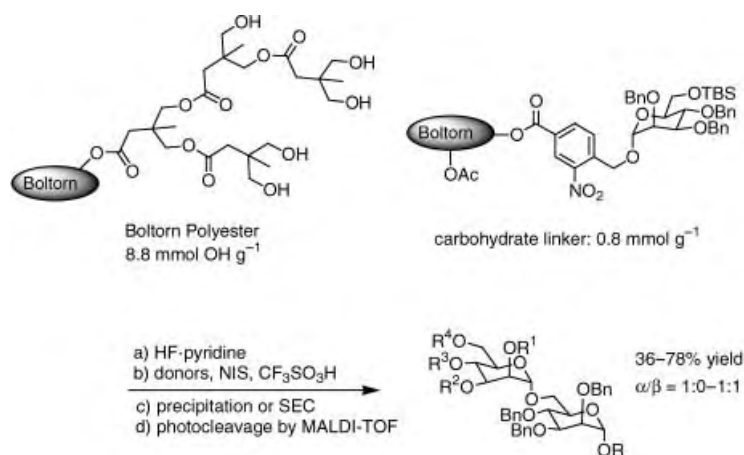
3.4.1.1. Size-Exclusion Chromatography

Size-exclusion chromatography (SEC; also known as gel permeation chromatography (GPC)) is used for the separation and fractionation of macromolecules on analytical and preparative scales.^[350] The separation occurs predominantly by the difference in the hydrodynamic volume of the macromolecules in solution, however, in some cases the polarity of the molecules can also influence the retention times. The SEC technique, like HPLC, generally gives very reproducible elution times (typically of < 1 h) and hence can be used for automated synthesis. However, the high cost of an automated SEC system means it must be considered as a serial separation technique.

Nevertheless, SEC has been applied in combinatorial synthesis to the separation of dendritic high-loading polymeric supports from low-molecular-weight reaction products.^[355, 356] Monodisperse polyamidoamine (PAMAM) dendrimers (generation 1) with an HMB-linker have been used to generate a small library (27 compounds) of indoles in a split-and-pool synthesis.^[356] Separation was performed on a 25 mg (10 μ mol) scale on a Sephadex LH-20 stationary phase to give good yields (> 90%) for individual examples.

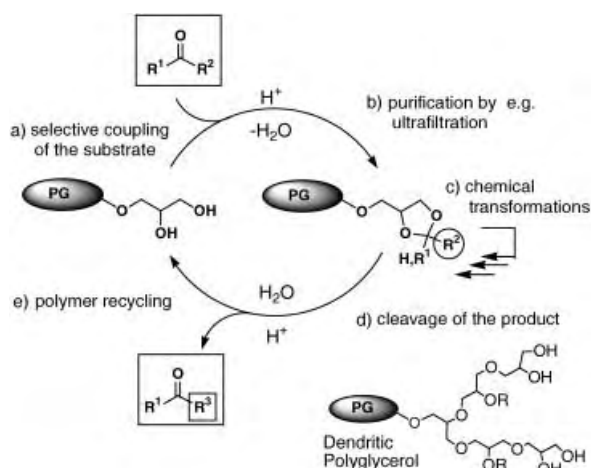
Carbosilane dendrimers (generation 0 and 1)^[357] and star-like PEGs^[358] have been used as multifunctional supports for the synthesis of β -lactams and guanidines, respectively. Preparative SEC was again used for the purification of the lactam and guanidine products, however, it was noted^[357] that the application of membrane technology (see Section 3.4.1.2) could make an improvement. Another example of the use of SEC is the purification of dendrimer-bound salen ligands, which were employed in the enantioselective opening of epoxides.^[359]

Most synthetic applications do not require the use of monodisperse polymeric supports (that is, perfect dendrimers) as long as the molecular-weight distribution of the polymer is narrow (< 1.5).^[348] For example, dendritic aliphatic polyesters and polyethers have been used for the parallel syntheses of disaccharides (Scheme 63)^[355] and functional



Scheme 63. Synthesis of disaccharides using a dendritic polyester support and SEC purification. In all cases thioglycoside donors were employed.

carbonyl compounds (Scheme 64),^[360] respectively. In the case of the dendritic polyesters, separation was performed by SEC on a 50 mg scale, and high purities (> 90%) and moderate yields (40–60%) were obtained. MALDI-TOF analysis of the reaction products could be directly performed on the polyester support by using a photolabile linker. A general problem of polyester supports, however, is their limited chemical stability for a general application in organic synthesis. Although the separation of dendritic polyethers by SEC can be successfully performed, membrane separation techniques (dialysis and ultrafiltration) seem to be more promising with respect to parallelization and automation of the process.^[360]



Scheme 64. Usage and separation of dendritic aliphatic polyethers as high-loading supports, for example, carbonyl compounds.

3.4.1.2. Dialysis

Dialysis is a fairly established technique for the purification of soluble polymers.^[354] Originally, dialysis was mainly used for the separation of biopolymers in aqueous media because of the incompatibility of the membrane materials with organic solvents. Nowadays, however, dialysis can be performed in nearly any organic solvent as a result of improved membrane materials. Typical molecular weight cut-offs (MWCO) are 1000, 5000, and 20000 g mol^{-1} (based on linear polymer standards in water). In organic solvents, however, the MWCO can slightly vary because of the different swelling ability of the membrane materials in different solvents.

Recently, Haag et al. introduced dialysis as a multiparallel separation technique for soluble polymers on a multigram scale (Figure 5a, b).^[360] In this way, dendritic polyglycerol,^[361] a chemically stable, high-loading, soluble polymeric support, can be separated from low-molecular-weight impurities in multistep reactions. A fundamental advantage of this technique is the separation of large quantities (up to 10 mmol of substrate) in multiparallel approaches. Hence this material is attractive for the preparation of smaller libraries (10–100 compounds) on a relatively large scale. The limitations of this technique are the relatively long separation times (typically 12–36 h) and in some cases incompatibility with membrane materials, for example, for the separation of highly reactive or ionic compounds. Dialysis is also unsuitable for the final cleavage step of a multistep polymer-supported synthesis because the cleaved low-molecular-weight compound would be diluted into a large amount of solvent when diffusing through the membrane. In this case, ultrafiltration (see Section 3.4.1.3) can be used advantageously.

3.4.1.3. Ultrafiltration

A very efficient membrane separation technique for soluble macromolecules is ultrafiltration (UF), which was originally introduced by Bayer and co-workers for the automated synthesis of peptides in solution.^[362] Like dialysis, it can be employed for the separation of low-molecular-weight compounds from soluble polymeric supports. Membrane materials (organic and inorganic) with high chemical stability and

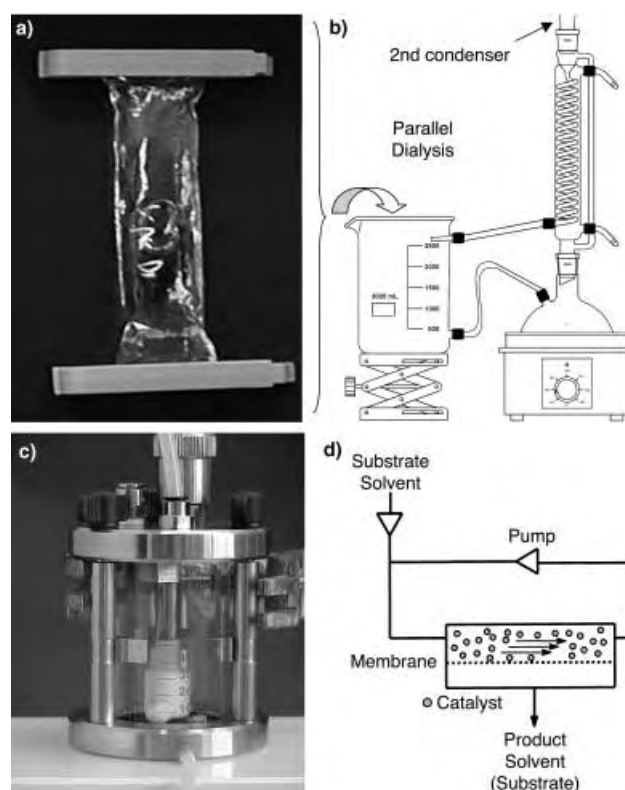


Figure 5. a) Dialysis tubing for the separation of soluble polymeric supports on a millimolar scale, b) apparatus for parallel dialysis for up to 12 reaction mixtures, c) chemically resistant UF unit for pressures up to 6 bar, d) continuous flow setup for a membrane reactor (with kind permission from Dr. S. Mecking).

compatibility to most organic solvents are now commercially available.^[363] In contrast to dialysis, much shorter separation times (ca. 1–3 h) can be achieved with UF because of the application of pressure (3–30 bar). It is necessary to use stirred UF cells or continuous flow systems for efficient separations to avoid clogging of the membrane. A chemically stable and commercially available set-up for pressures up to 6 bar is shown in Figure 5c.^[364] For higher pressures and continuous flow membrane reactors, however, it is necessary to use HPLC-type systems to avoid gas bubbles in the system (Figure 5d). As a result of the high costs of the automated systems, UF must be considered as a serial separation technique.

Ultrafiltration has been used for the separation of polymeric supports during multistep syntheses as well as for the separation of products after the final cleavage step (Scheme 64).^[348, 360] However, this technique is employed most frequently for the separation of polymer-supported catalysts.^[352] In this case, continuous flow UF systems (so-called membrane reactors) have been used for homogeneous catalysis. In these cases, the catalysts are complexed to amphiphilic dendritic macromolecules^[365, 366] or attached covalently through ligands to dendritic macromolecules.^[367–371] Although UF was originally introduced for the separation of linear polymeric supports, dendritic polymeric supports have been employed in many recent applications. Oxazaborolidine-functionalized microgels have also been used as homogeneous catalysts in enantioselective reduction of prochiral ketones and separated by UF.^[372]

3.4.1.4. Centrifugation

Centrifugation can also be used to generate the required “pressure” for ultrafiltration and is frequently used in biochemistry in multiparallel approaches for purification of biopolymers (for example, proteins, DNA).^[373] A major drawback of this technique, however, is the limited availability of membrane vials which are stable towards a broad range of organic solvents. Also, for analytical purposes, ultracentrifugation can directly separate large molecules from small molecules, similar to SEC. In both cases the separation times depend on the rotation speed of the centrifuge.^[373]

3.4.2. Separation of Soluble Polymeric Supports Based on Physicochemical Properties

3.4.2.1. Precipitation/Filtration

Other separation techniques for soluble polymers, such as precipitation/filtration and liquid–liquid phase separation, rely on polymer properties (for example, solubility) rather than their hydrodynamic volume. Precipitation is frequently used in polymer chemistry to purify the respective polymer from low-molecular-weight impurities. This method works especially well when the polymer is crystalline and the glass transition temperature is above room temperature. It has been frequently applied to the separation of functionalized PEG and non-cross-linked PS supports.^[349] Precipitation, however, is less suitable for multistep syntheses because impurities often remain trapped in the precipitated polymer. In addition, large solvent volumes are required to perform quantitative precipitation and hence automation of the process is difficult.

3.4.2.2. Liquid–Liquid-Phase Separation of Polymers

Another simple separation technique which is suitable for the separation of organic molecules from water-soluble polymers is based on liquid–liquid-phase separation between an organic phase (which contains the cleaved organic product) and an aqueous phase (containing the water soluble polymer).^[348, 360] Bergbreiter also used these biphasic systems for the recovery of polymer-supported catalysts.^[374] Although phase separation can be performed by a robot in a serial fashion, it is limited to systems in which the components have different solubilities in the two phases. Further examples of biphasic systems for simple separation (ionic liquids, fluoruous phases, and supercritical fluids) are discussed in Section 2.

3.4.2.3. Column Filtration for Separation of Soluble Polymeric Supports

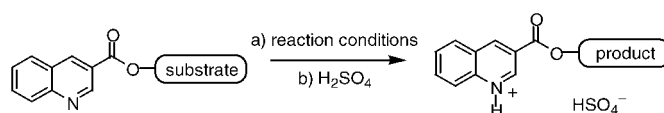
Although column filtration does not offer any advantages over conventional work-up protocols, filtration through a small amount of silica is often used as an additional purification step after the final cleavage of the product from the polymeric support. It also has been used for the separation of polymer-supported reagents from low-molecular-weight unpolar products.^[375]

4. Miscellaneous Separation Techniques

The techniques mentioned in the following section are rather specific and so far have only been described for a limited number of examples. Many of them are restricted to certain functionalities or can be used only under special reaction conditions. The potential of these techniques to be automated has not yet been explored.

4.1. Phase Switch

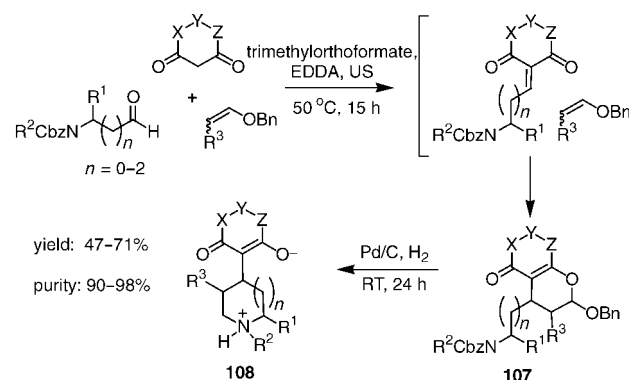
Phase-switchable tags can be used to precipitate a product from organic solutions either through salt formation^[376, 377] or by configurational change (for example, *cis/trans* isomerization).^[378, 379] Perrier and Labelle described a simple solution-phase/solid-phase work-up protocol in which a phase-switchable tag was employed.^[377] They covalently linked a substrate to a quinoline derivative, which is soluble in many organic solvents (Scheme 65). However, the conjugate can be precipitated after each reaction step in good yield (68–91 %) by



Scheme 65. Application of a quinoline tag for phase switching.

protonation to the corresponding quinolinium salt. Cleavage of the quinoline after the final reaction step, followed by precipitation liberates the desired products in high purities (>95 %). In many cases the quinoline derivative was sufficiently pure for reuse in the next synthesis. Several benzylic alcohols and aromatic carboxylates have been prepared by this approach as individual compounds and also as mixtures. This purification strategy, however, might be limited by incomplete reactions, which result in mixtures of quinoline derivatives.

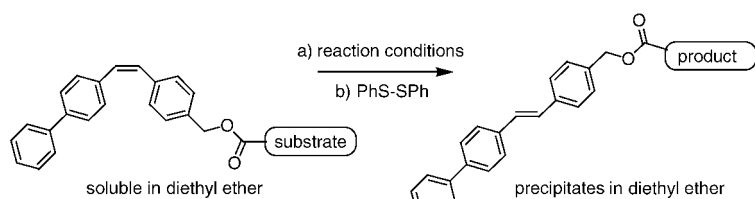
A very elegant phase-switch approach was recently described by Tietze et al. for the preparation of pyrrolidine, piperidine, and azepan derivatives.^[376] In this case, the formation of a zwitterionic compound induces precipitation after a multicomponent domino reaction (Scheme 66). Sev-



Scheme 66. Synthesis of pyrrolidine, piperidine, and azepan derivatives as betains.

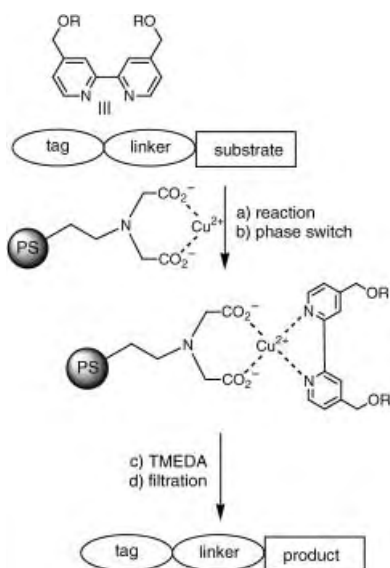
eral functionalized bicyclic compounds **107** can be formed from aminoaldehydes, 1,3-dicarbonyl compounds, and enol ethers through a Knoevenagel condensation and a hetero-Diels–Alder reaction. After hydrogenolytic cleavage of the protective groups and subsequent reductive amination, the corresponding betaines **108** are obtained in good yields (47–71 %) and high purities (90–98 %) as mixtures of diastereomers. The products are readily soluble in water and methanol and can easily be precipitated by the addition of diethyl ether. Although this approach is limited to betain formation, it does not require any coupling or cleavage of a phase-switchable tag, and hence saves time and synthetic effort.

A rather unconventional phase-switchable tag was recently designed by Wilcox and co-workers.^[378, 379] In this case, *cis/trans* isomerization of a stilbene derivative was used to induce precipitation from the reaction mixture (Scheme 67). 4-Phenylstilbene was chosen as the phase-switchable tag because the *cis* isomer is readily soluble in many organic solvents, while the *trans* isomer can be precipitated with, for example, diethyl ether or methanol. The isomerization can be induced either photolytically or by addition of diphenyldisulfide. A small library of isoxazolines was prepared in high yields (73–90 %) and high purities (88–95 %) by this approach.



Scheme 67. Stilbene tags for phase switching by *cis/trans* isomerization.

Recently, Ley et al. introduced a solid-phase Cu complex as a scavenger for dipyriddy tags (Scheme 68).^[380] This method is related to metallochelate chromatography in biochemistry in



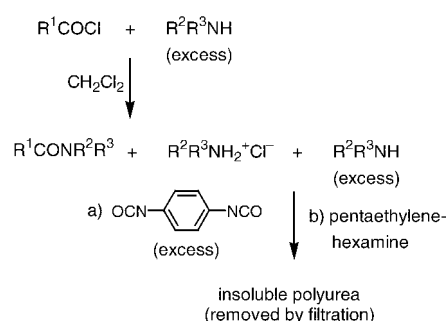
Scheme 68. Solid-phase bound Cu complex as a phase switch for bipyridyl tags.

which (His)₆ tags, which are isolated by stationary Ni complexes bound to a dicarboxylate resin, are used.^[373] The commercially available iminoacetic acid resin is first used to immobilize copper salts. This solid-phase Cu complex can now be used as a phase switch for the bipyridyl derivatives. Cleavage from the resin is easily induced in excellent yields (92–95 %) and high purities (>90 %) with TMEDA. The broad utility of this approach was demonstrated in the synthesis of hydantoine and benzodiazepine derivatives.

Although all these phase-switchable-tag protocols seem rather complicated they allow for reactions to be performed under homogenous conditions with monitoring by standard methods, as well as in concentrated solutions on a large or small scale.

4.2. Purification through In Situ Polymerization

Another purification strategy is the removal of excess reagent by polymerization. A recent example of the removal of secondary amines from the reaction mixture was presented by Barrett et al.^[381] Six simple amines were converted into the corresponding 3,5-dichlorobenzoic amides in high yields (85–96 %) and purities (92–99 %, Scheme 69). The excess amine was removed by subsequent addition of 1,4-phenylene diisocyanate (excess) and the cross-linking agent pentaerythritolhexamine. The insoluble polyurea can then be filtered off and the product isolated.



Scheme 69. Removal from impurities by in situ polymerization.

4.3. Nanofiltration

While ultrafiltration (see Section 3.4.1.3) typically requires particle sizes above 1 nm, nanofiltration can separate even smaller species. Vankelecom and co-workers described a simple approach in which Ru and Rh catalysts with bulky binap-type ligands ($M_w > 300 \text{ g mol}^{-1}$) were separated directly with a nanofiltration membrane in a continuous system.^[382] They obtained very high turnover frequencies and *ee* values for the hydration of unsaturated carbonyl compounds. Although the system is limited by the working conditions, such as solvent, temperature, and pressure, it can be applied to a number of catalysts and substrates, especially in the field of fine-chemical synthesis.

4.4. Magnetic Bead Separation

Magnetic particles that have been encapsulated within highly cross-linked polystyrene beads and then functionalized with, for example, antibodies have found various applications in the area of immunodiagnoses.^[383] The use of magnetic separation in the field of solid-phase organic synthesis has been limited because of the instability and/or relatively poor loading capacities exhibited by the currently available paramagnetic supports.^[384] Recently, Sucholeiki and Perez^[385] as well as Bradley and co-workers^[386] independently presented an approach for the preparation of higher loading (up to 1 mmol g⁻¹) magnetic solid-phase beads. The composite beads were found to compare favorably with the standard Merrifield resin under typical chemical conditions in organic solvents. These materials were used as scavengers in the synthesis of sulfonamides and tetrapeptides.^[385, 386]

5. Summary and Outlook

The separation techniques presented in this review illustrate alternatives for the traditional methods, such as crystallization, distillation, and column chromatography. While solid-phase chemistry has successfully demonstrated that it can be employed for the high-throughput synthesis and purification of large compound libraries on a small scale, it has several limitations. Thus, the various solution-phase techniques available should be reconsidered. This shift in paradigm is also observed in the pharmaceutical industry, which has partially returned to the solution-phase synthesis of individual compounds in a parallel format. In addition, sustainability (recycling of the support, catalyst, etc.), which was almost forgotten in the area of solid-phase chemistry, has become increasingly important.

Also, there are great industrial efforts towards a “green chemistry”. Consequently, maximum efficiency of all resources and minimum environmental impact are crucial features for all future chemical processes. Ionic liquids are among the few reaction media which could contribute to reaching these goals by replacing volatile organic solvents, minimizing the consumption of catalyst, and enhancing the overall activity and selectivity of chemical processes. Although there is little parallelization and automation in this area yet, the work-up protocols are simple enough to fulfill the requirements.

Fluorous-phase strategies must be viewed in comparison with other phase-labeling strategies. As with any of those, fluorous biphasic systems do not provide solutions to all the conceivable problems encountered in organic synthesis. Rather they should be seen as a possible specialized solution for a specific problem.

Combinatorial chemistry might become a major application for perfluoro-tagged catalysts, reagents, and products, since they offer a quite general method for work-up. Here, it is likely that solid-phase extraction will replace liquid–liquid extraction, because a lower fluorine content in the molecule is needed and because such filtration steps are easily performed in a parallel fashion, either manually or by a robot. The widespread use of perfluorinated solvents is undesirable

because of their negative long-term environmental impact. Fluorous silica gel certainly is a less problematic, easily recovered, and reusable alternative for small-scale operations. Besides combinatorial chemistry, fluorous-tagged catalysts may find application in industrial-scale operations either in fluorous biphasic systems or in synthesis in scCO₂. In contrast to laboratory-scale synthesis, where efficient containment and recovery of fluorous solvents can hardly be ensured, high-boiling fluorocarbons can be used in industrial processes for catalyst immobilization in closed circuit operations. Efficient quantitative recovery of fluorocarbons is imperative because of environmental concerns and the high cost of such solvents as well.

While fluorous reagents are a viable alternative in combinatorial chemistry, they are not likely to enter rapidly into the broad field of everyday synthesis, since they have to compete with established conventional reagents and a variety of solid-phase-bound reagents. Again, they might find specialized application in the commercial synthesis of fine chemicals, where their easy separation and regeneration presents a significant advantage.

One major advantage of SCF techniques over all other solution-phase techniques is the ease of product isolation. Simple depressurization suffices to obtain completely dry products if SCFs are used that are gaseous at normal pressure. This is an extremely important aspect, especially for the production of pharmaceuticals, where traces of solvents are not tolerated. Also, the tunable solvent power of SCFs allows for the development of a number of more elaborate separation schemes which are attractive for the separation from catalysts. Furthermore, scCO₂ has the potential to become the ideal “green solvent” which can be used to replace many potentially hazardous organic solvents. This may prove to be particularly advantageous in the preparation of pharmaceuticals, cosmetics, and food additives.

In contrast to these alternative solution-phase systems, solid-phase supports have so far dominated the field of combinatorial chemistry as well as the automation of separation techniques. After ten years of intensive research, however, there is still no polymeric support for general application in combinatorial chemistry. Every polymer has its drawbacks (for example, chemical stability, polarity, loading capacity). Soluble polymeric supports have also had a similar, but less pronounced, revival over the past decade. Aliphatic polyethers and non-cross-linked polystyrene are among the most promising candidates in terms of stability. Dendritic and linear polyfunctional soluble polymers have by far the highest loading capacities and show great potential as supports for reagents and catalysts in combinatorial synthesis. Although many separation techniques for soluble polymeric supports have been developed for solution-phase organic synthesis (some, even in a parallel format), further progress in the automation of solution-phase separation techniques is required. For example, membrane stability towards all organic solvents and better size selectivity are still insufficient in the case of membrane separation (dialysis, ultrafiltration).

There are still many new developments in the field of polymer-based separation techniques, such as smart cleavage protocols and phase-switching protocols (including catch-and-

release). Even though predictions about the future impact of this area are very speculative, the number of polymeric support based separations will certainly increase tremendously.

Among the various alternative separation approaches presented, there is nothing approaching “the best method”! Instead, it is more a search for an appropriate separation technique. Each individual chemical problem can only be successfully solved if the separation technique has been well-chosen and optimized. This becomes even more important for parallel approaches where small separation problems are amplified into a whole library. In the search for new separation strategies one should always bear in mind that it has to be a general tool for achieving the synthetic goal and not vice versa.

Abbreviations

acac	acetylacetonate
BARF	tetrakis(3,5-di(trifluoromethyl)phenyl)borate
binap	2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl
binaphos	2-(diphenylphosphanyl)-1,1'-binaphthyl-2-yl-1,1'-binaphthyl-2,2'-diyl-phosphite
binol	2,2'-dihydroxy-1,1'-binaphthyl
BMIM	1- <i>n</i> -butyl-3-methylimidazolium
Boc	<i>tert</i> -butoxycarbonyl
BSA	bis(trimethylsilyl)acetamide
CESS	catalysis and extraction using supercritical solution
CMS-DVB	poly(chloromethylstyrene- <i>co</i> -divinylbenzene)
cod	cyclooctadiene
CSS	crystallization from supercritical solution
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dca	dicyanamide anion
DCT	dichlorotriazene
DIC	5-(3,3-dimethyl-1-triazenyl)-1 <i>H</i> -imidazole-4-carboxamide
DIEA	diisopropylethylamine
DIPT	diisopropyl tartrate
DME	dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMFP	1,3-dimethyl-2-fluoropyridinium 4-toluenesulfonate
DMSO	dimethylsulfoxide
DuPhos	1,2-bis(2,5-dimethylphospholanyl)benzene
EDDA	ethylenediammonium diacetate
<i>ee</i>	enantiomeric excess
EMIM	1-ethyl-3-methylimidazolium
FBC	fluorous biphasic catalysis
FBS	fluorous biphasic system
FC-72	perfluoroalkane solvent, mainly C ₆ H ₁₄
FRPSG	perfluorous reversed-phase silica gel
GPC	gel permeation chromatography
HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
hfacac	hexafluoroacetylacetonate
HMB	4-hydroxymethylbenzoic acid

HPLC	high pressure liquid chromatography
LC	liquid chromatography
MTO	methyl trioxorhenium
MWCO	Molecular weight cut-off
NBS	<i>N</i> -bromosuccinic imide
NMP	<i>N</i> -methylpyrrolidone
PAM	phenylacetamidomethyl
PAMAM	polyamidoamine
PEG	polyethylene glycol
PFMCH	perfluoromethylcyclohexane
PG	protecting group
PS	polystyrene
PyBroP	bromo-tris(pyrrolidine)phosphonium hexafluorophosphate
RCM	ring-closing metathesis
RESS	rapid expansion of supercritical solutions
ROMP	ring-opening metathesis polymerization
salen	<i>N,N'</i> -bis(2-hydroxybenzylidene)-1,2-diaminoethane
SASP	supercritical antisolvent precipitation
scCO ₂	supercritical carbon dioxide
SCWO	supercritical water oxidation process
SEC	Size-exclusion chromatography
SER	sequestration-enabling technique
SFE	supercritical fluid extraction
TBAB	tetrabutylammonium bromide
TBHP	<i>tert</i> -butylhydroperoxide
TBME	<i>tert</i> -butyl methyl ether
TBTU	benzotriazolyl-tetramethyluronium tetrafluoroborate
TEMPO	2,2,6,6-tetramethylpiperidin- <i>N</i> -oxide
TFA	trifluoroacetic acid
<i>T_g</i>	glass transition temperature
THF	tetrahydrofuran
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TLC	thin-layer chromatography
tolbinap	2,2'-bis(ditoluylphosphanyl)-1,1'-binaphthyl
UF	ultrafiltration
US	ultrasonication

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- [84] The mutual solubility increases with rising temperature, which makes it difficult to distinguish between homogeneous and heterogeneous reactions. Naturally, questions arising in traditional phase-transfer reactions in aqueous biphasic mixtures also arise in fluorous biphasic systems. In a heterogeneous mixture the reaction can still proceed homogeneously (with the catalyst fraction dissolved in the organic phase or with the substrate fraction dissolved in the fluorous phase), heterogeneously across the liquid–liquid interface, or in any combination of these pathways. Little information about these details is available in the literature. The oxymoron “homogeneous biphasic catalysis” has been used in this and similar contexts. We feel that new terms should be coined very carefully and only if they contribute to clarifying a complex situation. We suggest the term “homogeneous biphasic catalysis” to be restricted to those rare cases, where the reaction pathways have been investigated and the homogeneous catalysis pathway dominates.
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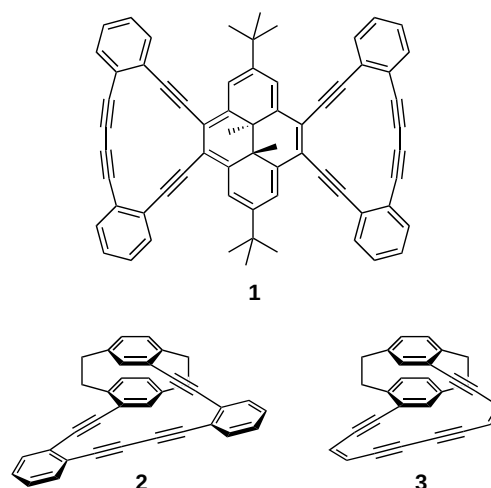
“Polyunsaturated” Cyclophanes**

Graham J. Bodwell* and Teizi Satou

Cyclophane chemistry has a long and colorful history.^[1] Although this discipline has evolved in many ways, several of the fundamental sources of interest in cyclophanes remain unchanged. These include the conception of novel, aesthetically pleasing and interesting structures, the challenge of synthesizing them, and the study of their properties once they have been prepared.

As with other areas of synthetic chemistry, the development of new methodology has played a crucial role in the development of cyclophane chemistry. An early example of this is the emergence of the sulfur-based ring-contraction strategies that were developed in the 1960s and 1970s,^[2] which paved the way for the synthesis of a very wide range of [2.2]cyclophanes and [2.2]cyclophanedienes. That these approaches are still in use today speaks to their lasting value. A more recent example is the advent of palladium-catalyzed cross-coupling reactions,^[3] which opened the door for the design and synthesis of whole new families of cyclophanes, that is, those that have multiply unsaturated bridges. A selection of such “polyunsaturated” cyclophanes is presented in Scheme 1.

When considering compounds that are composed of aromatic units linked by unsaturated bridges, the distinction between a cyclophane and a dehydrobenzannulene (DBA) can become blurred, or even disappear entirely. A crude criterion for distinguishing these two fascinating classes of compounds is that a DBA has only 1,2-disubstituted aromatic units, whereas a cyclophane has at least one non-1,2-disubstituted aromatic unit.^[4] Thus, the aptly named “dehydrobenzannulene–dimethyldihydropyrene hybrid” **1** reported by Haley, Mitchell, and co-workers^[5] falls under the DBA category, whereas the “[2.2]paracyclophane-dehydrobenzannulene hybrids” **2** and **3** described by Hopf, Haley, and co-workers^[6] fall under the heading of cyclophanes. Comparison of the electronic absorption spectra of **2** and **3** with appropriate DBAs and “broken” DBA analogues provided



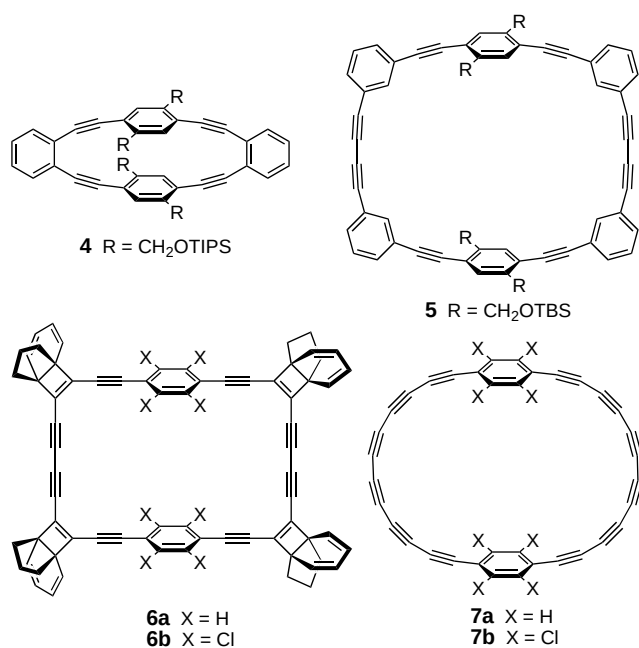
Scheme 1. Some examples of cyclophanes with multiply unsaturated bridges, made by using palladium-catalyzed cross-coupling.

evidence of global transannular delocalization between the fully conjugated decks of the cyclophane.

The use of electrocyclic reactions that result in the formation of new aromatic systems to generate strained systems is a strategy that has been successfully applied to a variety of small cyclophanes for some time.^[7] More recently, this approach has been enlisted in the construction of much larger strained systems. For example, Tsuji and co-workers' syntheses of cyclophanes **4** and **5** (see Scheme 2)^[8] featured tethered Dewar benzenes as precursors to the *para*-phenylene units. Their shape facilitated the palladium- or copper-catalyzed dimerization of the two halves to afford macrocyclic precursors. Removal of the tether and photochemical valence isomerization afforded the *para*-phenylene units, the substituents of which render the systems both chiral and amenable to further synthetic manipulation. Tobe et al., on the other hand, employed [4.3.2]propellane units as masked alkynes, which can be liberated by a [2+2] cycloreversion reaction. Again, their geometry permitted the construction of the comparatively unstrained precursor cyclophanes **6a** and **6b** by oxidative coupling of the two halves.^[9] Photolysis of **6a** at 77 K resulted in changes in the UV/Vis spectrum that were attributed to the formation of cyclophene **7a**. Laser-desorption time-of-flight mass spectrometry of **6b** gave rise not only to a signal caused by C₃₆Cl₈[−] (**7b**[−]), but also to a relatively

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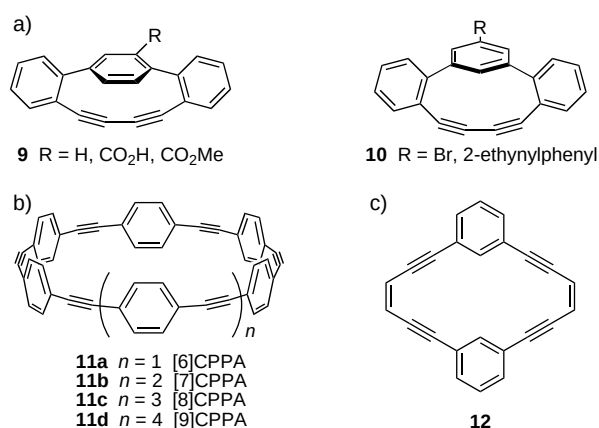
Scheme 2. Cyclophanes synthesized by a dimerization route. TIPS = triisopropylsilyl, TBS = *tert*-butyldimethylsilyl.

strong signal arising from C_{36}^- , which was speculated to correspond to the D_{6h} -symmetric carbon cluster.

Cyclophanes **6a** and **6b** are structurally related to a number of arene-alkyne cyclophanes **8a–g** (Table 1) that have been reported recently.^[10–12] These consist of two linear arylene units and four angular arylene units, all linked by varying numbers of alkynyl groups. Sonogashira and copper-mediated oxidative couplings feature prominently in the syntheses of these compounds. In the case of the cyclophanes of Marsella et al., **8a–c**, the comparatively high yield of **8c** (yield of **8c** = 30% vs. 12% for **8a** and 10% for **8b**) was ascribed to favorable aryl-perfluoroaryl electrostatic interactions. This result is a rare example of such interactions being of importance in solution. The linear arylene units in Baxter's "twistophane"

8d are 4,4'-(2,2'-bipyridyl)ene units, which allow the system to function as a sensor for Co^{2+} , Ni^{2+} , Cu^{2+} , and Zn^{2+} ions.^[11] Of particular interest is that **8d** responds differently to the different analytes. Fallis and co-workers reported the synthesis of the cyclophanes **8e–g**.^[12] The crystal structure of **8e** revealed the helically chiral nature of the cyclophane core. The incorporation of long side chains (**8f** and **8g**) was performed with an eye to preparing new liquid crystalline materials. Indeed, **8g** melted to provide a gray, opaque solution, which is typical of liquid crystal behavior.

The Fallis group has also produced some novel strained cyclophanes, which include **9**^[13] and **10**, shown in Scheme 3.^[14] These compounds can be viewed as dibenzododecahydro[8]para- and -metacyclophanes, respectively. Oda and co-



Scheme 3. Strained cyclophanes made by a) the Fallis group;^[14] b) Oda and co-workers;^[15] c) Sankaraman and co-workers.^[16]

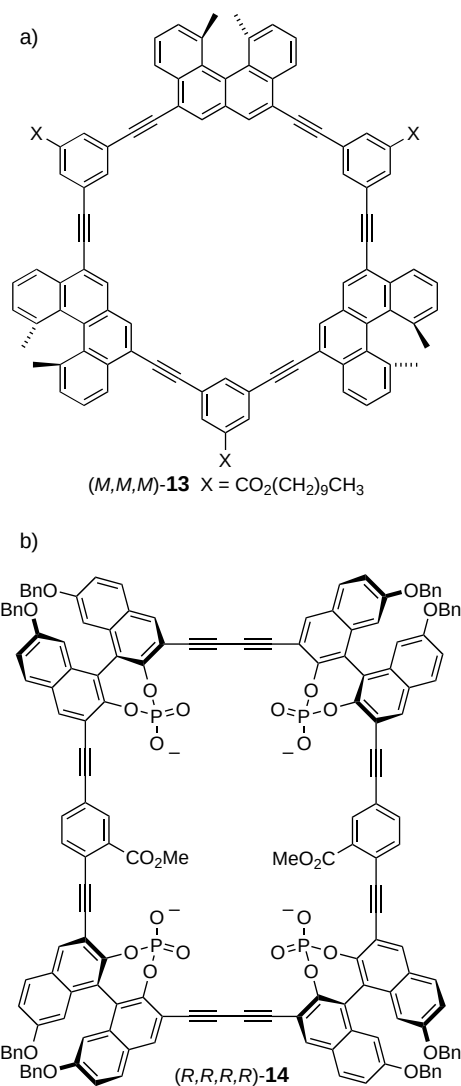
workers' cyclic *para*-phenylacetylenes (CPPA) **11a–d** stand out, not only because of their braceletlike structures, but also because their synthesis does not involve the use of palladium.^[15] The precursor cyclophanepolyenes were generated by an intramolecular McMurry-type reaction and the triple

Table 1. Some structurally related arene-alkyne cyclophanes.

Compound	Linear arylene unit	Angular arylene unit	Alkynes	
			m	n
8a	1,4-phenylene	2,3-thiophendiyl	1	1
8b	1,4-perfluorophenylene	2,3-thiophendiyl	1	1
8c	1,4-phenylene and 1,4-perfluorophenylene	2,3-thiophendiyl	1	1
8d	4,4'-(2,2'-bipyridyl)ene	1,2-phenylene	1	2
8e	1,4-phenylene	1,2-phenylene	1	2
8f	1,4-(2-undecyloxyphenyl)ene	1,2-phenylene	1	2
8g	1,4-(2-(11-methoxy-11-oxoundecyloxy)phenyl)ene	1,2-phenylene	1	2

bonds were installed by an addition–elimination sequence. No evidence for cyclic conjugation in these systems has been obtained to date, but they were reported to form inclusion complexes with C_{60} , C_{70} , and hexamethylbenzene. Another interesting cyclophane is Sankararaman and co-workers' [6.6]metacyclophane **12**, which features enediyne bridges.^[16] We await with interest the outcome of studies on the reactivity of the bridges in this and related systems.

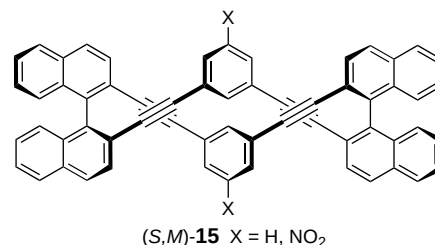
A new wrinkle in the synthesis of enantiomerically pure cyclophanes is the use of enantiomerically pure chiral aromatic systems as building blocks. Yamaguchi and co-workers employed single enantiomers of a [4]helicene derivative to prepare every possible stereoisomer of **13** (Scheme 4).^[17] The various stereoisomers of **13** aggregated in organic



Scheme 4. a) One isomer (M,M,M) of the Yamaguchi^[17] cyclophane; b) the cyclophane reported by Droz and Diederich.^[18]

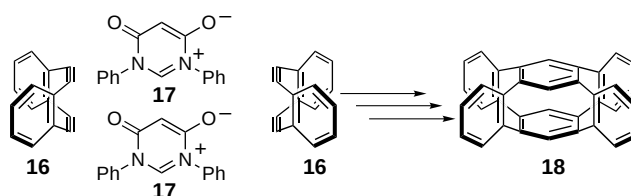
solvents (dimer formation) and the stereochemistry of the helicene units influenced the aggregation. The (R)-binol-derived tetraphosphate (R,R,R,R)-**14** was reported by Droz and Diederich,^[18] and exhibited a high affinity for two disaccharides in the competitive solvent mixture

CD_3OD-CD_3CN . Finally, Otera's group used the 1,1'-binaphthyl unit as the source of chirality for some enantiopure double-helical cyclophanes, for example, (S,M)-**15** (Scheme 5).^[19] In addition to the sheer beauty of these structures, a noteworthy feature of this work is that the solution and solid-state CD spectra agree with one another. This led the authors to suggest that the structures of these cyclophanes change little on going from solution to the solid state. Once again, palladium played a key part in the syntheses of **13–15**.



Scheme 5. Otera and co-workers' double-helical cyclophanes.^[19]

Hot off the press is Wudl and co-workers' tetrabenzannulated 1,2,4,5-cyclophanetetraene (**18**), which was prepared by a remarkably short and imaginative route (Scheme 6).^[20] Two units each of the DBA **16**^[21] and the mesoionic heteroaromatic diene **17**^[22] were united through successive hetero-Diels–Alder/retro-hetero-Diels–Alder reactions to produce **18**. This strained $[2_n]$ cyclophane, which sets a new standard for the number of unsaturated and/or benzannulated two-carbon-atom bridges, reacts rapidly with tetracyanoethylene (TCNE) to form a Diels–Alder adduct with no apparent formation of a charge-transfer complex.



Scheme 6. A strained cyclophane made by Wudl and co-workers through a series of cycloaddition reactions.

Palladium-catalyzed cross-coupling reactions have clearly worked wonders for the field of cyclophane chemistry. We look forward with great enthusiasm to subsequent developments in this area and, of course, to the next methodological revolution and the novel, interesting, and useful cyclophanes that it will surely produce.

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Odd-Electron Bonds and Biradicals in Main Group Element Chemistry**

Hansjörg Grützmacher* and Frank Breher

Radicals play a crucial role in bond-forming and bond-breaking processes.^[1] In hydrocarbon chemistry, however, carbon-centred radicals are usually observed as rather short-lived intermediates.^[2] Some selected recent examples serve as highlights to demonstrate that in main group element chemistry (apart from C) such reactive intermediates can be stabilized even to such an extent that they can be isolated in crystalline form.

Odd-Electron Bonds

To study the generation of a new type of a genuine two-center, one-electron (2c1e) P–P bond, Geoffroy, Mathey, Le Floch et al.^[3] developed the macrocyclic system **1**. Compound **1** contains two phosphinine units, PC₅R₅, which are linked by two flexible siloxane bridges to form a twelve-membered heterocycle. In the ground state conformation, the two phosphinine ring planes are almost coplanar and the two

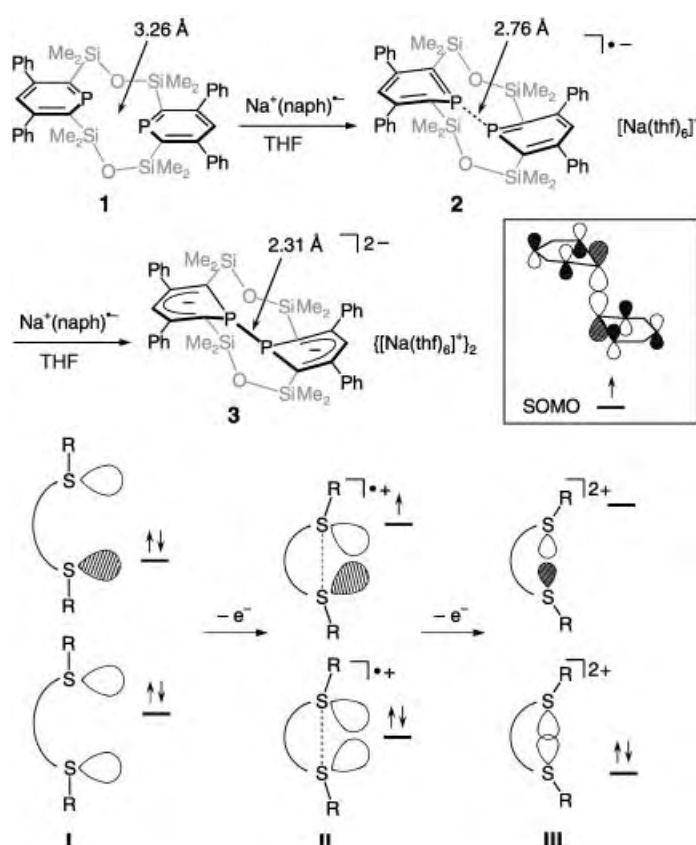
phosphorus atoms approach each other to a distance of 3.26 Å (Scheme 1).

This neutral precursor can be reversibly reduced at a potential of $E_{1/2}^{\circ} = -1.85$ V and $E_{1/2}^{\circ} = -2.10$ V (scan rate 5 V s⁻¹, THF) to give the radical anion **2** and the dianion **3**, respectively. Chemically, **1** was reduced with sodium naphthalenide. The combination of the results from X-ray analyses of the neutral precursor **1** and the fully reduced dianion **3** with the results from EPR spectroscopy and DFT calculations for the persistent phosphorus radical anion **2**, demonstrated that in this case the unpaired electron resides in the single-occupied molecular orbital (SOMO; Scheme 1). This SOMO is partially delocalized over both phosphinine rings, but mainly localized in a P–P σ bond. Notably, the P–P distance in **2** has shortened considerably and lies between that of the neutral compound **1** and that of the fully reduced form **3**, in which a 2c2e P–P bond has formed and the phosphinine rings deviate strongly from planarity.

The formation of the P–P bond in **2** and **3** resembles the creation of S–S bonds in the intensively studied radical cations of type **II** and dications of type **III** of polysulfur compounds (Scheme 1, bottom).^[4] The chemical process of bond making and the electronic configuration is different in these sulfur compounds. In the neutral precursor **I**, the nonbonding electron pairs of the two –S– entities interact to

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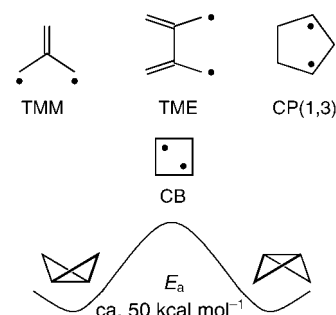
Scheme 1. Generation of a 2c1e P-P bond (top) and 2c3e S-S bond (bottom).

give a bonding and antibonding combination. One-electron oxidation leads to the radical cation [$>\text{S}\cdot\cdot\text{S}<$]^{•+} **II** with a 2c3e bond.^[5] Note that although the bond orders in **2** and **II** are the same (b.o. = 0.5), the single electron occupies an S-S antibonding orbital in **II** but a P-P bonding orbital in the radical anion **2**. Often, the radical cations **II** have lower oxidation potentials than their precursors which make their direct observation difficult.

Biradicals (Biradicaloids)

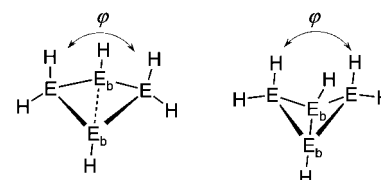
In the above-mentioned radicals, one unpaired electron is delocalized over two main group element centers forming either a 2c1e or 2c3e bond. Even closer to bond-forming and bond-breaking processes are biradicals,^[6] which in many cases are more appropriately designated as biradicaloids.^[7] These may be roughly divided into two classes: 1) delocalized biradicals (non-Kekulé molecules)^[8] for which trimethylenemethane (TMM)^[9a] and tetramethylethane (TME)^[9b] are the archetypal examples; 2) localized biradicals with two well-defined radical substructures that are not conjugated by way of a classical π system. Typical examples of this class are cyclopentane-1,3-diyl (CP(1,3))^[10] or cyclobutanediyl (CB).^[11] In all of these radicals the single electrons reside in π -type orbitals and the individual spins may either couple to give a triplet (TMM, TME) or a singlet state (CP(1,3)). The triplet states of CBs could be observed because the barrier for spin conversion impedes the ring closure to the corresponding bicyclo[1.1.0]butanes. On the other hand, singlet cyclobuta-

nediyls are only predicted as transition states for the ring inversion of [1.1.0]cyclobutanes at about 50 kcal mol⁻¹ (Scheme 2).^[12]



Scheme 2. Formulas of the delocalized biradicals trimethylenemethane (TMM), tetramethylethane (TME) (non-Kekulé molecules) and localized cyclopentane-1,3-diyl (CP(1,3)) and cyclobutanediyl (CB).

Strained Group 14 element compounds were identified as suitable candidates for the synthesis of stable biradicaloids (Scheme 3).^[13] For the silicon, germanium, tin, and lead

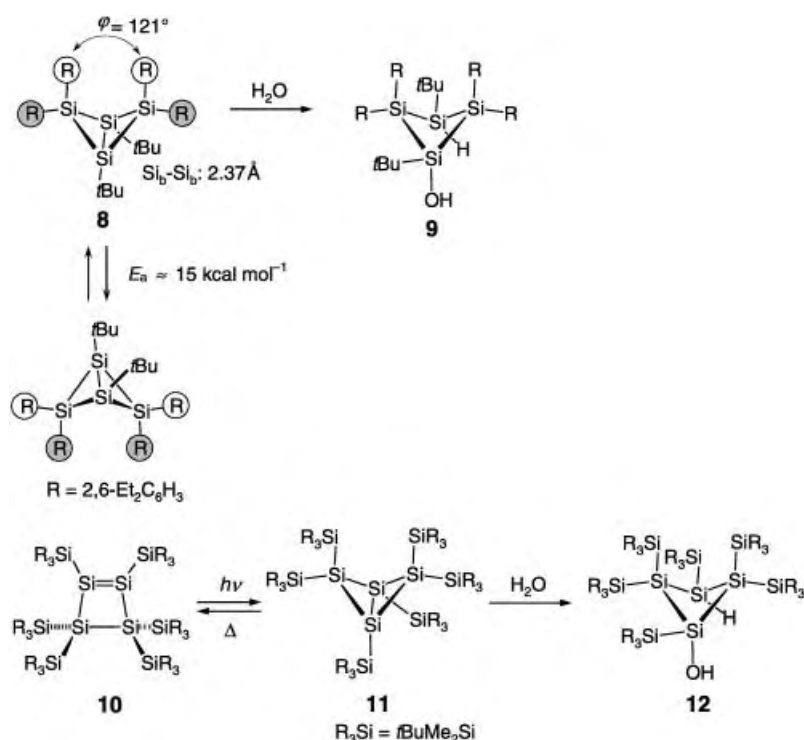


	E_b-E_b [Å]	φ [°]		E_b-E_b [Å]	φ [°]
4 E = Si	2.78	142	4'	2.37	123
5 E = Ge	3.03	144	5'	2.48	118
6 E = Sn	3.71	144			
7 E = Pb	3.90	152			

Scheme 3. Calculated bridgehead E_b-E_b bond lengths [Å] and interplane angles φ [°] for tetrametallabicyclo[1.1.0]butanes of Group 14.

analogues of bicyclo[1.1.0]butanes, quantum-chemical calculations^[13b, 14a-c] predict the phenomenon of bond stretch isomerism,^[15] that is two distinct minima on the potential energy surface (PES) which mainly differ by the length of one bond, as a result of the high ring strain and intrinsically low σ -bond energies. For the silicon and germanium compounds, the bond stretch isomers **4** and **5**, which can be regarded as coupled π -type biradicaloids, are more stable by about 8 and 16 kcal mol⁻¹, respectively, than the isomers **4'** and **5'** which possess usual E-E bond lengths. For E = Sn, Pb only the isomers **6** and **7** with an elongated E_b-E_b bond between the bridgehead atoms are found as minima.

Synthetically accessible and structurally characterized tetrasilabicyclo[1.1.0]butanes are rare. The sterically encumbered derivative **8** has a normal Si-Si bond length of 2.37 Å (Scheme 4).^[16] This is in accord with computations which predict that σ -electron-donating groups, for example *t*Bu, at the bridgehead silicon atoms favor the closed form, while σ -electron-withdrawing substituents, for example F, at the bridging silicon atoms favor the open form.^[13b, 14a] However, the physical and chemical properties of **8** indicate the energetically close relationship to the biradicaloid form.

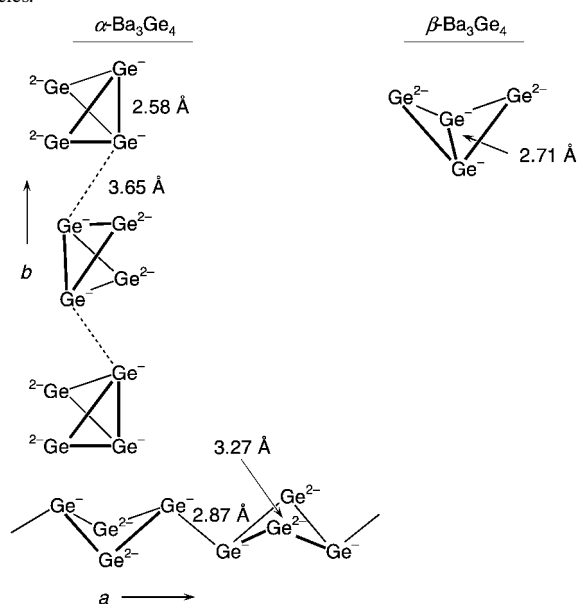


Scheme 4. Experimentally studied tetrasilabicyclo[1.1.0]butanes **8** and **11**. The inequivalent R groups that are interconverted by ring inversion are indicated by white and gray circles.

Crystals of **8** are thermochromic (intensely yellow at 170°C , colorless at -196°C) and the ring-inversion barrier for **8** is low ($E_a \approx 15 \text{ kcal mol}^{-1}$), as estimated by NMR methods from the coalescence of the inequivalent R groups. Also, the central $\text{Si}_b\text{--Si}_b$ bond is unusually reactive; even water can be quantitatively added to give the hydroxy derivative **9**. A similar observation was made for the silyl-substituted tetrasilabicyclo[1.1.0]bicyclobutane derivative **11**, which was generated from the tetrasilacyclobutene derivative **10** under irradiation with light ($\lambda > 420 \text{ nm}$).^[17] In the photostationary state, 91 % conversion was reached, and **11** was quenched by hydrolysis at 0°C to give **12**. No further spectroscopic data were obtained for **11** because in the dark it rearranges quantitatively to the cyclobutene **10** (Scheme 4). Remarkably, this isomerization cycle can be repeated more than 10 times without notable side reactions. In contrast to these results, computations for the parent system predict that the bicyclobutane isomer should be thermodynamically more stable.^[14d] On the other hand, such rearrangements, biradicaloid $\rightleftharpoons$ cyclobutenoid, have some common character and predictions concerning the relative stabilities of the individual isomers may be highly substituent dependent (for another example see **20** $\rightleftharpoons$ **23** in Scheme 7).

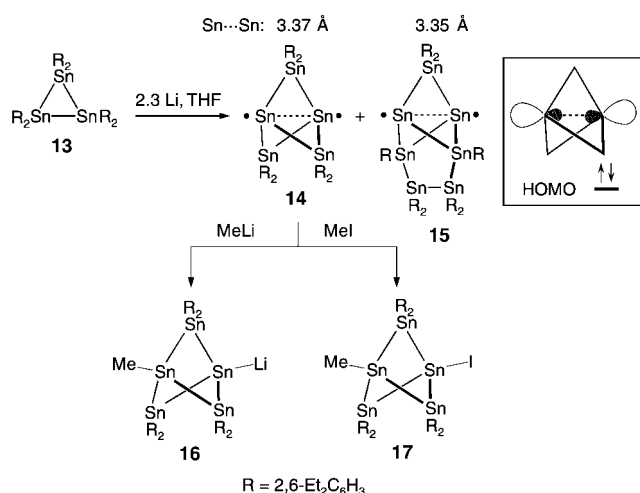
To our knowledge no other stable molecular metallabicyclobutanes of the heavier Group 14 elements have been reported to date; however, an interesting example of bond stretch isomerism and indications for biradicaloids in solid-state chemistry has been reported for the Zintl phase Ba_3Ge_4 . This system is prepared from a stoichiometric reaction of the elements between 1120 and 1360 K.^[18] In the high-temperature β -modification only isolated $[\text{Ge}_4]^{6-}$ ions with the butterfly bicyclo[1.1.0]butane structure are formed. The bridgehead $\text{Ge}_b\text{--Ge}_b$ bond is long ($2.71 \text{ \AA}$), although shorter

than the computationally predicted bond length of $3.03 \text{ \AA}$. In the room-temperature stable α -modification, one half of the $[\text{Ge}_4]^{6-}$ units exist as isolated ions with short $\text{Ge}_b\text{--Ge}_b$ bonds ($2.58 \text{ \AA}$) that are aligned along the crystallographic b axis (intermolecular Ge--Ge contacts: $3.65 \text{ \AA}$). The other half forms a polymeric $[\text{Ge}_4]_\infty^{6-}$ chain along the a axis. In this polymeric anion, the intermolecular Ge--Ge bonds of $2.87 \text{ \AA}$ replace the intramolecular $\text{Ge}_b\text{--Ge}_b$ bonds which are elongated to $3.27 \text{ \AA}$. As indicated in Scheme 5, neither the number of Ge--Ge bonds nor the charges change during the polymerization process nor the bivalent and trivalent germanium atoms are interchanged. Quantum-chemical considerations show that the intermolecular $\text{Ge}_b\text{--Ge}_b$ bonds in the polymeric anion have considerable biradicaloid character. Surprisingly, although all calculations indicate a diamagnetic ground state a sizable temperature-dependent paramagnetism was observed which leaves the question open whether this is due to accessible triplet states or to impurities in the sample.



Scheme 5. Section of the anionic substructure of the α - and β -modification of Ba_3Ge_4 . The long intermolecular contacts between the isolated $[\text{Ge}_4]^{6-}$ ions represented by dotted lines. In the polymeric anion $[\text{Ge}_4]_\infty^{6-}$ these distances are shortened and replace the elongated bridgehead $\text{Ge}_b\text{--Ge}_b$ bonds.

As one might expect, when the intrinsic σ -bond strength is weakened by taking an element from a higher period and the number of annulated three-membered rings is increased, the open biradicaloid form is stabilized even more. This was impressively demonstrated by Sita and Kinoshita who succeeded in isolating the pentastanna[1.1.1]propellane **14** (31 % yield) and the derivative **15** (1 % yield) from the reduction of the cyclotristannane **13** with lithium in THF (Scheme 6).^[19]



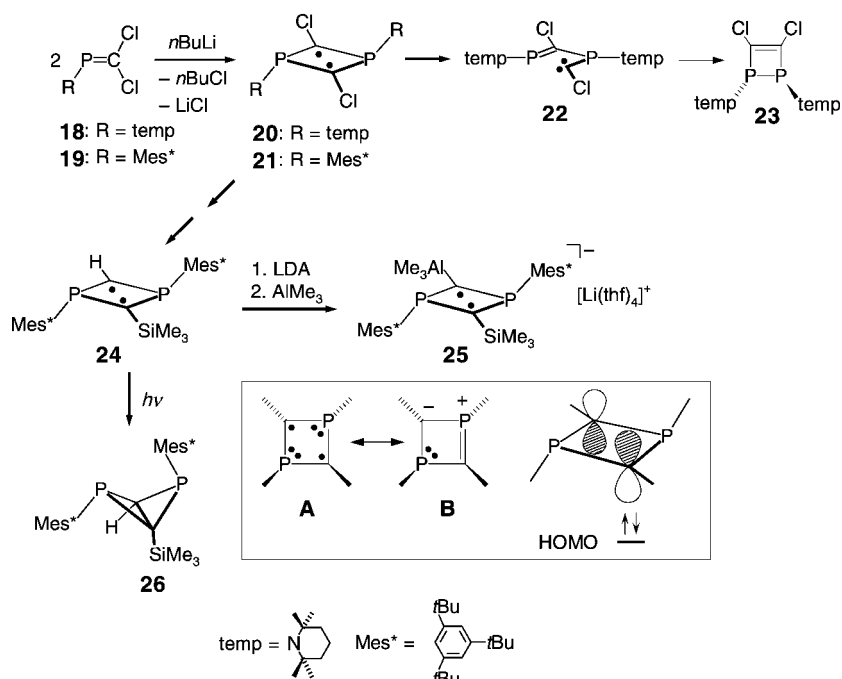
Scheme 6. Synthesis and reactivity of pentastanna[1.1.1]propellanes.

The experimentally determined distances (X-ray analyses) between the bridgehead tin atoms Sn_b are 20% longer than a regular Sn–Sn single bond. That **14** and **15** have considerable singlet biradicaloid character is further corroborated by the ease by which both compounds can be reduced stepwise to give the radical anions **14**^{•−} and **15**^{•−} ($E_{1/2}^{\circ} \approx -1.4$ V versus NHE) and the dianions **14**^{2−} and **15**^{2−} ($E_{1/2}^{\circ} \approx -1.9$ V versus NHE), respectively. The formally electron-deficient bridgehead tin centers (seven valence electrons) are converted into eight-valence-electron-configured (SnR₂)₃Sn[−] entities. Also, **14** showed some unusual reactivity; for example, MeLi or MeI are cleanly added to the central Sn_b–Sn_b bond to give **16** and **17**, respectively (Scheme 6). Extensive ab initio calculations performed for E₅[1.1.1]propellanes (E = C, Si, Ge, Sn),^[20] support the idea that although a bond-critical point indicative of a classical covalent bond can be found only for the carbon compound, there is a strong through-space interaction between the bridgehead centers in the σ-type biradicaloids for E = Si–Sn.

The first biradicaloid species prepared in gram quantities (yields >60%) were the 1,3-diphosphacyclobutane-2,4-diyls **20** and **21**. These were isolated when two equivalents of the *C*-dichlorophosphaalkenes **18** or **19**, respectively, were allowed to react with one equivalent of *n*BuLi at −100 °C (Scheme 7).^[21] The ring skeleton of these highly unusual P₂C₂ heterocycles is planar but both the carbon and the phosphorus centers are embedded in pyramidal coordination spheres. The comparatively high inversion barriers at phosphorus impede the formation of a planar 6π-conjugated heterocycle (like in the isoelectronic S₂N₂)^[22] and **20** and **21** have a high biradicaloid character. On the other hand, the coordination sphere at the phosphorus atoms is less pyramidal than in common phosphanes, which indicates some degree of π-donation from the phosphorus lone pairs to the carbon radical centers.

Simplistically, the electronic ground state may be approximated by the resonance structures **A** and **B** shown in Scheme 7 and diphosphacyclobutane-2,4-diyls may be described as weakly π-conjugated (delocalized) biradicaloids. Recent calculations by Schoeller et al. show that especially the substituents at the radicaloid carbon centers influence the electronic configuration of these Niece biradicals; for example, C-bonded silyl groups (σ donor, π acceptor) stabilize the singlet state, while the combination, NR₂ group at phosphorus and alkyl group at carbon, lowers the energy of the triplet state, thus providing the opportunity to easily control the biradical spin state.^[21e]

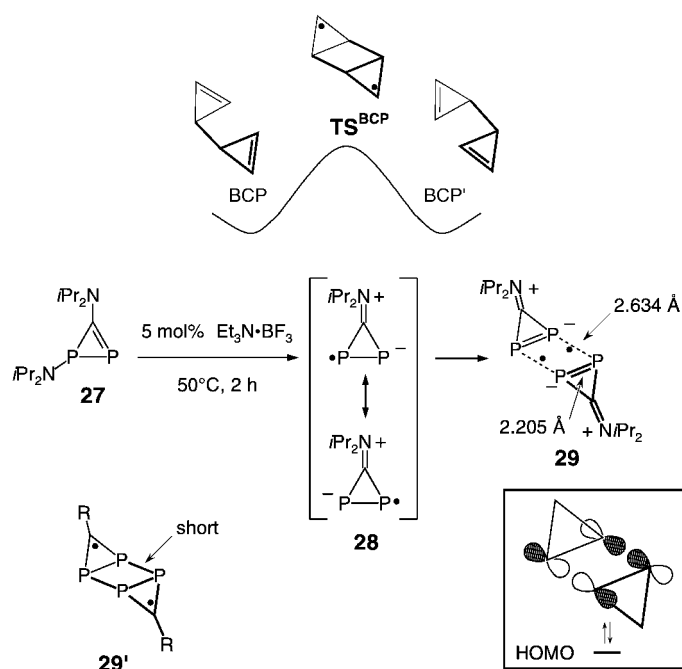
The pioneering preparative work to these biradicaloids was performed by Niece et al. While the *P*-amino derivative **20** is unstable at room temperature and isomerizes rapidly and quantitatively in solution, and slowly even in the solid state, to the 1,2-dihydrodiphosphete **23**, the Mes⁺-substituted compound **21** is stable up to 150 °C. The chloro substituents in **21**



Scheme 7. Syntheses of 1,3-diphosphacyclobutan-2,4-diyls (Niece biradicals).

can be exchanged for a silyl group and a H atom to give **24**. This compound can then be deprotonated by lithium di(isopropyl)amide (LDA) to give an unusual anionic carbene which subsequently reacts with AlMe₃ to give the anionic Niece biradical **25**. The symmetry of the HOMO shown in Scheme 7 does not allow a thermal ring closure of the open P₂C₂ heterocycles to the thermodynamically more stable valence isomer 2,4-diphosphabicyclo[1.1.0]butane; however, photolysis leads almost quantitatively to **26**.

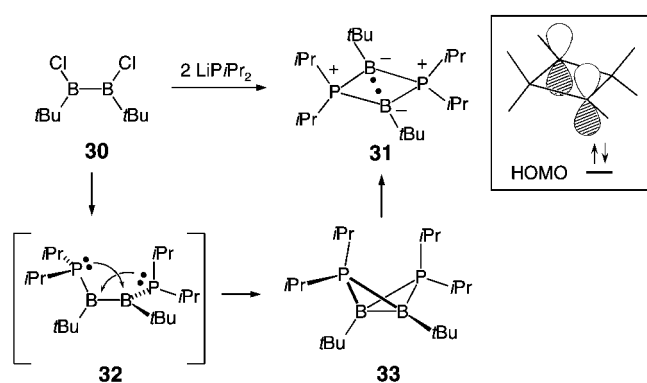
Biradical structures are also found among the more than 200 possible valence isomers of the formula C₆H₆. For the Cope rearrangement of the bicyclopent-2-enyl BCP one such structure is proposed as a transition state TS^BCP (Scheme 8).^[23] Replacement of the four carbon atoms in the central four-



Scheme 8. Cope rearrangement of bicycloprop-2-enyl $\text{BCP} \rightleftharpoons \text{BCP}'$ and synthesis of the stable diphosphirenyl dimer **29**.

membered ring by phosphorus atoms leads to compounds of type **29** which are no longer transition states but are stable.^[24] Bertrand et al. synthesized **29** from the reaction of the 1*H*-diphosphirene **27** with a catalytic amount of $\text{NEt}_3 \cdot \text{BF}_3$, and isolated it in the form of red crystals in 45% yield. It seems likely that the diphosphirenyl radical **28** is generated as the intermediate in this reaction. According to calculations by Schoeller the unpaired electron in **28** is equally distributed over both phosphorus atoms and localized in the π^* orbital of the $\text{P}=\text{P}$ bond. It is hence understandable that dimerization of **28** occurs through a $\pi^*-\pi^*$ interaction^[25] and leads to the observed product **29**. The central P_4 framework can be best described as a $4c6\pi$ -electron system in which four π electrons are hosted in two $\text{P}=\text{P}$ bonds within each CP_2 ring and the remaining two π electrons are localized in the HOMO (Scheme 8). Thus formally the two CP_2 units are held together by two one-electron $\text{P}-\text{P}$ bonds, as indicated by the formula given in Scheme 8. This description is consistent with the observation that the intra-ring $\text{P}-\text{P}$ bonds are quite short, while the inter-ring $\text{P}-\text{P}$ bonds are very long (c.f. **2** in Scheme 1). A further inspection of the electronic properties of compounds of type **29** by quantum-mechanical calculations^[24, 26] predict that they can be transformed into genuine biradicals like **29'** by compression of the central P_4 ring along the long $\text{P}-\text{P}$ vectors. This could be achieved either by changing the amino groups at the ring carbon atoms for alkyl or especially aryl groups, whereby the unpaired electrons will localize at the C-carbon atoms.^[26] It may also be possible to achieve this transition by applying pressure on the system.^[26] These exciting possibilities await, however, experimental verification.

As the icing on the cake, Bertrand, Schoeller et al. have recently successfully synthesized the crystalline, localized



Scheme 9. Synthesis of the Bertrand biradical **31**.

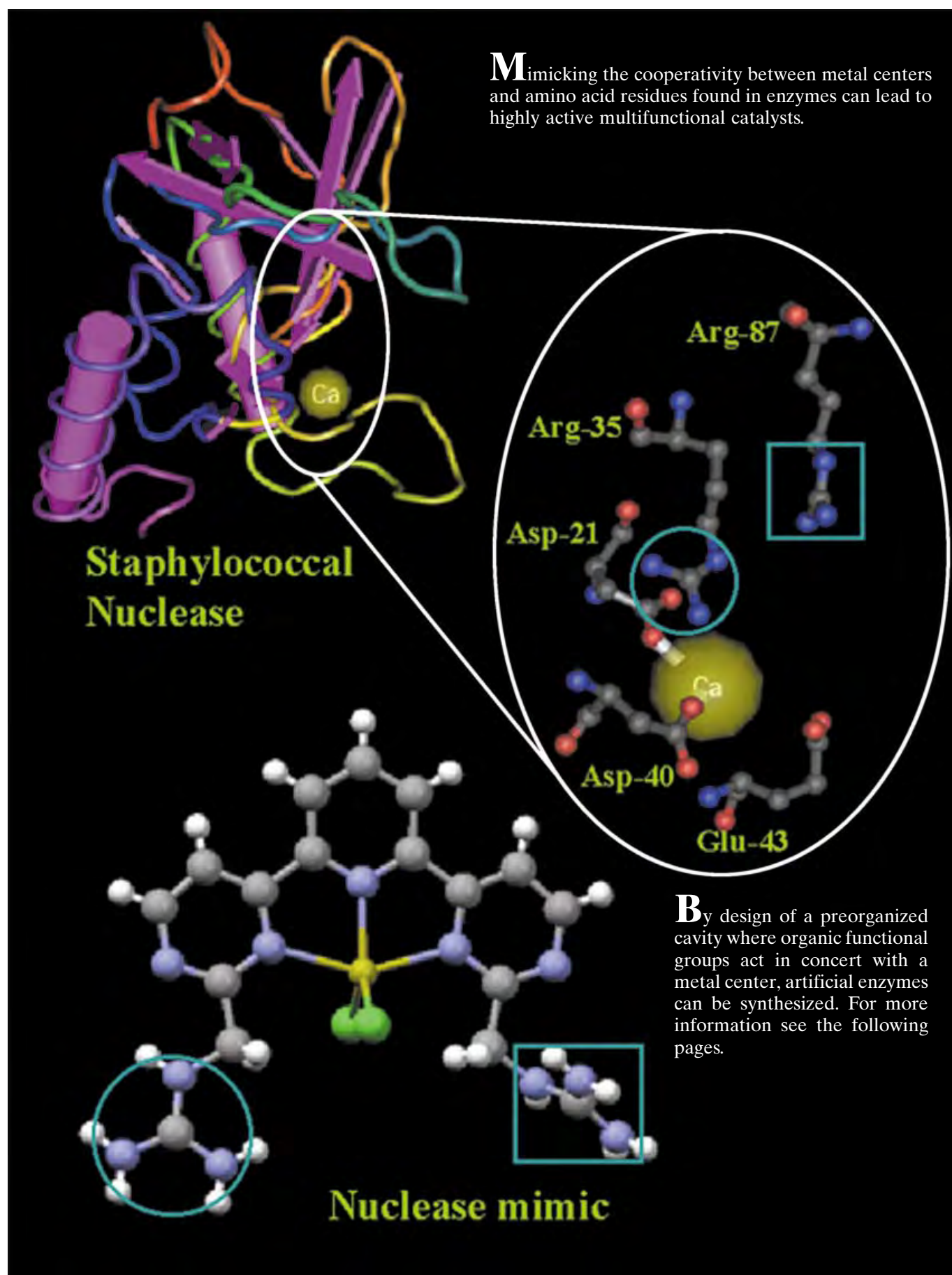
singlet, boron-centered biradicaloid **31** (Scheme 9).^[27] The $(\text{RP})_2(\text{CR})_2$ motif of the Niece radicals was replaced by the isoelectronic $(\text{R}_2\text{P})_2(\text{BR})_2$ unit (both contain 22 valence electrons for $\text{R}=\text{H}$). This had two important consequences for the stability: 1) the contribution of resonance structure **B** (Scheme 7) to the electronic ground state is largely diminished because the phosphorus lone pair has been transformed into a $\text{P}-\text{C}$ σ bond; 2) the heterocycle in **31** is expanded because of the intrinsically longer $\text{P}-\text{B}$ bonds (1.89 Å; the $\text{P}-\text{C}$ bonds in **20**, **24**, and **25** are 1.73–1.76 Å). Both factors favor an open singlet-biradical form.

The synthesis of **31** proved to be simple: reaction of the 1,2-dichlorodiborane(4) **30** with two equivalents of the secondary lithium phosphide $\text{LiP}(\text{iPr})_2$ furnished **31** as yellow, air-sensitive but thermally highly stable ($>200^\circ\text{C}$) crystals in 63% yield. The X-ray structure analysis revealed a perfectly planar P_2B_2 ring in which the transannular $\text{B}-\text{B}$ distance (2.57 Å) is 38% longer than the longest $\text{B}-\text{B}$ bond reported so far.^[28] Interestingly, ab initio calculations show that for the parent molecule $(\text{H}_2\text{P})_2(\text{BH})_2$ the planar form would be the transition state at 16.4 kcal mol⁻¹ for the inversion of the 1,3-diphospha-2,4-diborabicyclo[1.1.0]butane **33**. Note also that the symmetry of the HOMO shown in Scheme 9 allows a thermal disrotatorial electrocyclic ring closure. Although the mechanism is not known in detail, it can be assumed that the 1,2-diphosphanyldiborane(4) **32** should be one of the initial reaction intermediates. This structure, likely in a staggered conformation, should rapidly rearrange into the 1,3-diphospha-2,4-diborabicyclo[1.1.0]butane **33** which contains enough potential energy from the bulky groups to spring apart to give **31**. In other words, the choice of the sterically demanding substituents that can be comfortably accommodated in the planar form of **31** allowed the crystallization of a strictly iso(valence)electronic and *isostructural* transition state analogue for the bicyclo[1.1.0]cyclobutane, C_4H_6 , inversion. Using other substituents, it should be possible to adjust the $\text{B}-\text{B}$ distance such that any conformation on the internal reaction coordinate (IRC) for the bicyclo[1.1.0]butane inversion can be investigated. Furthermore, such studies on the transition of biradicaloids to biradicals (where 100% unpaired spin density would be confined to one radical site) would allow fundamental deep insights into the coupling of electronic spins.

Conclusion

Clearly, biradical(oid)s with main group elements are intrinsically more stable than their hydrocarbon counterparts. And many combinations are offered by the periodic system! Furthermore, the properties of biradicaloids can be fine-tuned by varying the substituents. Generally, the potential energy surfaces containing isomers of main group element compounds are much flatter than for comparable hydrocarbons. This facilitates the control over their distribution and mutual interconversions within a reasonable temperature range. From a purely synthetic point of view, the introduction of sterically demanding but electronically very different substituents is often easier to achieve in main group element chemistry than in classical hydrocarbon chemistry (simple salt metathesis reactions were involved in most of the above-cited examples, $E-Hal + R^- \rightarrow E-R + Hal^-$). Quantum-chemical calculations proved to be a highly valuable tool to guide the synthetic efforts for bi- and polyradicals, for the design of the electronic configuration, and finally for the development of new materials. As Berson wrote:^[6c] “In this domain of chemistry one has to expect the unexpected and to be ready to find it.” Hopefully, this highlight will stimulate further interest and research efforts in this direction.

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Remarkable Cooperativity between a Zn^{II} Ion and Guanidinium/Ammonium Groups in the Hydrolysis of RNA**

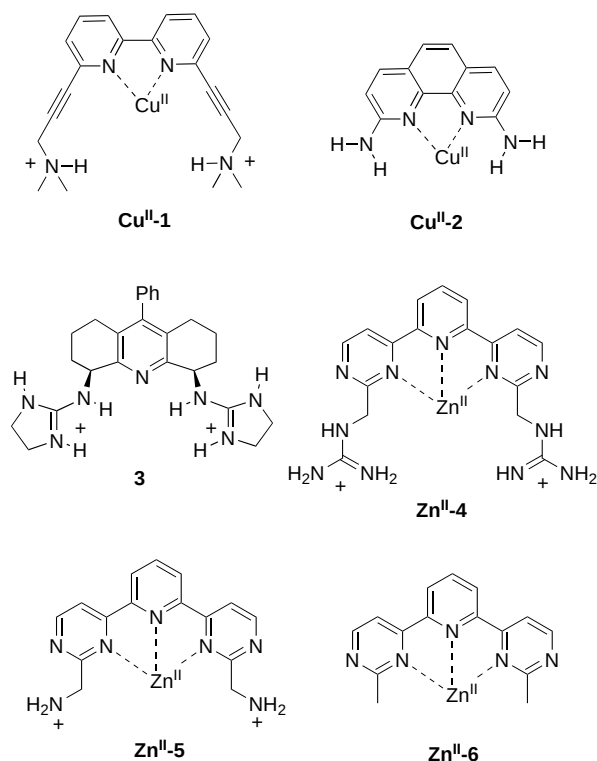
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In nature, the hydrolysis of the phosphodiester in DNA and RNA is often performed with enzymes that exploit cooperation between metal centers and amino acid residues, which act as general acid/base catalysts.^[1] The positively charged residues of lysine, arginine, and histidine are thought to stabilize phosphorane-like transition states by electrostatic interactions, hydrogen bonding, and/or proton transfer.^[2] In the case of the metalloenzyme staphylococcal nuclease (SNase), site-directed mutagenesis studies have revealed the extent of cooperativity between a Ca^{II} metal center and guanidinium residues.^[3] For example, the native enzyme containing guanidinium groups has a k_{cat} approximately 35000-fold higher than a mutant lacking the guanidinium groups. Furthermore, it was found that replacement of the Ca^{II} center with an Mn^{II} center, which maintains the tertiary structure but is catalytically inactive, dropped the reactivity approximately 36000-fold. Hence, the guanidinium and Ca^{II} units enhance each other's reactivity by factors of nearly 3×10^4 , which can be considered a measurement of their cooperativity.

The hydrolysis of RNA is a two-step reaction. The first step is a transesterification of the phosphodiester by the 2'-OH group, to create a 2',3'-cyclic phosphodiester, and the second step is nucleophilic opening that completes the hydrolysis.^[2] Artificial enzymes that could efficiently catalyze this sequence would be very useful in gene therapy.^[4] Owing to this potential, there is considerable interest in creating catalysts that efficiently hydrolyze RNA.^[5] Taking their lead from enzymes, numerous catalysts containing metal centers or general acids/bases have been explored.^[6] Although catalytic systems have been created that are very active using either metal centers or acids and bases alone, few demonstrate the high cooperativity between the two moieties that are hallmarks of enzymatic catalysis. In fact, there are few artificial enzymes with which the cooperativity between a metal ion and a charged auxiliary have been explored,^[7] relative to the number of systems with which one of these effects was analyzed independently.

One potential way to achieve multifunctional catalysis is to create a rigid cavity where multiple functional groups converge upon and form contacts with the bound substrate. This strategy may promote cooperativity between the functional groups. We do not presume to be sophisticated enough

to create a cavity that complements the shape of the transition state over the substrate. We simply want the catalytic groups to reside within a cleft or groove so that they form contacts with the substrate. The precedent for this design concept, and the catalysts reported herein, resides primarily in three studies: to study the cooperativity between a metal ion and ammonium groups in phosphate ester hydrolysis, Krämer and Kávári designed the complex **Cu^{II}-1** (Scheme 1).^[8] This complex was found to be 2900 times more reactive in



Scheme 1.

promoting the hydrolysis of an activated phosphodiester, bis(*p*-nitrophenyl) phosphate, than a control structure missing the ammonium ions. This catalyst has a preorganized cleft, such that binding of the substrate to the metal center ensures close proximity of the ammonium groups. Similarly, the complex **Cu^{II}-2** (Scheme 1), reported by Chin and co-workers, has two amino groups proximal to the metal, which leads to a 2×10^4 enhancement of the rate of the hydrolysis of 2',3'-cyclic monophosphate (2',3'-cAMP) compared to a catalyst lacking the amino groups.^[9] Our current design is also influenced by solely guanidinium-based catalysts. The rigid bisguanidinium receptor **3** (Scheme 1), where each guanidinium unit interacts with the substrate, has been found to enhance the rate of hydrolysis of RNA by a factor of 20 under neutral conditions.^[10]

Based upon these three studies, it seemed reasonable that a rigid bisguanidinium cleft that also contained an appropriately positioned metal center could act as an efficient RNA hydrolysis catalyst. Consequently, **Zn^{II}-4** (Scheme 1) was designed.^[11] The compound **Zn^{II}-4** incorporates guanidinium "arms" capable of hydrogen-bonding, designed to make direct

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contacts to a phosphodiester that is bound to the Zn^{II} center. Herein, we report the reactivity of **Zn^{II}-4** and **Zn^{II}-5** (Scheme 1) in the hydrolysis of the RNA dimer adenylyl (3'→5')phosphoadenine (ApA), and compare it to the reactivity of **Zn^{II}-6** (Scheme 1), to ligand **4** alone, as well as to background hydrolysis. We observed high cooperativity between the guanidinium groups and the metal center.

The hydrolysis of ApA to adenosine 3'-monophosphate, adenosine 2'-monophosphate, adenosine 2',3'-cAMP, and adenosine, was monitored by reverse-phase high-performance liquid chromatography (HPLC). The k_{obs} for hydrolysis increases linearly with **Zn^{II}-4** concentration at pH 7.4 (Figure 1 A), which indicates a first-order dependence on **Zn^{II}-4**. It is important to note that in all cases, the concentration of catalyst is above that of the substrate, and therefore there is no turnover. The k_{obs} values increase with pH until an optimum rate is reached around pH 7.5 (Figure 1 B). This observation is in excellent agreement with the $\text{p}K_{\text{a}}$ value of a water molecule coordinated to the zinc(II) center in **Zn^{II}-4**, which was determined to be 7.3 by potentiometric titration. This result suggests that the Zn-hydroxide form of complex **Zn^{II}-4** is the active catalyst in ApA hydrolysis. The low $\text{p}K_{\text{a}}$ value for the metal-bound water is because of the close proximity of the guanidinium arms. Similarly, Krämer et al. showed that the $\text{p}K_{\text{a}}$ of the water molecule coordinated to the copper(II) center in **Cu^{II}-1** is lowered by the proximal ammonium groups.^[8] As shown in Figure 1 B, the reactivity of **Zn^{II}-4** drops at higher pH values. This effect is the result of two factors: the slight precipitation of the catalyst and the deprotonation of one of the two guanidinium groups, the $\text{p}K_{\text{a}}$ value (10–11) of which is lower than normal for guanidinium groups (around 13).

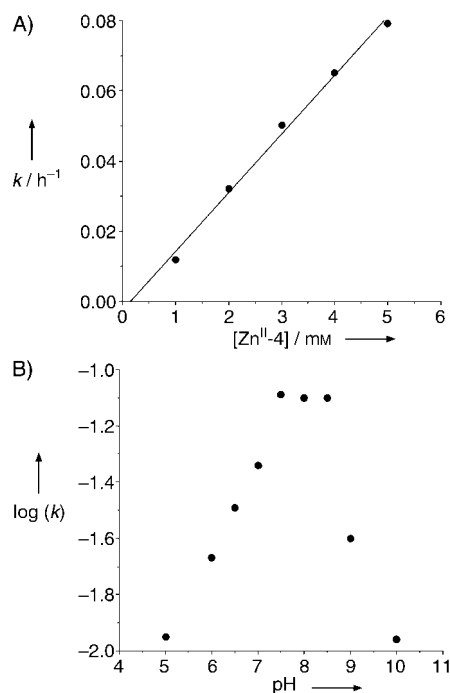
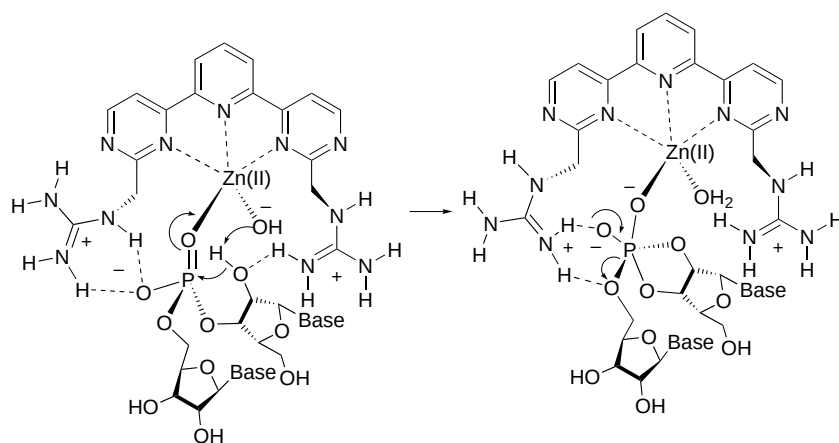


Figure 1. A) Pseudo first-order-rate constants (h^{-1}) for the hydrolysis of ApA promoted by **Zn^{II}-4**. B) Log-pseudo-first-order rate constants for hydrolysis of ApA as a function of pH value.

The pseudo-first-order rate constants for **Zn^{II}-4**, **Zn^{II}-5**, and **Zn^{II}-6** (5 mM) promoted hydrolysis of ApA (0.05 mM) at pH 7.4 (in water buffered with 10 mM of *N*-(2-hydroxyethyl)-piperazine-*N'*-2-ethanesulfonic acid (HEPES), at 37°C) are $8.0 \times 10^{-2} \text{ h}^{-1}$, $9.0 \times 10^{-3} \text{ h}^{-1}$, and $2.4 \times 10^{-5} \text{ h}^{-1}$, respectively. The reactions were followed to near 20% completion. Although these rate constants are very high, **Zn^{II}-4** is not as active as the most active catalysts previously reported. For example, a comparison of the rate constant for **Zn^{II}-4** to that of a very active dinuclear copper(II) complex reported by Chin and Young^[6b] shows that **Zn^{II}-4** is approximately 25 times less active. The key factor in this study is the degree of cooperativity achieved with **Zn^{II}-4**.

Mechanistically, the hydrolysis of ApA proceeds by an intramolecular attack by the 2'-OH group of the ribose. This step was confirmed by the fact that the 2'-deoxyadenylyl(3'→5')-2'-deoxyadenosine is not hydrolyzed to any measurable extent by **Zn^{II}-4**. However, the intermediate 2',3'-cAMP does not accumulate, but is rapidly hydrolyzed in situ. The rate constant of the hydrolysis of 2',3'-cAMP by **Zn^{II}-4** is fivefold larger than that of ApA. Therefore, the products of the hydrolysis reaction are adenine, and an equal mixture of 2'- and 3'-adenine monophosphate. The cooperativity is evidenced by the fact that there is no significant hydrolysis after 24 days using **4** alone, without the zinc center. Hence, **Zn^{II}-4** is about nine times more effective than **Zn^{II}-5**, over 3300 times more effective than **Zn^{II}-6**, and over 10^5 times more effective than **4** alone for enhancing the hydrolysis of ApA. To estimate the enhancement over the background hydrolysis by pure water at pH 7.4, a comparison to the buffer hydrolysis of cytidylyl(3'→5')cytidine (CpC) at 60°C was made.^[12] The half-life of this second-order reaction was estimated to be about 10000 days, which gives an extrapolated enhancement for **Zn^{II}-4** of near 10^6 at 37°C.

The rate enhancement of **Zn^{II}-4** over **4** is greater than that observed for native SNase containing the Ca^{II} center over SNase containing a nonproductive metal center. Clearly the enhancement obtained by adding metals to the guanidinium groups is very large in both the natural and synthetic systems. Yet, there is also a large enhancement as a result of adding a guanidinium to the metal centers in each case. The 3300-fold rate enhancement imparted by **Zn^{II}-4** compared to **Zn^{II}-6** is only one order of magnitude less than the enhancement attributed to the guanidinium groups for SNase, which demonstrates a very significant cooperativity between the Zn^{II} center and the guanidinium groups in **Zn^{II}-4**. The difference in reactivity cannot be entirely related to the $\text{p}K_{\text{a}}$ value of the water coordinated to the Zn^{II} center in each complex, although undoubtedly the $\text{p}K_{\text{a}}$ value of the Zn-bound water in **Zn^{II}-6** would be a unit or two higher than in **Zn^{II}-4** and **Zn^{II}-5**. Instead, some combination of the hydrogen bonding, electrostatic effects, and proton-donating ability of the guanidinium- and ammonium-containing arms must be the key to the enhanced reactivity. As these catalytic groups reside within a cleft containing the zinc ion, they form contacts with a bound substrate and play a role in the stabilization of the transition state. At this point we cannot rule out higher order complexes of **Zn^{II}-4** with itself, or with **4**, or with Zn^{II} as the catalytically active species.



Scheme 2. Proposed mechanism for nucleophilic attack and leaving-group departure facilitated by **Zn^{II}-4**.

A possible mechanism (Scheme 2) for the hydrolysis of ApA by **Zn^{II}-4** includes double activation of the phosphate by coordination to the zinc center and to one of the guanidinium fragments, followed by **Zn^{II}-OH** general-base-promoted delivery of the 2'-OH group. Hence the guanidinium and ammonium arms are postulated to play several roles:^[13] 1) to assist the binding of the phosphate group to the zinc ion, 2) to act as additional Lewis acids which polarize the phosphate group, 3) to lower the *pK_a* of a zinc-bound water molecule, and 4) potentially to protonate the leaving group.

In summary, a general strategy used by natural metal-nucleases is to achieve the hydrolysis of phosphodiester by cooperation between metal centers and amino acid residues. By creating a cleft that ensures guanidinium or ammonium groups and a zinc ion are proximal to one another, and preorganized to form contacts with a bound phosphodiester, we discovered cooperativity between the catalytic groups that is comparable to the enzyme SNase. The creation of other well-defined clefts wherein multiple productive contacts are made between catalyst and substrate may be anticipated to generate other efficient artificial enzymes.

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Fabrication of Ultrafine Conducting Polymer and Graphite Nanoparticles**

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The ability to selectively tune defects, electronic states, and surface chemistry has motivated the development of a variety of methods to fabricate metallic,^[1] inorganic,^[2] and polymeric nanoparticles.^[3] While metallic and inorganic semiconductor nanoparticles with dimensions of around 1 nm are routinely made, polymer nanoparticles with dimensions less than 5 nm have not been reported. Here we report the selective fabrication of amorphous polypyrrole (PPy) nanoparticles as small as 2 nm in diameter, using microemulsion polymer-

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ization^[4] at low temperature. In addition, we also describe a novel fabrication of graphite nanoparticles with dimensions less than 2 nm, by using ultrasmall amorphous PPy as the carbon precursor. The amorphous PPy nanoparticles are transformed into ultrafine graphite particles in the presence of an iron complex dopant, which promotes the graphitization of amorphous PPy during carbonization. Our results show that the graphite nanoparticles, when blended with polycarbonate, have an improved transparent conducting performance compared with carbon nanotubes. Low-temperature microemulsion polymerization is found to be a versatile route for the production of a wide range of new polymer nanoparticles and can be expanded to the fabrication of metallic and inorganic nanoparticles by using the concept of “nanoreactors”.

Cationic surfactants such as octyltrimethylammonium bromide (OTAB), decyltrimethylammonium bromide (DeTAB), and dodecyltrimethylammonium bromide (DTAB) were used to control the morphology of nanoparticles. Hexyltrimethylammonium bromide (HTAB) could not form highly ordered structures because of the weak hydrophobic interactions associated with short C_6 chains.^[5] Surfactants with hydrocarbon chains longer than C_{16} were not suitable for low-temperature microemulsion polymerization because of their liquid-crystalline state and high viscosity. Pyrrole monomers were polymerized in micelles, using iron(III) chloride as the oxidant, at 3 °C. The ^1H NMR spectrum of the nanoparticles showed no methyl resonances, which might have originated from residual surfactants. FTIR spectroscopy showed PPy ring-stretching bands at 1469, 1485, and 1549 cm^{-1} and an N–H stretching band at 3403 cm^{-1} . Therefore, it is certain that the surfactants were removed and PPy was successfully synthesized. Energy-dispersive X-ray analysis (EDAX) indicated the presence of carbon (54.2%), nitrogen (16.6%), and iron (15.3%). From these results, it is evident that the nanoparticles consist of PPy doped with an anionic iron complex.

Polymerization reactions using DeTAB (0.40 M) at 3 °C yielded PPy nanoparticles with an average diameter of approximately 2 nm, which was confirmed by high-resolution transmission electron microscopy (HRTEM) imaging and electron diffraction of the amorphous nanoparticles (Figure 1a). To our knowledge, there are no reports describing the manufacture of any kind of polymeric nanoparticles with dimensions less than 5 nm^[6] and this is the first experimental evidence for polymer nanoparticles in this size regime. Under these experimental conditions, PPy nanoparticles were fabricated between CMC I and CMC II (CMC = critical micelle concentration). This means that the product consisted mainly of PPy nanospheres. At room temperature the spherical nanoparticles were approximately 12 nm in diameter, while at 70 °C spherical mesoparticles (approximately 53 nm in diameter) were mainly obtained. As the polymerization temperature increases, the nanoparticle size also increases as a result of the increased mobility of surfactant chains. Figure 1b presents the change in average particle size as a function of surfactant concentration at 3 °C. The size of the nanoparticles decreased with decreasing surfactant chain length. The enhanced flexibility of longer spacers provides more free volume inside the micelles and, therefore, larger particles. The

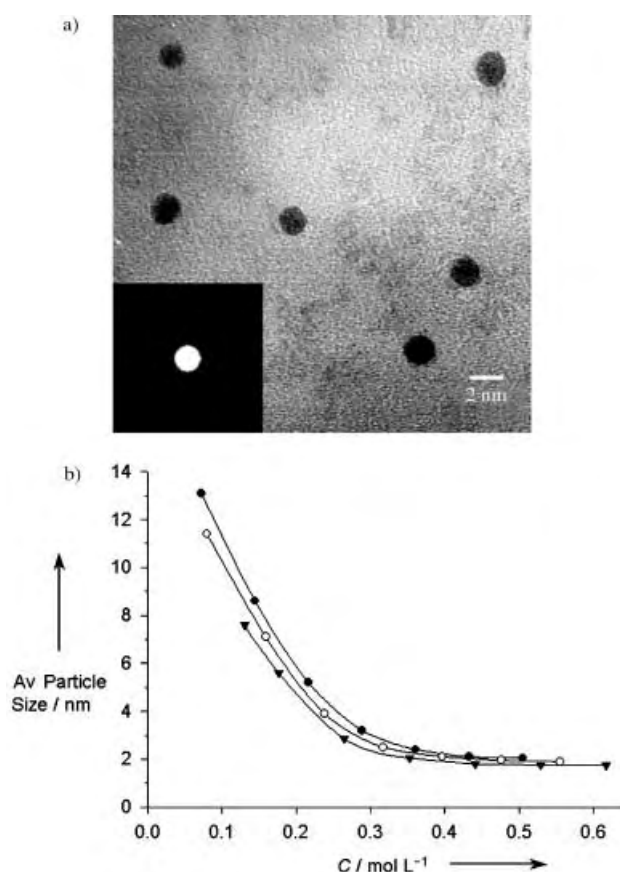


Figure 1. a) TEM image and nanobeam electron diffraction pattern of the PPy nanoparticles prepared using DeTAB (0.4 M) at 3 °C; b) Average change in nanoparticle size as a function of surfactant concentration (DTAB, ●; DeTAB, ○; OTAB, ▼). The average nanoparticle size was determined by TEM (50 particles counted).

micelle aggregation number (n) describes the number of surfactant molecules required to form a micelle; the value of n becomes smaller with shorter chain length.^[7] Thus, the number of micelles increases with shorter spacer length at the same surfactant concentration, which results in a reduction in the particle size. As surfactant concentration increases, the nanoparticle size decreases and approaches an asymptotic value. The morphological transformation occurs over this concentration range as a result of the relative changes in interfacial and packing forces.

The amorphous PPy nanoparticles can be transformed into ultrafine graphite particles by carbonization. It has been reported that transition metals promote the formation of graphite during the carbonization process.^[8] In our study, PPy nanoparticles were also synthesized by using ammonium persulfate as a comparative oxidant species. The control experiment showed that the doped iron complex anion facilitates the graphitization of PPy nanoparticles. For doped PPy nanoparticles, the loss of nitrogen atoms occurs between 400 and 600 °C, and carbonization reactions produce polycondensed aromatic hydrocarbons showing a high electrical conductivity.^[9] When the PPy nanoparticles were carbonized above 750 °C, the conductivity was found to be higher than that of pure PPy nanoparticles, which is a consequence of the presence of graphitic species.

Figure 2 shows a TEM image of carbonized PPy (CPPy) nanoparticles and their associated powder X-ray diffraction (XRD) pattern. The average particle size was 1.8 ± 0.4 nm, and the distribution was reasonably monodisperse; the carbonization temperature was 800 °C. The XRD pattern of CPPy confirms the presence of graphite in the nanoparticles, as the characteristic 002 and 100 Bragg reflections of graphenes are clearly displayed (Figure 2b). The electron diffraction pattern of CPPy nanoparticles also shows crystalline structure (Figure 2a). The degree of graphitization could be enhanced by treatment at higher temperatures. According to EDAX analysis, the graphite nanoparticles graphitized at 800 °C consist of carbon (73.8 %), nitrogen (1.3 %) and iron (8.6 %). The iron content could be removed without amorphization by heating the nanoparticles to reflux in nitric acid solution or by washing with excess methanol.

In general, powdered mixtures of vinyl polymers and metal oxides form graphite structures by heat treatment above 1000 °C.^[10] Compared with carbonization at an elevated temperature, graphite formation occurs at a mild temperature under our experimental conditions. The microemulsion system increases the extent of the π -conjugation length and optimizes the arrangement of the molecular chains.^[11] The size of polymer latex synthesized by microemulsion polymerization is much smaller than that synthesized by other synthetic methods. These effects probably bring about easier cyclization

and mass-transfer flow during carbonization. Our novel methodology describes the first demonstration of the fabrication of ultrafine graphite particles using amorphous polymer nanoparticulate precursors with a metallic dopant.

The ultrafine PPy and CPPy nanoparticles can be applied as optically transparent conducting materials. The PPy nanoparticles were blended with polycarbonate (PC), which is a typical transparent amorphous polymer used in glass substitutes and compact disks. Carbon nanofibers (CNs) are well-known as highly transparent conductive materials.^[12] For a comparison, CNs were also mixed with PC. Figure 3 shows the transparency and conductivity of PC/CN, PC/PPy, and PC/CPPy films. The transparencies of PC/PPy and PC/CPPy films were much higher (up to 17 %) than that of PC/CN films at the same filler content (Figure 3a). To obtain a transparent film, conductive powders should have an average particle diameter no larger (approximately 0.2 μ m) than half of the shortest wavelength of visible light.^[12] As a consequence of their large diameter and high aspect ratio, CNs easily form bulky aggregates, which causes blackening of the as-prepared films. The conductivity of a PC/pure PPy film was slightly lower than that of a PC/CN film (Figure 3b). As mentioned above, the conductivity of the PPy nanoparticles can be enhanced by the carbonization process. The PC/CPPy film showed higher conductivity than the PC/CN film. As the filler content increases, the generation of local electronic paths is favorable to small and uniform CPPy fillers. Judging from these results, PC/CPPy films could be used as a substitute for indium–tin

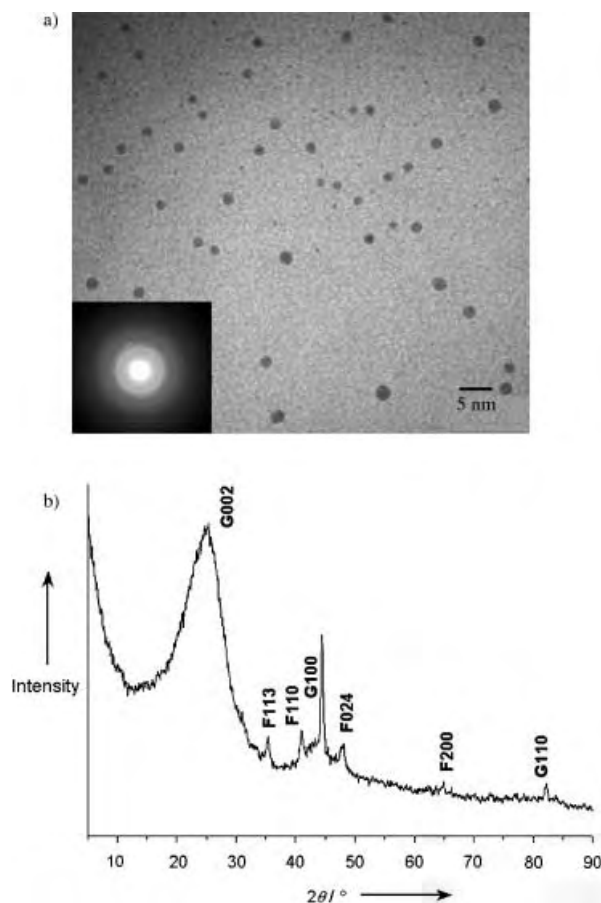


Figure 2. a) TEM image and nanobeam electron diffraction pattern of graphite nanoparticles fabricated by the carbonization of PPy nanoparticles prepared using DeTAB (0.4 M); b) powder X-ray diffraction pattern of the graphite nanoparticles (graphite, G; iron complex, F).

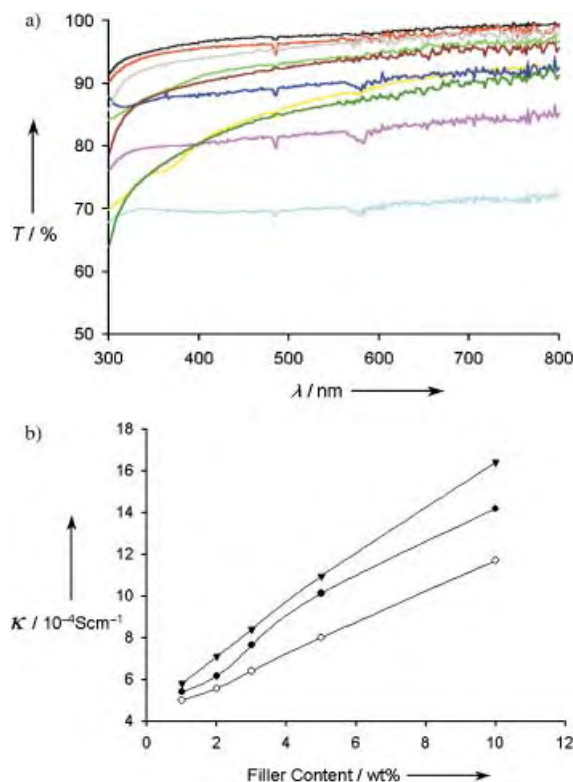


Figure 3. Transparency and conductivity of PC/CN, PC/PPy, and PC/CPPy films: a) Transparency (pure PC, black; PPy 1 wt %, red; PPy 3 wt %, green; PPy 10 wt %, yellow; CN 1 wt %, blue; CN 3 wt %, violet; CN 10 wt %, sky-blue; CPPy 1 wt %, gray; CPPy 3 wt %, brown; CPPy 10 wt %, deep-green); b) conductivity (PC/CN, ●; PC/PPy, ○; PC/CPPy, ▼).

oxide (ITO) as a potential transparent conducting material. In addition, CPPy nanoparticles could be applied as an anodic material in lithium-ion batteries because of their high conductivity and large surface area.

We have demonstrated a surfactant-mediated methodology for the synthesis of 2 nm spherical PPpy nanoparticles. The carbonized PPpy nanoparticles can be used as a highly transparent conductive material, which may possibly be a substitute for carbon nanofibers. Importantly, low-temperature microemulsion polymerization may provide a facile way to synthesize new polymer nanoparticles, and might be expanded to allow the fabrication of ultrafine metallic and inorganic particles, which embraces the concept of "nanoreactors".

Experimental Section

A variable amount of surfactant was magnetically stirred in distilled water (40 mL) at 3 °C. Pyrrole monomer (1.0 g, 14.9 mmol) was added dropwise to the surfactant solution, and iron(III) chloride hexahydrate (9.25 g, 34.3 mmol), dissolved in distilled water (5 mL), was added to the surfactant/pyrrole solution. Microemulsion polymerization proceeded while stirring for 3 h at 3 °C. The reaction product was placed in a separating funnel and excess methanol was added to remove the surfactants and the residual iron(III) chloride. The upper layer was discarded and the remaining nanoparticle precipitate was dried in a vacuum oven at room temperature.

The PPpy nanoparticles were placed in a quartz tube in a furnace under N₂ atmosphere. The sample was heated to 800 °C at a heating rate of 3 °C min⁻¹, held at 800 °C for 5 h, and then cooled to room temperature. PPpy nanoparticles and PC were combined in THF. The mixed solution was spin-coated onto a glass slide using a PWM32 spinner (Headway Research, Inc.). Transparency of the films was measured with a UV/Vis spectrometer and the conductivity was determined by the van der Pauw method. As-prepared (AP)-grade CNs were purchased from Aldrich. PC/CN and PC/PPpy films were prepared by the same method. Film thicknesses were estimated with an Alpha-Step 500 surface profiler (Tencor). All films were approximately 270 nm thick, the growth being controlled by changing the spinning speed. TEM images were taken by a JEOL 2010 high-resolution microscope and EDAX analysis was carried out using a Philips CM 20 microscope.

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Novel Capsules with High Stability and Controlled Permeability by Hierarchic Templating**

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Hollow capsules with high stability and controllable permeability have very interesting actual and potential applications, for example, as constrained environments for the preparation of nanostructured materials, the encapsulation of guest molecules, drug delivery, catalysis, and as host containers for nucleic acid storage and transport.^[1,2] However, deformation and rupture of hollow capsules under shear stress may limit these applications. The stability can be increased slightly by deposition of additional layers, but the permeability decreases simultaneously. While the loading has to be fast and the release slow in most applications, the permeability of the capsules has to be tuned according to the specific application.^[3] Therefore, it is desirable to develop a simple and reliable method to fabricate capsules with high stability and the desired permeability. A combination of tailorable and tunable silica nanoparticles with layer-by-layer (LbL) self-assembly^[4] provides a powerful tool for the creation of exciting nanostructured systems. Silica is extremely well-suited to this purpose since well-defined particles can be prepared. Since silica is itself charged, it can be assembled with cationic polyelectrolytes, and the chemistry to dissolve it without affecting the chemical composition of the organic film components is already well established.

Here we make use of these features to prepare capsule walls of defined porosity after removal of SiO₂ (Figure 1, left) or sphere-in-sphere (SiS) structures, again after removal of SiO₂, that is sandwiched in high concentration between two indestructible walls (Figure 1, right). Similar structures can be found in nature, for example, gram-negative bacteria possess two cell walls which are separated by an aqueous phase.^[5] To prepare nanoporous shells (NPS) we have used SiO₂ covered by polyallylamine hydrochloride (PAH@silica) as the cationic polyelectrolyte and polystyrene sulfonic acid (PSS) as the anionic polyelectrolyte and deposited multilayers of these by consecutive alternating adsorption on melamine formaldehyde particles (MF). The MF core is then removed by treatment with HCl, and the SiO₂ dissolved with HF. To form SiS shells, multilayers of PSS and PAH (2–3 double layers) are adsorbed alternately, followed by a variable number of silica and PAH layers (1–3 double layers) and then PSS and PAH to build-up a nondestructible outer shell.

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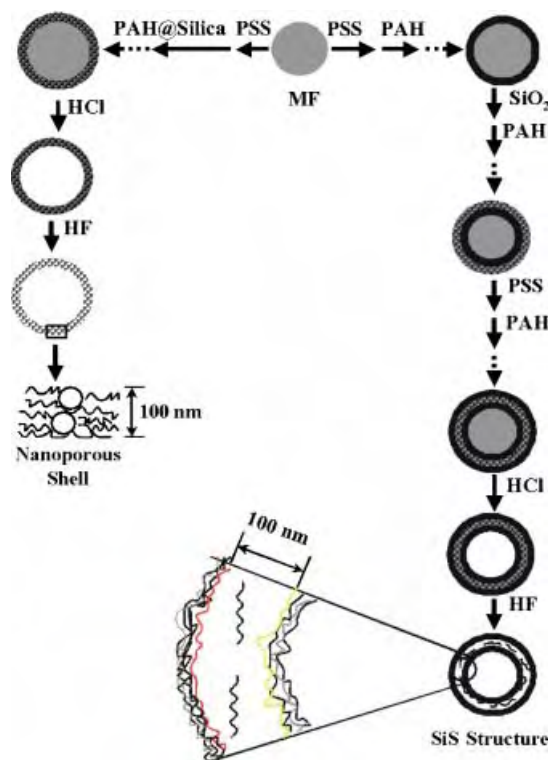


Figure 1. General procedure for the preparation of hollow capsules possessing nanopores and sphere-in-sphere shells.

To distinguish the inner and outer shells by optical spectroscopy we partly coadsorb PAH labeled with fluorescein isothiocyanate (PAH-FITC, green fluorescence) to the inner shell and PAH labeled with rhodamine B (PAH-RhB, red fluorescence) to the outer shell. Removal of the MF core by treatment with HCl again yields a hollow capsule. Subsequent removal of the SiO₂ by HF yields a liquid interlayer in which excess PAH is dissolved. This space between the outside volume and inner core volume is itself interesting as a reaction space, but here we use it merely to tune the properties of the capsule wall as a whole.

The wall thickness of both NPS and SiS capsules was measured by means of scanning-force microscopy (SFM) and shows there is a large difference in the capsules in the dried state before and after removal of the silica particles. A typical SFM image is shown in Figure 2. NPS capsules of (PSS/PAH@silica)₄ have average diameters of about 6.0 and 4.3 μm. The wall thickness of the dried particles can be deduced from SFM contour plots, since, for example, the height terraces correspond to folds and thus to a double wall thickness or multiples

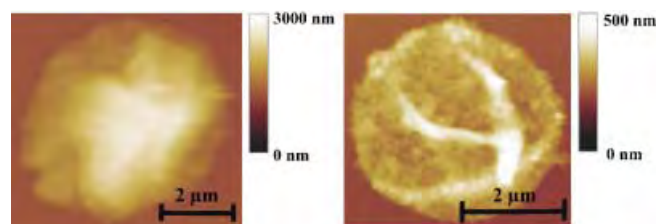


Figure 2. SFM images of air-dried hollow capsules of (PSS/PAH@silica)₄: a) before and b) after removal of silica nanoparticles from inside the walls.

thereof. In this case, one derives a value of 18 nm and, less accurately, of 500 nm for the wall thickness after and before removal of the SiO₂, respectively. An average diameter increment of approximately 120 nm per PAH@silica multi-layer indicates that about two monolayers (on average) of silica nanoparticles are adsorbed with each deposition cycle. This may be a result of the formation of agglomerates of silica nanoparticles. Nevertheless, SiS capsules of (PSS/PAH/PSS/PAH-FITC)(silica/PAH/silica)(PAH-RhB/PSS/PAH/PSS/PAH) possess a capsule wall containing silica particles with a thickness of 120–126 nm. The removal of the silica layers left a wall thickness of approximately 20–26 nm. The difference of about 100 nm corresponds to the thickness of two silica layers. Thus, SFM measurements indicate silica nanoparticles were successfully incorporated into the wall of the capsules and removed by HF etching.

NPS capsules were resolved by ultramicrotom transmission electron microscopy (UM-TEM). It can be seen from UM-TEM images (Figure 3) that the resulting hollow capsules of

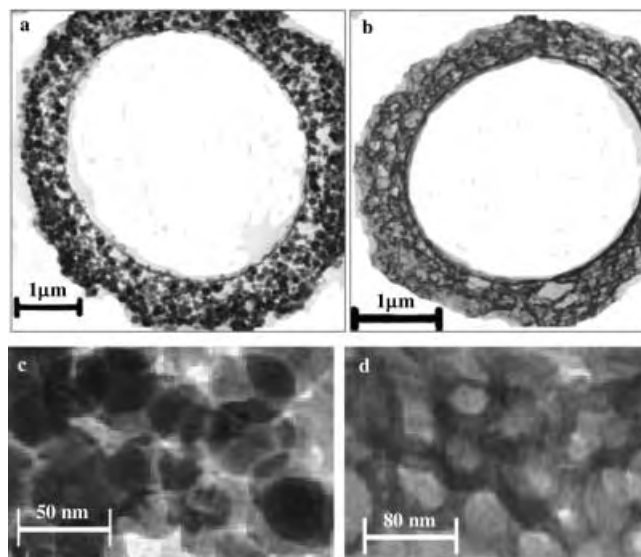


Figure 3. UM-TEM images of capsules of (PSS/PAH@silica)₄: before (a, c) and after (b, d) removal of silica particles from inside the walls.

(PSS/PAH@silica)₄ are almost spherical. Capsules with silica particles (dark dots with brighter surrounding) are shown in Figure 3 a. After the capsules have been subjected to HF acid to remove silica particles, the resulting pores (bright area with darker surrounding) are randomly distributed over the thin polymer shell of about 500 nm thickness, whereas the center with a diameter of about 4 μm is totally empty (Figure 3 b). The pore size distribution depends on the size of the silica particles and the osmotic pressure in the pores, and results in the thickness of the porous shell being similar to that of the shell possessing silica particles. The much smaller thickness measured by SFM after SiO₂ removal is thus the result of a collapse of the pores upon drying. Figure 3 c and d show the silica particles and the resulting nanopores at higher resolution.

It can be seen by means of confocal laser scanning microscopy (CLSM) that both the NPS and SiS capsules are

shape-persistent, with no agglomeration in solution before or after removal of the silica particles. More insight into the structure of the SiS shells in liquid has been obtained by high-resolution confocal two-color fluorescence microscopy. Removal of the silica layers should form an interlayer of approximately 100 nm thickness in between the inner shell of (PSS/PAH/PSS/PAH-FITC; approximately 8 nm thickness) and the outer shell of (PAH-RhB/PSS/PAH/PSS/PAH); approximately 10 nm thickness) that is filled by a PAH solution. Figure 4a shows the occurrence of two completely

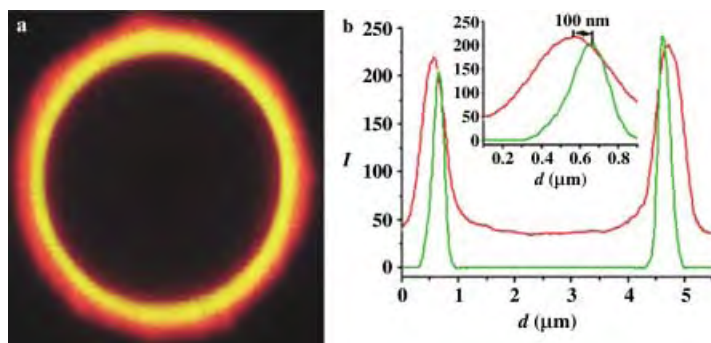


Figure 4. a) CLSM fluorescence image of a capsule of (PSS/PAH/PSS/PAH-FITC)(silica/PAH/silica)(PAH-RhB/PSS/PAH/PSS/PAH) after removal of the silica layers. Red emission results from the rhodamine B in the outer layers and yellow emission from the fluorescein in the inner layers mixed with the emission from the rhodamine B. b) Fluorescence profiles along a line through the capsule center; green: fluorescein fluorescence, red: rhodamine B fluorescence. I = fluorescence intensity.

co-centered fluorescent shells, which are attributed to the fluorescein-labeled inner shell of PSS/PAH/PSS/PAH-FITC and the rhodamine B labeled outer shell of PAH-RhB/PSS/PAH/PSS/PAH. Figure 4b shows the fluorescence distribution of both dyes detected simultaneously at different wavelengths. The insert of Figure 4b shows the distance between the inner and the outer shells at higher resolution. The difference between both maxima taken from five profiles yields an average distance of 100 ± 10 nm between the PAH-FITC on the inner shell and the PAH-RhB on the outer shell. This distance agrees well with the value of 100 nm determined by SFM for the silica-layer thickness.

The permeability was studied by confocal microscopy studies on the fluorescently labeled PAH and PSS, as well as on small dye molecules such as fluorescein and rhodamine B. NPS capsules are impermeable to the polymer but permeable to small dye molecules, both before and after removal of the silica particles. No difference in permeability was observed for SiS capsules before and after removal of the silica layers. However, annealing the SiS capsules with silica interlayers in the walls at 70 °C for 6 min and then cooling them down results in them becoming impermeable to small dye molecules, similar to the (PSS/PAH)₅ capsules. On the other hand, SiS capsules obtained by removal of the silica interlayers are permeable to small molecular dyes and impermeable to polymers.

The reduced permeability of the (PSS/PAH)₅ and (PSS/PAH)₂(silica/PAH/silica)(PAH/PSS)₂/PAH capsules was ascribed to a rearrangement of the macromolecular layer

constituents after annealing.^[6] This situation arises from a stronger coupling of the polyelectrolytes with each other which leads to an increased network in the wall. Macroscopically, the rearrangement reduces the capsule diameter by more than 20%. Simultaneously, the capsule wall contracts so that even small molecules cannot permeate through. Although the overall wall material of the SiS capsules after removal of silica is almost the same as for the (PSS/PAH)₆ capsules, the original continuous shell is divided into two subshells by the liquid interlayer. Thus, it is understandable that small dye molecules diffuse more easily into SiS capsules with a liquid interlayer than into (PSS/PAH)₆ capsules.

The mechanical stability of the capsules was elucidated by observing osmotically induced deformations. PSS ($M_w = 70000$ Da) does not permeate the capsule wall, hence, the capsule morphology can be tuned by adjusting the osmotic pressure external to the PSS solution. Starting with perfectly spherical capsules, a stepwise increase in concentration of PSS osmotically leads to permeation of water from the inside to the outside and concomitant deformation of the capsules. If (PSS/PAH)₅ and (PSS/PAH)₆ capsules are incubated in a 12% PSS solution, they invaginate and no longer show a spherical shape.^[6] However, no deformation was observed for either the NPS and SiS capsules before or after removal of the silica.

It can be easily understood that rigid organic–inorganic capsules are deformation-resistant, even under a considerable mechanical stress. After removal of the silica particles, capsules with water interlayers or nanopores have the same chemical composition as the capsules obtained from PSS/PAH. The much higher mechanical stability, which is attributed to the different shell structure, may arise from two factors: either the wall has become reinforced by the silica removal process (for example, by incomplete removal of silica or cross-linking of some chains) or the excess PAH resulting from the removal of silica particles has been excreted from the wall into the water interlayer or nanopores and build up an osmotic pressure. The latter offsets the external osmotic pressure of 10^6 Nm^{-2} corresponding to a weight of 12% PSS. The intermediate water layer must also exhibit a similar polyelectrolyte concentration. Such a concentration is not unreasonable because the PAH content in the silica-containing interlayer can be estimated to be about 11%. This estimate results from assuming a silica particle has a diameter of 50 nm and the polyelectrolyte coating has a thickness of 2 nm.

In summary, our results have shown that intriguing capsules with vastly different mechanical stability and controllable permeability can be prepared simply by changing the structure of the shell. We expect these novel capsules to be of particular interest for applications, such as delivery systems, catalysis, and chemical sensing or separation, for which structural features such as selective permeability, cavity shape, as well as a remarkable mechanical stability are critical. It is also clear that the liquid interlayer between the polymeric walls may be a reaction compartment suitable for reactions to enable the wall properties to be changed further. Further experiments need to be carried out to increase the efficiency and sophistication of encapsulation, delivery, and separations with these capsules.

Experimental Section

PSS ($M_w = 70\,000$ Da) and PAH ($M_w = 70\,000$ and $15\,000$ Da) were obtained from Aldrich. Silica particles (50 nm) were prepared according to the method reported by Stöber et al.^[7] MF particles (3.99 μm) were purchased from Microparticles GmbH, Germany.

The procedure employed for the deposition of PSS, PAH, silica, and PAH-coated silica nanoparticles onto the surface of MF microparticles is as follows: A solution (1.5 mL) of the species with a charge opposite to that of the MF templates or the last layer deposited (1 mg mL^{-1} PSS or PAH in 0.5 M NaCl or $2\text{ wt\%}$ silica or PAH-coated silica nanoparticles in 0.1 N NaCl) was added to a template latex solution (0.3 mL) and left to adsorb for 15 min. The excess added species was removed after each layer was deposited by centrifugation (2000 g, 2 min)/washing/redispersion cycles ($\times 3$) with dilute aqueous NaCl. After the final washing step, the particles were redispersed in water (0.3 mL). Subsequent layers were deposited until the desired number of multilayers was achieved. Silica particles (50 nm) were covered with one PAH layer by using a similar procedure except that centrifugation (10000 rpm, 10 min) was used for the particle separation. Hollow capsules were prepared by dissolving the MF cores with 0.1 M HCl solution. Silica particles in the walls of the capsules were removed with 0.1 M HF solution.

Confocal micrographs were taken with a confocal laser scanning microscope "Aristoplan" from Leica (Germany) equipped with a $100\times$ oil immersion objective.

The morphology of the capsule wall was investigated by transmission electron microscopy of ultrathin sections. The sections were made on an ultramicrotome "Ultracut E" after embedding them in a mixture of methyl methacrylate and *n*-butyl methacrylate. The sections were observed through a Zeiss EM 902 transmission electron microscope.

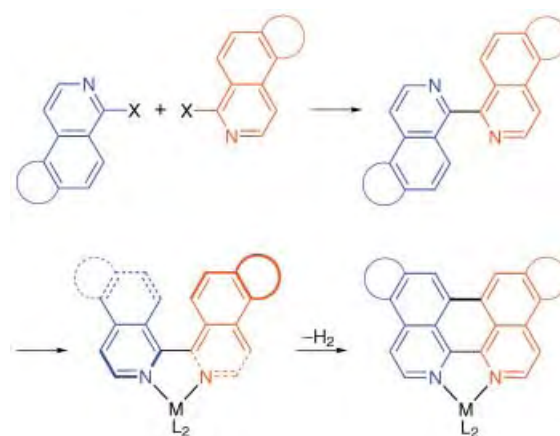
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Ru^{II} Complexes of "Large-Surface" Ligands**

Edith C. Glazer and Yitzhak Tor*

Ru^{II}-polypyridyl complexes have traditionally been synthesized by a complexation reaction of the ligand of interest with the appropriate Ru^{II} precursors.^[1] Although significant advances have been made in synthesizing modified 2,2'-bipyridine-, 1,10-phenanthroline-, and 2,2':6,2''-terpyridine-type ligands, these methodologies provide access to a rather constrained set of structural motifs.^[2] In particular, the range of Ru^{II} complexes that contain large, extended surfaces is limited,^[3] despite their enormous potential as nucleic acid intercalators, luminescent probes, as well as energy and electron donors and acceptors.^[4,5] We envisage a new methodology for the fabrication of extended polypyridyl systems from modular building blocks by the dehydrogenation reaction of a strained metal-complexed ligand (Scheme 1).^[6,7]



Scheme 1. Extended symmetric and asymmetric bipyridine-type ligands are synthesized in a modular fashion from simpler heterocycles. The chelating ligand is enforced into a *syn* orientation within an octahedral complex and can then undergo a dehydrogenation reaction to a planar "large-surface" metal-polypyridine complex.

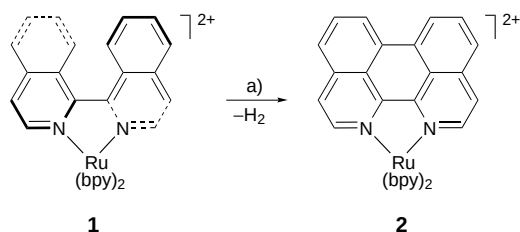
In this modular approach, nitrogen-containing heterocycles are homo- or heterocoupled to give extended bipyridines that can subsequently be coordinated and dehydrogenated to give the desired coordination complexes (Scheme 1).^[8] Here we report the successful implementation of this strategy for the preparation of biologically active eilatin-containing complexes as well as Ru^{II} complexes of previously unknown "large-surface" ligands.

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

The 1,1'-biisoquinoline-containing Ru^{II} complex (**1**) was selected as a model system for exploring the dehydrogenation procedure (Scheme 2). This coordination compound is easily



Scheme 2. Dehydrogenation of $[\text{Ru}(\text{bpy})_2(1,1'\text{-biisoquinoline})]^{2+}$ (**1**) to $[\text{Ru}(\text{bpy})_2(1,12\text{-diazaperylene})]^{2+}$ (**2**). Reagents and conditions: a) Pd/C, ethylene glycol–acetone 10:1, 175–195 °C, 24 h, 30 % yield. All complexes were isolated as their PF_6^- salts.^[10]

prepared by treating $[\text{Ru}(\text{bpy})_2\text{Cl}_2]$ (bpy = 2,2'-bipyridyl) with the known biisoquinoline ligand.^[9] Heating a solution of complex **1** in ethylene glycol with preactivated Pd/C to 175–195 °C for 24 h leads to the formation of complex **2** (30 % yield), which contains the fused 1,12-diazaperylene ligand.^[10] This “subtle” transformation can be monitored by spectroscopic techniques. The presence of distinct, slowly interconverting diastereomeric complexes of the unfused coordination compound **1**^[11] results in complicated ¹H and ¹³C NMR spectra that are simplified upon dehydrogenation to the racemic product **2** (Figure 1 a). Additionally, fusing the two isoquinoline rings results in dramatic changes in the UV/Vis absorption spectrum. Characteristic transitions, particularly the visible metal-to-ligand charge-transfer (MLCT) bands, are significantly shifted to longer wavelengths (Figure 1 b). Cyclic and square-wave voltammetry measurements further support the planarization of the biisoquinoline moiety in **1** to the diazaperylene core in **2**. While the metal-centered $\text{Ru}^{3+/2+}$ wave remains essentially unchanged ($E_{1/2} = 1.28$ V versus a saturated calomel electrode (SCE)),^[12] the first two reduction waves in **2** show a significant shift to lower potentials when compared to **1** ($\Delta E_{1/2} \geq 0.2$ V), as anticipated for the dehydrogenated product (Figure 1 c). Final confirmation of the successful dehydrogenation of **1** into **2** is obtained by mass spectrometry and by synthesizing an authentic sample of **2** by an independent synthetic route.^[13] It is important to note that the free 1,1'-biisoquinoline ligand does not undergo the corresponding dehydrogenation reaction to the fused 1,12-diazaperylene under identical conditions.

Having demonstrated the feasibility of the above approach, we were prompted to apply it to more complex systems where the synthesis of the free large-surface ligand is significantly more challenging.^[8] Toward this end, Ru^{II} complexes of eilatin,^[14] a marine alkaloid bearing two distinct coordinating faces (Scheme 3),^[15] are particularly intriguing since they have recently been shown to exhibit anti-HIV activity.^[16,17] The unfused ligand, trivially named here pre-eilatin, has been synthesized and used to prepare the dark-red Ru^{II} complex, $[\text{Ru}(\text{bpy})_2(\text{pre-eilatin})]^{2+}$ (**3**).^[10] Exposure to Pd/C in ethylene glycol at elevated temperatures (175–190 °C) cleanly converts complex **3** into the corresponding deep-green eilatin complex **4** after 1 h in essentially quantitative yield.^[10] It is worth noting

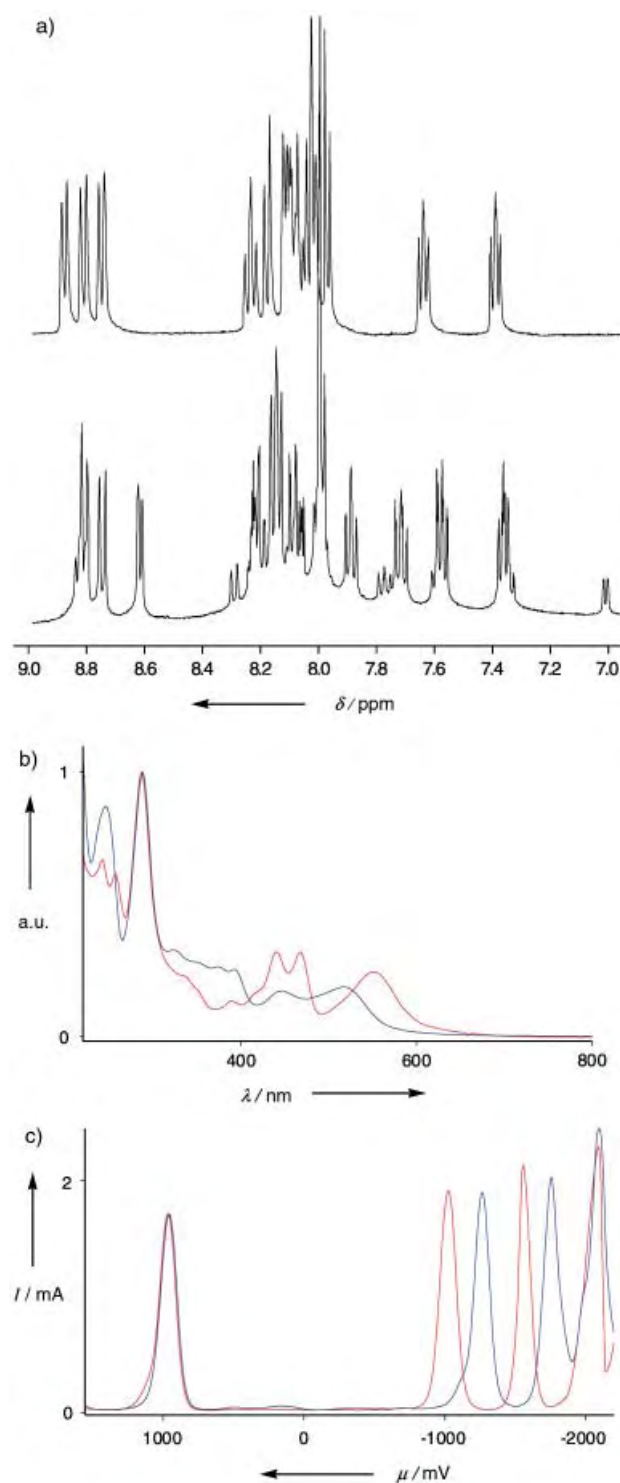
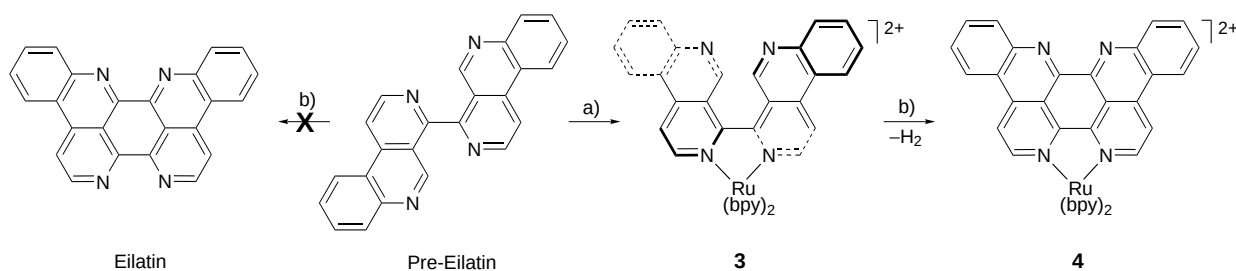


Figure 1. a) ¹H NMR spectra of **1** (bottom) and **2** (top) in $[\text{D}_6]\text{acetone}$ at room temperature. b) UV/Vis spectra of **1** (blue) and **2** (red) in CH_3CN . c) Square-wave voltammograms of **1** (blue) and **2** (red) in CH_3CN containing 0.1 M $[\text{nBu}_4\text{N}][\text{PF}_6]$ as supporting electrolyte. Potentials are shown with reference to the ferrocene–ferrocenium couple at 0.08 V.^[12]

that, as for the biisoquinoline system, treatment of the free pre-eilatin ligand with Pd/C under similar conditions does not yield eilatin (Scheme 3).

The structural and electronic reorganization that accompanies the transformation of **3** to **4** is manifested in a simplified NMR spectrum, a dramatic red-to-green color



Scheme 3. Dehydrogenation of $[\text{Ru}(\text{bpy})_2(\text{pre-eilatin})]^{2+}$ (**3**) to $[\text{Ru}(\text{bpy})_2(\text{eilatin})]^{2+}$ (**4**). Reagents and conditions: a) $[\text{Ru}(\text{bpy})_2\text{Cl}_2] \cdot 5\text{H}_2\text{O}$, ethylene glycol–water 1:1, 100 °C, 3 h, 62 % yield; b) Pd/C, ethylene glycol–acetone 10:1, 175–190 °C, 1 h, 97 % yield. All complexes were isolated as their PF_6^- salts.^[10] Note that identical reaction conditions do not convert the free pre-eilatin ligand to eilatin.

change (Figure 2), and a substantial change in electrochemical characteristics.^[10] As anticipated, complex **4**, containing the large-surface eilatin ligand, exhibits electronic transitions at lower energy than the bpy-type complex **3**. Most notable is the appearance of a low-energy band around 580–600 nm that has

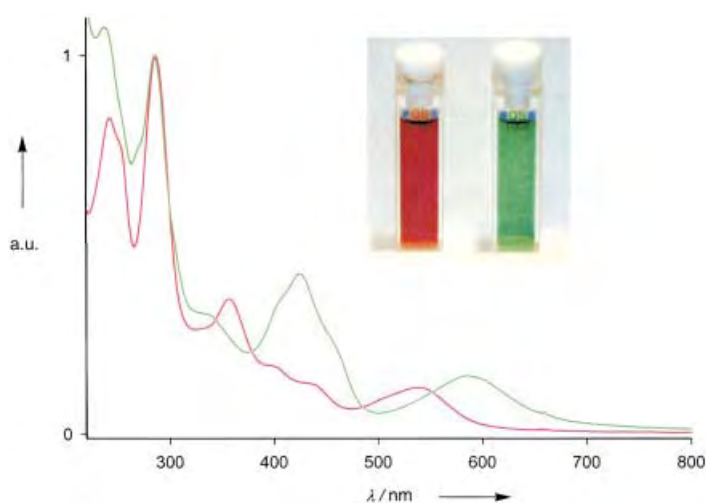
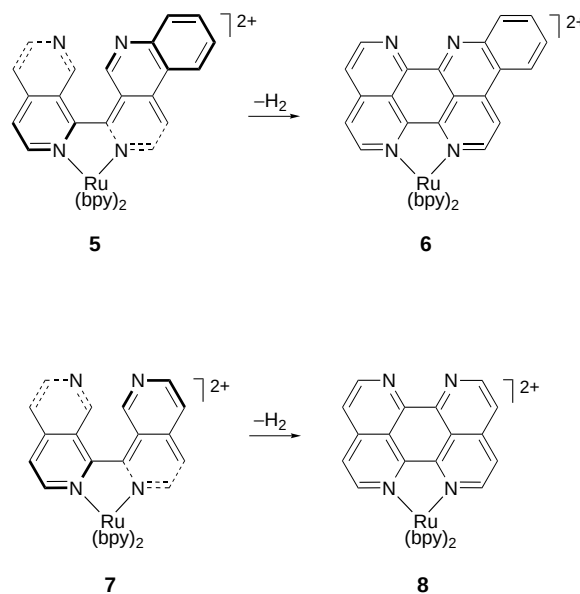


Figure 2. UV/Vis spectra of **3** (red) and **4** (green) in CH_3CN . Inset: a picture of the corresponding solutions.

previously been assigned to a Ru–eilatin MLCT transition (Figure 2).^[14] Planarization of the large heterocyclic ligand also stabilizes the reduced states of **4** when compared to **3**. While the $E_{1/2}$ values for the $\text{Ru}^{3+/2+}$ couple in **3** and **4** are almost identical (1.38 and 1.40 V versus SCE, respectively), a significant shift to less negative potentials is apparent for the reduction waves, with the $E_{1/2}$ value for the first reduction couple changing by more than 0.3 V ($E_{1/2} = -0.70$ and -0.39 V versus SCE, for **3** and **4** respectively).^[10,18]

The approach reported here naturally lends itself for the fabrication of coordination compounds bearing asymmetric “large-surface” ligands, since fluxional heterobiaryl ligands are accessible through cross-coupling reactions.^[19] Such ligands are particularly attractive because of their potential photophysical as well as nucleic acid recognition properties.^[4,20] As shown in Scheme 4, we have targeted the previously unknown debenzo-eilatin system **6**. Coordination of the free ligand to yield **5**, followed by dehydrogenation over Pd/C in ethylene glycol affords the desired compound **6**.^[10,21,22]

Interestingly, the 1,6,7,12-tetraazaperylene core of eilatin has never been reported. This heterocycle is an attractive



Scheme 4. Dehydrogenation reactions of **5** and **7** to yield the novel complexes **6** and **8**, respectively. All complexes were isolated as their PF_6^- salts.^[10]

bifacial bridging ligand that can be utilized for investigating charge-transfer phenomena in bimetallic complexes.^[23] Complexation of 1,1'-bis-2,7-naphthyridine to $[\text{Ru}(\text{bpy})_2]^{2+}$ to give **7** is followed by a facile dehydrogenation to afford the monometallic complex **8** (Scheme 4).^[10,22,24] In the case of both complexes **5** and **7**, dehydrogenation to **6** and **8**, respectively, produces the same extraordinary color change as with the eilatin system. The successful synthesis of complexes **6** and **8** highlights the significant advantages presented by the new approach for the modular construction of coordination compounds that are currently inaccessible by traditional routes.

The results reported in this contribution illustrate an elegant methodology to novel metal complexes where the “classical” $[\text{Ru}(\text{bpy})_2]^{2+}$ core is coordinated to unique large-surface ligands. The approach takes advantage of metal coordination to promote a dehydrogenation reaction, where extended bpy-type ligands are forced into a *syn* orientation within octahedral complexes. It is likely that the enforced proximity and enhanced steric repulsion within the bound ligand facilitates the single carbon–carbon bond-forming step during the dehydrogenation/cyclization reaction.^[25] In addi-

tion to the efficient synthesis of biologically active eilatin-containing complexes, Ru^{II} complexes of previously unknown ligands have also been prepared. It is anticipated that this methodology can be applied for the fabrication of other coordination compounds that contain different metal centers and coordination geometries.

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Modular, Well-Behaved Reversible Polymers from DNA-Based Monomers**

Elizabeth A. Fogleman, Wayne C. Yount, Jun Xu, and Stephen L. Craig*

Reversibly formed linear polymers (Figure 1a) have received increasing attention in recent years.^[1–8] Reversible association of monomers leads to extended assemblies whose structure and properties depend on the strength and specificity of the association, the conformational flexibility of the molecule, the concentration of the monomer, and the chemical and physical environment of the system. These dissipative polymers undergo conformational changes and diffusion on much shorter timescales than their covalent counterparts, assemble with minimal imperfections, and repair themselves on useful timescales.^[1,9] They encompass a range of structural motifs, phase behaviors,^[1,3,10] solution and solid-state mechanical properties,^[2,11,12] and environmental responsiveness,^[12] and offer promise as environmentally benign materials as a result of the ease of processing and recycling and the absence of a polymerization catalyst. Meijer and co-workers^[2,13,14] were the first to show that reversible polymers may possess properties that are similar to traditional covalent polymers despite the transient interaction (approximately seconds) defining the main chain.

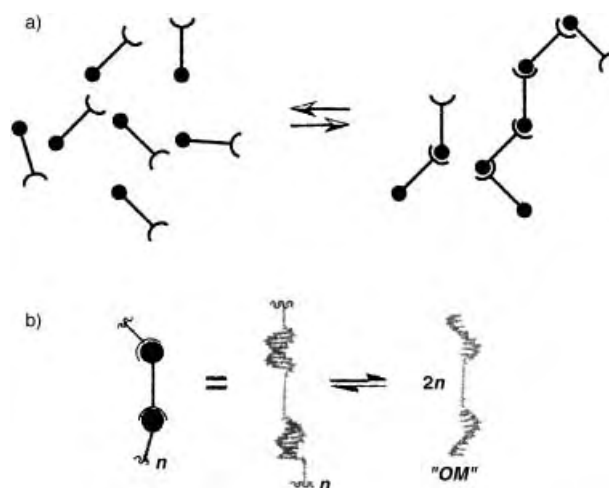


Figure 1. a) Schematic representation of reversible polymers; b) an OM-based reversible polymer. The spacer is extended for illustrative clarity only.

Here we report that the reversible polymeric properties of a system based on oligonucleotide base pairing are well-behaved. The system is intrinsically modular and is therefore amenable to “physical organic chemistry of materials”, that is, systematically varying the structure of the components and observing the concomitant changes in the properties of the assemblies. The monomers (hereafter, oligonucleotide-based monomers (OMs)) comprise oligonucleotide sequences that are covalently linked directly or through a synthetic spacer (Figure 1b). Duplex formation creates a linear, polymeric assembly that resembles larger duplex DNA,^[15] but in which the main chain is defined by the reversible base pairing. The specificity between complementary DNA strands is such that monomers can be synthesized that associate head-to-tail or in alternating patterns. DNA base pairing is a popular motif for self-assembly,^[16,17] and similar systems have been used to characterize DNA curvature and ring-closure probabilities,^[18,19] to sequentially align synthetic moieties,^[20,21] and to fabricate linear DNA–protein nanostructures.^[22] Surprisingly, their properties in the context of reversible polymerization have not been previously reported. We find that OMs are well-suited to systematic studies of reversible polymerization.

Representative OMs are reported in Table 1. OMs **1a–d** are self-complementary and form single-component homopolymers, while **2A:2B** and **3A:3B** are two-component heteropolymer systems. Melting curves give effective free energies of dimerization^[23] (ΔG_{dim}) that are in line with empirically derived expectations;^[24,25] polymerization does not have a significant impact on duplex formation. Polymer formation is revealed in all cases by an increased viscosity in the OM solutions relative to solutions of nonpolymerizing analogues. For example, the viscosity of **2A:2B** (3 mg mL^{−1} or 0.29 mM in each monomer, 1M NaCl/10 mM sodium phosphate buffer, pH 7.0, 25.0 °C, Cannon–Ubbelohde viscometer) is 1.25 times that of the same concentration of **2B** alone, and that of **3A:3B** (5.8 mg mL^{−1} or 0.22 mM) is 2.5 times that of **3A** alone. The molecular weight of the polymer can be easily controlled by varying the ratios of **2A:2B** and **3A:3B**; an excess of any monomer serves as an effective “chain

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Table 1. Composition, complementarity, and free energies of dimerization of oligonucleotide-based monomers. Red and blue colors denote complementarity within each OM system.

OM	Sequence	$\Delta G_{\text{dim}}(298)$ [kcal mol ⁻¹] ^[21]
1	(5'→3')GGTATACC-X-GCTTAAGC	
1a	no spacer	-10.0
1b	X = -T-	-8.5
1c	X = -CH ₂ CH ₂ CH ₂ -	-8.5
1d	X = -(CH ₂ CH ₂ O) ₆ -	-9.2
2A	(5'→3')GGCTCCCTTCTACCAC	-12.4
2B	(5'→3')AGGGAGCCGTGGTAGA	
3A	(5'→3')GCCCCGGCTCTCAAAAACCTCTCGGGCCCTAGAGGGGCCCTAGA	-13.2
3B	(5'→3')CCCGGGCTCTAGGGCCCCTCTAGGGCCCGAGAGTTTTTGAGAG	

terminator" for the polymerization. Expected molecular weights are calculated from the free energies of the duplexes and monomer ratio, and the viscosity observed scales as $MW^{(1.2 \pm 0.1)}$ for **2** and **3** (Figure 2). The exponents indicate semirigid rod polymers, which is consistent with the known structure of duplex DNA.

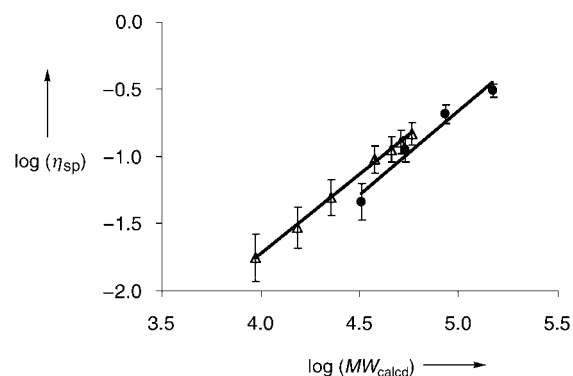


Figure 2. Specific viscosity η_{sp} as a function of calculated molecular weight determined from chain-termination studies for **2AB** (Δ , 3.0 mg mL⁻¹, 20 °C) and **3AB** ($\bullet$, 2.9 mg mL⁻¹, 20 °C).

The concentration dependence of the solution viscosity also reveals the reversible nature of the system. The specific viscosity of **1a** scales with $[\mathbf{1a}]^{3.3 \pm 0.2}$, which is in good agreement with theoretical expectations^[26] and previous observations for reversible systems.^[2,12] Static multiangle and dynamic light scattering studies on 1 mM solutions of **1a** confirm the expected average molecular weights of approximately 200 kDa and the presence of semirigid rod structures with persistence lengths of about 50 nm. The OM polymers behave like true reversible counterparts of high MW duplex DNA.

Enzymatic manipulations provide further insight. Quick T4 DNA ligase (New England Biolabs) covalently captures polymers of **1a** on the timescale of OM dissociation (approximately minutes), and the ligated polymers can be characterized by gel electrophoresis (Figure 3). All equilibrium polymerizations are candidates for some degree of cyclization, and these can be characterized for **1a**. Digestion by Lambda exonuclease removes any linear polymers,^[27] and the remaining small band of cyclic structures (approximately 10 % of total) is clearly seen in the gel.

Polymeric properties are determined not only by primary and secondary structure but also by inter- and intrachain

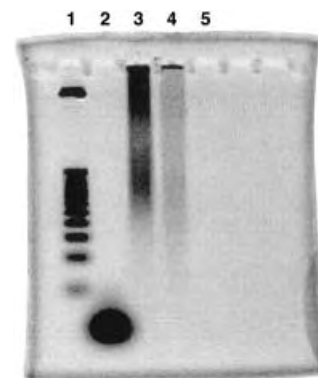


Figure 3. Denaturing polyacrylamide gel electrophoresis (PAGE) of OM **1a** samples. Lane 1: 25-bp step ladder; lane 2: OM **1a**; lane 3: ligated polymer of **1a**; lane 4: ligated and exonucleased **1a**; lane 5: exonucleased **1a**.

interactions. In OMs, the interactions—reflected by the Huggins constant (k')—are largely electrostatic, and they are mediated by the ionic strength of the buffer. Similar to the results of Shruggs and Ross,^[28] k' varies from 0.49 to 0.84, and passes through a maximum value at about 1 M NaCl. The nonlinear dependence on ionic strength can be ascribed to screening effects,^[29] and its consequence is that polymer–polymer interactions can be varied from good solvent to strongly interacting conditions. The variation is pseudo-independent of duplex thermodynamics, thus providing another handle for fundamental studies.

In conclusion, DNA-based modules appear to be generally suitable systems for fundamental studies of reversible polymerizations. As such, they possess several attractive characteristics. The thermodynamics and kinetics of association are determined by the variable OM base sequence. The linear density of the reversible interactions and the conformational flexibility along the polymer backbone are each dependent on a spacer in which much variation is possible. Inter- and intrachain interactions may be tuned by the salt concentration in the buffer. Finally, robust enzymology offers covalent capture of transient structures and structural analyses of cyclizations. Many properties of assembled materials directly reflect the nature of the reversible interaction defining the polymerization. An understanding of the relationship between the structural, mechanical, and dynamic properties of the polymer and the structural, thermodynamic, and dynamic properties of the molecular constituents might therefore create an avenue for the rational synthesis of materials with

specific properties. Studies with OM s should therefore provide insight into the molecular basis of novel properties of reversible polymeric systems, for example, at surfaces and interfaces.^[8]

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Molecular Clips that Undergo Heterochiral Aggregation and Self-Sorting**

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Biological systems offer exquisite examples of the ways in which spatially and temporally controlled self-processes—self-organization, self-assembly, and self-recognition—can lead to the creation of higher order functional structures.^[1] To approach the design of supramolecular systems that display complex biomimetic behavior, chemists have developed metal coordination, donor-acceptor interaction, and hydrogen-bond-driven self-assembly to a level of sophistication that has allowed these assemblies to be endowed with desirable chemical or physical properties.^[2] Within the area of self-assembly driven by hydrogen bonds, these activities have resulted in intriguing discoveries including quadruple hydrogen bonding modules^[3] that form the basis of supramolecular polymers,^[4] molecular capsules,^[5] systems that display enantiomeric self-recognition,^[6] and complete asymmetric induction.^[7] The use of hydrogen bonding as a tool in these applications depended on the design of robust, functionalizable, and tightly associated H-bonding modules. The further implementation of H-bonding modules as instructed components^[1] in self-organizing systems additionally requires systems capable of self-sorting.^[8] Such systems display high levels of discrimination between self and non-self species and consequently operate simultaneously and orthogonally within complex mixtures. One strategy to create robust H-bonding modules relies on increasing the number of hydrogen bonds and tailoring their geometrical arrangement. In this paper we employ a strategy using molecular clips,^[9,10] based on molecular shape and chirality. We report that compounds **1a**, **1b**, ($\pm$)-**2a**, and ($\pm$)-**2b** form tightly self-associated dimers in CDCl₃ driven by the simultaneous formation of π - π interactions and two hydrogen bonds. The dimers possess a confluence of properties—tight binding, high levels of chiral discrimination, and self-sorting—that make them prime modules for use in advanced applications.

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Figure 1 shows the chemical structures of the four molecular clips described in this paper. Compounds **1a** and **1b** are C_s -symmetric achiral meso forms, whereas $(\pm)$ -**2a** and $(\pm)$ -**2b** are chiral C_2 -symmetric compounds. All four compounds

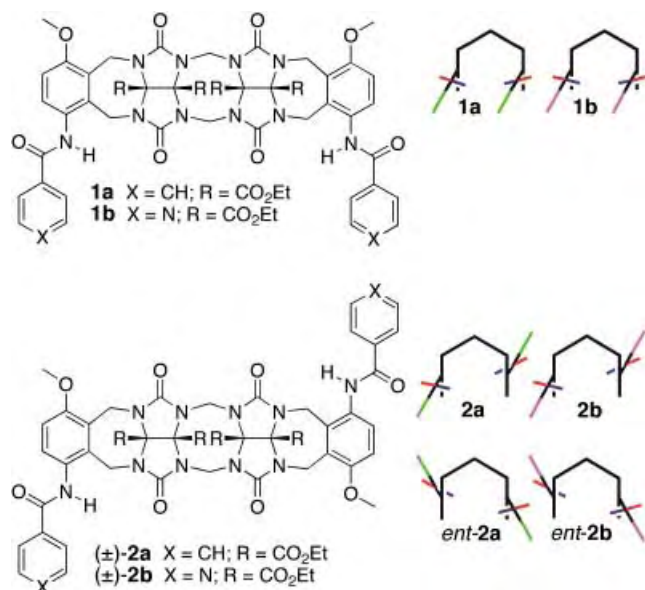


Figure 1. Structures of **1a**, **1b**, $(\pm)$ -**2a**, and $(\pm)$ -**2b**, and schematic representations of their three dimensional shapes; phenyl rings (green), pyridyl rings (purple), carbonyl oxygen atoms (red), amide NH groups (blue).

display remarkable self-association properties. In particular, the ^1H NMR spectra of **1a**, **1b**, $(\pm)$ -**2a**, and $(\pm)$ -**2b** (Figure 2a, b, e, and f) displayed two sets of resonances for the amide NH groups and the protons on substituted *o*-xylylene side-walls. These observations suggested the formation of kinetically and thermodynamically stable dimeric aggregates in CDCl_3 .^[11]

The X-ray crystal structures obtained for **1a** and $(\pm)$ -**2b** provide corroborating evidence for the dimerization of **1a**, **1b**, $(\pm)$ -**2a**, and $(\pm)$ -**2b** and suggest plausible geometries for these aggregates in CDCl_3 (Figure 3).^[12] The geometrical features of these dimers are dictated by the formation of only two $\text{C}=\text{O}\cdots\text{HN}$ hydrogen bonds.^[13] Their high thermodynamic stability, however, is likely to be caused by favorable interactions between the four aromatic rings that occur as the aromatic side-walls penetrate deep into the cleft of the opposing molecular clip.^[9a,b] One consequence of this geometry is the parallel orientation of the four amide groups, a feature which may prove valuable in the preparation of dynamic functional group arrays.^[14] In the dimerization of $(\pm)$ -**2b**, three outcomes are theoretically possible: enantiomeric self-recognition $((+)\text{-}2\text{b})_2$ and $(-)\text{-}2\text{b})_2$, formation of a heterochiral aggregate $((+)\text{-}2\text{b}\cdot(-)\text{-}2\text{b})$, or a mixture of the two processes. In reality, the heterochiral aggregate $((+)\text{-}2\text{b}\cdot(-)\text{-}2\text{b})$ is formed exclusively. The origin of this highly diastereoselective process is simple to explain; in the heterochiral dimer the simultaneous formation of π - π interactions and two hydrogen bonds is possible, whereas the hypothetical homochiral dimer benefits from π - π interactions and only a single hydrogen bond.

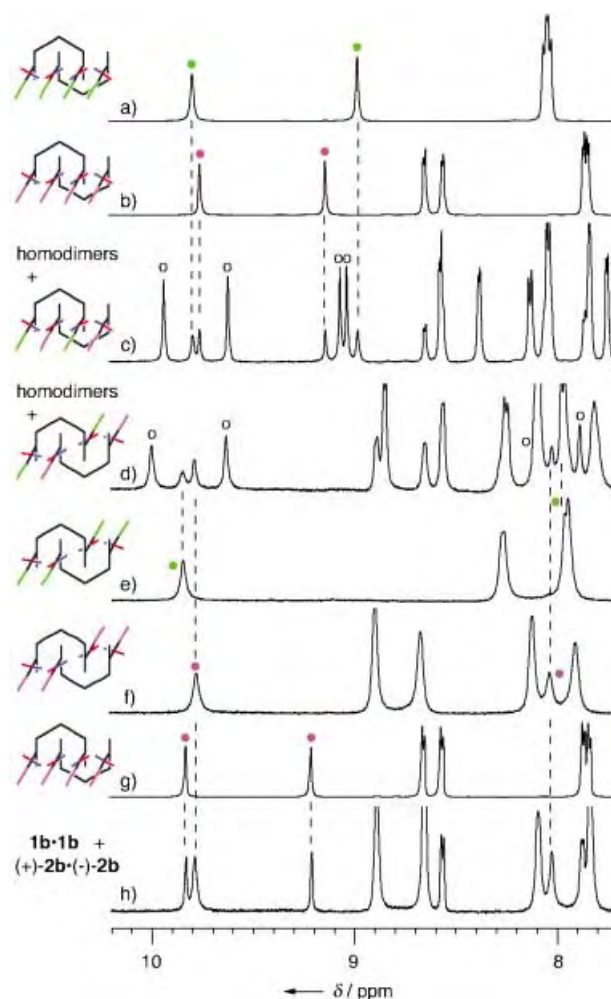


Figure 2. Hydrogen bonding region of the ^1H NMR spectra (CDCl_3 , 500 MHz, 2 mm) recorded for a) **1a-1a** (298 K), b) **1b-1b** (298 K), c) a mixture of **1a-1a**, **1b-1b**, and $(\pm)$ -**1a-1b** (298 K), d) a mixture of $(+)\text{-}2\text{a}\cdot(-)\text{-}2\text{a}$, $(+)\text{-}2\text{b}\cdot(-)\text{-}2\text{b}$, $(+)\text{-}2\text{a}\cdot(-)\text{-}2\text{b}$, and $(-)\text{-}2\text{a}\cdot(+)\text{-}2\text{b}$ (263 K), e) $(+)\text{-}2\text{a}\cdot(-)\text{-}2\text{a}$ (263 K), f) $(+)\text{-}2\text{b}\cdot(-)\text{-}2\text{b}$ (263 K), g) **1b-1b** (263 K), and h) a mixture of **1b-1b** and $(+)\text{-}2\text{b}\cdot(-)\text{-}2\text{b}$ (263 K). The schematic representations depict the species present in solution and their geometries. The resonances for amide NH groups of the homodimers are identified with green (●) and purple (●) bullets, whereas those of the heterodimers are marked with open bullets (○). The unmarked resonances arise from the appended pyridyl and phenyl rings.

Having established that **1a**, **1b**, $(\pm)$ -**2a**, and $(\pm)$ -**2b** form strong homodimeric aggregates, we decided to investigate the formation of heterodimers. When **1a** and **1b** were dissolved in CDCl_3 , a roughly statistical mixture of the homodimers **1a-1a** and **1b-1b** and the heterodimer **1a-1b** was observed (Figure 2c). Unlike the homodimers, the heterodimer $(\pm)$ -**1a-1b** does not possess a C_2 -axis, and each of the four amide NH groups give rise to separate resonances in the ^1H NMR spectrum. Similarly, when a mixture of $(+)\text{-}2\text{a}\cdot(-)\text{-}2\text{a}$ (Figure 2e) and $(+)\text{-}2\text{b}\cdot(-)\text{-}2\text{b}$ (Figure 2f) was analyzed by ^1H NMR (Figure 2d) we observed a mixture of the two heterochiral homodimers and a racemic mixture of heterodimers $((+)\text{-}2\text{a}\cdot(-)\text{-}2\text{b})$ and $(-)\text{-}2\text{a}\cdot(+)\text{-}2\text{b})$. These heterodimers are noteworthy as, for example, $(+)\text{-}2\text{a}$ exhibits complete enantioselective discrimination between $(+)\text{-}2\text{b}$ and $(-)\text{-}2\text{b}$.

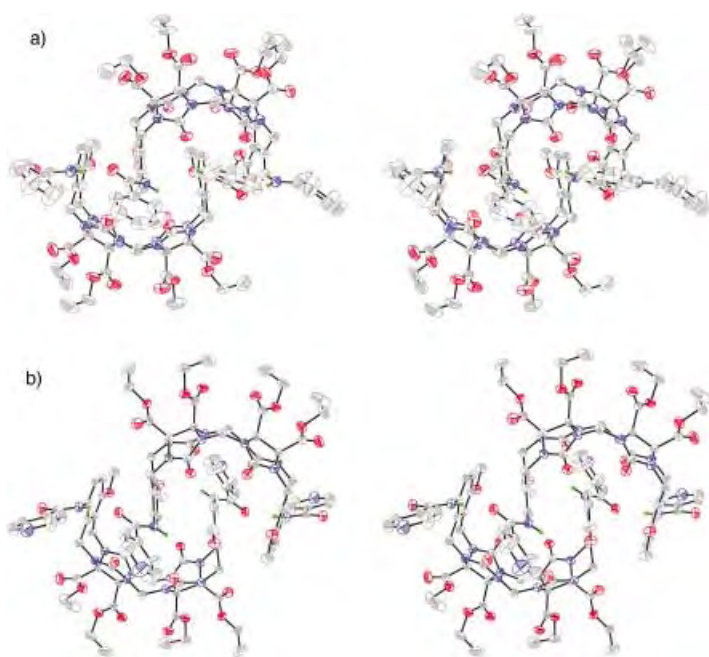


Figure 3. Cross-eyed stereoscopic ORTEP plots of the crystal structures of a) **1a-1a** and b) **(+)-2b(-)-2b**. The solvating PhCH₃ and CHCl₃ molecules in these complexes, as well as H atoms not bonded to amide N atoms have been removed for clarity. Two of the CO₂Et groups of **1a** adopt two orientations in the crystal structure; here, the major orientation component is depicted. Colors: C (grey), O (red), N (blue), and H (green).

The high level of enantioselectivity exhibited by **2a** and **2b** based on molecular shape and chirality led us to consider the behavior of a solution containing mixtures of achiral and chiral molecular clips. For example, upon mixing solutions containing **1b-1b** (Figure 2g) and **(+)-2b(-)-2b** (Figure 2f) we observed a simple superposition of the ¹H NMR spectra (Figure 2h) of the two homodimeric aggregates, a result which indicates that this class of compounds is self-sorting.^[8,15] The constraints placed on the system by the arrangement of the H-bonding groups, relative to the cleft of the molecular clip, dictate that optimal noncovalent interactions are achieved only through self-sorting.

In summary, we have developed two tightly self-associated H-bonding modules that are driven by the formation of only two hydrogen bonds, reinforced by π - π interactions. The relative geometry of the two H-bonding groups with respect to the cleft of the molecular clip controls the self-association process by favoring aggregates that simultaneously form both H-bonds and participate in π - π interactions. These aggregates display high levels of chiral discrimination and self-sorting. We anticipate that these characteristics will make them desirable for a variety of applications including noncovalent polymer chemistry, enantioselective recognition and catalysis, and as an instructed component in supramolecular chemistry.

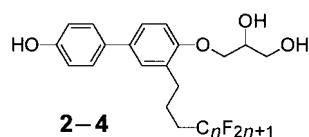
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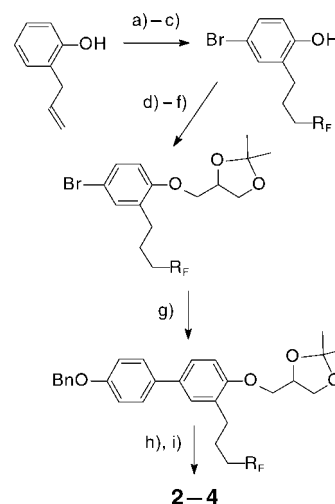
interior of these cylinders is filled with columns of the microsegregated fluid lateral chains. Figure 1 gives an overview of the obtained mesophase structures. First, the mesophase type depends on the length of the lateral chain, that is, their space requirement. Second, it depends on the space available for the chains within the cylinders, which is determined by the length of the bolaamphiphilic core.^[4] The question arose what would happen if the ratio of the size of the nonpolar chains and the length of the bolaamphiphilic core is shifted further, so that the formation of cylinders becomes disfavored.

Here we report novel mesophases obtained with the new mesogenic block molecules **2–4**. They have the same fundamental structure as compounds of the type **1**, but replacement of one of the terminal 2,3-dihydroxypropoxy groups by a single OH group makes the bolaamphiphilic core shorter and reduces the number of possible hydrogen bonds. Additionally, the lateral alkyl chains are replaced by semiperfluorinated chains,^[6] which require much more space than related hydrocarbon chains.^[7] Moreover, the stronger segregation^[8] of such fluorinated chains from the polar and rigid molecular parts (PR parts) increases the mesophase stability and thus compensates for the mesophase destabilization that results from the reduced cohesive forces between the bolaamphiphilic cores (fewer hydrogen bonds). Both structural variations lead to a dramatic change in self-organization in comparison to compounds **1**.



These compounds were synthesized as shown in Scheme 1.^[13] The products were investigated by differential scanning calorimetry (DSC), polarized light microscopy, and X-ray diffraction of well-aligned samples. The observed mesophases and their transition temperatures are collected in Table 1.

Compound **3** has the richest polymorphism and will be discussed in more detail. Three distinct mesophases can be detected by polarized light optical microscopy (see Figure 2). The high-temperature mesophase behaves like a conventional SmA phase, characterized by a typical fan texture (Figure 2a) which can easily be aligned homeotropically. These homeotropically aligned areas are optically isotropic and appear completely dark between crossed polarizers (Figure 2b). On cooling, at 153 °C a schlieren texture appears in these regions (Figure 2e) and indicates the transition to a new optically biaxial mesophase. A characteristic feature of this schlieren texture is the absence of four-brush disclinations. This excludes an SmC-like organization in which the molecules are tilted with respect to the layer planes and



Scheme 1. Synthesis of **2–4**. a) R_FI , $[Pd(PPh_3)_4]$;^[9] b) $LiAlH_4$, Et_2O ; c) HBr , $AcOH$, $DMSO$;^[10] d) $BrCH_2CH=CH_2$, K_2CO_3 , $MeCN$; e) *N*-methylmorpholine *N*-oxide, cat. OsO_4 , acetone, H_2O ;^[11] f) 2,2-dimethoxypropane, $Py\cdot TosOH$; g) $(4-BnO)C_6H_4B(OH)_2$, $[Pd(PPh_3)_4]$, $NaHCO_3$, glyme;^[12] h) 10 % HCl , $EtOH$; i) H_2 , Pd/C , $EtOAc$. $R_F = C_nF_{2n+1}$ ($n = 8, 10, 12$).

which is often found in conventional LC materials below an SmA phase. In samples with a fanlike texture only a significant change in the birefringence can be observed at the phase transition. The color changes from yellow through red, violet, blue, and green to yellow again, but the fans do not break or change their shape (Figure 2d). These textural features were predicted for biaxial SmA phases (SmA_b, McMillan phase)^[14] and were recently observed experimentally for such a mesophase.^[15] The transition to the third mesophase at 152 °C can be seen by the transformation of the schlieren texture into a paramorphic mosaiclike texture (Figure 2h),^[16] whereas no change is observed in the regions with fan-shaped texture. Here only the color changes, from deep yellow to red (Figure 2g). This suggests that the layer structure itself remains nearly unchanged in all three phases, whereas the order within the layers changes dramatically. This is additionally confirmed by X-ray scattering. The X-ray diffraction pattern does not change at the phase transitions between the three distinct phases. As shown in Figure 3 it is characterized by diffuse scattering in the wide-angle region,

Table 1. Transition temperatures T [°C] and corresponding enthalpy values ΔH [kJ mol⁻¹] (lower lines) of compounds **2–4**.^[a]

Comp	n	Cr	Lam _A	SmA _b	SmA	IS
2	8	●	118 [0.8] ^[b]	–	–	139 [6.0]
3	10	●	135 ^[c] [37.2]	● [2.0] ^[d]	153 142	156 [1.7]
4	12	●	154 ^[c] [18.6]	–	–	188 [2.0]

[a] Abbreviations: Cr = crystalline solid state; Lam_A = laminated smectic A phase, see Figure 2i;^[20] SmA_b = biaxial smectic A phase, see Figure 2f; SmA = smectic A phase, see Figure 2c; Iso = isotropic liquid phase. Transition temperatures and enthalpies were determined by DSC (Perkin-Elmer DSC-7, first heating scan, rate: 10 K min⁻¹) and confirmed by polarized light optical microscopy. Values in parentheses refer to monotropic (metastable) phases which were determined in the second heating scan. [b] Only partial crystallization, glassy solidification at $T_g = 18$ °C. [c] Multiple melting and Cr–Cr transitions were observed. [d] Not resolved.

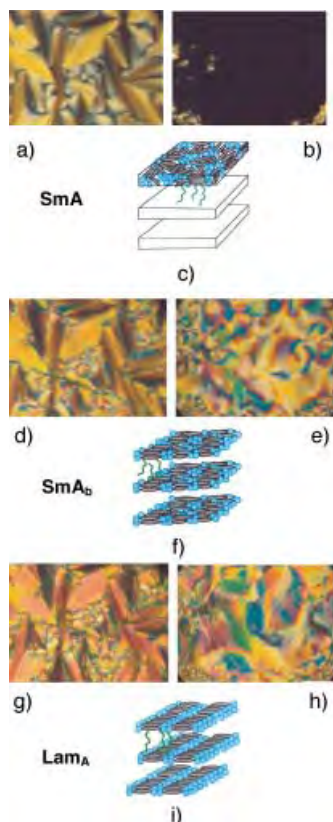


Figure 2. Textures of the mesophases of compound **3**, as observed between crossed polarizers, and suggested models of the organization of the molecules in the distinct mesophases. a) Fan-shaped texture of the SmA phase at 155°C. b) Homeotropically aligned SmA phase at 155°C. c) Organization of the molecules in the SmA phase. d) Fan-shaped texture of the SmA_b phase at 152.5°C. e) Schlieren texture of the SmA_b phase at 152.5°C. f) Organization of the molecules in the SmA_b phase. g) Fan-shaped texture of the Lam_A phase at 140°C. h) Paramorphic mosaic texture at 145°C. i) Organization of the molecules in the Lam_A phase.^[20]

which indicates the fluid state of this mesophase. Additionally, the small-angle region contains three sharp equidistant reflections that indicate the presence of a well-defined layer structure. The layer thickness is $d = 3.41$ nm at $T = 137^\circ\text{C}$ and is nearly temperature independent. No change of the layer thickness can be detected at the phase transitions. However, the layer spacing significantly increases with elongation of the lateral alkyl chain (**2**: $d = 3.0$ nm, **4**: $d = 3.8$ nm). The most remarkable feature of the X-ray diffraction pattern of well-oriented samples shown in Figure 3^[17] is that the diffuse wide-angle scattering forms a ring ($D = 0.49$ nm) with a maximum intensity at the meridian, that is, in the same direction as the layer reflections. This diffraction pattern is completely different from those of conventional smectic A phases, for which crescentlike halos are located perpendicular to the direction of the layer reflections.

The microscopic observations together with the peculiarities of the X-ray pattern led to the models of the mesophase structures shown in Figure 2c, f, and i. Accordingly, the layer structure should be the result of segregation of the nonpolar lateral chains from the bolaamphiphilic PR parts (biphenyl units and terminal diol groups). The layers are formed parallel to the molecular long axes, and this means that, in contrast to

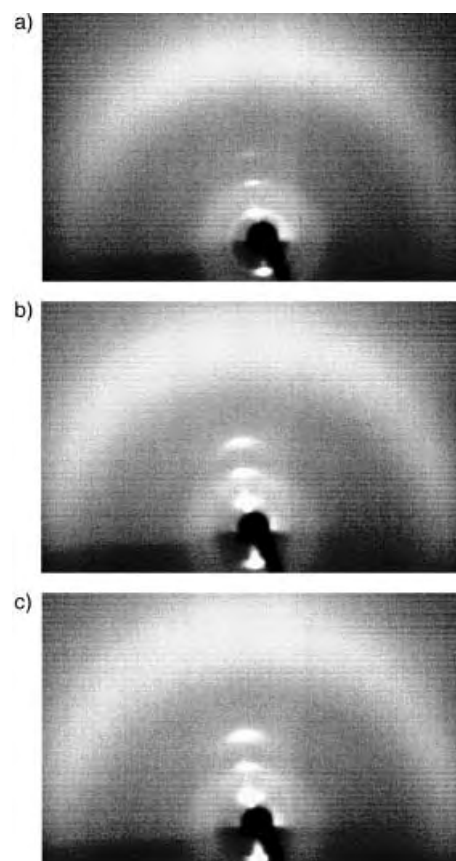


Figure 3. X-ray diffraction pattern of an aligned sample of compound **3** a) in the SmA phase at 155°C, b) in the SmA_b phase at 152.5°C, and c) in the Lam_A phase at 144°C.

all conventional smectic phases, the calamitic biphenyl cores are organized parallel to the layer planes. The PR layers are separated by the nonpolar layers of the lateral chains, which are strongly disordered (liquidlike). This special organization should be provided 1) by the unique topology of connection of the nonpolar chains in a lateral position at the rodlike cores, 2) by the parallel alignment of the biphenyl cores, and 3) by the cohesive hydrogen bonds at the termini of the biphenyl cores, which stabilize the PR layers. The experimentally determined layer distance requires that the thickness of the PR sublayers correspond on average to about three parallel aligned biphenyl cores. According to X-ray scattering and optical investigations, the layer structure is maintained in all three mesophases. Therefore, the phase transitions should result from a reorganization of the biphenyl cores within the PR layers.

Let us at first consider the biaxial smectic phase SmA_b, shown in Figure 2f. Here, the biphenyl cores should adopt long-range orientational order within the PR sublayers, and the individual layers are orientationally correlated with each other, so that optical biaxiality of the bulk sample results. Hence, this biaxial smectic phase is built up by a regular sequence of thin layers of the ordered PR cores, separated by the layers of the lateral chains. Since only orientational order of the PR cores exists within the layers, this phase can be regarded as a nematic phase which is laminated parallel to the long axis of the calamitic molecules.

At the transition to the high-temperature mesophase SmA either the long-range parallel alignment of the rigid cores within the PR layers or the orientational correlation between adjacent layers may be lost. It is, however, most likely that the two processes occur simultaneously. This means that the formation of a long-range orientational order within the individual layers at the transition from the uniaxial SmA to the biaxial SmA_b phase is accompanied by the formation of a long-range orientational correlation between adjacent layers. Hence, the phase structure of this SmA phase is related to those of conventional SmA phases, with the difference that in this new phase the biphenyl cores should be aligned on average parallel to the layer planes (see Figure 2c).^[18]

The transition from the SmA_b phase to the low-temperature phase is characterized by a reduction in the fluidity, as indicated by the transition from a schlieren texture to a paramorphic mosaiclike texture. This means that additional order should occur at this phase transition. In analogy to the phase sequence Iso-N-SmA, which is often observed in conventional LC systems on decreasing the temperature, it can be assumed that in the low-temperature mesophase of **3** the bolaamphiphilic cores adopt a positional order within the PR sublayers. This results from the segregation of the hydrogen-bonding networks from the aromatic cores which leads to a smecticlike organization within these sublayers (see Figure 2i). Hence, microsegregation occurs in two distinct directions: Segregation of the nonpolar chains from the PR cores leads to the "bulk" layer structure, and segregation of polar and aromatic subunits within the PR layers gives rise to an additional periodicity within these sublayers which occurs parallel to the layer planes. As the wide-angle scattering remains diffuse in all three mesophases, no additional order between the aromatic cores (e.g., SmB-like) or within the sublayers of the lateral chains should occur in this low-temperature mesophase. In other words, this mesophase can be regarded as a fluid smectic phase which is laminated parallel to the molecular long axes by the fluid layers of the lateral chains. Because we have no particular indication for a tilted arrangement of the molecules within these quasi-2D smectic sublayers^[19] the simplest possibility for a laminated SmA structure (Lam_A)^[20] is suggested for this mesophase (Figure 2i). Surprisingly, however, the additional repeat distance within the PR sublayers, which is expected to occur perpendicular to the layer reflection at the equator of the two-dimensional X-ray pattern, cannot be found in the X-ray diffraction pattern. This could be explained by assuming that the electron-density modulation within the 2D smectic sublayers is low;^[21] hence, the intensity of the corresponding reflections is very low. Additionally, there is no positional correlation between adjacent layers, and this means that there is only an orientational correlation of adjacent layers, but the individual layers can still slide with respect to each other. This phase structure has some similarities to the sliding columnar^[22] and lamellar columnar mesophases.^[23]

These results show that the competitive combination of microsegregation and rigidity is an appropriate way to obtain exciting new mesophase morphologies that are quite distinct from conventional mesophases. The individual sheets of these lamellar arrangements can be regarded as quasi-2D analogues

of the classical 3D mesophases. Hence, it could be expected that a diversity of different higher-order structures related to those known from conventional smectic phases could also be obtained within the layers of these laminated mesophases. Additional new mesophases could be expected at the transition between the columnar phases of compounds **1** and the smectic phases of **2–4**, and as a result of the positional correlation between adjacent layers of the laminated smectic phases, and this would lead to numerous novel mesophases with two- and three-dimensional organization.^[24]

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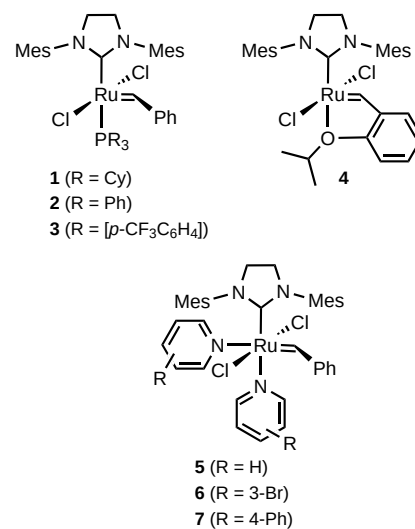
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- [16] The texture of the Lam_A phase of compound **2** which occurs directly from the isotropic liquid state is not a paramorphic texture and therefore typical mosaic and spherulitic textures can be observed.
- [17] The alignment is obtained by spreading the samples on a glass substrate, without applying external electric or magnetic fields.

- [18] A related phase structure should be present in the SmA phases of a TTF derivative with four branched lateral chains (R. A. Bissell, N. Boden, R. J. Bushby, C. W. G. Fishwick, E. Holland, B. Movaghar, G. Ungar, *Chem. Commun.* **1998**, 113.) and was suggested for 1,4,5,8-tetraalkyl-substituted derivatives of anthracene and anthraquinone (S. Norvez, F. G. Tournilhac, P. Bassoul, P. Hersonn, *Chem. Mater.* **2001**, *13*, 2552).
- [19] In this case, which would correspond to laminated SmC or SmC_A structures, the aromatic cores would be tilted with respect to the direction of the periodicity within the aromatic sublayers, but parallel to the layer planes of the bulk organization.
- [20] To distinguish such phases from conventional smectic phases, in which the calamitic molecules are arranged perpendicular to or tilted with respect to the layer planes, it is proposed to designate such phases as laminated mesophases (Lam), whereby a subscript designates the organization within the ordered sublayers (Lam_A = laminated SmA phase, see Figure 2i). In principle, the SmA_b and SmA phases of **2–4** can alternatively be described as a laminated nematic phase (Lam_N) and laminated isotropic phases (Lam_{iso}), respectively, but the phase symmetry of these phases is the same as in conventional SmA_b and SmA phases, so that this well established nomenclature should still be used in these cases.
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A Practical and Highly Active Ruthenium-Based Catalyst that Effects the Cross Metathesis of Acrylonitrile**

Jennifer A. Love, John P. Morgan, Tina M. Trnka, and Robert H. Grubbs*

The N-heterocyclic carbene-coordinated ruthenium benzylidene complex [(H₂IMes)(PCy₃)(Cl)₂Ru=CHPh] (**1**) is a highly active catalyst for a wide variety of olefin-metathesis reactions,^[1] including those with sterically demanding^[2] and electron-deficient olefins (Scheme 1).^[3] In spite of recent advances, there are several processes that remain challenging,



Scheme 1. Ruthenium-based olefin metathesis catalysts. Mes = 2,4,6-trimethylphenyl.

such as olefin cross metathesis (CM) with directly functionalized olefins.^[4] For example, acrylonitrile CM has only been successful with Schrock's arylimido molybdenum alkylidene catalyst^[5] and the ether-tethered ruthenium alkylidene derivative [(H₂IMes)(Cl)₂Ru=CH(*o*-iPrOC₆H₄)] (**4**).^[6,7] Phosphane-ligated ruthenium catalysts have given poor results for this transformation,^[3a,5c,6c,8,9] except for one report of efficient CM between purified acrylonitrile and 1-decene mediated by **1**.^[10] We have determined that dissociation rates of ligands are related to catalyst efficiency during CM with acrylonitrile. On this basis, we have developed a new, highly efficient ruthenium complex to perform acrylonitrile CM with unpurified acrylonitrile; this catalyst is the *fastest initiator* of any ruthenium-based catalyst reported to date.^[11]

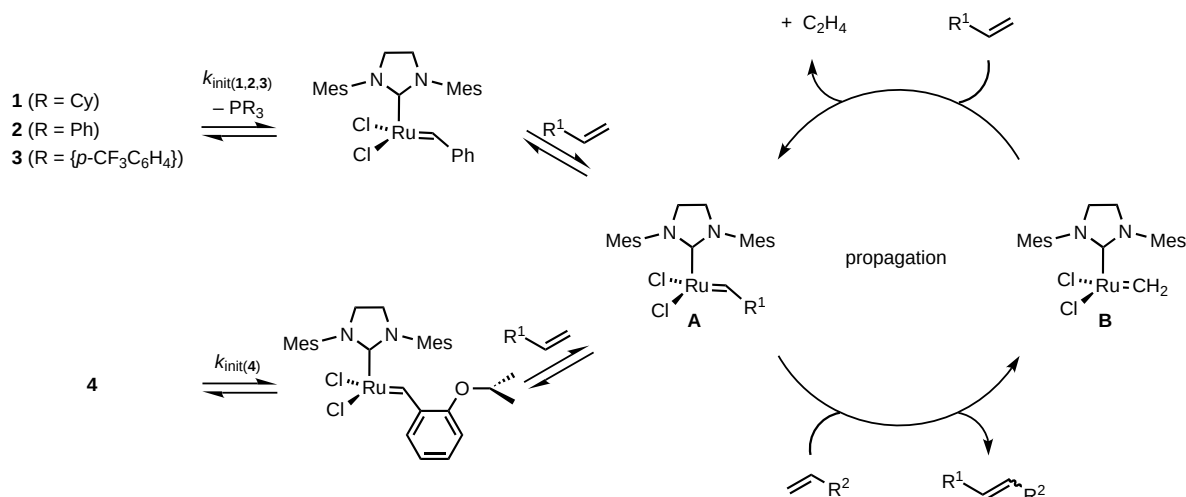
Previous studies have shown that precatalysts of the type [L₂X₂Ru=CHR] initiate by dissociating one L-type ligand before entering the catalytic cycle (Scheme 2);^[12] in complexes **1–3**, L is a phosphane (PR₃), and in complex **4**, L is a tethered ether ligand (*i*PrO). Importantly, complexes **1–4** all provide the *same* propagating species (**A** and **B**) after a *single* turnover.^[13] If either **A** or **B** is trapped by L, dissociation of L must occur before catalysis can continue. The relative affinity of **A** and/or **B** for the olefin in preference to L (i.e., favoring propagation) controls how long these species remain in the catalytic cycle. Consequently, the differences in activity between catalysts **1–4** depend on their rates of initiation and rebinding of L, both of which can be tuned by the nature of L.^[12b,14–16]

Complexes **1–4** are all active for a variety of metathesis processes, such as CM, ring-closing metathesis (RCM), and ring-opening-metathesis polymerization (ROMP). However, the situation involving acrylonitrile CM is more complex; CM between acrylonitrile and allylbenzene proceeds efficiently with **4** (68 % yield) but not with **1–3** (21 %, 35 %, and 36 % yields, respectively; Table 1).^[17] Clearly, this difference cannot simply be an issue of precatalyst initiation; **2** and **4** have roughly the same initiation rates and initiation is faster with **3** than **1**, **2**, or **4** Table 2. The difference is also not a result of

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.



Scheme 2. Mechanism of olefin cross metathesis.

Table 1. Cross metathesis of acrylonitrile with allylbenzene.^[a]

Catalyst	Yield [%]	<i>E/Z</i> ^[b]
1	21	1:1.7
2	35	1:4
3	36	1:1.8
4	68	1:1.9
5	26	1:1.2
6	67	1:1.8
7	29	1:1.8

[a] Conditions for CM: acrylonitrile (1.0 equiv), allylbenzene (2.5 equiv, 0.2 M in CH₂Cl₂), ruthenium catalyst (2.5 mol %), 40 °C, 12 h. [b] Ratios determined by means of ¹H NMR spectroscopy.

Table 2. Initiation rate constants of various ruthenium alkylidene complexes.^[a]

Catalyst	k_{init} (at 5 °C) [$\times 10^{-3} \text{ s}^{-1}$]
1	0.0032 $\pm$ 0.0006 ^[b]
2	1.8 $\pm$ 0.1 ^[b]
3	35 $\pm$ 9 ^[b]
4	2.6 $\pm$ 0.1 ^[c]
5	> 200 ^[d]
6	> 4000 ^[d]
7	> 200 ^[d]

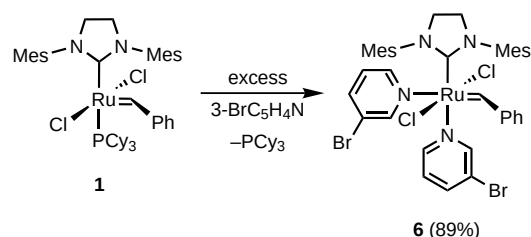
[a] Experimental details are given in the Supporting Information, unless otherwise indicated. [b] Ref. [12b]. [c] Ref. [14]. [d] Lower limit estimate.

changes in the propagating species because **1–4** converge to the *same* intermediate after a *single* turnover (Scheme 2). Furthermore, a cyano-substituted alkylidene is observed in solution during CM of acrylonitrile using **1**. This species has a slower initiation rate than **1**, which suggests that a cyanocarbenic intermediate, if trapped by phosphane, only reenters the catalytic cycle with difficulty. Consequently, the activity of complexes **1–4** in acrylonitrile CM must be strongly influenced by the rates of both dissociation and rebinding of L.

We have shown that an improvement in initiation without a substantial increase in the rate of rebinding of L improves the rate of catalysis.^[12,14] We previously noted that the pyridine ligands in [(H₂IMes)(py)₂(Cl)₂Ru=CHPh] (**5**, py = pyridine) can be readily replaced with phosphanes; even the electron-deficient phosphane P(*p*-CF₃C₆H₄)₃ reacts with **5** to provide

3.^[18,19] On this basis, it was anticipated that pyridine-ligated complexes would be useful catalysts in acrylonitrile CM.

A variety of bipyridine complexes can be prepared by adding an excess of the appropriate pyridine to **1**. These reactions are complete within minutes, require little or no solvent, and can be easily performed with commercial, unpurified reagents. For example, reaction of **1** (0.5 g) with 3-bromopyridine (10 equiv) provides [(H₂IMes)(3-Br-py)₂(Cl)₂Ru=CHPh] (**6**) within minutes (Scheme 3).^[20] The prod-



Scheme 3. Synthesis of bipyridine complex **6**.

uct is isolated in 89% yield simply by precipitation with pentane and without further purification. In comparison, the synthesis of **4** is considerably less efficient and more time-consuming, especially because chromatography is required for purification and not all reagents are commercially available.^[6,7]

We attempted to measure the initiation rates of **5–7** by using both NMR spectroscopy and UV/Vis kinetic studies (Table 2).^[15] The reaction of complex **6** with ethyl vinyl ether was complete within 0.5 seconds at 5 °C; this is by far the fastest initiation measured in a ruthenium-based system. The rate constants (k_{init}) for **5–7** increase linearly with olefin concentration even with up to 3750 equivalents of olefin, which suggests that these reaction conditions do not approach saturation kinetics.^[21] We consider the values obtained under these nonsaturation conditions as lower-limit estimates for the initiation rate constants of **5–7**.^[22] In particular, complex **6** initiates the reaction at least three orders of magnitude faster than **4** and at least six orders of magnitude faster than **1**! The

superior initiation properties of **6** over those of **3** and **4** is further illustrated by their relative activities in the ROMP of cyclooctadiene (cod; Figure 1).^[12b,14,16a,23]

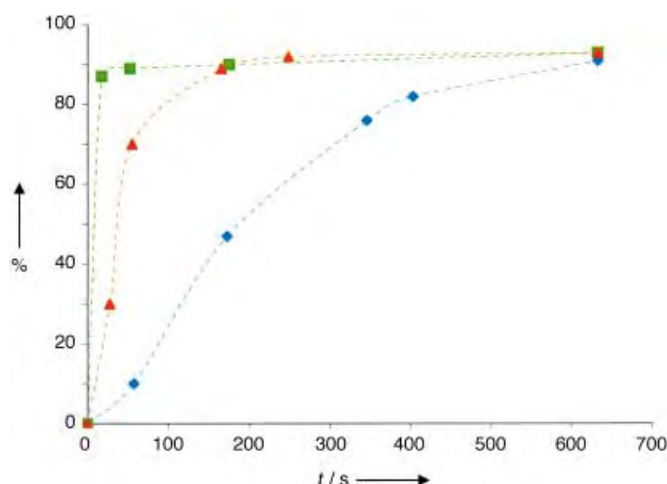


Figure 1. ROMP of cod at 10°C with catalysts **3**, **4**, and **6** (cod/Ru 3000:1, [Ru] = 0.5 mM in CD₂Cl₂). The progress of the reaction was monitored by ¹H NMR spectroscopy. ▲ complex **3**; ◆ complex **4**; ■ complex **6**. Dotted lines are intended as visual aids and are not curve fits.

Complexes **5–7** were compared for their ability to mediate CM between acrylonitrile and allylbenzene (Table 1). Although complexes **5** and **7** provide only modest yields of cross product (26% and 29%, respectively), the 3-bromopyridine derivative **6** provides a respectable yield of 67%, similar to that obtained with **4**. From these results, we conclude that the complexes with pyridine and 4-phenylpyridine ligands (**5** and **7**, respectively) do not achieve a sufficient steady-state concentration of the propagating species for CM to occur readily. Complex **6** is a considerably better catalyst, presumably because dissociation of the electron-deficient 3-bromopyridine ligand is extremely rapid and/or because rebinding is slow, both of which contribute to favorable turnover conditions.

We have shown that tuning the electronics of the L-type ligand can provide a catalyst that is capable of performing acrylonitrile CM with high efficiency. [(H₂IMes)(3-Brpy)₂(Cl)₂Ru=CHPh] is an exceptionally fast initiator for the metathesis of simple olefins and is synthetically accessible in one step from commercially available starting materials.

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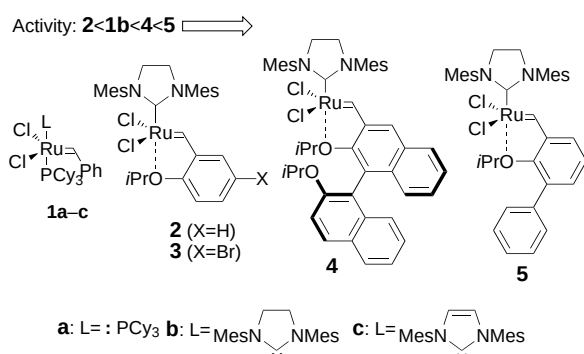
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A Highly Efficient Ruthenium Catalyst for Metathesis Reactions**

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The development of accessible metathesis catalysts that combine high activity with excellent tolerance to a variety of functional groups has been key to the widespread application of olefin metathesis in organic synthesis. In spite of the general superb application profile of the ruthenium carbene **1a**, its limited thermal stability and the low activity towards substituted double bonds are major drawbacks.^[1]

Specifically, the preparation of substituted olefins with electron-withdrawing functionality (such as α,β -unsaturated carbonyl compounds, nitriles, sulfones, etc.) through cross metathesis (CM) with terminal alkenes remains a difficult task. The newly introduced highly active ruthenium alkylidene complexes with sterically demanding N-heterocyclic carbene (NHC)^[3] ligands have dramatically alleviated this limitation.^[2] Compounds of type **1b** and **1c** were found to be efficient catalysts in the reactions of previously metathesis-inactive substrates, including α,β -unsaturated olefins (Scheme 1).^[2,4]



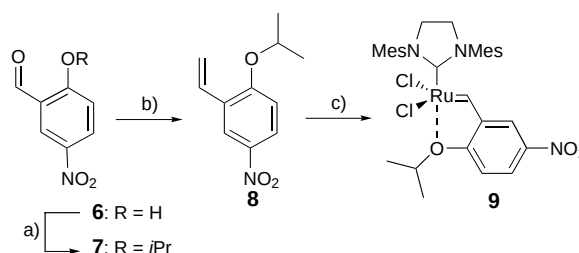
Scheme 1. Evolution of ruthenium precatalysts for alkene metathesis. Cy = cyclohexyl; Mes = 2,4,6-trimethylphenyl.

Hoveyda and co-workers have recently established **2** as a remarkably robust complex, which promotes olefin metathesis by a “release–return” mechanism.^[5] Despite the fact that phosphane-free catalyst **2** was found to be more sluggish than **1b**,^[6] it has a superior general reactivity toward electron-deficient olefins.^[7] The fact that the ruthenium carbene **2** is air-stable and can be easily purified by standard silica-gel chromatography and recycled after the reaction is a particularly appealing facet of this chemistry.^[5,8]

Blechert and Wakamatsu have shown recently that the replacement of the isopropoxystyrene “ligand” in **2** by binol- or biphenyl-based styrene results in a large improvement in the activity of the catalyst, as complexes **4** and **5** are much more reactive than both **2** and the “second-generation” Grubbs catalyst **1b**.^[9]

During our project aimed at the preparation of the immobilized metathesis catalyst, we prepared the bromo analogue **3** of Hoveyda's catalyst **2**.^[10] Although the reactivity patterns of complexes **2** and **3** were in general similar, the latter system was visibly less reactive in some model reactions.^[4b] This result once again shows that even a small variation in the isopropoxystyrene “ligand” can result in a change in the activity of the catalyst. Impressed by results published recently by Blechert and Wakamatsu,^[9] we decided to investigate the electronic effects in the isopropoxystyrene “ligand” sphere of complex **2** which are not fully understood.^[11] At first, we decided to test whether a decrease in the electron density of the styrene part of **2** would result in increased catalyst reactivity.

As illustrated in Scheme 2, we used commercially available **6** as a starting material for preparation of the corresponding ruthenium carbene **9**. The green microcrystalline complex **9**



Scheme 2. Synthesis of catalyst **9**. a) *i*PrI, K₂CO₃, Cs₂CO₃ (cat.), DMF, 2 days, room temperature, 86%; b) Ph₃P=CH₂, THF, –78°C→RT, 1 h, 57%; c) **1b**, CuCl, CH₂Cl₂, 30°C, 1 h, 83%.

was easily obtained in good yield (83%) by the reaction of **1b** (1 equiv) and CuCl (1 equiv) with styrene **8** (1 equiv), followed by routine flash chromatography. Having secured an efficient method for the preparation of complex **9**, we tested its catalytic activity. As the reactions of standard model substrates diallyltosylamide or diallylmalonate are too fast for an accurate measurement of their conversions,^[12] we decided to use more challenging ring-closing metathesis of **10a**. This model reaction showed that precatalyst **9** is significantly more reactive than **2** and **3** in the formation of trisubstituted double bonds (Figure 1). Notably, **9** is not only highly active but also stable, as it can be stored in air (+4°C) for more than four weeks without decomposition or loss of activity.

The metathesis of selected benchmark substrates was then examined. The results compiled in Table 1 illustrate the remarkably wide scope of this catalyst: 1) The RCM and enyne variant of the metathesis reaction can be performed efficiently at 0°C (Table 1, entries 2–4); 2) Various degrees of substitution of the double bond are tolerated, and even trisubstituted olefins can be synthesized in good yields at ambient temperature (Table 1, entries 1 and 5); 3) The CM reaction of terminal alkenes and α,β -unsaturated compounds

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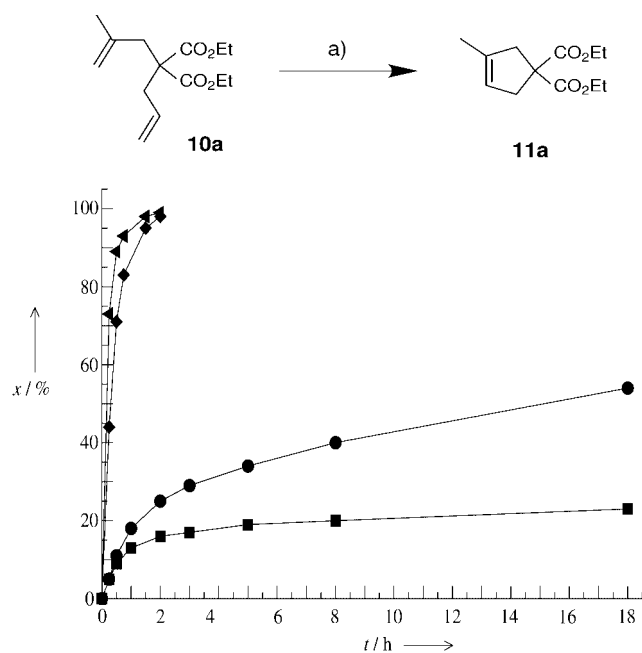


Figure 1. RCM of **10a** with precatalysts **1b** (▲, 1 mol %), **2** (●, 2.5 mol %), **3** (■, 2.5 mol %), and **9** (◆, 1 mol %). a) cat. (1–2.5 mol %), CH_2Cl_2 , room temperature, x = conversion.

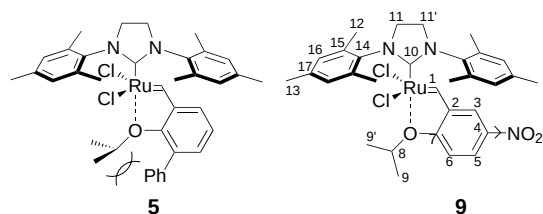
can be also performed at room temperature (Table 1, entries 6–9). The more demanding CM reactions of phenyl vinyl sulfone^[4] (Table 1, entry 8) and acrylonitrile^[7a] (Table 1, entry 9) show that also in this particular case complex **9** is superior to **1b** and **2**. Most remarkably, the new precatalyst **9** can be used for CM of methacrylonitrile; the transformation is *beyond the scope* of the “second generation” Grubbs’ carbene **1b** (Table 1, entry 10).

In conclusion, we have shown that the catalysts related to that of Hoveyda can be significantly improved by changing not only the steric^[11] but also the electronic character of the Ru-chelating isopropoxy fragment. For example, introduction of a strong electron-withdrawing group at the 2-isopropoxy-styrene ring of **2** leads to complex **9**, which is equally stable but dramatically more reactive than the parent catalyst **2**. We assume that the decrease in the electron density^[13] of the oxygen atom of the isopropoxy fragment reduces its chelating ability, thus facilitating formation of the catalytically active 14-electron Ru–carbene species, and suppressing repeated reassociation to the metal center. Therefore, this mode of catalyst activation is, in fact, similar to that of **4** and **5**, in which the increase in steric bulk improves the leaving-group ability of the styrene “ligand” (Scheme 3).^[9] Complex **9** is attractive

Table 1. Comparative investigation of **9**.

Entry	Substrate 10	Product 11	Yield using 9 [%] ^[a]	Yield using ref. catalyst [%] ^[a]
1	10a	11a	99 % ^[b] (1 mol %, RT, 2 h)	2 : 50 % ^[b] (2.5 mol %, RT, 18 h)
2			98 % (1 mol %, 0°C, 1 h)	1c : 85 % ^[c] (1 mol %, 80°C, 1 h)
3			99 % (1 mol %, 0°C, 1 h)	1b : 99 % ^[d] (1 mol %, RT, 1 h)
4			78 % (2.5 mol %, 0°C, 8 h)	1b : 99 % ^[d] (1 mol %, RT, 1.5 h)
5			99 % ^[b] (2.5 mol %, RT, 4 h)	
6 ^[e]	10f TBSO-(CH ₂) ₄ -CH=CH ₂		82 % (2.5 mol %, RT, 30 min)	5 : 90 % ^[d] (1 mol %, RT, 40 min)
7 ^[f]	10f		95 % (1 mol %, RT, 30 min)	5 : 91 % ^[d] (2.5 mol %, RT, 20 min)
8 ^[g]	10f		90 % (2.5 mol %, RT, 16 h)	1b : 85 % ^[h] (5 mol %, 40°C, 16 h)
9 ^[i]			87 % ^[b] (5 mol %, RT, 30 min)	2 : 79 % ^[i] (8 mol %, 40°C, 6 h)
10 ^[k]	10f		58 % (5 mol %, 40°, 16 h)	1b : 0 % ^[b] (5 mol %, 80°C, 24 h)

[a] Yield of isolated product, unless stated otherwise. [b] Yield determined by GC. [c] Ref. [2g]. [d] Ref. [9b]. [e] Reaction with methyl vinyl ketone (2 equiv). [f] Reaction with methyl acrylate (2 equiv). [g] Reaction with phenyl vinyl sulfone (2 equiv). [h] Ref. [4]. [i] Reaction with acrylonitrile (2 equiv). [j] $E/Z = 1:3$, ref. [7a]. [k] Reaction with methacrylonitrile (4 equiv).



Scheme 3.

from a practical point of view as it is active and easy to obtain in a three-step synthesis. This catalyst operates under very mild conditions (0°C to room temperature) and can be successfully applied in various types of metathesis reactions (RCM, CM, enyne). Further investigations to determine the full scope and limitations of **9** and similar systems are under way.

Experimental Section

9: Carbene complex **1b** (153 mg, 0.18 mmol), CuCl (18 mg, 0.18 mmol), and CH₂Cl₂ (10 mL) were placed in a Schlenk tube. A solution of **8** (38 mg, 0.18 mmol) in CH₂Cl₂ (4 mL) was then added and the resulting solution was stirred under argon at 30°C for 1 h. After this step, all manipulations were carried out in air with reagent-grade solvents. The reaction mixture was concentrated in vacuo, and the resulting material was purified by column chromatography on silica. Elution with cyclohexane/EtOAc (5:2) led to the isolation of **9** as a green band. The solvent was evaporated, the residue was washed with *n*-pentane and dried under vacuum to afford **9** as a green microcrystalline solid (100 mg, 83%). *R*_f = 0.30 (cyclohexane/EtOAc 8:2); ¹H NMR (500 MHz, CD₂Cl₂): δ = 16.42 (s, 1H; 1-H), 8.46 (dd, *J* = 9.1, 2.5 Hz, 1H; 5-H), 7.80 (d, *J* = 2.5 Hz, 1H; 3-H), 7.10 (s, 4H; 16-H), 6.94 (d, *J* = 9.1 Hz, 1H; 6-H), 5.01 (sept, *J* = 6.1 Hz, 1H; 8-H), 4.22 (s, 4H; 11-H, 11'-H), 2.47 (2 × s, 18H; 12-H, 13-H), 1.30 ppm (d, *J* = 6.1 Hz, 6H; 9-H, 9'-H); ¹³C NMR (125 MHz, CD₂Cl₂): δ = 289.1 (C1), 208.2 (C10), 156.8 (C7), 150.3, 145.0 (C2), 143.5 (C4), 139.6 (C15), 139.3, 129.8 (C16), 124.5 (C5), 117.2 (C3), 113.3 (C6), 78.2 (C8) 52.0 (C11, C11'), 21.3 (C9, C9'), 21.2 (C12), 19.4 ppm (C13) (where assignments of the NMR signals are given (based on 2D ¹H, ¹³C-chemical shift correlated spectra: GHSQC, GHMBC), they are unambiguous and refer to the arbitrary numbering shown in Scheme 3); IR (KBr): $\tilde{\nu}$ = 2924, 2850, 1606, 1521, 1480, 1262, 1093, 918, 745 cm⁻¹; HRMS (IE): *m/z* calcd for C₃₁H₃₇N₃O₃³⁵Cl₂Ru: [*M*⁺] 671.1255, found 671.1229; elemental analysis (%) calcd for C₃₁H₃₇N₃O₃Cl₂Ru (671.63): C 55.44, H 5.55, N 6.26; found: C 55.35; H 5.70, N 6.09.

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Nanoscopic Pt Colloids in the “Embryonic State”

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It is generally accepted that when metal colloids are synthesized by wet chemical reactions, the first step is a reduction of the metal salt to give zerovalent metal atoms.^[1] During the “embryonic stage” of the nucleation these atoms can collide in solution to form an irreversible “seed” of stable metal nuclei. Alternatively, the single metal atoms may be stabilized by complexation with ligands such as olefins and phosphanes, a process that is the basis of a rich organo-transition metal chemistry.^[2] On repeating an old experiment for the formation of Ni colloids, published by Karl Ziegler in the context of the famous “nickel effect”^[3,4] as early as 1954, we recently developed a novel, straightforward, general pathway to mono- and bimetallic nanoparticulates by the “reductive stabilization” of colloidal transition metals using trialkylaluminum compounds, which act both as reducing agents and as colloid stabilizers.^[5] We now report that in the case of Pt we have been able to establish the mechanism of the colloid formation by a combination of NMR, ASAXS (anomalous small-angle X-ray scattering), XAS (X-ray absorption spectroscopy), DFT (density functional theory) computations, and electron microscopy.

When [Pt(acac)₂] (**1**; acac = acetylacetonate) and AlMe₃ (**2**) react in toluene the reaction mixture turns from bright yellow to black over the course of about 24 h. ¹H NMR measurements were carried out in situ to monitor the reaction and to identify the products. In the initial ¹H NMR spectrum recorded about 30 min after the reagents had been mixed, a signal was observed at $\delta = 0.51$ that is assigned to methyl groups in an intermediate platinum complex **3** on account of

the coupling with ¹⁹⁵Pt ($I = 1/2$, 33.8% natural abundance). Over the course of the next few hours this Pt–methyl signal became more intensive and at the same time the number of signals from other products increased (Figure 1).

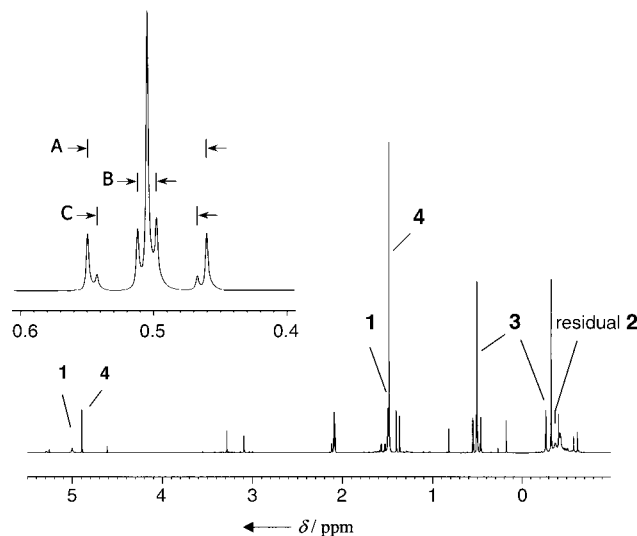


Figure 1. 400 MHz ¹H NMR spectrum of the mixture of **1** and **2** after 5 h at 27°C. The inset shows an expansion of the multiplet for the platinum-bound methyl group of **3** at $\delta = 0.51$. A: $|^2J(^{195}\text{Pt}, ^1\text{H})| = 35.7$ Hz; B: $|^4J(^{195}\text{Pt}, ^1\text{H})| = 5.7$ Hz; C: $|^2J(^{195}\text{Pt}, ^1\text{H})| + ^4J(^{195}\text{Pt}, ^1\text{H})|$ (AA'X₁₂X'₁₂ spin system, ²*J*(¹⁹⁵Pt, ¹H) and ⁴*J*(¹⁹⁵Pt, ¹H) have opposite signs).

The multiplet of the platinum-bound methyl group provides detailed information about the structure of the intermediate complex **3**. The intensity distribution is consistent with a binuclear platinum complex. The multiplet comprises the superimposed signals of isotopomers containing no ¹⁹⁵Pt nucleus (43.8%), one ¹⁹⁵Pt nucleus (44.8%), and two ¹⁹⁵Pt nuclei (11.4%); the latter is the most informative part of the signal and can be analyzed as the X region of an AA'X_nX'_n spin system (A = ¹⁹⁵Pt, X = ¹H). The complex must therefore be symmetrical but the platinum nuclei are not magnetically equivalent^[6]—that is, the methyl groups must be terminal and not located in bridges between the platinum atoms. Furthermore, an exchange of the methyl groups between the platinum atoms on the NMR time scale can be ruled out.

EXAFS (extended X-ray absorption fine structure^[7–11]) analyses were performed to obtain further insight into the structure of the intermediate complex **3** (Figure 2). The Fourier transform of **3** clearly differs from that of **1**, the analysis of which yields a Pt–O bond length of (2.00 ± 0.01) Å in the first coordination shell, in agreement with previously published crystal structure data.^[11] The detailed EXAFS analysis of **3** shows that the Pt absorber atom is directly surrounded by a light back scatterer, either C atoms at a distance of (2.11 ± 0.02) Å or O atoms at a distance of (2.09 ± 0.04) Å and Al atoms at a distance of (2.45 ± 0.02) Å. Surprisingly no back scattering from Pt was observed, revealing that there is no Pt–Pt bond in the complex. This clearly indicates the existence of a bridging group between the two Pt atoms.

Evidence for a bridging group was obtained from a long-range COSY experiment (optimized for small H,H couplings).

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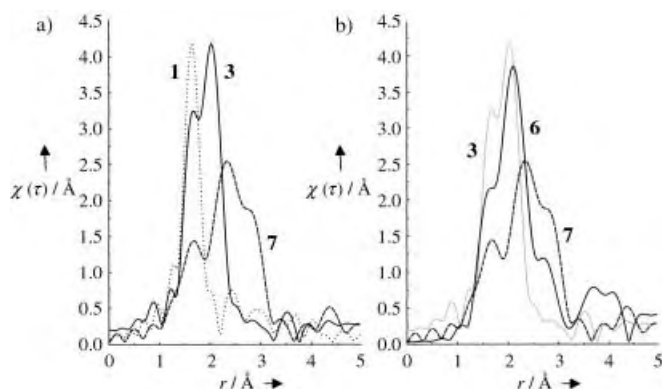
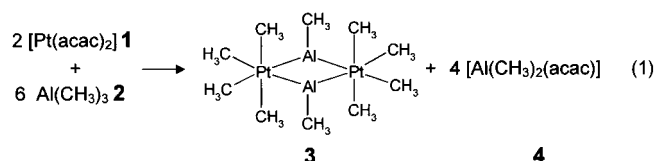


Figure 2. Fourier transform of Pt L_{III} EXAFS signals. a) The intermediate complex **3**, [Pt(acac)₂] (**1**), and the Pt colloid **7**. b) Pt particles **6** in solution, the intermediate complex **3**, and the Pt colloid **7**. The deviation between the distances displayed in the figure and the extracted distances in the material is due to the phase correction.

A cross peak was observed between the methyl signal at $\delta = 0.51$ ppm and a singlet (no coupling to ¹⁹⁵Pt) at $\delta = -0.27$ ppm in the region for aluminum-bound methyl groups. The integrated intensity of this resonance signal is one quarter of that of the platinum-bound methyl group. Further evidence was obtained when the complex was isolated from the reaction mixture. The pure complex **3** is rather unstable and decomposes rapidly in solution; however, in the presence of a fivefold excess of AlMe₃ it can be kept in solution for up to two days. Besides the signal for the platinum-bound methyl group, the ¹H NMR spectrum of **3** only shows the signal of the aluminum-bound methyl group at $\delta = -0.27$ ppm, verifying that acetylacetonate can be excluded as a component of the bridge.

The spectra are consistent with the formation of a complex of structure **3** being formed in the initial stage of the reaction together with the aluminum acetylacetonate **4** [Eq. (1)]. Crystallographic data for a diiridium complex with bridging AlMe groups have been reported;^[12] however, this is apparently the only literature reference to a binuclear transition metal complex with such bridging groups.



Further support for the unusual structure proposed for **3** is provided by density functional calculations (Figure 3). Starting from the proposed structure of **3**, the potential energy surface was explored at the BP86/ECP1 level of DFT.^[13] The two most stable isomers that could be located are **3a** (*C*_{2v} symmetry) and **3b** (*C*_{2h} symmetry), both of which display four partially Pt–Al-bridging methyl groups. Isomer **3a** is the more stable, but **3b** lies only 1–2 kcal mol^{−1} higher in energy. On searching for a transition state connecting **3a** and **3b**, a low-lying second-order saddle point **3c** (*C*_{2h} symmetry) was located that is only 3.5 kcal mol^{−1} above **3a**, indicative of a highly fluxional character for **3**. This saddle point would scramble all four methyl groups attached to one Pt atom, in

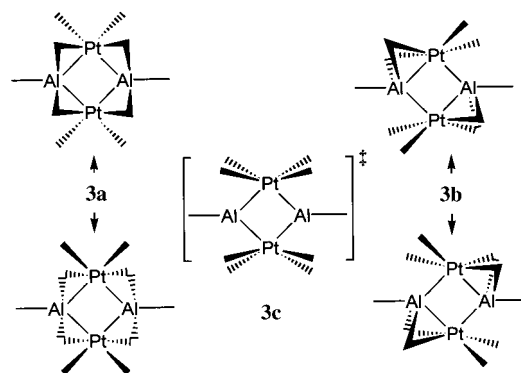


Figure 3. Results of the density functional calculations for the intermediate complex **3**.

accordance with the equivalence of these four groups on the NMR time scale. Isomers **3a** and/or **3b** are thus plausible candidates for the structure of **3** in solution.

Further experiments were performed to obtain more information on the way Pt atoms are formed from the complex **3**. Mass spectrometric analyses showed that [Pt(CH₃)₂(cod)] (**5**) is formed when the isolated complex **3** decomposes in solution in the presence of 1,5-cyclooctadiene (cod; see Scheme 1), which indicates that Pt(CH₃)₂ fragments are likely to be the first step towards single metal atoms. The decomposition of Pt(CH₃)₂ fragments by cleavage of the methyl groups is supported by the gas evolving during the colloid synthesis, which consists mainly of methane and small amounts of ethene and ethane.

The nucleation process was studied by time-resolved in situ ASAXS measurements for a reaction period of 1000 h.^[14] Stable Pt particles **6** of 1.2 nm diameter were detected in solution after **3** had reacted for three days in the presence of **4** and an excess of **2**. The increase in the intensity of the small-angle scattering by almost an order of magnitude indicates the onset of cluster formation in the solution. Anomalous small-angle X-ray scattering was employed to confirm that the observed scattering arises from Pt particles. This method provides unbiased information on the distribution of the particle sizes even when there are significant contributions from other nanostructures.^[15–17] These experiments show that the scattering arises from Pt particles with a diameter of 1.2 nm and with a rather narrow monomodal size distribution. Remarkably, the size remains unaltered during the course of the experiment (Figure 4a).

The increase in the mass fraction of Pt atoms transformed into particles (Figure 4b) is accounted for by the increase in

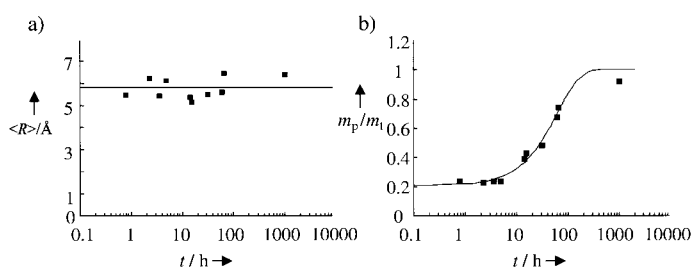


Figure 4. a) Time dependence of the mean particle radius $\langle R \rangle$, b) mass fraction m_p/m_t of Pt atoms transformed into particles (m_p = mass of platinum in particles, m_t total mass of platinum).

the number of these stable particles **6**. Complementary results are obtained by EXAFS. After four days in solution, Pt back scatterers at $r = (2.71 \pm 0.1)^\circ\text{C}$ can be detected by Fourier analysis of the EXAFS data, proving that dissolved Pt particles **6** have been formed (Figure 2b).

The redispersible Pt colloid **7** can be isolated from the solution of the Pt nanoparticles in the form of a black solid. This colloid was investigated by a combination of high-resolution transmission electron microscopy (HRTEM), ASAXS, and XANES/EXAFS. The TEM images show that 1.2 nm globular Pt nanoparticles are present and that nearly all of the particles are amorphous, which was confirmed by optical Fourier transformation (Figure 5a). The particle size distribution is narrow and exhibits features of a monomodal log-normal distribution (Figure 5b).

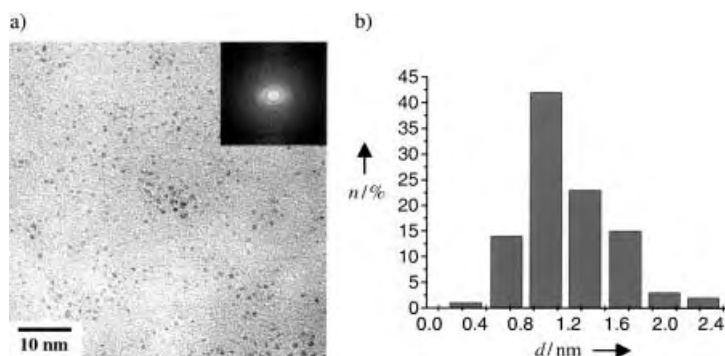


Figure 5. a) High-resolution transmission electron micrograph with optical diffractogram (Fourier transform) from different regions of the sample showing the amorphous character of the particles. b) Histogram of the particle size distribution. n = number of particles, d = particle diameter.

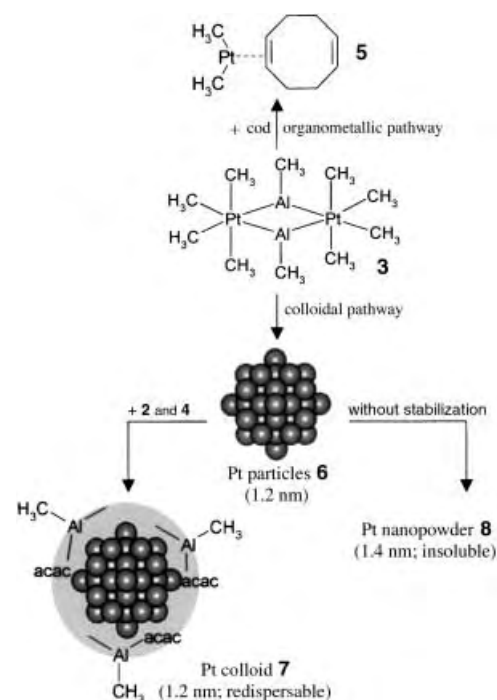
We conclude from these experiments that complexes of type **3** are general precursors from which organometallic complexes such as **5** can be synthesized by trapping reactions, or from which Pt nanoparticles such as **6** can be obtained by decomposition (Scheme 1).

In the presence of excess $\text{Al}(\text{Me})_3$ (**2**) and $[\text{Al}(\text{Me}_2)(\text{acac})]$ (**4**) a redispersible Pt colloid **7** (1.2 nm) can be isolated. When **3** decomposes in the absence of external stabilizers, a non-dispersible Pt nanopowder **8** with particles of 1.4 nm diameter is formed. The mean diameter is slightly greater than in the redispersible Pt colloid (**7**) as a result of agglomeration. Thus the products of the reaction between **2** and **4** act as a protecting shell which keeps the particles in solution. The reactivity of this protecting shell is a prerequisite for using the colloids **7** as building blocks for Pt nanoparticle networks.^[18]

Experimental Section

For the in situ experiments $[\text{Pt}(\text{acac})_2]$ (60 mg, 0.15 mmol) was dissolved in $[\text{D}_8]\text{toluene}$ (5 mL) under an argon atmosphere. A solution of $\text{Al}(\text{CH}_3)_3$ (43.2 mg, 0.6 mmol) in $[\text{D}_8]\text{toluene}$ (5 mL) was then added. After the solutions had been thoroughly mixed, the reaction mixture was transferred to a sealed sample tube (e.g. NMR tube, capillary) and subsequently to the respective instrument for characterization (NMR, ASAXS, XAS).

The NMR measurements were carried out at 300 K in $[\text{D}_8]\text{toluene}$ on a Bruker AMX 400 NMR spectrometer equipped with a 5 mm inverse probehead.



Scheme 1. Schematic representation of the synthetic pathways starting from the intermediate complex **3**.

The experimental setup and data analysis for the X-ray absorption measurements (XANES/EXAFS) carried out at ELSA (Bonn, Germany) are described elsewhere.^[7] A specially designed liquid cell similar to the one described in reference [8] was used for the in situ measurements. The Pt L_{III} edge EXAFS data were analyzed by using the UWXAFS analysis package.^[9]

ASAXS measurements were carried out at the JUSIFA beamline (<http://www.fz-juelich.de/iff/personen/H.-G.Haubold>) at the Hamburg Synchrotron Radiation Laboratory HASYLAB-DESY. To compensate for contributions from background scattering, additional measurements were performed at a second X-ray energy $E_2 = 11\,543\text{ eV}$ close to the L_3 X-ray absorption edge of the Pt atoms. At this energy, the squared atomic scattering amplitudes of the Pt atoms are reduced by about 10% by anomalous scattering^[15–17] and consequently the scattering cross section of Pt structures becomes smaller, whereas background scattering contributions remain unaffected and can be subtracted.

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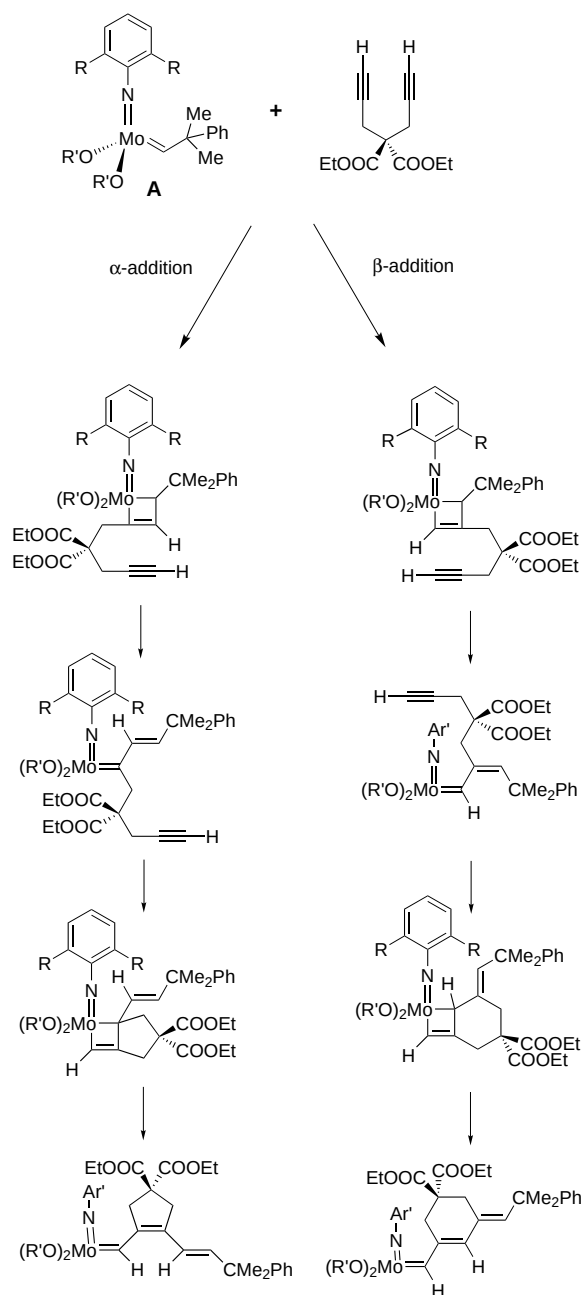
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Stereoselective Cyclopolymerization of 1,6-Heptadiynes: Access to Alternating *cis-trans*-1,2-(Cyclopent-1-enylene)vinylenes by Fine-Tuning of Molybdenum Imidoalkylidenes

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Soluble, conjugated organic polymers are of great potential because of their intriguing optical and electronic properties.^[1] Areas of interest include their use as conducting or semi-conducting polymers, organic light-emitting polymers, plastic solar cells, or more general, one or two-dimensional molecular wires. Any successful utilization depends on a high degree of definition as well as on the variability in the polymer structure. The cyclopolymerization of 1,6-heptadiynes containing suitable substituents at the 4-position offers an attractive access to polyenes with cyclic recurring units along the backbone.^[2,3] The synthesis of such polymers requires the use of Ziegler-type catalysts,^[4] Pd catalysts,^[5] binary/ternary Mo- or W-based catalysts,^[6] and anionic polymerization^[7] Unfortunately, these methods lead to mostly insoluble, ill-

defined polymers, variable repeating units (i.e. 1,2-(cyclopent-1-enylene)-vinylenes and 1,3-(cyclohex-1-enylene)-methylidene), and broad molecular-weight distributions (polydispersity index (PDI) $\gg 2$). However, well-defined high-oxidation-state Schrock-type molybdenum carbenes cyclopolymerize 1,6-heptadiynes in a living manner, yet result in polyenes that contain a mixture of five- and six-membered rings.^[2,3,8] Usually these polymers display good solubility in common organic solvents (e.g. C_6H_6 , toluene, CH_2Cl_2 , CHCl_3), good long-term stability towards oxidation and high effective conjugation lengths (N_{eff}).^[2,3,9] The two different reaction pathways that are responsible for the formation of five- and six-membered ring structures are shown in Scheme 1.^[2] The ring size of the polyene is influenced by steric and electronic effects of the ligands of the Schrock initiator **A**. Polymers



Scheme 1. Mechanisms for the cyclopolymerization of DEDPM with a Schrock-type initiator **A**.^[2,3]

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exclusively consisting of six-membered rings can be prepared using the molybdenum complex $[\text{Mo}(N\text{-}2\text{-}t\text{Bu-C}_6\text{H}_4)(\text{CH-}t\text{Bu})(\text{O}_2\text{CCPh}_3)_2]$, where the bulky triphenylacetate ligands force the monomer to undergo selective β -addition.^[9] While such selective β -additions are comparably easy to accomplish both in cyclopolymerization and 1-alkyne polymerization,^[9,10] a Schrock-initiator-based synthesis of polyenes solely based on five-membered rings has not been accomplished to date, though diethyldipropargylmalonate (DEDPM) derived poly(1,2-(cyclopent-1-enylene)vinylene)s were formed with classical MoCl_5 -based initiators. However, only oligomers with a low degree of polymerization ($\text{DP} < 6$) and broad polydispersities ($\text{PDI} \leq 4.2$) were reported.^[11]

To gain access to polymers containing exclusively five-membered rings, variations in both the imido and alkoxy ligand in complexes **A** were carried out. Based on the concept of small alkoxides developed by Schrock,^[12] and on our results in 1-alkyne polymerization,^[10,13] a small ligand sphere was believed to be necessary for, but not a guarantee of, selective α -addition. Additional information on the influence of the electronic nature of the alkoxide ligands as well as on steric effects of the aryl imido substituents was required.

We synthesized a variety of new Mo-based Schrock-type initiators based on fluorinated and non-fluorinated alkoxides (**A**), of which three were capable of selective α -addition (as indicated by ^1H NMR spectroscopic investigations of the first insertion products). Both **1** ($\text{R} = i\text{Pr}_2$, $\text{R}' = t\text{Bu}$) and **2** ($\text{R} = \text{Me}$, $\text{R}' = t\text{Bu}$) Figure 1^[14] cyclopolymerized DEDPM in the presence of additional base (quinuclidine) to give ferrocene (Fc) terminated poly-DEDPM with a five-membered-ring content of more than 95%. With **3** ($\text{R} = \text{R}' = i\text{Pr}$), a starting temperature of -30°C was sufficient for reaction. Polymer structures were identified according to standard procedures using 4,4-bis(ethoxycarbonyl)cyclopent-1-ene and 4,4-bis(ethoxycarbonyl)cyclohex-1-ene as model compounds (the relative error in structure determination was $< 3\%$).^[2] Thus, a typical ^{13}C NMR spectrum of a polymer containing both five- and six-membered ring structures shows at least two sets of carbonyl resonance signals that can be ascribed to carbons in different chemical environments within the polymer chain

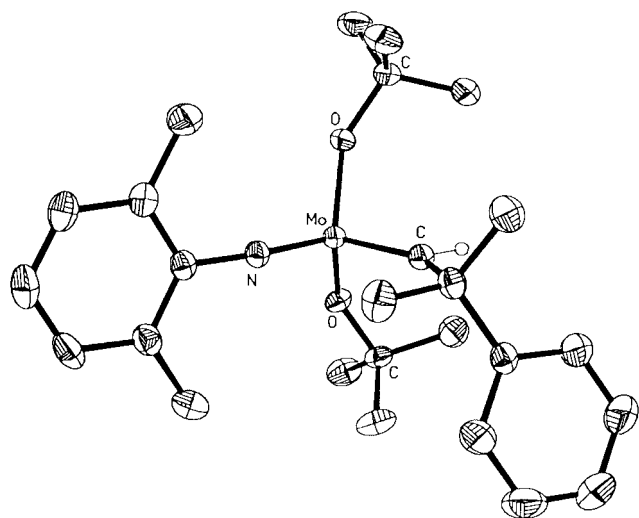


Figure 1. ORTEP drawing of **2** (thermal ellipsoids set at 40 % probability).

(Figure 2 top). The ^{13}C NMR spectra of polymers containing solely five-membered rings show one, sharp carbonyl resonance signal (Figure 2 bottom).

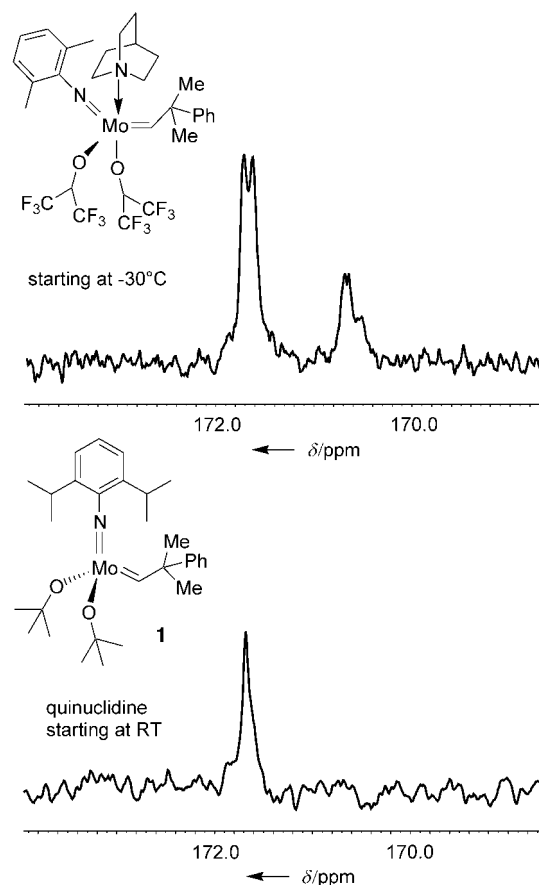


Figure 2. ^{13}C NMR spectra of poly-DEDPM₅₀ samples containing 70 % five-membered rings (top) and $> 95\%$ five-membered rings (bottom).

A plot of the number-average molecular weight (M_n) versus the number of monomer equivalents of DEDPM (N) showed linear dependences for initiators **1–3**, that of initiator **1** is shown in Figure 3 and clearly underlines the necessity of an absolute method for molecular-weight determination such as light scattering. From this linear plot, the low PDIs (< 1.4) and

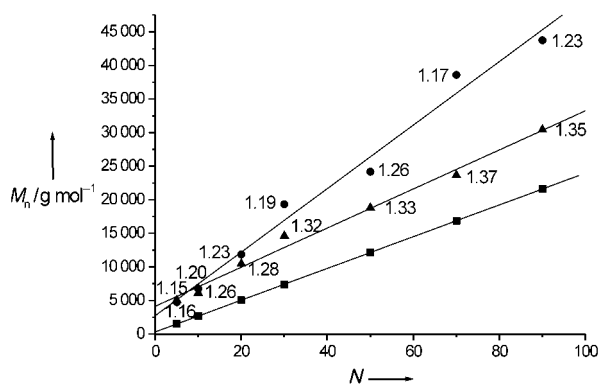


Figure 3. Plot of M_n versus number of monomer equivalents N for poly-DEDPM samples prepared using **1**-quinuclidine as initiator. The PDIs for the poly-DEDPM produced are given; ● gel permeation chromatography (polystyrene standard), ▲ light scattering, ■ calculated.

the complete consumption of monomer we conclude that chain transfer or termination are absent. The existence of at least a class V living system was confirmed by the stepwise synthesis of poly-DEDPM.^[15] Furthermore, this plot perfectly fits the kinetic data obtained for initiators **1–3**. Thus, values for k_p/k_t were found to be 9, 14, and 114 for initiators **2**, **3**, and **1**, respectively, and serve as an excellent explanation for the small (positive) deviation of the light-scattering-derived values for M_n from theoretical values. We have demonstrated the broad applicability of the new initiators by the fact that other polyenes based on bulky monomers such as di-(1*S*, 2*R*, 5*S*)-(+)-menthyl dipropargylmalonate prepared by the action of **1** at -30°C and terminated by ferrocene aldehyde also contain >95% five-membered rings.

While ring sizes and ratios of ring sizes may be determined conveniently by ^{13}C NMR spectroscopy, investigations on tacticity and *E/Z*-ratios of the vinylenes require some additional changes in the monomer. As has already been outlined for various norborn-2-ene and norbornadiene derivatives,^[16,17] an additional element of chirality is required to break the symmetry between the repeating units. Therefore, 4-(ethoxycarbonyl)-4-(1*S*, 2*R*, 5*S*)-(+)-menthoxy carbonyl-1,6-heptadiyne (**4**) was synthesized and cyclopolymerized by **1** in the presence of quinuclidine. The ^{13}C NMR spectrum of poly-**4** (Figure 4) displays two sharp resonance signals around

$\delta \approx 171$ ppm attributed to the two different ester carbonyl groups of a polymer that again contains >95% five-membered rings. The single, sharp resonance signal for the C-4 atoms at $\delta = 57$ ppm and the vinylenes carbon at $\delta = 123$ ppm further support a highly regular five-membered-ring structure. For reasons of symmetry, one can distinguish between the few possible structures (*cis*, *trans*, *iso*-, or *syndiotactic*) by ^1H NMR spectroscopy.^[16] An absolute assignment of tacticity would be possible if the resonance signal of the olefinic protons were sufficiently resolved. A ^1H , ^1H COSY NMR spectrum was recorded for poly-**4**₅₀ (500 MHz, $[\text{D}_8]$ toluene, 85°C). Two sets of *trans*-coupled protons were unambiguously identified by their resonance signals at $\delta = 6.19, 6.83$ ppm, $J = 16.5$ Hz and $\delta = 6.60, 7.16$ ppm, $J = 16.0$ Hz, respectively. These two sets were assigned to the end groups, $\text{FcCH}=\text{CH}-\text{P}$ and $\text{P}-\text{HC}=\text{CHCMe}_2\text{Ph}$ (P = polymer chain), respectively. A (broadened) signal at $\delta = 7.1$ ppm resulting from the overlap of the two resonance signals for the protons along the conjugated backbone did not show any observable coupling. Though this is indicative for a highly tactic structure, we cannot completely exclude that any existing coupling is not observable because of small chemical-shift differences, which thus, does not allow the unambiguous assignment of any tacticity.

Despite the large set of data, mechanistic considerations, which would allow formulating a general rule for the synthesis of regular structures, are still speculative. The fact that non-fluorinated alkoxides are required for a selective backbone formation as well as the significant effects of additional base and temperature on the final polymer structure suggest that the rates of interconversion between the *syn* and *anti* forms of the initiators play an important role. Initiators based on non-fluorinated alkoxides show fast *syn-anti* interconversion^[18] whereas a base favors the formation of the (base-coordinated) *anti* isomer.^[19] Nevertheless, a quantitative description would necessitate kinetic data for the interconversion in non-fluorinated Mo-alkoxides. Unfortunately this interconversion is too fast for the reactivity differences between a *syn*- and *anti*-rotamer to be determined by current methods.

In summary, chiral polyenes with an alternating *cis-trans* structure containing solely five-membered rings and defined polymer end groups have been prepared. The physical properties of the new polyenes strongly differ from existing poly(heptadiyne) systems with a lower degree of definition in the polymer backbone. Thus, the new polyenes show significantly bathochromic shifts in the UV/Vis spectrum (591 nm versus 511 nm for six-membered ring structures, corresponding to $N_{\text{eff}} = 52$) as well as an entirely different solubility. They are stable under air over months in the solid state as well as in solution. Furthermore, no thermal decomposition is observed under He up to temperatures of 180°C . They possess excellent film-forming properties with DP-dependant glass transitions around 25°C .

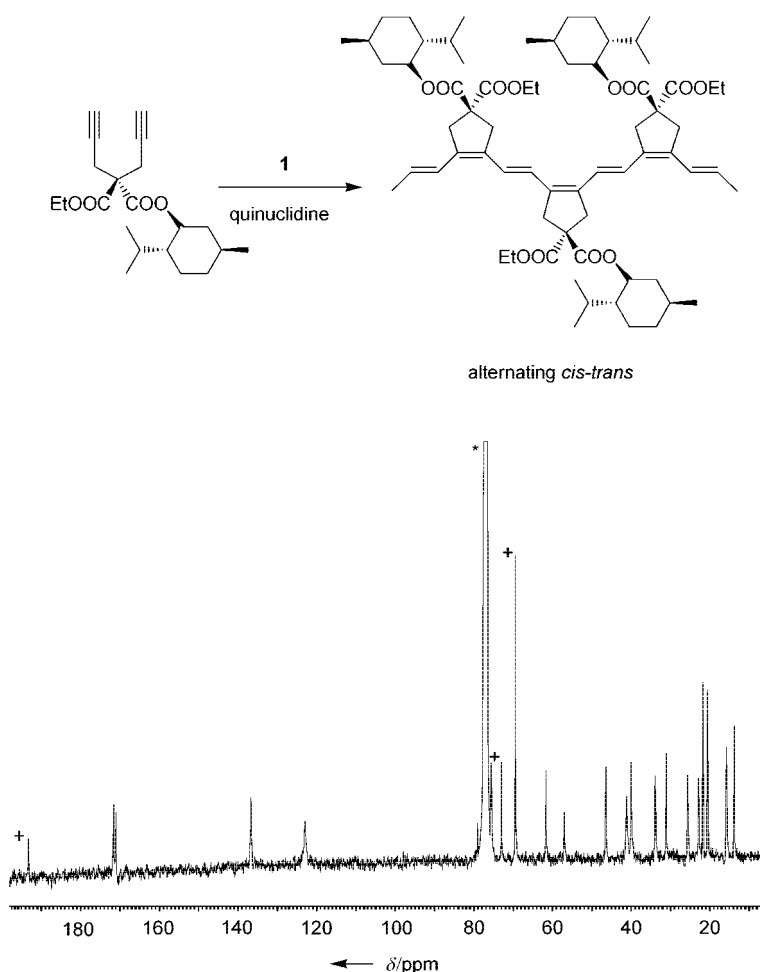


Figure 4. Synthesis and ^{13}C NMR spectrum of chiral, alternating *cis-trans* poly-**4** (DP = 50, $M_n = 18600$ g mol $^{-1}$, PDI = 1.26, * CDCl_3 ; + residual ferrocene aldehyde).

Experimental Section

All experiments were performed under a nitrogen atmosphere in a glove box (MBraun) or by using standard Schlenk techniques. $[\text{Mo}(N\text{-}2,6\text{-}i\text{Pr}_2\text{-C}_6\text{H}_3)(\text{CHCMe}_2\text{Ph})(\text{OTf})_2]\text{DME}$, $[\text{Mo}(N\text{-}2,6\text{-Me}_2\text{-C}_6\text{H}_3)(\text{CHCMe}_2\text{Ph})(\text{OTf})_2]\text{DME}$, and $[\text{Mo}(N\text{-}2,6\text{-}i\text{Pr}_2\text{-C}_6\text{H}_3)(\text{CHCMe}_2\text{Ph})(\text{OC}(\text{CH}_3)_2)_2]$ (**1**) as well as other compounds were prepared following literature procedures.^[20] Experimental details can be found in the Supporting Information.

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Ambiphilicity: A Characteristic Reactivity Principle of π -Bound Phosphorus Heterocycles**

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Dedicated to Professor Gottfried Huttner
on the occasion of his 65th birthday.

Cyclooligomerization of phosphalkynes, such as $t\text{BuC}\equiv\text{P}$ (**1**), in the coordination sphere of reactive metal complexes predominantly leads to π complexes of the cyclodimer 1,3-diphosphete^[1–4] or the cyclotrimer 1,3,5-triphosphabenzene.^[5] However, pentaphosphametalloenes, such as the pentaphosphapherrocene derivative **2**, are obtained with reactive iron complexes^[6,7] or free metal atoms.^[8] Their formation requires that at least one P–C triple bond be broken (Scheme 1).

Oligophosphametalloenes are easily accessible substances with a series of interesting properties.^[9] Thus, there is much interest in determining the mechanism of their formation. Because complete cleavage of **1** is very unlikely, even at a transition-metal center, we assume that initially formed cycloaddition products from **1** undergo intra- or intermolec-

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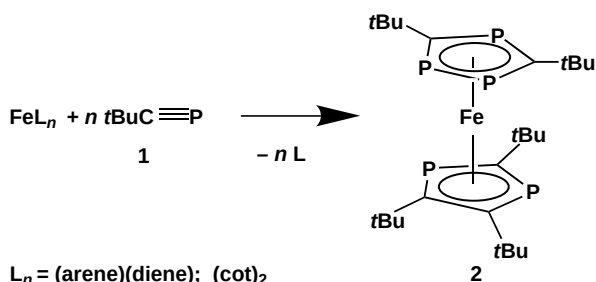
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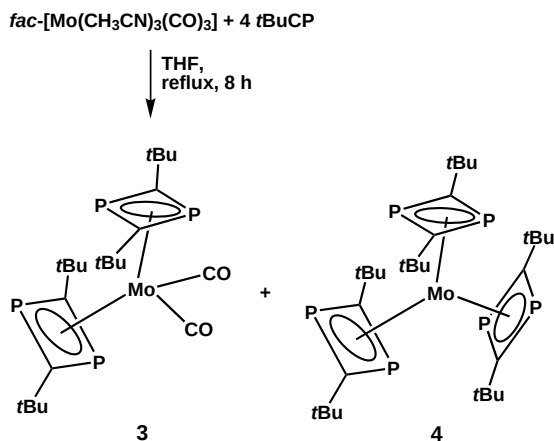
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Scheme 1. Formation of pentaphosphaferrocene **2**.

ular interactions with each other that allow the exchange of phosphorus atoms or *t*BuC-fragments under mild conditions. One convincing indication that this is the case, the observation of strong intramolecular interactions between Mo-coordinated 1,3-diphosphete ligands is reported herein. These interactions serve as a novel model for the initial step in the exchange of ring components of π -coordinated P heterocycles.

We treated *fac*-[Mo(CH₃CN)₃(CO)₃] with **1**, with the aim of synthesizing [Mo(CO)₂(2,4-di-*t*Bu-1,3-diphosphete)₂] (**3**). In contrast to earlier reactions of molybdenum–carbonyl complexes with **1**,^[10,11] we were able to isolate **3** as the main product. However, to our surprise we also found the known complex [Mo(2,4-di-*t*Bu-1,3-diphosphete)₃] (**4**) as a by-product. The published molecular structure of **4** in the solid state shows an unusual feature, the P–C separation between two of the rings is only 215 pm, a very short distance that is hard to explain (Scheme 2).^[12]



Scheme 2. Formation of (1,3-diphosphete)–Mo complexes.

Differences to the published data^[12] obtained at low temperatures led us to investigate the structural chemistry of **4** more closely. We therefore performed single-crystal analyses at temperatures of 100, 150, 200, 240, and 293 K. An intramolecular, fully reversible topotactic reaction between the ligands of **4** is observable in the crystal structures. Figure 1 shows the superposition of the two extremes of the molecular structures of **4** at 100 (**4a**) and 293 K (**4b**). Structure **4b** is identical to the published data within the margins of error (Figure 1).^[12,13]

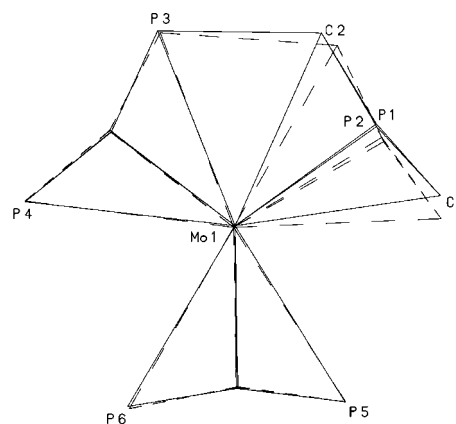
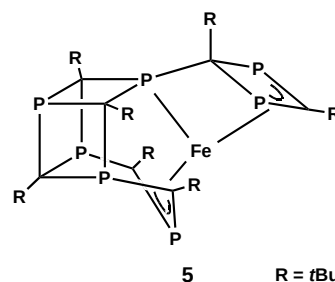


Figure 1. Side view of the superimposed molecular structures of **4** in the single crystal at 100 K (**4a**, full lines) and at 293 K (**4b**, dashed lines). The *t*Bu groups of the rings have been omitted for clarity.^[13] Selected distances **4a** [**4b**] [$\Delta = \text{4a} - \text{4b}$] in pm: Mo1–C2 256.69(19) [254.2(3)] [+2.48], C2–C21 157.6(3) [156.2(4)] [+1.4], C1–P1 179.3(3) [181.5(3)] [–2.2], C2–P1 189.3(2) [186.4(3)] [+2.9], C3–P3 181.5(2) [180.1] [+1.4], C1–P5 275.9(13) [251.0(21)] [+24.9], C2–P3 198.8(2) [215.1(4)] [–16.3].

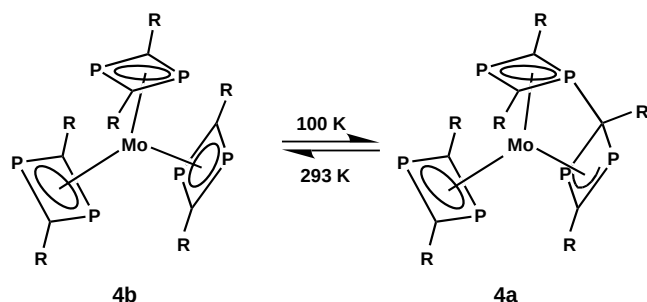
Structures **4a** and **4b** are very similar, in accord with the requirements of a topotactic reaction.^[14] The main fragment {Mo(C3P3C4P4)(C5P5C6P6)} only changes minimally, whereas in **4a** C1P1C2P2 has moved towards the C3P3C4P4 ring. The unusually short inter-ring separation C2–P3 decreases from 215.1 (**4b**) to 198.8 pm (**4a**), a distance that is consistent with a slightly stretched single bond.^[15] The shortening of this separation by 16.3 pm occurs concurrently with a lengthening of the inter-ring distance C1–P5 by 24.9 pm and a localization of the π interaction in the C1P1C2P2 ring in **4a**. The other rings, in contrast, are delocalized, with essentially equivalent bond lengths. The bonds C2–P1 and C2–P2 with an average length of 189.2 pm correspond to P–C single bonds, whereas the C1–P1 and C1–P2 separations (179.2 and 179.3 pm, respectively, see Supporting Information for numbering scheme) suggest significant P–C double bond character.

An almost identical structural unit is found in **5**, the iron complex of a polycyclic heptamer of **1**. The four-membered



ring in **5** is clearly 1,3-diphosphetenyl, an sp³-carbon-bridged π -coordinated diphosphaallyl system. The two P–C separations of the diphosphaallyl unit in **5** are 178 pm and the intraannular P–C single bonds are 191 and 192 pm long (Scheme 3).^[16]

The same interpretation seems appropriate for **4a**. The P–C contact between the rings, which is short even at room temperature, is so strengthened at low temperatures that the



Scheme 3. Molecular description of the topotactic bond formation.

C2–P3 interaction can be seen as a covalent bond. Atom C2 is converted into an sp^3 -hybridized center on formation of this bond and thus C2 no longer contributes to the delocalized π system of the ring and the Mo1–C2 bond is broken. Both the formation of the P3–C2 bond and the lengthening of the inter-ring distance between C1 and P5 occur continuously within the temperature range investigated and are fully reversible (Figure 2).

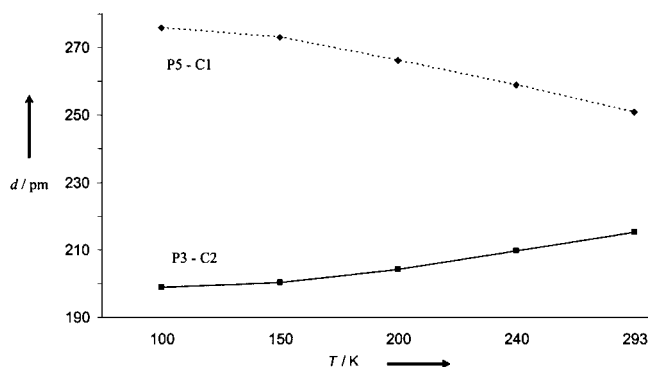
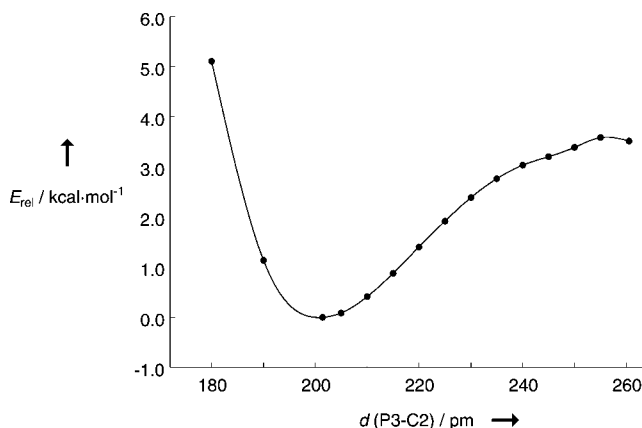


Figure 2. Temperature dependence of the P3–C2 and P5–C1 separations in pm. 100 K: P3–C2 198.8(2), P5–C1 275.9(13); 150 K: 200.3(6), 273.0(14); 200 K: 204.0(1), 266.2(16); 240 K: 209.6(1), 259.0(15); 293 K: 215.1(4), 251.0(21).

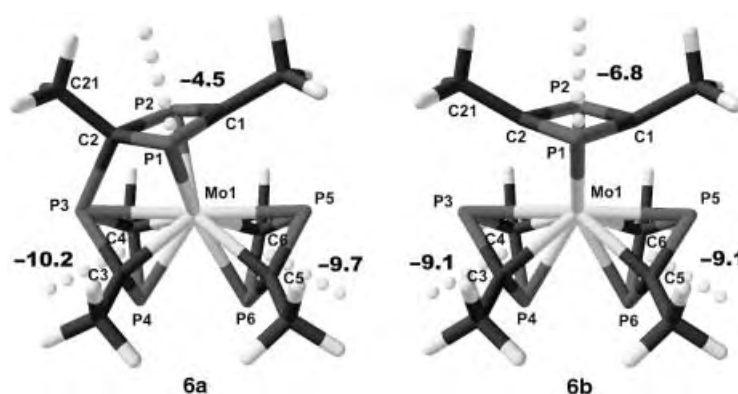
To our knowledge such intramolecular bond-formation reactions between π ligands at metal centers have not been described before. The structural type of the new bicyclic ligand is also without precedence. Reversible chemical reactions in which single crystals are conserved are also very rare, at least for metal complexes.^[17] To explain this phenomenon qualitatively we assume a nucleophilic attack of the lone pair of P3 on C2. The total number of electrons supplied by the ligands in **4a** remains constant despite the loss of the Mo1–C2 bond because the 1,3-diphosphaallyl fragment can be regarded as a formal anion. In contrast, the aromaticity of the C3P3C4P4-ring is retained, as shown by quantum-mechanical calculations (see below). Thus, P3 formally forms a pyramidal phosphonium center, a further interesting structural detail.^[18]

DFT calculations on the model compound [Mo{tris(2,4-dimethyl-1,3-diphosphet)}] (**6**) and the un-

substituted prototype compound **7** were performed to aid the analysis of the bonding situation in **4**. The calculations used Gaussian 98^[19] with the B3LYP hybrid functional^[20] and the LanL2DZ basis set.^[21] The basis set was extended with a set of d-functions with exponents of 0.6 and 0.34 on C and P, respectively, and p-functions with an exponent of 0.072 on the Mo center.^[22] Reaction paths in which the P3–C2 separation (comparable to C1–P5) was varied from 180 to 260 pm were calculated for the model compounds. The resulting energy profile for **6** is shown in Figure 3.

Figure 3. Calculated reaction profile for **6a**→**6b**.

Two isoenergetic minima with C_s symmetry and P3–C2 (or P5–C1) distances of 201.4 pm (**6a**) and a 3.5 kcal mol^{−1} less stable C_{2v} transition structure (**6b**) were obtained for the methyl-substituted compound (Figure 4). In contrast, the prototype compound **7** gives a broad, flat energy profile without a definitive structural preference. The C_s structure **6a** agrees surprisingly well with that found experimentally at 100 K in the crystal (**4a**). Even the critical C2–P3 and Mo1–C2 distances are almost identical. Larger differences are found for the nonbonding inter-ring distances C1–P5 (306.0 com-

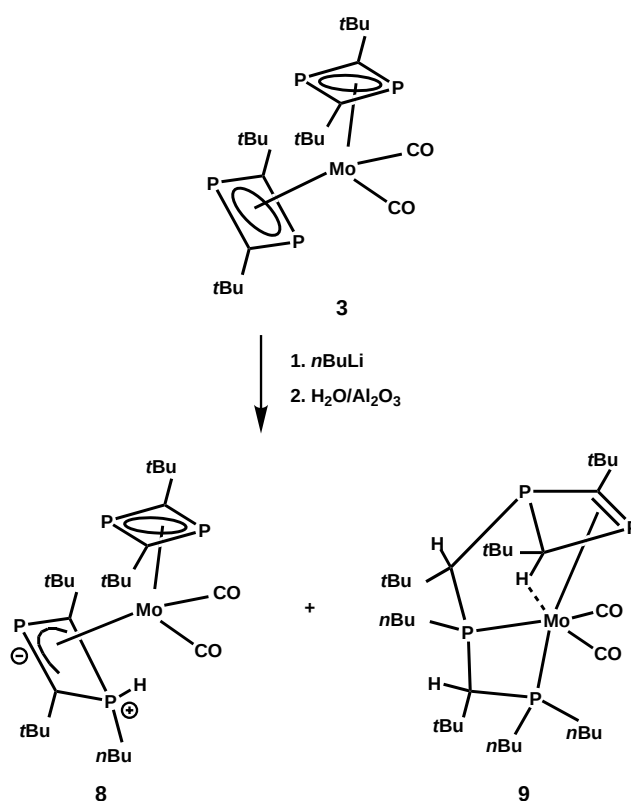
Figure 4. Calculated structures and NICS-1-values for the minimum-energy structure **6a** and the transition state **6b** from **6**. Selected distances **6a** [**6b**] [$\Delta = \mathbf{6a-6b}$] in pm, the numbering is analogous to **4**: Mo1–C2 256.9 [245.8] [+11.1], C2–C21 154.2 [152.3] [+1.9], C1–P1 180.3 [184.5] [−4.2], C2–P1 192.7 [184.5] [+8.2], C3–P3 186.6 [182.3] [+4.3], C3–P4 185.4 [185.1] [+0.3], C1–P5 306.0 [260.7] [+45.3], C2–P3 201.4 [260.7] [−59.3]. Selected Wiberg bond orders **6a** [**6b**]: Mo1–C2 0.1966 [0.3688], Mo1–P3 0.2678 [0.3177], C2–C21 1.0253 [1.0611], C1–P1 1.0995 [0.9808], C2–P1 0.8577 [0.9808], C3–P3 0.9063 [1.0081], C3–P4 0.9686 [0.9525], C1–P5 0.1044 [0.2458], C2–P3 0.6940 [0.2458].

pared to 275.9 pm) and P4–P6 (263.0 compared to 278.0 pm). These differences are probably caused by simplifying the substituents from *t*Bu to methyl and do not decrease the value of the modeling exercise significantly.

Wiberg bond orders^[23] were used to analyze the bonding situation. These support the interpretation derived from the structural data. This is most clearly seen in the P3–C2 interaction, for which a bond order of 0.69 is found in **6a**, compared with only 0.25 in **6b**. The value for the Mo1–C2 interaction decreases significantly (from 0.37 to 0.20) on going from **6b** to **6a**, but the Mo1–P3 interaction is weakened far less (from 0.32 to 0.27). Thus the Mo1–C3P3C4P4 fragment is almost unaffected by the inter-ring P3–C2 bond formation, whereas the Mo1–C2 bond is weakened significantly, which results in the Mo–diphosphaallyl system Mo1–C1P1P2. The C1–P1 and C1–P2 bonds become stronger (bond order: 0.98→1.10) and those between C1–P1 and C2–P2 weaker (bond order: 0.98→0.86). Identical conclusions can be reached from the calculated nucleus independent chemical shifts (NICS)^[24] (Figure 4), which describe the cyclic delocalization of the π electrons (i.e. the aromaticity of the ligands), and from the net atomic charges obtained from a natural population analysis (NPA).^[25] According to these criteria, the aromaticity of the 1,3-diphosphetenyl ring C1P1C2P2 decreases significantly, whereas it actually increases slightly for the C3P3C4P4-ring. The NPA shows P3 in **6a** to be 0.1 more positive than in **6b**, whereas C2 becomes –0.15 more negative. This suggests a partial charge-transfer from P3 to C2. The NPA charges are thus in accord with the formal view of a nucleophilic attack of P3 on C2. As all the calculated parameters for **6a** agree well with the experimentally determined structure for **4a**, we conclude that **4a** represents the real thermodynamic minimum for the complex **4**. The influence of the *t*Bu substituents and the crystal lattice on the bonding within the ligands is therefore of secondary importance. However, the lattice forces allow for the synchronization of the intramolecular reaction in the crystal, which can thus take place topotactically.

Thus, 1,3-diphosphete ligands display electrophilic character additionally to their inherent nucleophilicity; they are thus ambiphilic. There is only one report of the electrophilicity of neutral diphosphete complexes.^[26] Therefore, to test our hypothesis, we treated **3** with *n*BuLi as the nucleophile and protonated the resulting reaction products. In this way we were able to add one or three *n*-butyl groups to obtain [Mo(CO)₂(1,3-diphosphete)(1,3-diphosphetenyl)] (**8**) and [Mo(CO)₂(1,3-diphospheten-3-diphosphaoctyl)] (**9**; Scheme 4, Figure 5).^[27]

Both of these complexes have structures that make a detailed theoretical analysis necessary. These investigations are not yet complete. The bonding situation of the P1C1P2C6 four-membered ring in **9** is particularly difficult to understand. Although there seem to be no obstacles to the formation of a phosphaaallyl system in the protonation step, as found in **8**, this does not occur, but rather a 1,3-diphosphetene ligand that can only contribute two π electrons to the metal center is formed. The metal attempts nevertheless to attain an 18 valence electron structure by an agostic interaction (C6H1...Mo1).^[28] The unequivocally determined connectivity of the molecular



Scheme 4. The addition of nucleophiles.

components leads us, however, to the central question of this project. The constitution and the molecular structures of **8** and **9** show that Mo⁰-coordinated 1,3-diphosphete ligands are electrophilic. However, the initial attack of the nucleophile occurs at the phosphorus atom, analogously to the situation found for the cation of the salt [Mo(CO)₂(indenyl)(2,4-di-*t*Bu-1,3-diphosphete)]⁺BF₄[–].^[29] The reaction sequence is completed for **8** by a stereoselective protonation of the metal side of the phosphorous atom, which is evidence for the entry of the carbanion from outside.^[26] A heteroallyl system is formed, as in the case of **4a**, but in this case it is a 2-phosphaallyl. Because, however, a ring carbon atom plays the role of the electrophile in the intramolecular reaction, but a phosphorous atom plays the role of the electrophile in the intermolecular version, the electrophilicity of these two different types of ring atom in (1,3-diphosphete)Mo⁰ units cannot be very different.

The ambiphilicity of 1,3-diphosphete ligands caused by the phosphorus atoms is a characteristic that has not been observed previously in this type of complex. We can only begin to judge the effect of this ambiphilicity on the reactivity of the complexes because 1,3-diphosphete complexes have proven to be very robust.^[30] The polydentate ligand in **9** shows that the ambiphilic intramolecular reactivity of 1,3-diphosphete ligands can also operate despite strong competition from other nucleophiles. The P2–C18 bond between the remaining ring and its new side chain is the result of an intramolecular step although three carbanions are added to one ring. The ring that is attacked thus not only loses its π system, but is also ring-opened.

1,3-Diphosphetes, and probably other unsaturated P heterocycles, can, by reason of their ambiphilicity, take part in

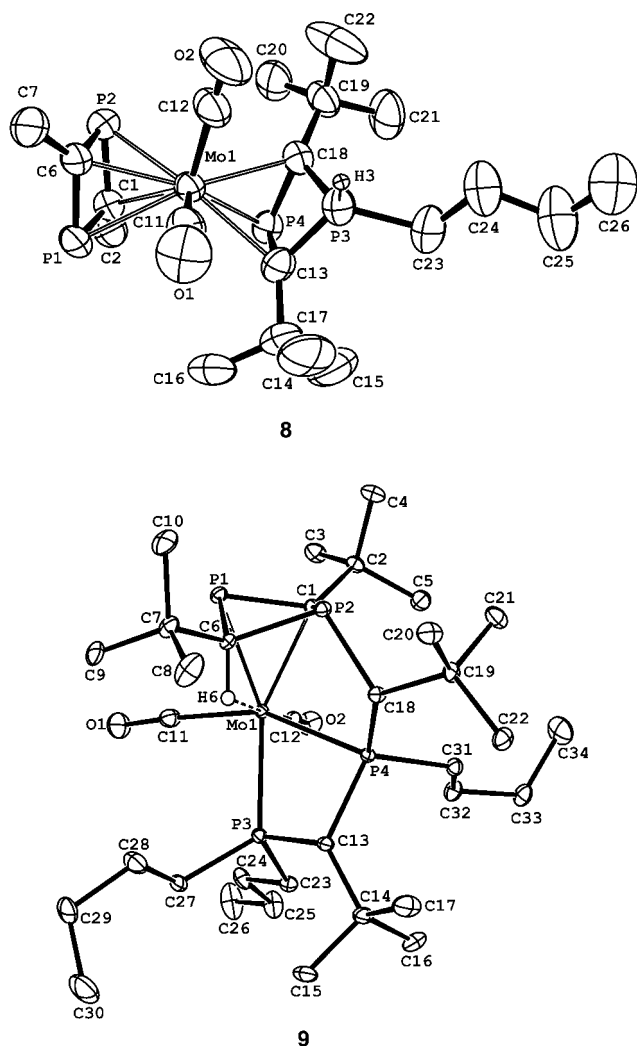


Figure 5. Molecular structures of **8** (298 K) and **9** (100 K). All hydrogen atoms except H3 and the methyl groups on the quaternary carbons C2 and C7 in **8** have been omitted for clarity. All hydrogens are omitted in **9** except H6.^[27]

nucleophilic or electrophilic intramolecular interactions. This situation is a new starting point for determining the complex reaction sequences of π ligands with lone pairs in the coordination spheres of metal centers, which, for instance, we must assume to take place in the formation of pentaphosphametalocenes from phosphalkynes. If we assume the process that forms 1,3-diphosphite and 1,3,5-triposphinine ligands^[1–5] to be the first step, as discussed in the introduction, a P–C bond can be formed between the ligands as in **4**. We have used preliminary DFT calculations for [Fe(1,3-diphosphite)(1,3,5-triposphinine)] to investigate the viability of this approach. Given this linkage between the ligands, there are no more fundamental theoretical problems in the exchange of ring components.

Other ligand-construction reactions that are at present not understood may also be traced back to the ambiphilicity of P atoms in coordinated heterocycles. This is, for instance, the case for [W(2,4-di-*t*Bu-1,3-diphosphite)₃] with a P–C inter-ring distance of 207.1 pm at 200 K,^[31] for the P–C bond between the pentamer cage and the four-membered ring of

the heptamer ligand in **5**,^[16] or the formal addition product of coordinated 1,3-diphosphites or 1-phosphites with phosphalkynes. In these cases, π -coordinated phosphalkyl structures are found once again.^[32]

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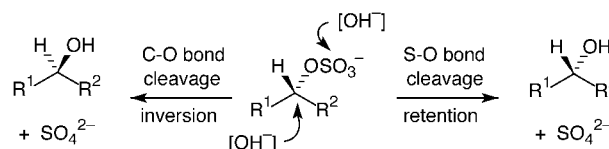
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Enantioselective Stereoinversion in the Kinetic Resolution of *rac*-*sec*-Alkyl Sulfate Esters by Hydrolysis with an Alkylsulfatase from *Rhodococcus ruber* DSM 44541 Furnishes Homochiral Products**

Mateja Pogorevc, Wolfgang Kroutil, Sabine R. Wallner, and Kurt Faber*

Sulfatases catalyze the hydrolytic cleavage of the sulfate ester bond by liberating inorganic sulfate and the corresponding alcohol.^[1] Depending on the nature of the enzyme and its catalytic mechanism, enzymatic hydrolysis of *sec*-alkyl sulfates may proceed through retention—by cleavage of the S–O bond—or inversion—by the cleavage of the C–O bond—of configuration at the chiral carbon atom (Scheme 1).^[2,3]



Scheme 1. Stereochemical pathways of enzymatic sulfate ester hydrolysis.

The ability of *sec*-alkylsulfatases to effect stereoinversion during catalysis makes them prime candidates for their application in so-called enantioconvergent processes,^[4] which allow the enantioselective transformation of enantiomers by opposite stereochemical pathways to furnish a single stereoisomeric product in 100% theoretical yield. Other enzymes, which potentially show this ability are a) epoxide hydrolases,^[5] b) dehalogenases,^[6] and c) glycosidases.^[7] A limited number of alkylsulfatases have been biochemically characterized^[1] but to date, these enzymes have not been applied to preparative biotransformations.^[8]

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From a screening of bacteria of the genus *Actinomyces* with *rac*-2-octyl sulfate as substrate,^[9] seven active strains were identified that hydrolyzed the substrate to produce 2-octanol and inorganic sulfate. The alkylsulfatase activity of the most active strain—*Rhodococcus ruber* DSM 44541—was investigated in more detail:

- 1) The *sec*-alkylsulfatase activity was constitutive with respect to substrate induction and was present in resting cells which were grown on a complex medium.^[5a]
- 2) The activity could be preserved upon lyophilization in Tris-HCl buffer (pH 7.5, 10 mM) and was maintained for several months when stored at +4°C.
- 3) The activity was associated with a soluble, monomeric protein (termed RS2) independent of any known cofactor.^[10]
- 4) The stereochemical pathway of sulfate ester hydrolysis was found to proceed with inversion of the chiral center. Thus, when enantiopure (*R*)-2- or (*R*)-3-octyl sulfate was used as substrate, (*S*)-2- and (*S*)-3-octanol, respectively, were obtained without racemization in >99% *ee*.
- 5) To evaluate the stereo- and enantioselectivity of this biocatalytic activity, the substrate tolerance and the respective enantioselectivities were investigated. The data in Table 1 reveal a clear trend: The enzyme showed excellent regioselectivity in favor of *rac*-*sec*-alkyl sulfates *rac*-**1a–d**^[9] of medium-chain length, which were readily accepted as substrates. In contrast, *prim*-sulfate ester **1e** was not converted at all. The enantioselectivity—expressed as the enantiomeric ratio (*E* value^[11]) was optimal for substrate **1b** where the relative size of substituents R¹ and R² was significantly different, which facilitates the chiral recognition process. Lower selectivities were observed when the functional group was gradually moved towards the center of the molecule, with R¹ and R² becoming similar in size to give near-symmetrical compounds *rac*-**1c,d**.
- 6) In general, the stereopreference was shown to be *R*, that is *R* configured substrate enantiomers were transformed with inversion of configuration to give the corresponding *S* alcohols, while *S* sulfate esters remained untouched.

Almost identical results were obtained when lyophilized whole cells were used as biocatalysts, which indicates that no

competing alkylsulfatase (showing different enantioselectivities or opposite stereopreference) was present. To improve the low enantioselectivity for *rac*-**1c** (*E*=4.3), a range of additives (such as metal ions, carbohydrates, and detergents) that are known to influence the chiral recognition of enzymes^[12] were tested as “selectivity-enhancers”. Whereas a modified polysaccharide (DEAE-dextran, *E*=9.5) and a detergent (cetyltrimethylammonium bromide, *E*=30) had a positive, but limited effect, the addition of metal ions resulted in a breakthrough: A dramatic selectivity-enhancement was achieved in the presence of Fe^{III} (5 mM), which raised the *E* value of *rac*-**1c** from 4.3 to >200, going in hand with a decrease in reaction rate.

In conclusion, a stereoselective *sec*-alkylsulfatase acting with inversion of configuration was found in *Rhodococcus ruber* DSM 44541. The remarkable feature of this biotransformation is the fact that—in contrast to the action of lipases, esterases, and proteases—the absolute configuration of the formed product and the remaining nonconverted substrate are identical to furnish homochiral *S* configured products from a racemate. This constitutes an important step en route towards the deracemization of *sec*-alcohols by stereo- and enantioselective biohydrolysis of their corresponding sulfate esters.

Experimental Section

Synthesis of substrates: Alkyl sulfates **1a–e** were prepared by sulfatation of the corresponding alcohol using NEt₃·SO₃ according to a known procedure.^[9] In the same manner, (*R*)-2- and (*R*)-3-octyl sulfate were obtained from (*R*)-2- or (*R*)-3-octanol, respectively.

Screening for alkyl sulfatase activity: Lyophilized cells (50 mg)^[5a] were rehydrated in Tris-buffer (pH 7.5, 0.1 M, 0.6 mL) for 0.5 h, *rac*-2-octyl sulfate solution was added (end concentration 22 mM, total volume 0.8 mL) and the vials were shaken for 5 days at room temperature. The conversion was determined by GC analysis after extraction of the formed alcohol with ethyl acetate using menthol as internal standard. The absence of spontaneous (nonenzymatic) hydrolysis for all substrates was proven by blank experiments in the absence of enzyme. When using whole-cell systems, a small amount of 2-octanone was formed as side product due to oxidation of 2-octanol.

Determination of enantiomeric composition: Alcohols **2a–d** were analyzed as the corresponding trifluoroacetate derivatives ((CF₃CO)₂O/EtOAc/60°C/20 min) on GC (Chrompack CP7500 (cyclodextrin-B-2, 25 m × 0.25 mm, 25 μm film); Chirasil-Dex CB/G-PN (propionyl γ-cyclodextrin, 30 m × 0.32 mm; H₂)), and their absolute configuration was elucidated by co-injection using an independent reference sample.

Partial purification of *Rhodococcus* sulfatase (RS2): Cells were disrupted by using a bead mill and the cell-free extract was subjected to HIC (Phenyl Sepharose, Pharmacia) using a stepwise gradient. Active fractions were pooled and lyophilized.

Table 1. Stereoselectivities of enzymatic sulfate ester hydrolysis

$ \begin{array}{c} \text{OSO}_3^- \\ \\ \text{R}^1 - \text{C} - \text{R}^2 \\ \\ \text{1e} \end{array} \xrightarrow[\text{Tris-buffer pH 7.5}]{\text{Alkylsulfatase}} \begin{array}{c} \text{H} - \text{C} - \text{OSO}_3^- \\ \\ \text{R}^1 - \text{C} - \text{R}^2 \\ \\ \text{2e} \end{array} + \begin{array}{c} \text{H} - \text{C} - \text{OH} \\ \\ \text{R}^1 - \text{C} - \text{R}^2 \\ \\ \text{1e} \end{array} + \text{SO}_4^{2-} $					
Substrate	R ¹	R ²	Conversion [%]	<i>ee</i> _p [%]	Enantioselectivity (<i>E</i>) ^[11]
<i>rac</i> - 1a	<i>n</i> -C ₅ H ₁₁	CH ₃	3.6	— ^[a]	—
<i>rac</i> - 1b	<i>n</i> -C ₆ H ₁₃	CH ₃	46	82	21
<i>rac</i> - 1c	<i>n</i> -C ₅ H ₁₁	C ₂ H ₅	38	52	4.3
<i>rac</i> - 1d	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₃ H ₇	68	9	<2
1e	<i>n</i> -C ₇ H ₁₅	H	0	—	—
<i>rac</i> - 1c	<i>n</i> -C ₅ H ₁₁	C ₂ H ₅	33	74	9.5 ^[b]
<i>rac</i> - 1c	<i>n</i> -C ₅ H ₁₁	C ₂ H ₅	25	90	30 ^[c]
<i>rac</i> - 1c	<i>n</i> -C ₅ H ₁₁	C ₂ H ₅	9	99	>200 ^[d]

[a] Very slow reaction. [b] Partially purified enzyme RS2 in presence of DEAE-Dextran (5% (w/v)). [c] In presence of cetyltrimethylammonium bromide (0.2% (w/v)). [d] In presence of Fe^{III} (5 mM).

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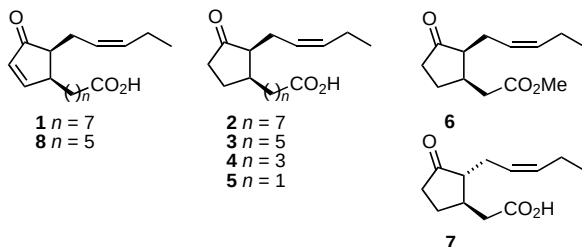
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A New Synthesis Route to Enantiomerically Pure Jasmonoids**

Martin Ernst and Günter Helmchen*

*Dedicated to Professor Volker Jäger
on the occasion of his 60th birthday*

12-Oxophytodienoic acid (12-OPDA) (**1**), ubiquitous in the plant kingdom, is the biosynthetic precursor for the jasmonoids **2–7**. These compounds result from **1** via the so-called octadecanoid cascade and participate as signaling compounds in a variety of processes.^[1] 12-OPDA (**1**) itself originates from

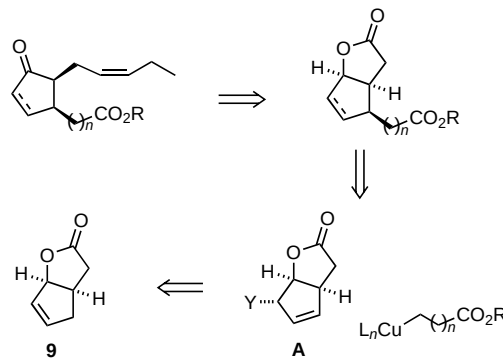


linolenic acid by oxidative cyclization. In 1997, dinor-oxophytodienoic acid (**8**), a hexadecanoid compound that is derived from hexadecatrienoic acid, was discovered and was shown to also possess pronounced biological activity.^[2]

All of the jasmonoids possess an epimerizable *cis*-disubstituted cyclopentenone or cyclopentanone system. Many

EPC syntheses exist for methyl epijasmonate (**6**) which is of great economical importance due to its use in fragrances.^[3] For the other octadecanoids, a broadly applicable, diastereoselective route to the racemic compounds has been worked out by Crombie and Mistry.^[4] The only asymmetric synthesis of enantiomerically pure **1**, presented by Grieco and Abood, employs an enzyme-catalyzed kinetic resolution.^[5,15] We here report the development of an enantioselective synthetic route that could be applied to all of the jasmonoids, **1–8**, on the basis of a catalytic enantioselective process.

The concept of the synthesis is presented in Scheme 1 in the form of a retrosynthetic analysis. The key compound is an enantiomerically pure building block of general formula **A**



Scheme 1. General synthesis strategy for jasmonoids.

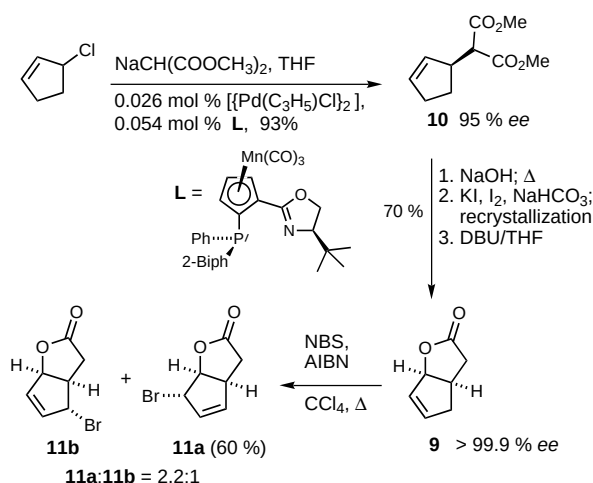
with a leaving group Y in allylic position. Herein, we could draw on studies by Roberts, Newton et al. who used the corresponding bromide, **A** with Y = Br, in the synthesis of prostaglandins, that is cyclopentanoids with *trans* configuration of the side chains.^[6] They obtained the bromide by radical bromination of an isomer of lactone **9**. We wanted to introduce the carboxyalkyl side chain *cis* to the lactone function of the jasmonoids by an *S_N2'*-*anti*-reaction of intermediate **A** with an appropriate cuprate. Compound **A** was planned to be prepared from lactone **9** which was previously obtained in low selectivity by Pd-catalyzed asymmetric allylic alkylation of cyclopentenyl chloride using second-generation chiral phosphanyloxazoline ligands.^[7]

With a third-generation phosphanyloxazoline, the ligand **L**,^[8] we now obtained an enantiomeric excess of 95% *ee* and a yield of 93% in the allylic substitution with sodium dimethylmalonate (Scheme 2). The alkylated malonate was converted into the crystalline iodolactone whose enantiomeric purity was increased by recrystallization to > 99.9% *ee*.^[7] Dehydrohalogenation furnished the allylic lactone **9** in 70% yield from **10**.

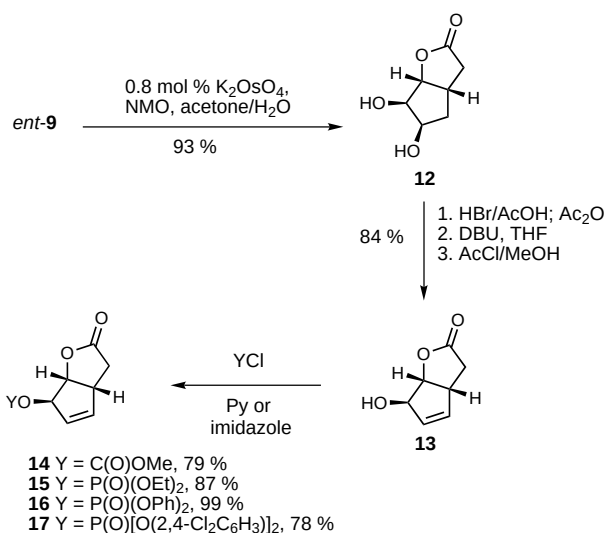
Bromolactone **11a** was prepared by radical bromination of **9** in CCl_4 under reflux in 60% yield. In contrast to the racemate,^[9] enantiomerically pure **11a** is an oil, and its purification by column chromatography laborious. Therefore, the series of allyl derivatives **14–17** was additionally prepared (Scheme 3). To access the non-natural enantiomers of the jasmonoids, *ent*-**9** was stereoselectively dihydroxylated,^[10] and the resulting diol **12** was transformed into the allylic alcohol,^[11] which was acylated. Both **12** and **13** as well as

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Scheme 2. Preparation of the bromolactone **11a**. Compound **11b** can be converted into a mixture of **11a** and **11b** by heating in toluene. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, NBS = *N*-bromosuccinimide, AIBN = 2,2'-azobisisobutyronitrile, Biph = biphenyl.



Scheme 3. Preparation of allylic substrates with different leaving groups. NMO = 4-methylmorpholine-*N*-oxide, Py = pyridine.

phosphate **16**, which proved to be particularly well suited for further transformations, are crystalline and, thus, the preparation of oxygenated allyl derivatives should be amenable to scale-up.

The $\text{S}_{\text{N}}2'$ -*anti* reaction of **11a** with various organocopper reagents was investigated by using the introduction of a *n*-butyl substituent as model system (Table 1).^[6] Use of exactly one equivalent of the organocopper compound afforded the monosubstitution product **18** in high yield. With an excess of monoorganocopper reagents or cyanocuprates, a domino reaction occurred, even at low temperature, in which allylic lactone **18** was opened, and a mixture of disubstituted carboxylic acids **19** was formed. Less reactive zinc cyanocuprates ("Knochel cuprates")^[12] selectively displaced only bromide, even when used in high excess. Dependence on the type of organometallic precursor or the cuprate employed for transmetalation was not observed.

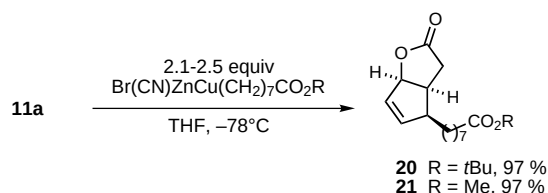
Table 1. Reactions of allylic substrates with *n*-butylcopper compounds.

Substrate	Reagent	Equiv	18 [%]	19 [%]
11a	<i>n</i> BuLi/Li(2-thienyl)Cu(CN)	1.0	96	—
11a	<i>n</i> BuMgCl/CuBr·SMe ₂	1.8	24	64
11a	<i>n</i> BuZnI/Li ₂ Cl ₂ Cu(CN)	13	quant.	—
11a	<i>n</i> BuLi/ZnCl ₂ /Li(2-thienyl)Cu(CN)	4.7	95	—
16	<i>n</i> BuLi/ZnCl ₂ /Li ₂ Cl ₂ Cu(CN)	2.5	95 ^[a]	—
17	<i>n</i> BuLi/ZnCl ₂ /Li ₂ Cl ₂ Cu(CN)	2.7	85 ^[a]	—

[a] In these cases *ent*-**18** resulted as the product.

The optimized reaction conditions were also applied to substrates **14–17** (Table 1). Only the phosphates reacted with zinc cyanocuprates, the electron-poor **17** displaying the highest reactivity, while **16** gave the highest yield. With diethylphosphate **15**, conversion was not complete even at prolonged reaction times.

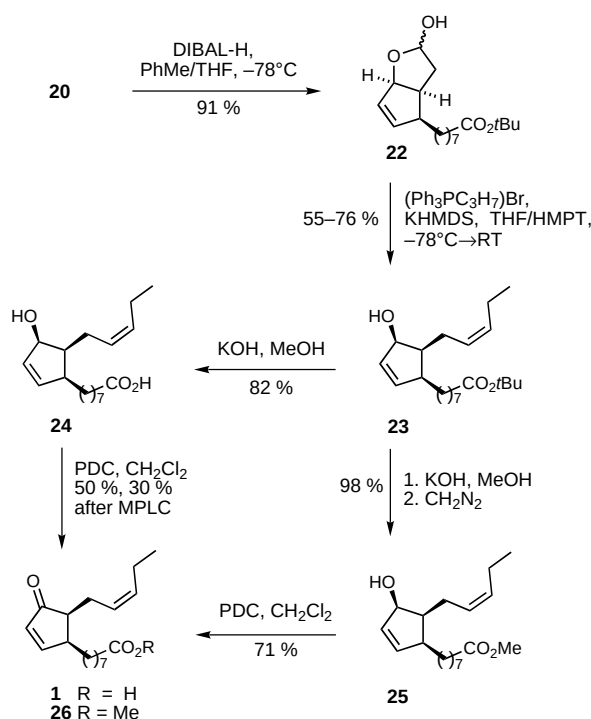
Ester groups are tolerated in the preparation of organozinc compounds by reaction of halogen compounds with activated zinc in polar solvents.^[13] Thus, the carboxyalkyl side chain needed for 12-OPDA (**1**) could be derived from methyl *ω*-bromooctanoate as well as *tert*-butyl *ω*-bromooctanoate (Scheme 4). The corresponding zinc cyanocuprates furnished yields of up to 97% in the reaction with **11a**. Phosphate **16** was transformed into the enantiomeric product *ent*-**20** in 89% yield.



Scheme 4. Introduction of the C₈ side chain by using a zinc cyanocuprate.

Lactone **20** was reduced with DIBAL-H to give the lactol which was transformed into the olefin in a *Z*-selective Wittig reaction (Scheme 5). The *Z/E* selectivity was in the range of 10:1. After separation of the isomers by flash chromatography, the pure *tert*-butyl ester was obtained in 55–76% yield. Saponification of the *tert*-butyl ester and oxidation of the free acid with PDC afforded crude **1** in 50% yield and pure **1** in 30% yield after purification by MPLC. The methyl ester **26** was obtained in 71% yield by oxidation of **25**. In analogy to **26**, the methyl esters of OPC-8:0 (**2**) and dinor-OPDA (**8**) were prepared, from **11a**, for the first time by enantioselective syntheses. In addition, *ent*-12-OPDA methyl ester was prepared from **16**.

The biological activity of the methyl esters of the various enantiomerically pure synthetic jasmonoids and their corresponding reduced precursors was assessed in the *bryonia*



Scheme 5. Synthesis of 12-OPDA (**1**) and 12-OPDA methyl ester (**26**). DIBAL-H = diisobutylaluminum hydride, KHMDS = potassium hexamethyldisilazide, HMPT = hexamethylphosphoric acid triamide, PDC = pyridinium dichromate.

dioica tendril coiling assay.^[14] This allowed us to confirm that **26** is more active than *rac*-**1**.

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Palladium-Catalyzed Coupling of Alkyl Chlorides and Grignard Reagents**

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Organometallic cross-coupling reactions have proven extremely important in recent years for the synthesis of organic building blocks, and pharmaceutical and agrochemical derivatives. A topic of current interest in this area is the catalytic activation and subsequent functionalization reactions of C–Cl bonds not only for laboratory-scale synthesis but also for industrial applications.^[1] To date the main focus has been the refinement of aryl and vinyl chlorides. Important contributions have been made, for example, in the area of Heck, Suzuki, and amination reactions of aryl chlorides.^[2–8]

While catalytic nucleophilic substitution of C(sp²)–Cl bonds is nowadays well established, the palladium-catalyzed refinement of alkyl chlorides has been largely neglected so far. The difficulty of catalytic nucleophilic substitution at C(sp³)–Cl has been attributed to the ease of β-hydride elimination reactions of the corresponding alkylpalladium complexes. Nevertheless, Suzuki et al.^[9] and Knochel et al.^[10] demonstrated the possibility of palladium- and nickel-catalyzed coupling of alkyl bromides and alkyl boranes as well as organozinc derivatives. Furthermore, we were also able to show that palladium-catalyzed carbonylations of in situ generated α-amidoalkyl bromides proceed in good yields to the corresponding amino acid derivatives.^[11]

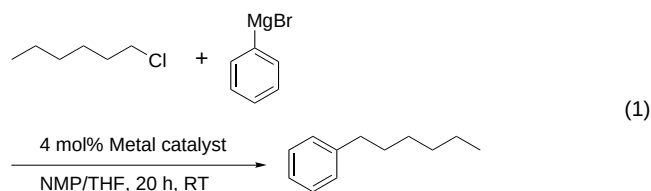
Fu et al.^[12] recently described the first catalytic coupling reactions of alkyl chlorides through a palladium-catalyzed Suzuki reaction. Kambe et al.^[13] developed the efficient

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nickel-catalyzed Kumada coupling of 1-chlorooctane with butylmagnesium chloride in the presence of 50 mol % of butadiene. As most arylboronic acids are synthesized from the corresponding Grignard reagents, the Kumada coupling reaction offers a more direct access to the desired products than the Suzuki reaction. Therefore, we have studied the Grignard coupling of alkyl halides (Kumada coupling) in the presence of various metal catalysts. Herein, we describe the first successful development of such a palladium-catalyzed method using alkyl chlorides.

Initially, we performed the coupling of 1-chlorohexane (**1**) and phenylmagnesium bromide (**2**) in the presence of different metal catalysts as a model reaction [Eq. (1)]. Selected



results are shown in Table 1. In general, all reactions were run with 4 mol % of metal catalyst at room temperature. A commercially available solution of phenylmagnesium bromide in THF was added to a solution of **1** and catalyst in such a way that the reaction temperature does not exceed 40 °C. No conversion was observed in the absence of catalyst. Simple salts of Cu,^[14] Ni, or Fe, which have been shown to be active in Grignard coupling reactions of alkyl bromides or aryl chlorides, did not catalyze the desired reaction to an appreciable amount (Table 1, entries 1–3). For palladium as catalyst metal, we studied the effect of different phosphane ligands, solvents, and substrate concentration. Although a high conversion was observed in the presence of Pd(OAc)₂

and triarylphosphanes, the selectivity of the reaction was low (Table 1, entries 4 and 5). Side products were hexene and hexane. In agreement with the results reported by Fu et al. for Suzuki reactions, tricyclohexylphosphane (PCy₃) proved to be the best ligand for the Grignard coupling of **1** (Table 1, entries 7–9). However, the ligand effect was not pronounced, as Pd/PtBu₃ also gave a significant amount of product. Further optimization of the amount of Grignard reagent (Table 1, entries 13–18) led to excellent yield (96 %) of 1-phenylhexane in the presence of 1.5 equivalents of **2**. Apart from the influence of the ligand, the efficiency of the reaction was found to be largely dependent on the solvent (Table 1, entries 10–12). So far, only *N*-methylpyrrolidinone (NMP) and dimethylacetamide (DMAc) gave good yields of the coupling product.

After having optimized the model reaction, we were interested in extending the scope of the coupling reaction. As shown in Table 2, the coupling reactions of 1-chlorohexane and 1-chlorobutane with different tolyl, anisyl, and 4-fluorophenyl Grignard reagents proceeded in good to excellent yields (77–99 %; Table 2, entries 1–5). Isobutyl chloride led to a slightly lower yield (72 %). Unfortunately, *sec*-butyl chloride, and *tert*-butyl chloride did not react under the conditions described. On the other hand, the method was applicable to functionalized alkyl chlorides. 5-Chloropentanenitrile, methyl 6-chlorohexanoate, and 3-chloropropionaldehyde diethyl acetal gave the corresponding products (58–99 %; Table 2, entries 7–9). Even coupling reactions with 2-phenylethyl chloride, which is amenable to elimination of HCl to give styrene, proceeded with significant yields (43–76 %; Table 2, entries 10, 11). The coupling of **1** and **2** exhibited complete conversion within 30 min; the reaction times for the other reactions have not been optimized (in general 20 h).

Interestingly, the palladium-catalyzed coupling of organozinc reagents proceeded under similar conditions as described for the Kumada coupling. For example, the reaction of **1** with phenylzinc bromide proceeded in the presence of a Pd/PCy₃ catalyst at 60 °C in 41 % yield (44 % conversion).

In conclusion, we have developed a novel method for the palladium-catalyzed cross-coupling of alkyl chlorides and Grignard reagents. Good to excellent yields of the coupling products were obtained at room temperature, and functional groups such as ethers, esters, acetals, fluorides, nitriles, aryl and benzyl were tolerated by the procedure. We are currently investigating extensions of this methodology to alkyl–alkyl coupling reactions.

Experimental Section

General procedure: A 25-mL Schlenk flask was charged with Pd(OAc)₂ (0.0180 g, 0.080 mmol) and PCy₃ (0.0224 g, 0.080 mmol), sealed with a septum, and

Table 1. Coupling of 1-chlorohexane (**1**) and phenylmagnesium bromide (**2**).^[a]

Entry	Solvent	2 [equiv]	Metal compound	Ligand	Conversion [%]	Yield [%]
1	NMP	1.2	CuCl ₂ ·LiCl	–	27	3
2	NMP	1.2	[Fe(acac) ₃]	–	44	7
3	NMP	1.2	[Ni(acac) ₂]	–	45	2
4	NMP	1.2	Pd(OAc) ₂	PPh ₃	88	9
5	NMP	1.2	Pd(OAc) ₂	P(<i>o</i> -tol) ₃	92	11
6	NMP	1.2	Pd(OAc) ₂	PtBu ₃	70	27
7	NMP	1.2	Pd(OAc) ₂	PCy ₃	99	68
8 ^[b]	NMP	1.2	Pd(OAc) ₂	PCy ₃	99	70
9 ^[b,c]	NMP	1.2	Pd(OAc) ₂	PCy ₃	76	34
10	THF	1.2	Pd(OAc) ₂	PCy ₃	1	1
11	dioxane	1.2	Pd(OAc) ₂	PCy ₃	1	2
12	DMF	1.2	Pd(OAc) ₂	PCy ₃	70	3
13	NMP	1.0	Pd(OAc) ₂	PCy ₃	91	61
14	NMP	1.5	Pd(OAc) ₂	PCy ₃	99	73
15	NMP	2.0	Pd(OAc) ₂	PCy ₃	99	71
16	NMP	3.0	Pd(OAc) ₂	PCy ₃	99	72
17	DMAc	1.5	Pd(OAc) ₂	PCy ₃	95	84
18	NMP ^[d]	1.5	Pd(OAc) ₂	PCy ₃	99	96

[a] Reaction conditions: **1** (2 mmol), metal complex (4 mol %), ligand (4 mol %), solvent (5 mL; NMP was distilled over CaH₂, the other solvents were used as received from Aldrich (water-free, over molecular sieves)), 20 h, room temperature; NMP = *N*-methylpyrrolidinone, DMAc = *N,N*-dimethylacetamide, PCy₃ = tricyclohexylphosphane. [b] 40 °C. [c] 1 mol % Pd(OAc)₂/PCy₃, 1/1. [d] NMP from Aldrich water-free 99.5 %, sure/seal bottle, used as received.

Table 2. Palladium-catalyzed cross-coupling of alkyl chlorides with aryl Grignard reagents.

Entry	Alkyl chloride	Aryl Grignard Compound	Product	Conversion [%]	Yield [%]
1				99	91
2				99	83
3				100	99
4				99	77
5				nd ^[a]	89
6				100	72
7				100	99
8				80	58
9				85	74
10				90	76
11				96	43
12				100	84

[a] nd = not determined.

purged with argon for 15 min. NMP (5 mL) and **1** (0.27 mL, 2 mmol) were added by syringe. Then, **2** (3 mL, 3 mmol, 1M in THF) was added dropwise over 1 min to the stirred mixture. After 20 h at room temperature, the reaction was quenched with MeOH (1 mL) and water (1 mL). The solution was concentrated to about 6 mL by rotary evaporation, and subjected to silica gel column chromatography (heptane) to give a colorless liquid (0.276 g, 1.7 mmol, 85% yield). ¹H NMR (400 MHz, CDCl₃): δ = 7.25–7.00 (m, 5H; Ar), 2.51 (t, ³J(H,H) = 7.7 Hz, 2H; CH₂), 1.58–1.47 (m, 2H; CH₂), 1.30–1.15 (m, 6H; CH₂), 0.80 ppm (t, ³J(H,H) = 6.4 Hz, 3H; CH₃); ¹³C NMR (400 MHz, CDCl₃): δ = 143.4, 128.9, 128.7, 126.0, 36.5, 32.2, 32.0, 29.5, 23.1, 14.6 ppm; MS (EI, 70 eV): m/z (%): 162 (33) [M⁺], 105 (11) [Ph-C₂H₄⁺], 91 (100) [Ph-CH₂⁺], 77 (4) [Ph⁺], 43 (16) [C₃H₇⁺].

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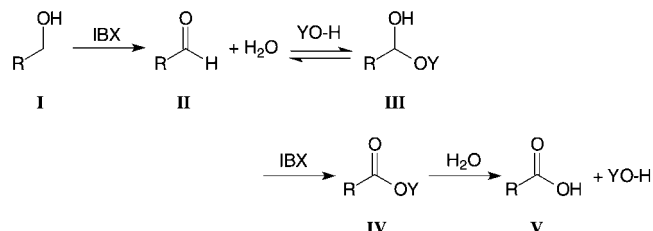
IBX-Mediated Oxidation of Primary Alcohols and Aldehydes To Form Carboxylic Acids**

Ralph Mazitschek, Marcel Mülbaier, and Athanassios Giannis*

Dedicated to Professor Peter Welzel on the occasion of his 65th birthday

During recent years the hypervalent iodine reagent 1-hydroxy-1,2-benziodoxole-3(1*H*)-one-1-oxide (IBX) was utilized for numerous novel and synthetically valuable oxidative transformations, including, among others, the cyclization of anilides,^[1] the preparation of amino desoxy sugars from glycals,^[2] the benzylic oxidation of aromatic compounds,^[3] and the synthesis of α,β -unsaturated aldehydes and ketones from homologous, saturated precursors.^[4]

IBX is safe and easily accessible, and is especially suited to the oxidation of alcohols in homogenous solution to yield the corresponding aldehydes and ketones.^[5,6] Recently, analogous reactions using polymer-supported IBX have been reported.^[7,8] The transformation of primary alcohols to carboxylic acids has never been observed using IBX. For the first time, we report here that primary alcohols are oxidized easily in the presence of IBX and certain O nucleophiles to give carboxylic acids at ambient temperature in high yields. Starting from the hypothesis that the aldehyde **II**, which is generated from a primary alcohol **I** and an excess of IBX, reacts with suited O nucleophiles (YO-H) to form the intermediate **III**. This intermediate can be oxidized to the corresponding active ester **IV**, which in turn is hydrolyzed to give the desired carboxylic acid **V** (Scheme 1).

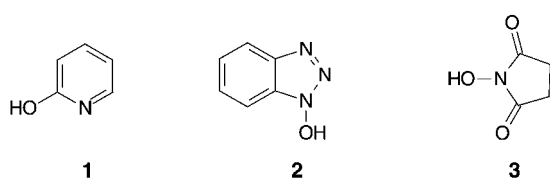


Scheme 1. Mechanism of the IBX-mediated oxidation of primary alcohols to give the carboxylic acids.

In our initial attempt 2-hydroxypyridine (**1**, HYP) was used as an O nucleophile. We were pleased to find that, in the presence of 2 equivalents of IBX and 4 equivalents of 2-hydroxypyridine, 1-decanol was oxidized to form decanoic acid in 48 h in 92 % yield. A series of other aliphatic alcohols (and aldehydes) was oxidized under the same reaction conditions in high yields to give the carboxylic acid analogues (Table 1). That only catalytic amounts of hydroxypyridine are

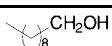
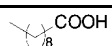
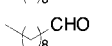
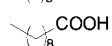
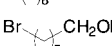
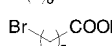
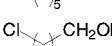
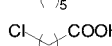
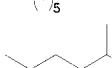
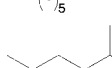
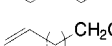
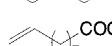
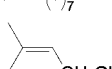
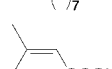
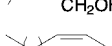
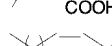
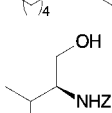
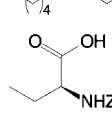
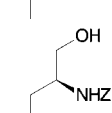
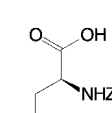
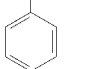
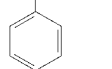
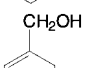
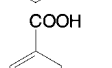
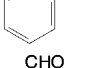
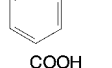
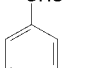
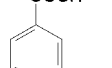
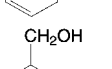
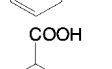
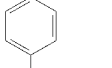
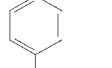
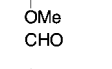
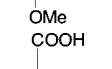
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[**] IBX = 1-hydroxy-1,2-benziodoxole-3(1*H*)-one-1-oxide.



required for the transformation is consistent with the proposed mechanism, however the reaction times also increase dramatically. Benzaldehyde (and benzylic alcohol) was not oxidized under these conditions. Also the oxidation of 2-decenal (and of 2-decen-1-ol) was not observed. We suppose that 2-hydroxypyridine is insufficiently nucleophilic to form

Table 1. Oxidation of primary alcohols and aldehydes to form carboxylic acids.

Entry	Substrate	Method	Product	Ratio A:AE ^[a]	Yield ^[b] of A [%]
1		HYP		–	91
2		NHS		1:10	80
3		HYP		–	91
		NHS		1:10	40
4		HYP		–	85
5		HYP		–	74
6		NHS		1:10	67
7		NHS		0:1	64
8		HYP		–	90
		NHS		1:10	40
9		HYP		–	79 ^[c]
10		HYP		–	85 ^[c]
11		NHS		2:3	79
12		NHS		1:2	93
13		NHS		1:4	76
14		NHS		1:2	90
15		NHS		1:1	68
16		NHS		1:0	64
17		NHS		1:0	95

[a] A: acid, AE: active ester. [b] Yield of product isolated. [c] The enantiomeric purity was determined by chiral HPLC.^[10]

the semiacetals of type **III** with these compounds. Therefore we decided to test 1-hydroxybenzotriazole (**2**, HOBT), as its hydroxy group shows an increased nucleophilic character, caused by the α effect. Actually, using benzaldehyde, IBX, and HOBT (1:1:1) we were able to detect the formation of benzoic acid within a few minutes. However, the yield was only 20%. The reason for this is the decomposition of **2** under the reaction conditions. To circumvent this problem, we decided to substitute HOBT with *N*-hydroxysuccinimide (NHS) **3**, because this compound is stable to IBX. Indeed, we could oxidize aromatic aldehydes as well as α,β -unsaturated aldehydes to the corresponding carboxylic acids. Identical products were obtained from benzyl and allyl alcohols. Aliphatic aldehydes were also oxidized to form carboxylic acids. Interestingly, the NHS-mediated oxidation yielded the preparatively valuable active esters (*O*-succinimidyl) in most cases.^[9] This observation endorses the mechanism postulated in Scheme 1. The addition of water (approximately 10 vol%) did not influence the reaction. The hydroxypyridine and the NHS-mediated methods both tolerate a wide variety of functional groups, such as isolated and conjugated double bonds, alkyl halogenides, urethanes, and electron-rich and -poor aromatic compounds. Starting from *N*-protected α -amino alcohols, the corresponding amino acids can be generated without racemization.^[10]

In the past, various highly efficient methods for oxidizing alcohols to give carboxylic acids have been developed. However, all of these methods have inherent disadvantages.^[11–14] For example, using the TEMPO/NaOCl/NaOCl₂ method, electron-rich aromatic alcohols are scarcely oxidized and the chlorination of the aryl ring is often a side reaction. Double bonds require special reaction conditions. Similar is true for the Sharpless-Katsuki-method as well as for the recently reported Pd-mediated oxidation of alcohol groups to give carboxylic acids.

Our method is mild, efficient, and avoids the use of toxic metals. It is compatible with various functional groups and the iodosobenzoic acid can be separated from the reaction mixture and easily reoxidized to form IBX.

Experimental Section

HYP method: IBX (2.6 equiv, 13 mmol; 1.6 equiv of IBX or 8 mmol, when starting from the aldehyde) were dissolved in DMSO (10 mL). The alcohol/aldehyde (5 mmol) was added in a single portion at room temperature. After oxidation of the alcohol (in most cases after 10–20 min) of HYP (5 equiv, 25 mmol) was added and the reaction mixture was stirred for an additional 72 h. It is not necessary to exclude moisture and oxygen. For the workup semisaturated NaHCO₃ solution (50 mL) was added and the reaction mixture extracted with diethyl ether (2 × 30 mL). The iodosocarboxylic acid, which precipitated as an off-white amorphous solid, was removed by filtration. After acidification to pH 1 with 10% sulfuric acid, the aqueous phase was extracted (3 × 50 mL) with diethyl ether. The combined organic phases were washed once with a 5% KHSO₄ solution and dried over Na₂SO₄. The solvent was removed under reduced pressure, to leave the acid containing traces of iodosobenzoic acid. Analytically pure product was obtained by column chromatography on silica gel.

NHS method: IBX (2.6 equiv, 13 mmol; 1.6 equiv of IBX or 8 mmol starting from the aldehyde) were dissolved in DMSO (15 mL). The alcohol/aldehyde (5 mmol) was added in a single portion at room temperature. After oxidation of the alcohol to the aldehyde, *N*-hydroxysuccinimide (5 equiv, 25 mmol) was added slowly so that the temperature did not exceed 30°C. The reaction mixture was stirred over 16 h.

To isolate the active esters, semisaturated NaHCO₃ solution (50 mL) was added. After stirring for 5 min the reaction mixture was extracted (3 × 50 mL) with diethyl ether. The iodosocarboxylic acid, which precipitated as an off-white amorphous solid, was removed by filtration. The organic phase was washed once more with 10% NaHCO₃ solution (50 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure. Analytically pure product was obtained by column chromatography on silica gel.

For isolation of the carboxylic acid, 1N NaOH (50 mL) was added to the reaction mixture and stirring was continued until a clear solution was obtained. This solution was washed with diethyl ether (1 × 50 mL) and acidified with 2N hydrochloric acid to pH 1. The aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed once with 5% KHSO₄ solution and dried over Na₂SO₄. The solvent was removed under reduced pressure. Analytically pure product was obtained by column chromatography on silica gel.

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Cation Control in Functional Helical Programming: Structures of a D,L-Peptide Ion Channel**

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The controlled folding of molecules into helical structures is a very important means to assemble functional entities. Helices can carry and process information (DNA double helix),^[1] provide the basis for rigid materials (collagen triple helix),^[2] can be used for transport purposes (single-stranded β -helix of D,L-peptides),^[3] or for arranging photo-, electro-, or transport-active groups^[4] in 3D space. The design of synthetic compounds with a predictable folding behavior (programmed folding) is actively pursued.^[5] However, most of the known examples of helical folding remain on the structural level.

Our interest in functional folding of synthetic ion channels^[6] led us to explore D,L-peptides, which we used as structural templates for ether- δ -peptide strands to yield ion channels with novel functions.^[7] The pivotal D,L-peptide is the gramicidin A (gA) ion channel (Figure 1a).^[3] gA itself can adopt a variety of conformations depending on the environment. In organic solvents, gA predominantly forms dimeric double helices, which vary in handedness and dimerization topology.^[8] The binding of cations can force this double helix to increase its diameter.^[9] Only in membranelike environments will gA form a unique head-to-head associated dimer of two right-handed, single-stranded β -helices.^[10] This conformation, with 6.3 residues per turn, is generally regarded to be the “active” ion-channel structure,^[11a-c] but as it has never been observed in isotropic solution or by X-ray crystallography, its nature has remained a source of debate.^[11d]

We found that the fully synthetic 22mer “minigramicidin” **1** (Figure 1a) acts as an ion channel in phospholipid bilayers (Figure 1b). A remarkable dependence of the channel activity on the membrane thickness was observed,^[12a] and preliminary

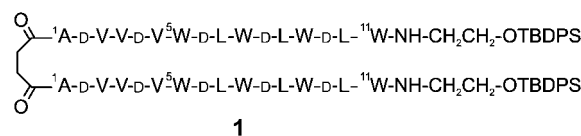
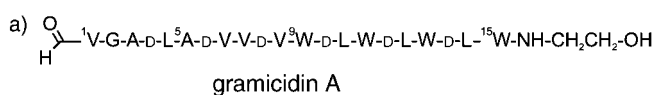


Figure 1. a) Primary sequence of **1** and gA; b) representative current trace of **1** in planar lipid bilayers (1 M CsCl, 120 mV, soy-bean lecithin). Consult Supporting Information for details.

investigations indicated a more confined conformational space for **1** than for gA.^[12b] With the goal of a detailed understanding of the ion-channel-active conformation of **1**, we focused on structural investigations in the absence and presence of Cs⁺ ions.

Compound **1** features the terminal 11mer domain of gA, covalently dimerized by use of succinic acid in a head-to-head fashion. This linkage avoids the lateral dissociation equilibrium,^[12b] which complicates structural studies of gA.^[13,14] The *tert*-butyldiphenylsilyl (TBDPS) capping groups in **1** enhance its solubility in organic solvents and facilitate the structural studies. Single-channel current measurements in planar phospholipid bilayers revealed that **1** forms a highly active Cs⁺-ion channel ([**1**] = 10^{−14} M in the aqueous bath solution, see Supporting Information). Only one type of channel is observed, which indicates a single channel-active conformation in the membrane (Figure 1b).

The structure of **1** in the absence of metal ions was determined in [D₆]benzene/[D₆]acetone 10:1 and CDCl₃/[D₃]MeOH 1:1 (v/v) by using NMR spectroscopy. Both solvent mixtures mimic membranes in their polarity.^[15] The same highly symmetric structure **A** was found in either case; this peptide dimer forms a left-handed double- β -helix with 5.7 residues per turn and a length of approximately 38 Å (Figure 2) with the succinate linker moiety in an antiperiplanar conformation. This type of secondary structure is adopted by gA only in the presence of CaCl₂.^[8g]

The entire structure transforms into a new species upon addition of Cs⁺ salts. After saturation with CsI, peptide **1** adopted the monomeric structure **B** in CDCl₃/[D₃]MeOH 1:1 or 3:1 (v/v, Figure 3). Each 11mer fragment forms a right-handed β -helix with approximately 6.3 residues per turn. The succinate moiety joins the two fragments symmetrically (C₂ axis) in an anticlinal fashion (mean structure) to yield a single helix with a total length of about 17 Å.

Structure **B** has all features of the presumed gA channel conformation—in contrast to the double β -helical structure **A** without Cs⁺. The pore diameter rises from 1.2 Å in the dimer **A** to 4.5 Å in the monomeric $\beta^{6.3}$ helix **B**, wide enough to host Cs⁺ ions. Structure **B** forms a continuous channel like the head-to-head dimer of gramicidin A in membranelike environments.^[11] The amide carbonyl groups of the anticlinal

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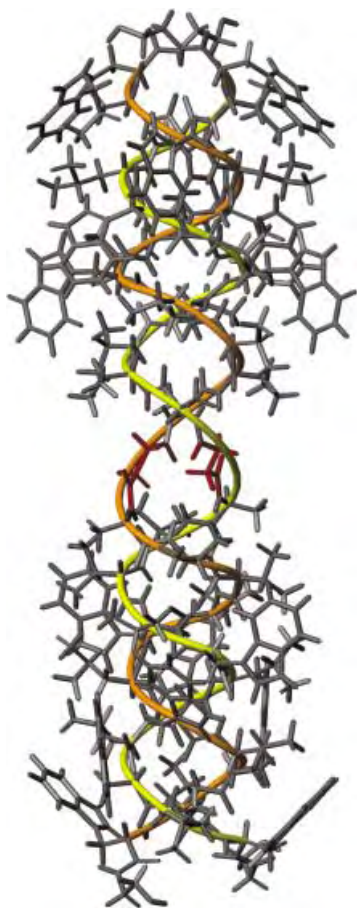


Figure 2. Averaged mean structure **A** (PDB = protein database accession code 1 KQE; calculated from the sixteen energetically favored structures) of **1** in $[D_6]$ benzene/ $[D_6]$ acetone 10:1. The TBDPS protecting groups were omitted from the structure determination because of overlapping signals. The linker region is colored in red. NMR spectra were acquired at 600 MHz (Bruker AMX). Assignments were obtained with the program Felix 2000 (Accelrys, San Diego, CA) by a combination of DQF-COSY and TOCSY experiments according to standard procedures.^[16] H–H distance restraints were extracted from NOESY spectra at 150 and 300 ms. 688 NOE cross-peaks (330 intraresidual, 138 sequential, and 220 medium-range) were used. For all amino acid residues $^3J(H^N, H^\alpha)$ coupling constants could be measured. They are all in the range typical for a β -sheet. The NOE restraints and the H^N, H^α couplings were used in a simulated annealing protocol^[17] with the program X-PLOR^[18] to calculate sixteen structures that have a root-mean-square deviation (rmsd) of the backbone positions of 0.61 Å.

succinate linker fit well into the overall pattern of the channel carbonyl groups, completing the coordination sphere of the Cs^+ ions which are putatively bound in symmetrical positions.^[19]

The conformational switch from **A** to **B** was monitored by NMR spectroscopic titration in $CDCl_3/[D_3]MeOH$ 1:1 with CsI (Figure 4a, see Supporting Information). A nonlinear least-squares fit for several scenarios (1–2 ions, no aggregation, dimer, trimer, or tetramer) revealed that only the scenario shown in Figure 4b could reproduce the data well: The dimer **A** dissociates into a monomeric state **C** first (K_D), which takes up two Cs^+ ions consecutively (K_1, K_2). It was not possible to extract a value for K_D reliably from the data, because K_D and K_1 are strongly coupled. With an approximated value of $K_D = 0.00126 M^{0.5}$ (98 % dimer at $[Cs^+] = 0$),

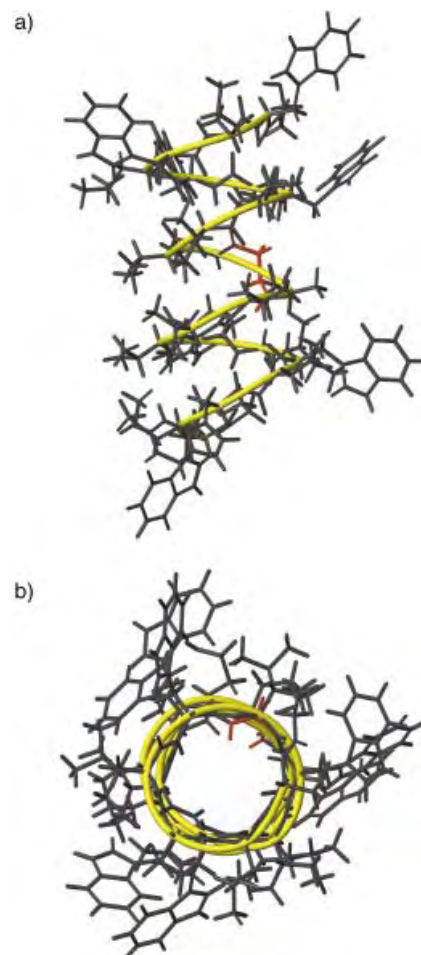


Figure 3. Averaged mean structure **B** of **1** in $CDCl_3/[D_3]MeOH$ 3:1 saturated with CsI, a) side view, b) top view. The structure was determined in the same way as described for **2**. In this case, 213 NOE cross-peaks (97 intraresidual, 51 sequential, and 65 medium-range) were used. The rmsd of the backbone positions of the ten best structures was 0.91 Å.

binding constants of $K_1 = (63 \pm 5) \times 10^3 M^{-1}$ and $K_2 = (36 \pm 20) M^{-1}$ were obtained (see Supporting Information). The much stronger binding of the first Cs^+ ion ($\Delta G_1 = -28 kJ mol^{-1}$) than the second one ($\Delta G_2 = -9 kJ mol^{-1}$) indicates that the conformational reorganization of the entire structure on binding of the first Cs^+ ion is less energetically costly than the coulomb repulsion encountered on the second binding event.

To relate these findings further to gA,^[8f,12b] circular dichroism (CD) spectra of these secondary structures were recorded (Figure 5). In organic solvents such as CH_3CN or $C_2H_4Cl_2/MeOH$, compound **1** shows two *negative* Cotton effects at $\lambda = 228$ and 208 nm (Figure 5a, spectra c and d),^[12b] in full accordance with the left-handed double- β -helical structure **A**.^[12b,20] The Cs^+ complexes **B** in $C_2H_4Cl_2/MeOH$ or pure MeOH instead display a single *positive* Cotton effect at $\lambda = 230$ nm (Figure 5a; spectra a and b), which indicates right-handedness of the β -helix. This spectrum differs significantly from the spectrum of **1** in 1,2-di-myristoyl-*sn*-glycero-3-phosphatidylcholine (DMPC) vesicles,^[20] which nearly coincides with that of gA (Figure 5b). The latter spectrum is normally assigned to the right-handed, single-stranded β .^{6,3}

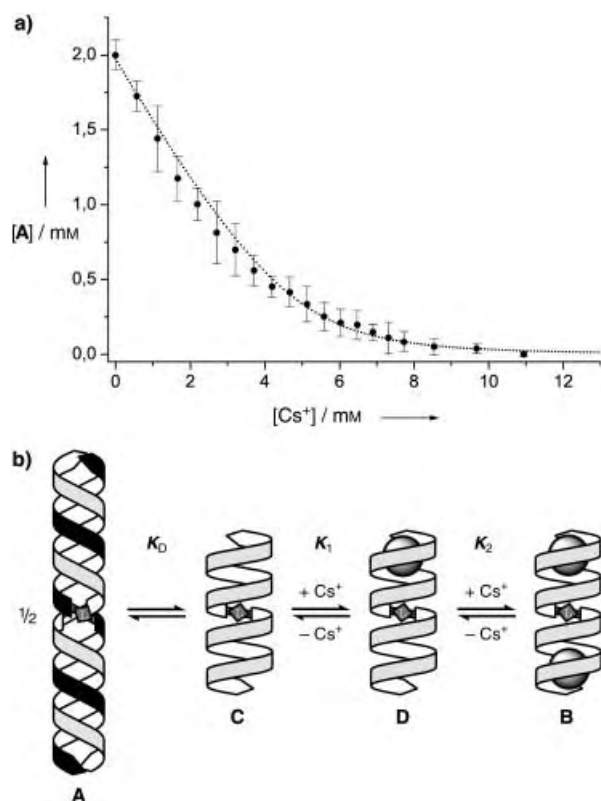


Figure 4. a) NMR spectroscopic titration of **1** with CsI in $\text{CDCl}_3/[\text{D}_3]\text{MeOH}$ 1:1; dotted line refers to the fitting; b) schematic representation of the equilibria involved in the conformational transition from **A** to **B** via the putative monomer **C** and the 1:1 complex **D** upon addition of Cs^+ ions.

helix,^[8f] which we found for the Cs^+ complex **B** in organic solvents. The origin of the different spectra remains unclear at this stage. We reason, however, that the differences in the CD spectra report subtle changes in local conformations of the gramicidines, which do not affect the global structure (to be published elsewhere).

To correlate the Cs^+ binding found for **1** in organic solvents with the ion-transport process, we studied the dependence of the channel conductance Λ on the concentration of Cs^+ ions in the solution (Figure 6a).^[21] The data displayed three remarkable features: 1) Conductance can be measured at very low concentrations of Cs^+ ions, 2) the curve is supralinear (shows an over-proportional increase) in the medium-concentration range (10–100 mM) and 3) a maximum is observed at approximately 1.5 M. These features indicate a multiple-binding-site transport process.^[21b] A kinetic rate model with two symmetrical binding sites and four states^[22] reproduces the data well (Figure 6b). The apparent rate constants thus obtained ($\pm 30\%$) are $A = 5.2 \times 10^8 \text{ L mol}^{-1} \text{ s}^{-1}$, $B = 4.9 \times 10^6 \text{ s}^{-1}$, $K = 5.1 \times 10^7 \text{ s}^{-1}$, $D = 4.4 \times 10^7 \text{ L mol}^{-1} \text{ s}^{-1}$, and $E = 5.4 \times 10^7 \text{ s}^{-1}$. Clearly, a doubly occupied state becomes transiently populated during the ion-transport process mediated by minigramicidin **1** at higher concentrations of Cs^+ ions.

In summary, the present study shows that the minigramicidin **1** forms a distinct double-helical rod **A** in media of low polarity. Its disaggregation into the channel-active conformation is triggered by membrane insertion or by Cs^+ -ion binding. The latter allowed us to study the right-handed β -helix of the D,L-peptides in solution for the first time. The structure **B** probably reflects the ion-channel-active conformation of **1** in the membrane—occupied by two Cs^+ ions.

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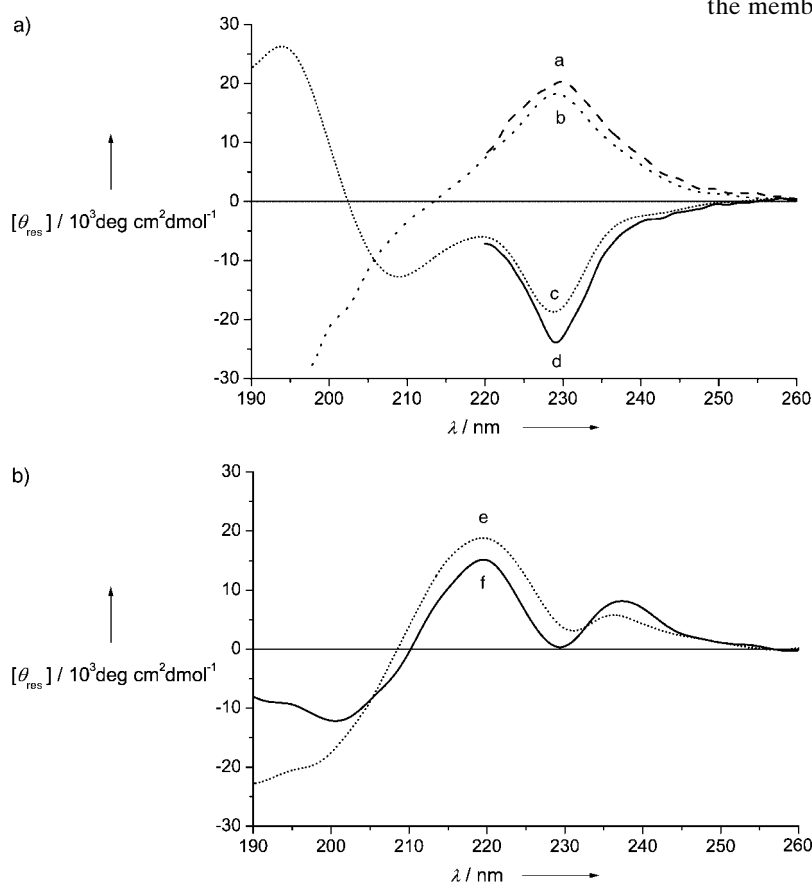


Figure 5. a) CD measurements of **1** in organic solvents ($T = 22^\circ\text{C}$, $[\mathbf{1}] = 10^{-5} \text{ M}$): Spectrum a: $\text{C}_2\text{H}_4\text{Cl}_2/\text{MeOH}$ 1:1, saturated with CsCl (---); b: 50 mM CsCl in MeOH (---); c: CH_3CN (••••); d: $\text{C}_2\text{H}_4\text{Cl}_2/\text{MeOH}$ 1:1 (—); b) CD measurements in DMPC vesicles^[20] ($T = 22^\circ\text{C}$, $[\text{gA}]$ or $[\mathbf{1}] = 10^{-5} \text{ M}$): spectrum e: gA (••••); f: **1** (—). The shape of the spectra a and d was unchanged at $[\mathbf{1}^+] = 10^{-3} \text{ M}$ (not shown). $[\theta_{\text{res}}]$ = mean molar ellipticity per residue.

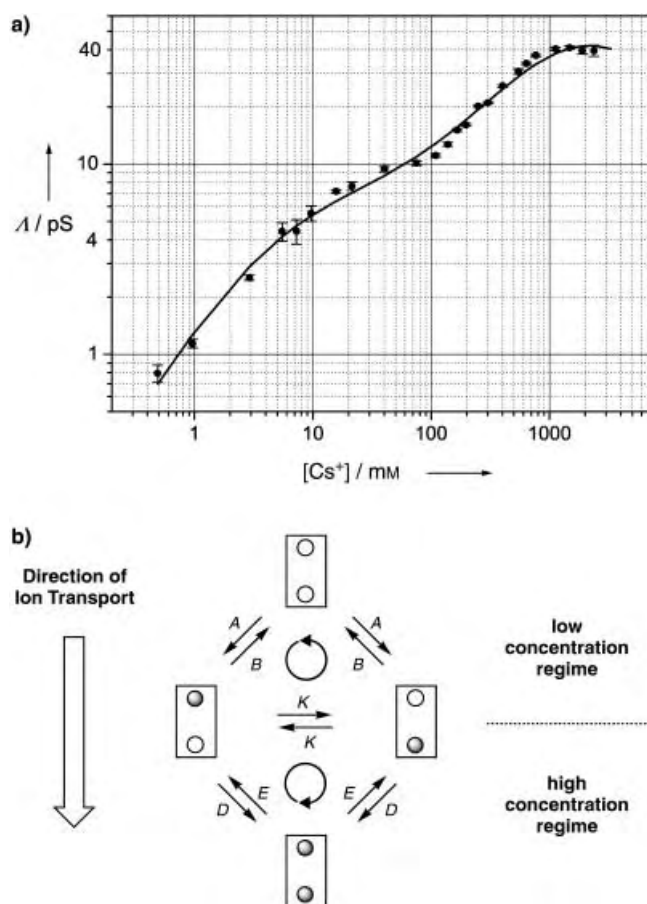


Figure 6. a) Concentration dependence of the channel Cs^+ -ion conductance of **1** at $T = 22^\circ\text{C}$ in soybean lecithin ($n > 50$ in each case); b) kinetic rate model (two binding sites—four states) used to model the ion transport through the channel **1**.^[22]

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 [19] The symmetrical structure **B** indicates an even number of bound Cs^+ ions. The NMR spectroscopic titration of **1** with CsI suggests that two Cs^+ ions are present, as does the ESI mass spectrum of the complex, which is dominated by the $[\text{1}+2\text{Cs}]^{2+}$ ion peak. Presumably, the Cs^+ ions reside in the respective upper and lower thirds of the channel pore. But as the positions of the Cs^+ ions in the complex could not be deduced from the present NMR spectroscopic data, they were not taken into account during the calculation of structure **B**.
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Global Replacement of Tryptophan with Aminotryptophans Generates Non-Invasive Protein-Based Optical pH Sensors

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Among the gene-encoded natural amino acids tryptophan occurs in proteins in only a low abundance (1.2%),^[1] but it occupies a unique position because of its ability to form numerous selective inter- and intramolecular interactions.^[2] It also represents the main source of UV absorbance and of fluorescence in proteins^[3] and has, therefore, recently been recognised as a useful intrinsic probe for structural and functional studies of proteins as well as an attractive target for classical protein engineering and design. More recently, the previously limiting factors of classical protein engineering procedures that rely solely on the standard set of canonical amino acids have been overcome by methods that allow for expansion of the amino acid repertoire (for example, see ref. [4]). In this context, our approach for the *in vivo* incorporation of noncanonical amino acids into proteins is based on the traditional use of auxotrophic *E. coli* host strains^[5] that are forced to undergo selective pressure incorporation (SPI).^[6] This method exploits the lack of absolute substrate specificity of aminoacyl-tRNA synthetases as the crucial enzymes in the interpretation of the genetic code,^[7] a process that leads to activation and transfer of a variety of structurally and chemically similar substrate analogues onto cognate tRNAs under defined conditions (see, for example, ref. [8]). The main principle of this engineering approach is the reassignment of the coding triplets, that is, differences in the interpretation of the genetic code under the experimentally imposed selective pressure. For example, the repertoire for the tryptophan coding triplet (UGG) has been expanded with novel translationally active chromophores such as 4-fluorotryptophan, 5-fluorotryptophan, 6-fluorotryptophan,^[9] 7-azatryptophan^[10] and 5-hydroxytryptophan^[11] or even with tryptophan-related amino acids such as β -(thienopyrrolyl)alanines^[12] or β -selenolo[3,2-*b*]pyrrolyl-alanine.^[13]

The main motivation for attempting global replacement of tryptophan residues in proteins with these analogues derived from earlier reports on the spectroscopic properties of substituted indoles.^[14,15] In fact, it is known that substitution of indole with electron-donating groups leads to intramolecular charge transfer being extremely sensitive to pH

changes.^[16] For example, amino substituents on aromatic ring systems are less basic in the excited than in the ground state.^[17] Thus, the protonation level in the excited states affects the resonant integration of their free electrons in conjugated ring systems which causes charge migration and is seen as blue- or red-shifted spectroscopic bands.

The amino acids **2–7** (Figure 1) were synthesised enzymatically from L-serine using commercially available amino- and hydroxyindoles as substrates for tryptophan synthase^[18] and characterized spectroscopically^[19] (the synthesis of the Trp analogues will be reported elsewhere).

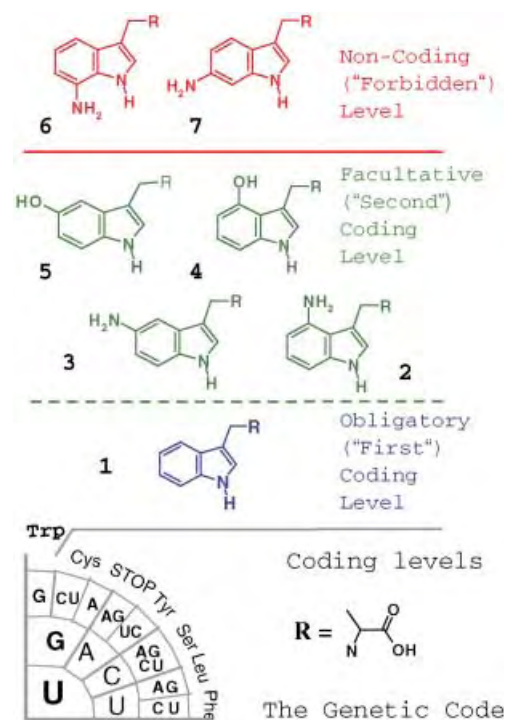


Figure 1. Genetic code engineering by expansion of the coding capacity of the tryptophan triplet UGG under the experimentally imposed selective pressure. The universal genetic code assigns UGG as the coding triplet for L-tryptophan (**1**), shown here as the obligatory or first coding level. By using the SPI method the entry of amino acids **2–5** into genetic code is allowed, thus creating a second or facultative coding level. Translationally inactive amino acids **6** and **7** can be regarded as prevented from entering into the genetic code (noncoding level) at this level of the development of SPI methodology.

The pseudo-wild-type variant C40A/C82A/P27A of barstar (**1-b***) was chosen as a model protein for the expression experiments as it contains three tryptophan residues, namely, the fully or partially solvent-exposed Trp38 and Trp44 as well as Trp53, which is completely buried within the protein hydrophobic core (Figure 2). The latter residue is known to be essential for the structural integrity of the protein, since it cannot be replaced by any of the other 19 canonical building blocks by routine site-directed DNA mutagenesis.^[20] The three Trp residues of barstar (**1-b***) were globally replaced with the analogues **2–5** by the SPI method using the Trp-auxotrophic *E. coli* strain ATCC49980 as the expression host.^[21] Variant proteins were produced in yields comparable to those of the **1-b*** protein (10–30 mg L⁻¹)^[22] and were stable

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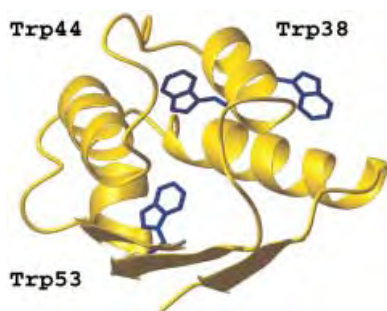


Figure 2. The structure of small ribonuclease inhibitor barstar,^[23] with the tryptophan positions marked, represented as a ribbon plot (derived from the program MOLSCRIPT).^[24]

in buffer solutions, with the exception of **4-b***, which exhibits a strong tendency for aggregation. Unexpectedly, incorporation of the analogues **6** and **7** failed, most probably because of their poor recognition by the protein translation machinery.

Absorbance and fluorescence profiles of the protein variants were used as qualitative analytical criterion to monitor successful incorporation. For example, the hydroxy group at position 5 of indole leads to significant enhancement of the ^1L_b transition band^[15] and thus to a pronounced spectral shoulder at 310 nm ($\epsilon_{310} = 8180 \pm 395 \text{ M}^{-1} \text{ cm}^{-1}$) in **5-b*** (see Supporting Information, Table 1). In contrast, the absorption maximum of **4**^[19] is similar to that of the tyrosine whose phenolic OH group in the ground state exhibits a pK_a value of about 10.^[3] Therefore, no shift in the UV spectrum of **4-b*** was observed in the examined pH range. Since the difference in molecular mass between **1** and **2**, **1** and **3**, (both 15 Da), **1** and **4**, and **1** and **5** (both 16 Da) is sufficiently large to be determined experimentally, mass spectrometry was used for quantitative analysis. While quantitative incorporation of both tryptophan analogues **2** and **3** in barstar was readily achieved (calcd: $M_r = 10298.2$; found: 10299 ± 2.0), the replacement level with the tryptophan analogues **4** and **5** never exceeded 80%. Although the parent protein could not be detected and globally substituted variants were the dominant forms (10300 ± 2.4 Da), contaminants with one 4-hydroxy- or 5-hydroxytryptophan (10269 ± 4.1 Da) and two 4-hydroxy- or 5-hydroxytryptophan residues (10285 ± 2.0 Da) were always present.

As expected, the UV properties of the tryptophan analogues **2–5** are fully reflected in the spectra of related barstar variants. In addition, the spectra of the **2-b*** and **3-b*** variants were found to be pH sensitive (Figure 3). The absorption profiles of **1-b***, **2-b***, and **3-b*** are very similar at pH 3.0 where protonation of the amino group leads to formation of a monocation. Conversely, at pH 7.0 and 9.0 the main absorption peak of **3-b*** is blue-shifted by almost 6 nm ($\lambda_{\text{max}} = 275$ nm) while the spectral shoulder is markedly red-shifted by 15 nm ($\lambda_{\text{max}} = 310$ nm) for **3-b*** (Figure 3). A similar trend, although weaker in its intensity, is observed for **2-b***. These changes may derive mainly from the increased basicity of the imino group in the indole moiety and, thus, from anion formation above pH 6. In fact, solution studies of 5-aminoindole revealed that a monoanion is formed by deprotonation of the indole imino group.^[17]

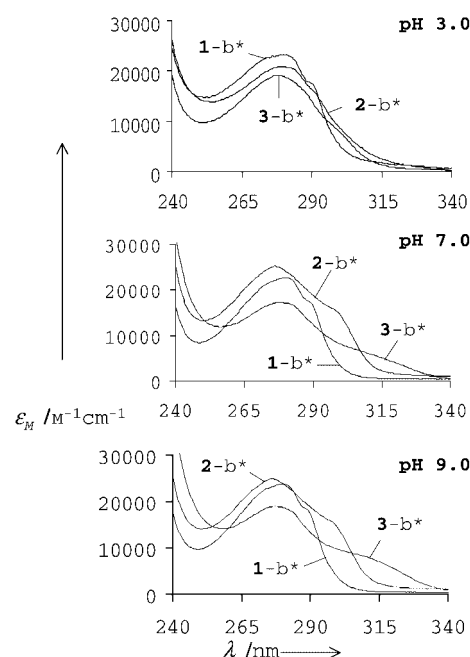


Figure 3. UV absorption spectra of **1-b*** and related variants **2-b*** and **3-b*** at different pH values. Note that under neutral and basic conditions a second prominent shoulder appears at 300 for **2-b*** and at 305 nm for **3-b***.

Both the UV spectrum and the fluorescence of indole is composed of the two overlapping transitions ^1L_a and ^1L_b that are nearly orthogonal in polarization.^[3] Similarly, the absorption profile of 5-aminoindole is a mixture of ^1L_a and ^1L_b bands, where the smaller absorption band (shoulder) at 285 nm derives from the transition of the ground to the ^1L_a state (long axis) and the main absorption, centred at 275 nm, derives from transition to the ^1L_b state (short axis). The amino group located along the longer axis (that is, at position 5) might perturb the ^1L_b state more than ^1L_a state. Therefore, the larger red shift observed for 5-aminoindole must be derived from the better delocalization of the nitrogen charge within the π cloud of the aromatic moiety than that of the oxygen atom of hydroxyindole. This is conceivable because the polarizability of the amino group is almost double that (1.44×10^{-24} mL per molecule) of the hydroxy group (0.733×10^{-24} mL per molecule),^[25] and clearly indicates a higher propensity of nitrogen electrons to be spatially distorted since they are much less tightly bound than oxygen electrons. Therefore, the observation that hydroxytryptophan- b^* variants **4-b*** and **5-b*** do not show significant changes in their absorbance properties in the pH range from 3.0 to 9.0 is not surprising. Correspondingly, the relative pH insensitivity of the **4-b*** and **5-b*** variants has to be attributed to the intrinsic spectroscopic properties of the hydroxytryptophan residues rather than to their protein environments—that is, the protein is only a carrier for the incorporated chromophores. Indeed, CD measurements revealed that secondary structures of the variant proteins are unchanged when compared to the **1-b*** protein variant in the pH range 6.0 to 9.0 where this protein is stable (unpublished data). Under acidic conditions ($> \text{pH } 4$) barstar is present in a molten globule form, while under stronger basic conditions ($< \text{pH } 10$) it is denatured.^[20]

It is also well known that the presence of electron-donating amino and hydroxy groups in different positions of the indole moiety leads to fluorescence spectra with two maxima at 350 and 520 nm.^[14–16] However, it is also known that the spectral properties of indoles are strongly dependent on the solvent polarity;^[3] for example, water acts as a proton donor in the S^0 state, while the intramolecular charge transfer from the amino group to the indole is most effective in the S^1 excited state.^[17] Therefore, the dramatic decrease in the relative fluorescence intensity of **2-b*** and **3-b***, compared to the native protein (Figure 4), can only be explained by interactions such as the hydrogen bonding of water molecules to the aminoindole in the S^1 state. This situation leads to enhanced rates of radiationless processes and explains the absence of the second fluorescence band in the related protein variants in aqueous buffered solutions as determined by steady-state fluorescence measurements. Indeed, the second band might be restored if such proteins are dissolved in suitable organic solvents, thus providing dual-fluorescence protein-based pH sensors in nonpolar media, such as membrane environments.

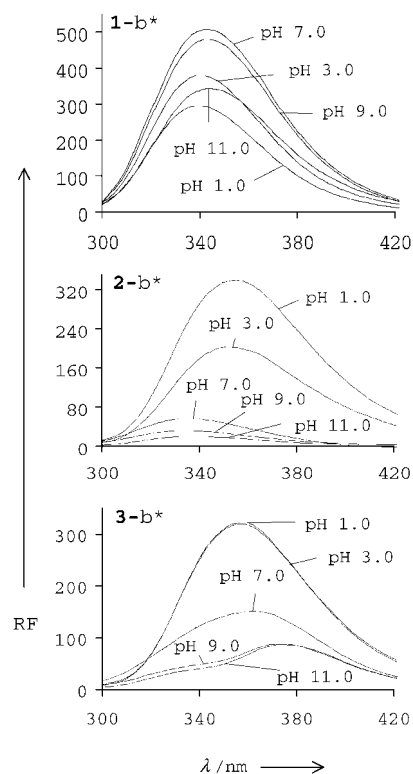


Figure 4. Effect of pH on the fluorescence emission profiles of **1-b***, **2-b***, and **3-b***.

Changes in the relative fluorescence intensity of the variants **1-b***, **4-b***, and **5-b*** are gradual and monotonic in the pH range studied (Figure 5). Only **4-b*** was found to exhibit remarkably decreased quantum yields, probably because of its high tendency towards aggregation. The lower

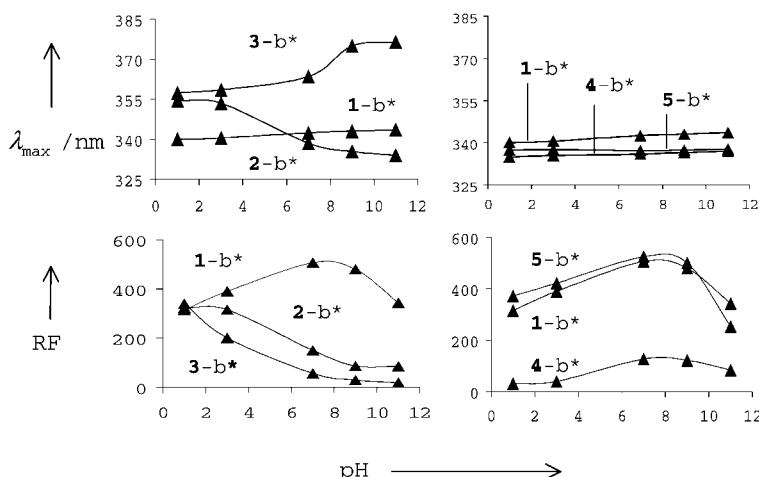


Figure 5. Plot of the variations in fluorescence emission maxima (λ_{max}) and relative intensities (RF) versus pH.

fluorescence intensity of these proteins under acidic conditions is the result of the transition of barstar to a molten-globule state below pH 4.0. Conversely, denaturing of barstar takes place under strongly basic conditions (pH > 10.0), and this accounts for the decreased fluorescence intensities in this pH range.^[20] On the other hand, the fluorescence intensities of **2-b*** and **3-b*** in the pH range 4.0 to 9.0 results in titration curves with significantly decreasing values of fluorescence at increasing pH values which reach a plateau at pH > 9.0 (Figures 4 and 5). Observed changes in the intensity of these substituted barstars show completely different trends than the **1-b***, **4-b***, and **5-b*** variants upon pH titration.

The position of the emission maxima at pH 3.0 is similar for **1-b***, **4-b***, and **5-b***, while for **2-b*** and **3-b*** it is red-shifted by 18 nm (Figures 4 and 5). The position of the emission maxima does not vary significantly at pH 7.0 and 9.0 for **1-b***, **4-b***, and **5-b***, while two different trends were observed for **2-b*** and **3-b***. A blue-shifted cooperative titration curve was obtained with a transition midpoint between pH 5 and 6 for the **2-b*** variant. Conversely, this cooperative transition of the emission maximum for **3-b*** is red-shifted with a transition midpoint at pH 8 (Figure 5). These large differences have to be assigned to the changes in the charge-density distributions along the indole aromatic ring which depend upon the nature, orientation, and position of the substituent in the parent indole molecule in a particular solvent. Taking this into account, the observed red shift for **3-b*** can be explained as follows: 5-aminoindole acts as a better proton donor than water in the S^1 state, that is, it is deprotonated to a greater extent in the excited state than is 4-aminoindole. Conversely, the blue shift measured for **2-b*** indicates there is a greater level of protonation in the 4-aminoindole in the excited state (that is, the solvent water molecules act as better proton donors than 4-aminoindole itself in the S^1 state). Clearly, the larger red shift is favored by the amino substituent being in position 5 of the indole (since it lays along the dipole transition moment) than in position 4, which is in full agreement with literature data on model compounds.^[3,16,17] Furthermore, the observed transition arises from an equilibrium between the ionized forms in the ground and excited states.

Such equilibrium is not only pH-dependent, but it also reflects the differences in the concentrations of corresponding species in the ground and excited states.

The pH sensitivity of the 2-b* and 3-b* variants, both in terms of fluorescence emission maximum and intensity, is the consequence of an intramolecular charge migration that originates solely from cation-to-anion transitions of the aminoindoles around pH 6. Thus, the conversion of barstar from a pH-insensitive to a pH-sensitive protein in terms of fluorescence is primarily the result of the intrinsic properties of the aminotryptophan analogues **2** and **3** integrated into the barstar structure. The multiple functions of tryptophan residues in proteins means it is indeed conceivable that proteins "tailored" with amino- and hydroxyindole or other indole-like side chains may represent useful non-invasive tools for in vivo or in vitro monitoring of protein folding as well as of protein-membrane, protein-protein, protein-ligand, and enzyme-substrate interactions. Protein variants in which tryptophan residues are globally replaced by related analogues with predefined spectral properties are readily accessible by the SPI methodology and could well offer an approach for the design of protein-based molecular sensors.

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L-alanine (L-HO₂CCHCH₃NH₂) and L-lysine (L-HO₂CCH-(CH₂)₄NH₂). These compounds can be represented by the general formula [XMo₆O₂₁(O₂CRNH₃)₃]ⁿ⁻ (*n* = 2, X = Se^{IV}, Te^{IV}; *n* = 3, X = As^{III}, Sb^{III}, Bi^{III}; R = CH₂, C₂H₄, C₃H₆, CHCH₃, CH(CH₂)₄NH₂). Polyanions **4**, **14**, and **18** are the first examples of chiral, functionalized heteropolymolybdates.

Polyanions **1–18** consist of a heteroatom X surrounded by a ring of six MoO₆ octahedra which alternately share edges and corners. Three amino acid molecules are each bound to two edge-sharing Mo centers by their carboxylate group on the same side of the ring (see Figures 1–4). The central heteroatom, located slightly above the plane of six molybdenum atoms, is coordinated to three μ₃-oxo groups which leads to a trigonal-pyramidal coordination geometry. The lone pair is on the same side of the ring as the amino acids.

The molybdenum–oxo framework of the title compounds has been seen before in the species **19–22**:

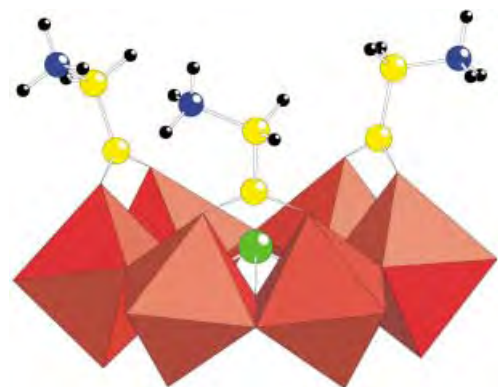
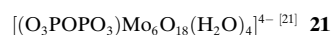
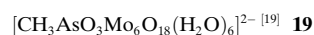


Figure 1. Combined polyhedral/ball and stick representation of **1**. The MoO₆ octahedra are shown in red and the balls represent selenium (green), carbon (yellow), nitrogen (blue), and hydrogen (black).

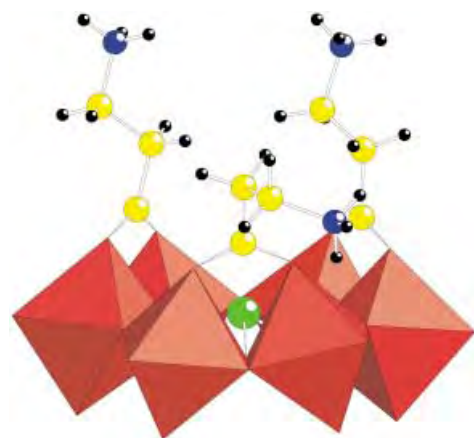


Figure 2. Combined polyhedral/ball and stick representation of **2**. The color code is the same as in Figure 1.

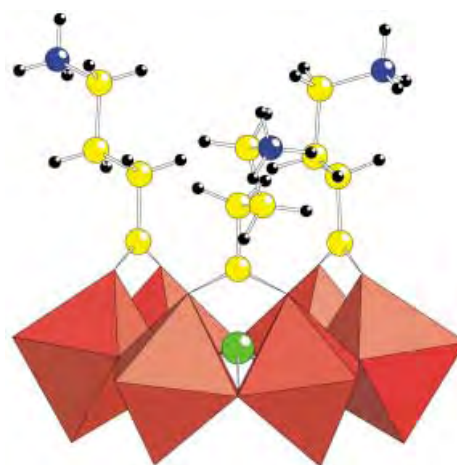


Figure 3. Combined polyhedral/ball and stick representation of **3**. The color code is the same as in Figure 1.

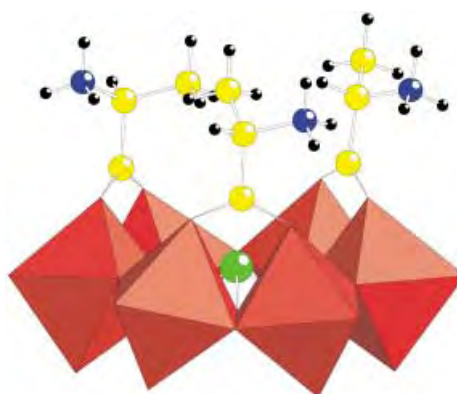


Figure 4. Combined polyhedral/ball and stick representation of **4**. The color code is the same as in Figure 1.

The new polyanions are synthesized by refluxing an aqueous solution containing sodium molybdate, heteroatom, amino acid, potassium chloride in the mole ratio 6:1.1:6:6 at pH 3.5 for 1 h.^[22] The yields range from 23–97%. Single crystals suitable for X-ray diffraction could be obtained for half of the compounds presented.^[23] The characterization of the remaining species is based on FTIR spectroscopy and elemental analysis.^[22]

In all the polyanions three amino acids are bound to the polyoxomolybdate framework by their carboxylate group. All species characterized by X-ray diffraction show complete protonation of the pendant amino groups, based on charge balance considerations. Therefore it can be concluded that glycine (**1**, **5**, **8**, **11**, **15**), β-alanine (**2**, **6**, **9**, **12**, **16**), 4-aminobutyric acid (**3**, **7**, **10**, **13**, **17**), L-alanine (**4**, **14**), and L-lysine (**18**) are bound as zwitterions. This is not a surprise keeping in mind that the pH value of the reaction mixture is 3.5, which is lower than the isoelectric point of the amino acids used (pH 6 for the neutral amino acids and pH 9.7 for L-lysine). Bond valence sum calculations did not indicate any protonation of the oxygen atoms bonded to the molybdenum atoms.^[24] Therefore, the negative charge of each polyanion corresponds to the charge of the XO₃ heterogroup (−2 for X = Se^{IV}, Te^{IV}; −3 for X = As^{III}, Sb^{III}, Bi^{III}), which is located in

the center of the metal–oxo framework. As a result **1–18** can be considered as “zwitteranions” and this property may be important for biological applications.

In addition to glycine, β -alanine, 4-aminobutyric acid, L-alanine, and L-lysine we investigated additional essential amino acids. It appears that some of them (e.g. L-asparagine) can also be bound to the title structure, but so far we have not been able to isolate pure products. Our studies allow us to conclude that it is more difficult to bind amino acids with bulky functional groups, most likely because of steric interactions.

Interestingly we observed little crystallographic disorder for the pendant alkyl amino groups of the amino acids. This is especially surprising for **3** and **7**, which contain 4-aminobutyric acid. A possible explanation involves the lone pair of the heterogroup, which seems to play an important structure-controlling role in all the polyanions. As a result, the three amino acids in each polyanion are orientated almost parallel to each other and perpendicular to the metal–oxo framework, this is especially true for the species with long alkyl groups (**3**, **7**, **10**, **13**, and **17**), which resemble a prawn with three legs.

To learn more about the solution properties of **1–18** we analyzed the freshly prepared polyanions by ^1H and ^{13}C NMR spectroscopy. We also measured the spectra of aqueous solutions of the redissolved salts of **1–18** as well as solutions of amino acids as references. However, we discovered that NMR spectroscopy did not allow us to distinguish free from bound amino acids. It is possible that binding of an amino acid to two molybdenum centers in **1–18** does not induce a detectable chemical-shift change for its hydrogen and carbon atoms. The hydrogen atoms on the α -carbon atoms should be most affected, but they are already four bonds away from the closest molybdenum atom. In addition, the bonds between molybdenum atoms and carboxylate oxygen atoms are weak (e.g. in **1**: $d_{\text{Mo-OC}} = 2.260\text{--}2.322(5)$). This observation indicates that in aqueous solution the amino acids are probably labile, which would lead to a relatively fast exchange of free and bound amino acids. We performed temperature-dependent NMR spectroscopy between 5–25 °C, but these studies did not allow us to draw additional conclusions.

Our work has shown that the structural type of the title polyanions can accommodate a variety of amino acids. Furthermore there appears to be variability related to the central heteroatom site. We were able to synthesize isostructural species although we changed the size of the heteroatom and its lone pair ($\text{As}^{\text{III}} < \text{Sb}^{\text{III}} < \text{Bi}^{\text{III}}$) as well as its charge ($\text{As}^{\text{III}}/\text{Sb}^{\text{III}}/\text{Bi}^{\text{III}}$ vs. $\text{Se}^{\text{IV}}/\text{Te}^{\text{IV}}$). Therefore, the open structural type of **1–18** is a rare example of a polyoxoanion family that can be easily and systematically derivatized at two different sites. In addition the terminal amino groups of the amino acids present sites for further functionalization.

Currently we are in the process of preparing additional derivatives of the title compounds, with an emphasis on phosphorus-containing species. A detailed investigation of the biological properties of the title polyanions is also underway and the results will be reported elsewhere.

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mission 0.634/0.756, 51123 reflections collected, 11056 independent reflections ($R_{\text{int}} = 0.056$), 8979 observed reflections with $I > 2\sigma(I)$, 308 parameters, max residual electron density 1.544 e Å⁻³, $R_1 = 0.040$, $wR_2 = 0.092$; K, Se, Mo, Cl refined anisotropically. $\text{K}_2[\text{Se}^{\text{IV}}\text{Mo}_6\text{O}_{21}(\text{O}_2\text{CCHCH}_3\text{NH}_3)_3] \cdot 4.5\text{H}_2\text{O}$: $0.30 \times 0.20 \times 0.10\text{ mm}^3$, orthorhombic, space group $P2_12_12_1$, $Z = 4$, $T = 293(2)\text{ K}$, $a = 11.2576(16)$, $b = 16.655(2)$, $c = 19.285(3)\text{ Å}$, $V = 3616.0(9)\text{ Å}^3$, $2\theta_{\text{max}} = 56.6^\circ$, $\rho_{\text{calcd}} = 2.587\text{ Mg m}^{-3}$, $\mu = 3.364\text{ mm}^{-1}$, min/max transmission 0.375/0.621, 40856 reflections collected, 8833 independent reflections ($R_{\text{int}} = 0.067$), 7967 observed reflections with $I > 2\sigma(I)$, 267 parameters, max residual electron density 1.316 e Å⁻³, $R_1 = 0.038$, $wR_2 = 0.097$; K, Se, Mo refined anisotropically. $\text{K}_2[\text{Te}^{\text{IV}}\text{Mo}_6\text{O}_{21}(\text{O}_2\text{CCH}_2\text{NH}_3)_3] \cdot 8\text{H}_2\text{O}$: $0.30 \times 0.14 \times 0.10\text{ mm}^3$, orthorhombic, space group $Pnma$, $Z = 4$, $T = 173(2)\text{ K}$, $a = 13.9561(18)$, $b = 20.805(3)$, $c = 12.3770(16)\text{ Å}$, $V = 3593.7(8)\text{ Å}^3$, $2\theta_{\text{max}} = 56.6^\circ$, $\rho_{\text{calcd}} = 2.709\text{ Mg m}^{-3}$, $\mu = 3.176\text{ mm}^{-1}$, min/max transmission 0.596/0.719, 39150 reflections collected, 4557 independent reflections ($R_{\text{int}} = 0.051$), 4156 observed reflections with $I > 2\sigma(I)$, 144 parameters, max residual electron density 1.663 e Å⁻³, $R_1 = 0.057$, $wR_2 = 0.132$; K, Te, Mo refined anisotropically. $\text{K}(\text{H}_3\text{N}(\text{CH}_2)_2\text{COOH})[\text{Te}^{\text{IV}}\text{Mo}_6\text{O}_{21}(\text{O}_2\text{C}(\text{CH}_2)_2\text{NH}_3)_3] \cdot 3\text{H}_2\text{O}$: $0.20 \times 0.16 \times 0.08\text{ mm}^3$, monoclinic, space group $P2_1/c$, $Z = 4$, $T = 173(2)\text{ K}$, $a = 10.7020(14)$, $b = 20.831(3)$, $c = 16.771(2)\text{ Å}$, $\beta = 97.527(2)^\circ$, $V = 3706.6(9)\text{ Å}^3$, $2\theta_{\text{max}} = 56.7^\circ$, $\rho_{\text{calcd}} = 2.657\text{ Mg m}^{-3}$, $\mu = 2.966\text{ mm}^{-1}$, min/max transmission 0.634/0.704, 42108 reflections collected, 9096 independent reflections ($R_{\text{int}} = 0.062$), 6903 observed reflections with $I > 2\sigma(I)$, 265 parameters, max residual electron density 1.660 e Å⁻³, $R_1 = 0.043$, $wR_2 = 0.090$; K, Te, Mo refined anisotropically. $\text{Cs}_2[\text{Te}^{\text{IV}}\text{Mo}_6\text{O}_{21}(\text{O}_2\text{C}(\text{CH}_2)_2\text{NH}_3)_3] \cdot 5.25\text{H}_2\text{O}$: $0.18 \times 0.16 \times 0.10\text{ mm}^3$, monoclinic, space group $P2_1/n$, $Z = 4$, $T = 293(2)\text{ K}$, $a = 11.3740(16)$, $b = 22.231(3)$, $c = 16.887(2)\text{ Å}$, $\beta = 102.535(2)^\circ$, $V = 4168.3(10)\text{ Å}^3$, $2\theta_{\text{max}} = 56.7^\circ$, $\rho_{\text{calcd}} = 2.697\text{ Mg m}^{-3}$, $\mu = 4.259\text{ mm}^{-1}$, min/max transmission 0.507/0.612, 46889 reflections collected, 10230 independent reflections ($R_{\text{int}} = 0.051$), 8117 observed reflections with $I > 2\sigma(I)$, 282 parameters, max residual electron density 1.471 e Å⁻³, $R_1 = 0.039$, $wR_2 = 0.086$; Cs, Te, Mo refined anisotropically. $\text{K}_2\text{Na}[\text{As}^{\text{III}}\text{Mo}_6\text{O}_{21}(\text{O}_2\text{CCH}_2\text{NH}_3)_3] \cdot 6\text{H}_2\text{O} \cdot 0.5\text{Cl}$: $0.22 \times 0.06 \times 0.04\text{ mm}^3$, monoclinic, space group $P2_1$, $Z = 2$, $T = 173(2)\text{ K}$, $a = 11.7166(17)$, $b = 13.753(2)$, $c = 11.8154(17)\text{ Å}$, $\beta = 115.121(2)^\circ$, $V = 1723.8(4)\text{ Å}^3$, $2\theta_{\text{max}} = 56.8^\circ$, $\rho_{\text{calcd}} = 2.749\text{ Mg m}^{-3}$, $\mu = 3.479\text{ mm}^{-1}$, min/max transmission 0.636/0.856, 20056 reflections collected, 7708 independent reflections ($R_{\text{int}} = 0.076$), 6330 observed reflections with $I > 2\sigma(I)$, 277 parameters, max residual electron density 1.320 e Å⁻³, $R_1 = 0.050$, $wR_2 = 0.102$; K, Na, As, Mo, Cl refined anisotropically. $\text{K}_{2.5}\text{Na}[\text{Sb}^{\text{III}}\text{Mo}_6\text{O}_{21}(\text{O}_2\text{CCH}_2\text{NH}_3)_3] \cdot 6\text{H}_2\text{O} \cdot 0.5\text{Cl}$: $0.10 \times 0.08 \times 0.02\text{ mm}^3$, monoclinic, space group $P2_1$, $Z = 2$, $T = 173(2)\text{ K}$, $a = 11.7166(17)$, $b = 13.753(2)$, $c = 11.8154(17)\text{ Å}$, $\beta = 115.121(2)^\circ$, $V = 1723.8(4)\text{ Å}^3$, $2\theta_{\text{max}} = 56.8^\circ$, $\rho_{\text{calcd}} = 2.877\text{ Mg m}^{-3}$, $\mu = 3.354\text{ mm}^{-1}$, min/max transmission 0.705/0.819, 20076 reflections collected, 8344 independent reflections ($R_{\text{int}} = 0.068$), 6870 observed reflections with $I > 2\sigma(I)$, 277 parameters, max residual electron density 1.682 e Å⁻³, $R_1 = 0.051$, $wR_2 = 0.097$. K, Na, Sb, Mo, Cl refined anisotropically. CCDC-190479–190487 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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Preparation and Characterization of a Model Bimetallic Catalyst: Co–Pd Nanoparticles Supported on Al₂O₃**

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The development of well-defined model systems is an important precondition for studies aimed at an understanding of catalytic mechanisms at the microscopic level. In this context, the bridging of the so-called “materials gap”, that is the adjustment of the model systems to the complexity of real catalysts, is essential. Accordingly, in the case of supported metal catalysts, the focus has shifted from single crystals, which were studied in the beginning to understand adsorption and reaction on extended surfaces, to metal particles deposited on oxide supports.^[1,2] The latter systems allow the investigation of particle size effects as well as metal–support interactions, that is factors that can equally be decisive for the overall catalytic performance. Although some progress has been achieved in recent years in this field, the question remains how model systems for more complex systems can be prepared in a defined and reproducible manner.

Herein, we deal with this question for bimetallic catalysts. Such materials represent a highly interesting class of catalysts because one metal can tune and/or modify the catalytic properties of the other metal as the result of both ligand (electronic) and ensemble (structural) effects.^[3] Bimetallic Pd–Co particles, for example, have shown improved selectivity over pure Co particles in Fischer–Tropsch reactions.^[4–8] Since the conversion of natural resources into syngas (CO + H₂) and then to clean fuels through the Fischer–Tropsch reaction will likely become evermore important with changing supplies and environmental concerns,^[9] a detailed understanding of such effects by means of suitable model systems is needed.

Our approach is based on metal vapor deposition on a suitable oxide support under ultrahigh vacuum (UHV) conditions. For the present study, a thin alumina film grown on a metallic NiAl(110) substrate was used,^[10] which enabled us to apply scanning tunneling microscopy (STM) as well as temperature-programmed desorption (TPD) for the charac-

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terization of the samples. On this film, nanometer-sized Pd–Co particles were generated by sequentially depositing the two constituents onto this support. Inspired by earlier work by Henry and co-workers,^[11,12] different structures and compositions of the particles were obtained in a controllable way by taking advantage of the different nucleation and growth properties of the two metals.

This is demonstrated in Figure 1 by STM images taken after depositing Pd and Co alone and together on the film. In the case of pure Pd, the data show that the majority of Pd particles nucleate and grow at line defects of the support. As discussed in detail elsewhere, these line defects, which appear as protruding lines in the differentiated part of the image (upper left corner), are antiphase and reflection domain boundaries of the alumina film.^[13] Another point to note is the regular shape of the aggregates which suggests that they have a crystalline structure. Closer inspection shows that the sides and top are mainly formed by (111) faces.^[14] In contrast, pure Co preferentially nucleates at point defects on the alumina film.^[15,16] As can be inferred from the corresponding STM image, this results in both a higher particle density and a more homogeneous particle distribution on the surface. Unlike for Pd, there are no indications of crystalline order of the Co aggregates.

Let us now assume that Pd is deposited on a surface already covered by Co particles. Owing to the higher mobility of Pd on the surface, it will be trapped at Co particles before reaching the line defects. The STM image presented in Figure 1 essentially corroborates this expectation. The arrangement of particles found for this sequence strongly resembles that for pure Co, thus suggesting particles with a Co core and a Pd shell. If, on the other hand, Pd is deposited first, the less mobile Co atoms should partly cover the Pd crystallites and partly nucleate between them. The STM image indeed shows triangular and hexagonal crystallites as well as the large number of new small clusters between them.

In addition to these sequential deposition experiments, we also performed a codeposition experiment. The corresponding STM image (Figure 1, lower row, center) reveals a situation intermediate to the results of the sequential preparation. As the structure of these particles (alloy particles or core/shell structures) is presently unclear, they will not be considered in the following.

To verify the surface composition of our model systems, we performed temperature-programmed desorption experiments using CO as a probe molecule. In this context, it is important to know that CO prefers *different adsorption sites* on the two metals. On Pd, CO is bound preferentially to threefold hollow sites, followed by bridge sites, and finally atop sites.^[17,18] On Co the order is reversed: CO is bound preferentially to atop sites, followed by more highly coordinated sites.^[19,20]

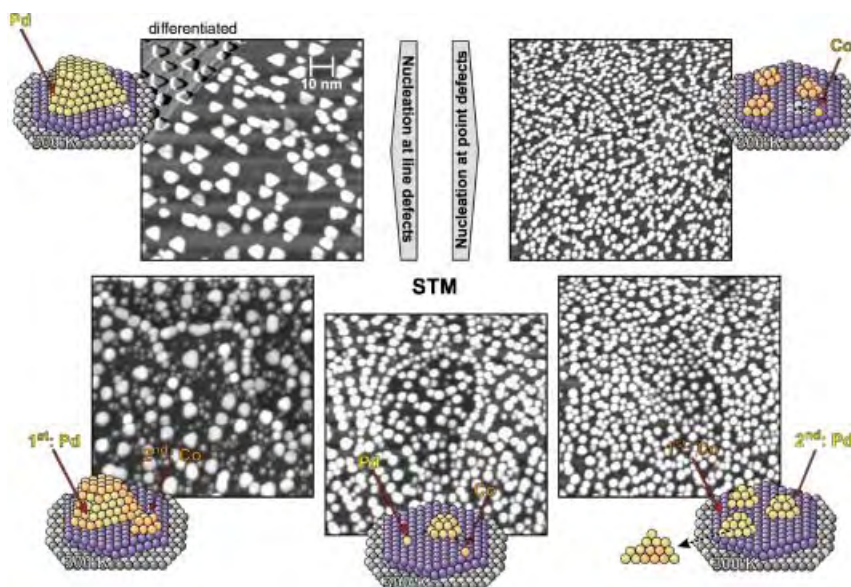


Figure 1. STM images (100 nm × 100 nm) taken after depositing 2 Å Pd and 2 Å Co alone (top row) and together (bottom row) onto a thin alumina film at 300 K. In the latter case the metals have either been deposited sequentially (left: 1st Pd, 2nd Co; right: 1st Co, 2nd Pd) or simultaneously (middle). The ball models schematically show the structure of the systems investigated: gray: NiAl substrate; blue: Al₂O₃ film; light blue: defects of the alumina film; yellow: Pd atoms; orange: Co atoms.

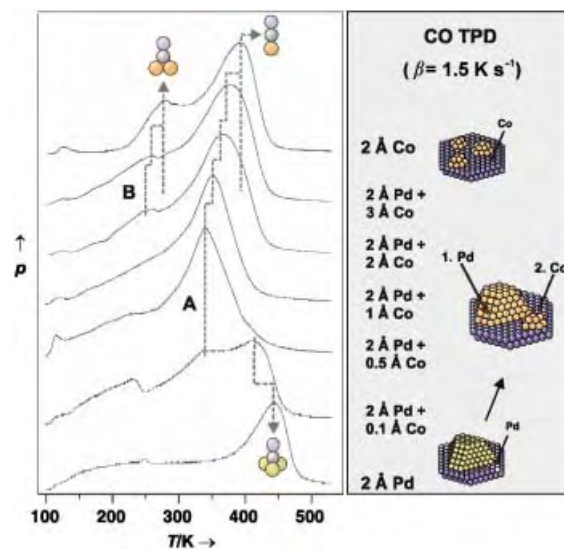


Figure 2. Temperature-programmed desorption spectra of CO from bimetallic Pd–Co particles supported on Al₂O₃/NiAl(110). The particles were prepared by depositing 2 Å Pd (1 Å Pd $\approx 6.8 \times 10^{14}$ cm⁻²) first and various amounts of Co subsequently. The spectra for pure Pd and Co particles are also shown for reference. An exposure of 20 L CO (1 L $\approx 10^{-6}$ Torr) was given at 100 K prior to TPD. The heating rate was 1.5 K s⁻¹. Color code for the models see Figure 1.

Two series of TPD spectra from the bimetallic particles are plotted in Figure 2 and 3 for the sequence 1st Pd/2nd Co and 1st Co/2nd Pd, respectively. The bottom spectrum of Figure 2 and the top spectrum of Figure 3 shows the desorption of CO from pure Pd. The main peak at about 450 K is due to desorption from threefold hollow sites, in agreement with data from Pd(111) single-crystal surfaces^[18] and with an IR spectroscopic study on metal particles.^[21] The broad shoulder

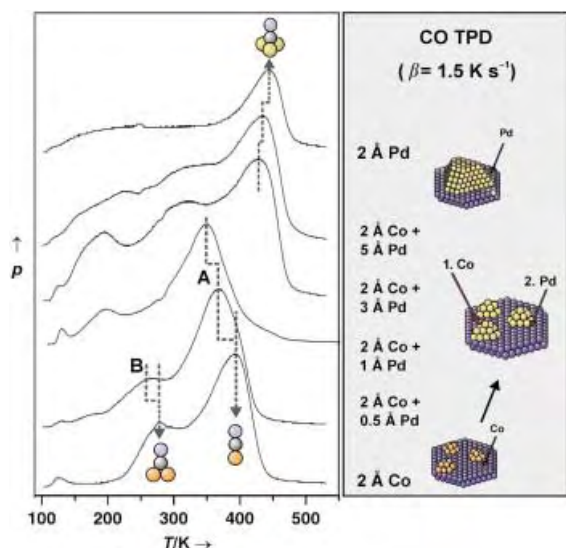


Figure 3. Temperature-programmed desorption spectra of CO from bimetallic Pd–Co particles supported on $\text{Al}_2\text{O}_3/\text{NiAl}(110)$. The particles were prepared by depositing 2 Å Co ($1 \text{ Å Co} \approx 9.0 \times 10^{14} \text{ cm}^{-2}$) first and various amounts of Pd subsequently. The spectra for pure Pd and Co particles are also shown for reference. An exposure of 20 L CO ($1 \text{ L} \approx 10^{-6} \text{ Torr s}$) was given at 100 K prior to TPD. The heating rate was 1.5 K s^{-1} . Color code for the models see Figure 1.

at lower temperatures most likely results from the gradual depopulation of bridge and atop sites. For pure Co particles (top spectrum of Figure 2 and bottom spectrum of Figure 3), we assign the desorption at about 390 K to atop sites and the shoulder at about 280 K to bridge sites, in analogy to literature data from single-crystal surfaces.^[20]

Turning to the bimetallic systems, for the deposition order 1st Pd/2nd Co it is interesting to note that small amounts of Co deposited onto a film covered by Pd particles result in large changes in the TPD spectrum. At the beginning of the deposition series, a significant lowering of the desorption temperature from Pd threefold hollow sites can be detected (ca. 25 K). Concomitantly, a new feature evolves at about 350 K, which becomes dominant with increasing Co coverage and finally suppresses the desorption from the Pd hollow site.

In principle, two effects can be responsible for the different adsorption and desorption behavior of an alloy as compared to the pure metals: electronic and structural effects.^[22,23] The first effect, also called ligand effect, is encountered if the interaction between an adsorbate and a particular adsorption site is modified by a second metal surrounding that site. Since bimetallic bonding generally weakens the strength of the Pd–CO bond,^[23] the downshift of the desorption maximum in the Pd spectrum can be readily explained by a ligand effect of Co covering the Pd crystallites. The second effect, called ensemble effect, is relevant only for highly coordinated sites, that is bridge or hollow sites. It is effective if one of the atoms constituting such a site is exchanged by the second metal so that the site is eliminated. As threefold hollow sites should be strongly affected by this effect, the early suppression of the corresponding peak in the Pd spectrum is not surprising.

With increasing Co coverage (Figure 2), the peak at 350 K shifts to higher temperatures until, at very high Co coverages, the desorption spectrum resembles that of pure Co. It is

therefore tempting to assign the peak, labeled **A** in the spectra (Figure 2), to the desorption of terminally bonded CO from Co atoms on the Pd crystallites. The shift can be explained by a decreasing ligand effect of Pd as the Co coverage increases. Also note the peak, labeled **B**, that points to Co bridge sites appearing later in the series due to the ensemble effect expected in this case.

So far only desorption from the Co-covered Pd crystallites has been considered. In the intermediate coverage regime, however, the broad desorption maximum with a clear contribution (shoulder) at higher temperatures reveals that, according to STM images (Figure 1), the small Co particles that form between the Pd crystallites are also detectable in the TPD spectra.

For the deposition order 1st Co, 2nd Pd the TPD experiments (Figure 3) corroborate the structure inferred from the STM results as well. Here, a new desorption peak from CO atop sites evolves at lower temperature (**A**), which can be assigned to Co particles partly covered by Pd. The shoulder at the original desorption temperature still visible in the first spectrum of the series apparently results from areas on the particles not covered at this stage. The shift of the maximum to lower temperatures induced by Pd can again be understood in terms of the ligand effect discussed above. As the Pd coverage increases and its electronic influence becomes stronger, the desorption shifts to even lower temperatures and the desorption from pure Co sites vanishes.

Finally, when a Pd shell completely covering the Co cores is formed, desorption from Pd threefold hollow sites is detected in the spectra. At a first glance, it might be surprising that relatively large amounts of Pd are needed to observe this site. Two reasons, however, can be responsible for that: 1) the strong ensemble effect expected for this site and 2) the smaller and less ordered particles as compared to the other deposition order (cf. Figure 1) which possibly offer less intact threefold hollow sites.

In conclusion, we have presented a method to prepare oxide-supported bimetallic Pd–Co nanoparticles by metal vapor deposition. By taking advantage of nucleation and growth processes on the surface, particles of different structure and composition can be obtained. CO TPD experiments corroborate the structures suggested by STM, revealing that both ensemble and ligand effects change the adsorption properties of these bimetallic model catalysts.

Experimental Section

The UHV system used in this study has been described in detail elsewhere.^[24] Briefly, it consists of a commercially built analysis chamber (Omicron) with an AFM/STM stage, as well as X-ray photoelectron spectroscopy (XPS) and low-energy electron diffraction (LEED) capabilities. Coupled to the analysis chamber by a transfer system is a preparation chamber containing Pd and Co metal evaporators, and facilities for sputtering, gas dosing, and TPD measurements. The flux of the metal evaporators was calibrated both with a quartz microbalance in a different chamber and checked by STM in the analysis chamber. To quantify the amount of material deposited, the nominal film thickness as measured by the microbalance is used in this article. The NiAl(110) crystal was cleaned by cycles of Ar^+ sputtering, and an Al_2O_3 film was prepared by previously described methods.^[10,13]

Before the TPD measurements, the sample was given a directed dose of CO at 100 K and then placed less than 1 mm away from the differentially

pumped cap of the quadrupole mass spectrometer. The sample was heated by radiation from a tungsten filament mounted directly behind it. A linear temperature ramp for TPD was programmed with a controller and power supply from Schlichting Physikalische Instrumente. The spectra were obtained by recording the temperature and the partial pressures of the species desorbing from the surface during such a ramp. Blank measurements from the oxide film without deposited metal particles showed desorption of small amounts of masses 2, 16, 18, 28, 32, and 44 below 150 K resulting from desorption from the heating filament (CO does not adsorb on the clean alumina film above 90 K^[13]); these signals were at least an order of magnitude smaller than those from the metal particles.

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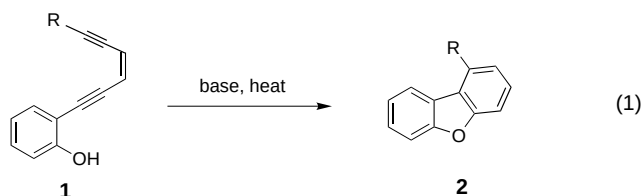
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A Route to 5-Substituted Dibenzofurans by Anionic Cycloaromatization of 2-(6-substituted 3-hexen-1,5-diynyl)phenyl *tert*-butyldimethyl ethers and Related Molecules**

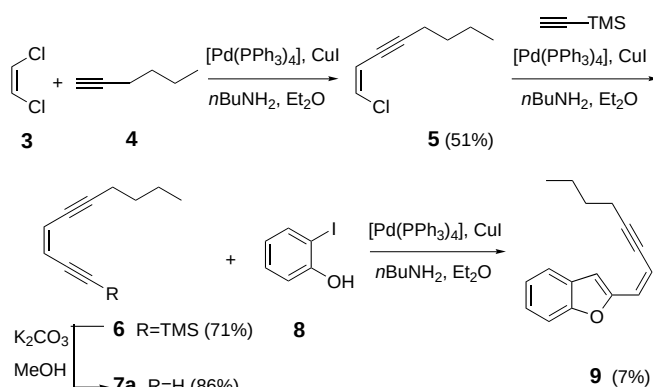
Ming-Jung Wu,* Chia-Ying Lee, and Chi-Fong Lin

It is well-known that in a certain period of the life cycle of lichens or living-plant wood tissues a number of unique antimicrobial compounds are produced. The production of such compounds is thought to be a result of the secondary metabolism or as a part of their dynamic defense systems.^[1] The biphenyl- or dibenzofuran-containing phytoalexins show manifold biological activities and have attracted much attention for chemical syntheses and biological studies.^[2]

The dibenzofuran skeletons were usually generated by an acid-catalyzed ring-closure reaction of 2,2'-dihydroxybiphenyl compounds^[3] or by cyclization of diaryl ethers with palladium.^[4] Recently, we reported the anionic cycloaromatization of enediynes promoted by nucleophilic addition to prepare a variety of aromatic compounds.^[5] We believe that 2-(6-substituted 3(*Z*)-hexen-1,5-diynyl)phenols (**1**) could undergo intramolecular anionic cycloaromatization to give dibenzofurans (**2**) under alkaline conditions. [Eq. (1)]

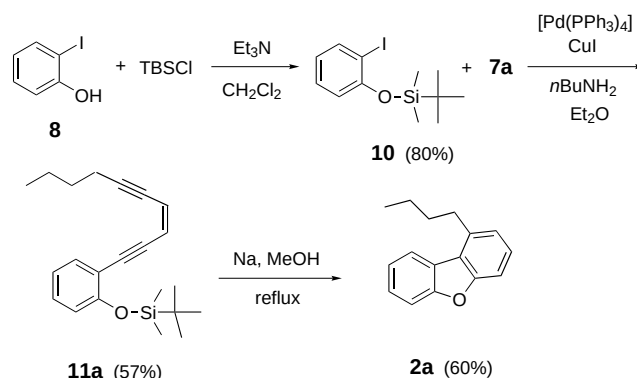


An attempt to synthesize compound **1** was carried out by using *cis*-1,2-dichloroethene (**3**; Scheme 1) as a starting material. The palladium-catalyzed coupling reaction of **3** with 1-hexyne (**4**) under Sonogashira reaction conditions^[6] gave the vinyl chloride **5** in 51% yield. Compound **5** was then coupled with trimethylsilylacetylene under the same reaction conditions to give the enediyne **6** in 71% yield. Desilylation of **6** was carried out by treatment of **6** with potassium carbonate in dry methanol to form **7a** in 86% yield. Finally, the enediyne **7a** was coupled with 2-iodophenol (**8**) using tetrakis(triphenylphosphane)palladium as a catalyst to give the benzofuran **9** in 7% yield and a recovered 50% yield of the starting phenol **8** (Scheme 1). The failure to obtain the desired 2-(3(*Z*)-decen-1,5-diynyl)phenol (**1a**) may be attributed to the acidic proton of the phenol, which could cause the acid-catalyzed cyclization to give the benzofuran **9** instead of the dibenzofuran **2a**.



Scheme 1. Synthesis of the benzofuran **9** from a dichloroethene precursor. TMS = trimethylsilyl.

We anticipated that the protection of the phenolic proton, following the treatment of the product with a base would allow us to synthesize dibenzofurans. Thus, 2-(3(*Z*)-decen-1,5-diynyl)phenyl *tert*-butyldimethylsilyl ether (**11a**; Scheme 2) was prepared by palladium-catalyzed coupling reaction of (*Z*)-3-decen-1,5-diyne (**7a**) with 2-iodophenyl *tert*-butyldimethylsilyl ether (**10**) in 57% yield. Treatment of compound **11a**



Scheme 2. Palladium-catalyzed coupling of **10** and **7a**, and subsequent cyclization of the product **11a** (see Table 1).

with sodium methoxide methanol heated under reflux for 16 h gave, after column chromatography, 5-butyldibenzofuran (**2a**) in 60% yield.

After the synthesis of dibenzofuran by the described method, we turned our attention to testing the generality of this cyclization reaction. Thus, various enediynylphenyl *tert*-butyldimethylsilyl ethers **11b–j** (Table 1) were prepared.^[7] Treatment of **11b–j** with sodium methoxide under the same reaction conditions gave compounds **2b–j** in 50–94% yields. Other reaction conditions have also been examined for this cyclization reaction to synthesize dibenzofurans. The results show that treatment of **11b** and **11e** with potassium carbonate in refluxing methanol gave the dibenzofurans **2b** and **2e**, respectively, in yields comparable to those obtained by Method A.

Compound **11k** was prepared from *p*-*tert*-butylphenol.^[8] Treatment of **11k** with sodium methoxide in refluxing

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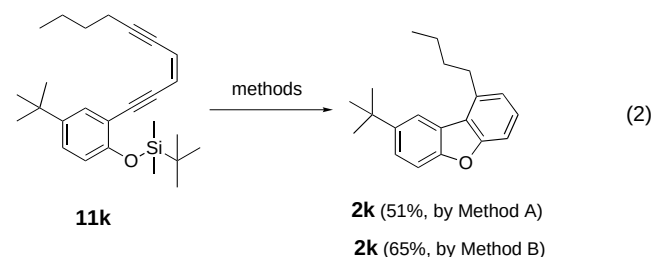
[**] We would like to thank the National Science Council of the Republic of China for financial support.

Table 1. Generation of 5-substituted dibenzofurans and related molecules.

Conditions			Yield
Method A: Na, MeOH			
X, X =	H, H	11b	R = C ₅ H ₁₁ 2b (56%)
		11c	R = C ₇ H ₁₅ 2c (50%)
		11d	R = C ₃ H ₆ OTHP 2d (57%)
X, X =		11e	R = C ₆ H ₅ 2e (93%)
		11f	R = C ₃ H ₁₁ 2f (94%)
		11g	R = C ₇ H ₁₅ 2g (92%)
		11h	R = C ₃ H ₆ OTHP 2h (91%)
X, X =		11i	R = C ₄ H ₉ 2i (75%)
		11j	R = C ₃ H ₁₁ 2j (75%)
Method B: K ₂ CO ₃ , MeOH			
		11b	2b (56%)
		11e	2e (93%)

THP = tetrahydropyran

methanol gave **2k** in 51 % yield. On the other hand, treatment of **11k** with potassium carbonate in refluxing methanol gave **2k** in 65 % yield. [Eq. (2)]



In conclusion, we have presented an efficient method for the synthesis of a series of 5-substituted dibenzofurans and related molecules in moderate to good yields by anionic cycloaromatization of enediynes.

Experimental Section

General procedure for methanolysis of **11** (Method A): Freshly cut sodium metal (5 mmol) was added to a solution of 2-(6-substituted 3(Z)-hexen-1,5-diynyl)phenyl *tert*-butyldimethylsilyl ethers (1 mmol) in 10 mL of methanol, the solution was heated to reflux and stirred for 16 h. After cooling to room temperature, the methanol was removed in vacuum. Saturated NaCl(aq.) was added to the residue, and extracted with EtOAc. The combined organic layer was dried over anhydrous MgSO₄(s). After filtration and removal of solvent, the residue was purified by column chromatography to give the separated products. Method B: The reaction conditions were the same as described in Method A, but the sodium was replaced with potassium carbonate (5 mmol).

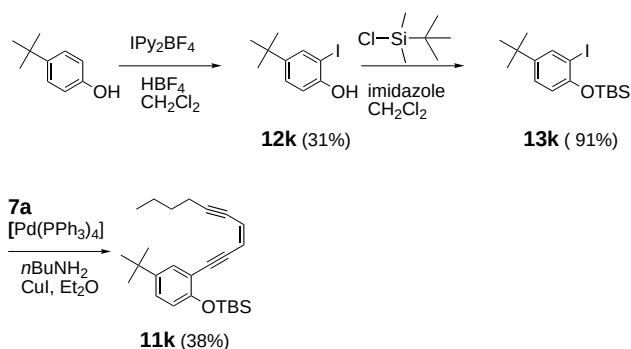
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- [7] Characterization data: **2a**: ¹H NMR (CDCl₃, 200 MHz): δ = 7.98 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.51–7.32 (m, 4H), 7.13 (dd, *J* = 6.6, 1.6 Hz, 1H), 3.15 (t, *J* = 7.4 Hz, 2H), 1.84–1.72 (m, 2H), 1.57–1.26 (m, 2H), 1.00 ppm (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 50 MHz): δ = 156.3, 156.0, 138.6, 126.9, 126.4, 124.3, 123.0, 122.6, 122.3, 122.2, 111.5, 109.0, 33.5, 31.9, 22.7, 14.0 ppm; HRMS (EI) calcd for C₁₆H₁₆O 224.1201, found 224.1207. **2b**: ¹H NMR (CDCl₃, 200 MHz): δ = 7.98 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.60 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.50–7.32 (m, 4H), 7.13 (dd, *J* = 7.0, 1.8 Hz, 1H), 3.13 (t, *J* = 7.6 Hz, 2H), 1.85–1.77 (m, 2H), 1.56–1.38 (m, 4H), 0.92 ppm (t, *J* = 7.6 Hz, 3H); ¹³C NMR (CDCl₃, 50 MHz): δ = 156.2, 156.0, 138.7, 126.9, 126.5, 124.6, 123.0, 122.6, 122.3, 122.1, 111.5, 109.1, 33.8, 31.9, 29.5, 22.6, 14.1 ppm; HRMS (EI) calcd for C₁₇H₁₈O 238.1358, found 238.1360. **2c**: ¹H NMR (CDCl₃, 200 MHz): δ = 8.01 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.63 (dd, *J* = 7.6 Hz, 1H), 7.56–7.41 (m, 2H), 7.32–7.21 (m, 2H), 4.61 (t, *J* = 3.2 Hz, 1H), 3.96–3.85 (m, 2H), 3.61–3.47 (m, 2H), 2.69 (t, *J* = 6.4 Hz, 2H), 2.04–1.84 (m, 2H), 1.75–1.48 ppm (m, 6H); ¹³C NMR (CDCl₃, 50 MHz): δ = 156.4, 156.0, 138.7, 126.9, 126.4, 124.3, 123.0, 122.6, 122.3, 122.2, 111.5, 109.0, 33.8, 31.9, 29.7, 29.6, 22.6, 21.0, 14.2 ppm; HRMS (EI) calcd for C₂₀H₂₂O₃ 310.1569, found 310.1570. **2d**: ¹H NMR (CDCl₃, 200 MHz): δ = 7.96 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.59 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.57–7.32 (m, 4H), 7.13 (dd, *J* = 7.6, 1.4 Hz, 1H), 3.13 (t, *J* = 7.6 Hz, 2H), 1.85–1.73 (m, 2H), 1.53–1.23 (m, 8H), 0.90 ppm (t, *J* = 7.8 Hz, 3H); HRMS (EI) calcd for C₁₉H₂₂O 266.1671, found 266.1672. **2e**: ¹H NMR (CDCl₃, 400 MHz): δ = 8.02 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.73 (d, *J* = 1.2 Hz, 1H), 7.62 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.55–7.51 (m, 2H), 7.36 (td, *J* = 8.0, 1.6 Hz, 1H), 7.31–7.22 (m, 3H), 2.57 (t, *J* = 6.8 Hz, 2H), 1.73–1.67 (m, 2H), 1.66–1.50 (m, 2H), 0.99 ppm (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ = 154.1, 154.0, 134.0, 131.1, 129.2, 127.6, 126.4, 124.5, 122.8, 120.5, 111.0, 105.4, 96.1, 80.5, 30.5, 22.0, 19.4, 13.6 ppm; HRMS (EI) calcd for C₂₀H₁₈O 274.1358, found 274.1346. **2f**: ¹H NMR (CDCl₃, 200 MHz): δ = 8.06 (dd, *J* = 7.0, 0.8 Hz, 1H), 7.78 (s, 1H), 7.67–7.54 (m, 3H), 7.46–7.23 (m, 4H), 2.58 (t, *J* = 7.0 Hz, 3H), 1.78–1.61 (m, 2H), 1.61–1.28 (m, 4H), 0.96 ppm (t, *J* = 7.4 Hz, 3H); ¹³C NMR (CDCl₃, 50 MHz): δ = 154.1, 154.0, 134.0, 131.1, 129.2, 127.7, 127.6, 126.4, 124.5, 122.7, 121.1, 120.5, 110.9, 105.4, 96.2, 80.5, 31.2, 28.2, 22.2, 19.8, 13.9 ppm; HRMS (EI) calcd for C₂₁H₂₀O 288.1515, found 288.1513. **2g**: ¹H NMR (CDCl₃, 200 MHz): δ = 8.03 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.75 (s, 1H), 7.74–7.52 (m, 4H), 7.44–7.21 (m, 4H), 2.56 (t, *J* = 7.0 Hz, 2H), 1.76–1.68 (m, 2H), 1.56–1.27 (m, 8H), 0.90 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 50 MHz): δ = 154.2, 154.1, 134.0, 131.1, 129.2, 127.8, 127.6, 126.4, 124.5, 122.7, 121.2, 120.6, 111.0, 105.4, 96.2, 80.5, 31.7, 29.0, 28.9, 28.5, 22.6, 19.8, 14.0 ppm; HRMS (EI) calcd for C₂₃H₂₄O 316.1828, found 316.1823. **2h**: ¹H NMR (CDCl₃, 400 MHz): δ = 8.42 (dt, *J* = 8.0, 1.2 Hz, 1H), 8.21 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.91 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.73 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.61–7.37 (m, 5H), 4.68 (t, *J* = 4.0 Hz, 1H),

3.98–3.91 (m, 2H), 3.60–3.53 (m, 2H), 3.40–3.35 (m, 2H), 2.21–2.14 (m, 2H), 1.93–1.57 ppm (m, 6H); ^{13}C NMR (CDCl_3 , 100 MHz): δ = 155.9, 152.2, 135.3, 133.0, 127.6, 126.1, 125.7, 125.5, 124.8, 122.9, 122.2, 121.9, 120.8, 120.0, 118.4, 111.7, 98.8, 66.8, 62.1, 30.9, 30.6, 29.6, 25.4, 19.5 ppm; HRMS (EI) calcd for $\text{C}_{24}\text{H}_{24}\text{O}_3$ 224.1201, found 224.1207. **2i**: ^1H NMR (CDCl_3 , 200 MHz): δ = 8.49 (s, 1H), 8.06 (s, 1H), 7.93–7.87 (m, 1H), 7.82 (s, 1H), 7.79–7.46 (m, 5H), 7.36–7.24 (m, 2H), 2.60 (t, J = 6.8 Hz, 2H), 1.77–1.37 (m, 4H), 1.00 ppm (t, J = 7.0 Hz, 3H); ^{13}C NMR (CDCl_3 , 50 MHz): δ = 154.5, 154.2, 134.0, 132.4, 132.3, 132.0, 131.3, 128.3, 127.9, 127.2, 127.1, 126.8, 126.8, 125.9, 124.6, 122.8, 121.2, 118.3, 110.9, 105.8, 30.6, 29.7, 19.5, 13.6 ppm; HRMS (EI) calcd for $\text{C}_{24}\text{H}_{20}\text{O}$ 324.1515, found 324.1512. **2j**: ^1H NMR (CDCl_3 , 200 MHz): δ = 8.50 (s, 1H), 8.07 (s, 1H), 7.84 (s, 1H), 7.80–7.29 (m, 8H), 2.60 (t, J = 6.8 Hz, 2H), 1.83–1.22 (m, 6H), 0.95 (t, J = 6.8 Hz, 3H); ^{13}C NMR (CDCl_3 , 50 MHz): δ = 154.3, 154.1, 134.1, 132.4, 132.3, 132.0, 131.4, 128.3, 127.3, 127.1, 126.9, 126.8, 126.5, 125.8, 124.6, 122.8, 121.2, 119.0, 111.0, 105.8, 31.3, 29.6, 22.3, 19.8, 14.0 ppm; HRMS (EI) calcd for $\text{C}_{25}\text{H}_{22}\text{O}$ 338.1671, found 338.1667. **2k**: ^1H NMR (CDCl_3 , 200 MHz): δ = 7.99 (t, J = 1.2 Hz, 1H), 7.52 (d, J = 1.4 Hz, 2H), 7.44–7.31 (m, 2H), 7.11 (dd, J = 6.8, 1.4 Hz, 1H), 3.15 (t, J = 7.6 Hz, 2H), 1.89–1.74 (m, 2H), 1.65–1.50 (m, 2H), 1.45 (s, 9H), 1.03 ppm (t, J = 7.6 Hz, 3H); ^{13}C NMR (CDCl_3 , 50 MHz): δ = 156.7, 154.2, 145.6, 138.4, 126.6, 124.1, 123.9, 122.9, 122.5, 118.7, 110.7, 109.0, 34.7, 33.8, 32.0, 31.8, 22.9, 14.0 ppm; HRMS (EI) calcd for $\text{C}_{30}\text{H}_{24}\text{O}$ 280.1828, found 280.1816.

[8] Treatment of *p*-*tert*-butylphenol with bis(pyridium)iodonium(i)tetrafluoroborate (IPy_2BF_4) gave 2-iodo-4-*tert*-butylphenol in 31% yield. Compound **12k** was treated with *tert*-butyldimethylsilyl chloride using imidazole as a base to give **13k** in 91% yield. Finally, compound **13k**



was coupled with **7a** using palladium as a catalyst to give **11k** (TBS = *tert*-butyldimethylsilyl) in 38% yield.

The HfCl_4 -Mediated Diels–Alder Reaction of Furan**

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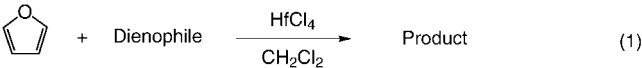
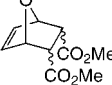
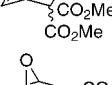
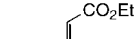
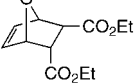
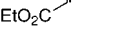
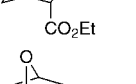
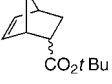
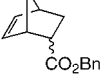
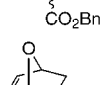
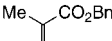
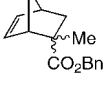
7-Oxabicyclo[2.2.1]hept-2-ene derivatives are useful intermediates for the synthesis of natural products such as carbohydrates and prostaglandins.^[1] One of the most straightforward methods for the construction of the 7-oxabicyclo[2.2.1]hept-2-ene skeleton is the Diels–Alder reaction between furan and appropriate dienophiles. However, the facile retro-Diels–Alder reaction and the low reactivity of furan as a diene, as a result of its aromatic character, make the Diels–Alder reaction of furan one of the most difficult cycloadditions.^[2] In addition to the use of highly reactive dienophiles in the Diels–Alder reaction,^[3] several methods have been developed to overcome these difficulties, such as the use of high pressure^[4] or Lewis acid mediated reactions.^[5] Although several Lewis acids have been reported to promote the reaction efficiently, there are problems in terms of generality. For example, $\text{BF}_3\cdot\text{OEt}_2$ is a good catalyst for methyl acrylate but a poor promoter for other dienophiles,^[5c] ZnI_2 is suitable for acrylonitrile but not for α,β -unsaturated esters,^[5a] while methyl vinyl ketone and acrylonitrile are activated by BiCl_3 .^[5i] Some Lewis acids supported on silica gel have also been utilized for the promotion of a particular dienophile with furan.^[5e,g,i,j] However, low *endo/exo* selectivity is generally obtained because of the facile retro-Diels–Alder reaction. Herein we report the *endo*-selective Diels–Alder reaction of furan with α,β -unsaturated esters catalyzed by HfCl_4 .

First, we looked for an appropriate Lewis acid using the reaction of furan and dimethyl maleate as a model and employing furan as the solvent (40 equiv). The reaction was performed in the presence of an equimolar amount of Lewis acid at room temperature for 15 h. Of the several Lewis acids screened,^[6] HfCl_4 was found to have suitable Lewis acidity to promote the Diels–Alder reaction in moderate yield (60%).^[7] Although most of the reported Lewis acids lose their Lewis acidity by coordination with furan, which acts as a Lewis base, HfCl_4 still activates α,β -unsaturated esters efficiently even in the presence of an excess amount of furan. Next, the use of a solvent was examined, and CH_2Cl_2 was found to be the best with respect to both yield and *endo/exo* selectivity.^[8] For example, the Diels–Alder reaction of dimethyl maleate and furan proceeds in CH_2Cl_2 at -20°C within 5 h to afford the cycloadduct in good yield (91%) and high diastereoselectivity

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Table 1. The Diels–Alder reaction of furan.^[a]

							
Entry	Dienophile	Product	Equiv of HfCl ₄	T [°C]	t [h]	Yield [%] ^[b]	endo/exo ^[c]
1			1.1	0	4	88	72/28
2			1.1	−20	5	91	93/7
3			1.1	−50	66	91	98/2
4			0.2	0	20	88	89/11
5			1.1	−20	7	84	–
6			1.1	−50	17	82	–
7			0.2	0	26	39	–
8			1.1	−50	25	84	69/31
9			1.1	−50	8	98	78/22
10			0.2	0	20	56	76/24
11			0.2	0	40	73	60/40
12			0.2	0	51	88	50/50
13			1.1	−10	48	34	18/82

[a] Furan/dienophile = 20/1. [b] Yield of isolated product. [c] The ratio (*endo*/*exo*) is determined by ¹H NMR analysis (400 MHz).

(*endo*/*exo* = 93/7; Table 1, entry 2). The effect of temperature on the yield and diastereoselectivity of the reaction is shown in entries 1–3. As the temperature is lowered, the diastereoselectivity increases, and very high *endo* selectivity (98/2) was attained when the reaction was conducted at −50 °C. This is only the second highly *endo*-selective Diels–Alder reaction of furan with a maleic acid derivative, the first being a reaction performed under high-pressure conditions,^[4a] and the present reaction is complimentary to the thermal Diels–Alder reaction of maleic anhydride and furan, which affords predominantly the thermodynamically stable *exo* isomer.^[3c]

The generality of this HfCl₄-mediated Diels–Alder reaction of furan with respect to dienophiles was investigated (Table 1). The reaction of diethyl fumarate proceeds smoothly at −20 °C to afford the Diels–Alder product in good yield (entry 5). The ester group has a large effect both on the yield and selectivity in the reaction of acrylate derivatives; the reaction of the benzyl ester is faster (8 h) and more selective (*endo*/*exo* = 78/22, entry 9) than that of the *tert*-butyl ester (25 h, *endo*/*exo* = 69/31, entry 8). Methyl methacrylate is not a reactive dienophile, and its Diels–Alder cycloadduct is formed in very low yield (8%), even under high-pressure conditions (15 kbar).^[4a] HfCl₄, however, accelerates the Diels–Alder reaction of benzyl methacrylate and furan to afford the cycloadduct in 34% yield, with the *exo* isomer predominating (entry 13). Though there is room for improvement of the yield, this is the first example of a Diels–Alder reaction of furan with a methacrylate derivative.

We found that HfCl₄ behaves as a true catalyst of this reaction. That is, when the reaction of furan and diethyl maleate was performed in the presence of only a catalytic amount (20 mol %) of HfCl₄, the reaction proceeded at 0 °C to afford the Diels–Alder adducts in good yield (88%), and with

high *endo*/*exo* selectivity (entry 4). On the other hand, fumarate ester is not a suitable substrate for the present reaction, with the Diels–Alder adducts being formed in low yield when the amount of HfCl₄ was reduced to 20 mol % (entry 7). The yield for the catalytic reaction using benzyl acrylate as the dienophile increased with increasing reaction time, while the diastereoselectivity decreased (entries 10–12). This observation can be attributed to thermodynamic equilibration in the presence of HfCl₄ at 0 °C in favor of the *exo* isomer. High *endo* selectivity in the reaction using an equimolar amount of HfCl₄ at low temperature can be achieved under kinetic control (Table 1, entry 9).

Next, substituted furans were employed in the Diels–Alder reaction (Table 2). Not only furan, but substituted furans also react efficiently with several dienophiles in the presence of both equimolar and catalytic amounts of HfCl₄. The higher HOMO levels of 2-methylfuran and 2,5-dimethylfuran relative to those of the parent furan means the reactions proceed much faster. Although a long reaction time (66 h) is necessary for the reaction of dimethyl maleate and furan at −50 °C in the presence of an equimolar amount of HfCl₄ (Table 1, entry 3), the reaction of the same dienophile with 2-methylfuran and with 2,5-dimethylfuran proceeds within 5 h at the same temperature with the same loading of the catalyst (Table 2, entries 1,3). High *endo* selectivity was attained in these reactions of dimethyl maleate (Table 2, entries 1–4). Diethyl fumarate also reacts with 2,5-dimethylfuran to give the cycloadduct in 81% yield (Table 2, entry 5). Benzyl acrylate also reacts with substituted furans to give the Diels–Alder products in good yield with moderate *endo* selectivity. Higher *endo*/*exo* selectivity was obtained in this reaction when a catalytic amount of HfCl₄ was employed, compared with that of the reaction using an equimolar amount of Lewis acid (Table 2, entries 6–9).

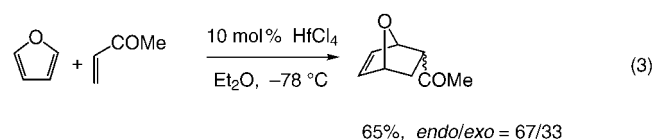
Table 2. The Diels–Alder reaction of substituted furan.^[a]

Entry	R	Dienophile	Product	Equiv of HfCl ₄	T [°C]	t [h]	Yield [%] ^[b]	endo/exo ^[c]
1	H			1.1	−50	5	82	> 98/2
2	H			0.2	−30	10	94	84/16
3	Me			1.1	−50	5	81	> 98/2
4	Me			0.2	−30	11	97	> 98/2
5	Me			1.1	−20	11	81	–
6	H			1.1	−50	4	85	69/31
7	H			0.2	−30	12	84	72/28
8	Me			1.1	−50	4	84	70/30
9	Me			0.2	−20	16	98	80/20

[a] Furan/dienophile = 20/1. [b] Yield of isolated product. [c] The ratio (*endo*/*exo*) is determined by ¹H NMR analysis (400 MHz).

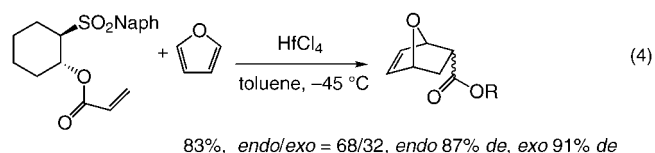
The regio- and stereochemistries of the Diels–Alder adducts of 2-methylfuran and benzyl acrylate (Table 2, entries 6, 7) were determined from NOESY spectra, and by conversion of the major isomer into the corresponding iodolactone.

Methyl vinyl ketone, however, did not afford the Diels–Alder product under the same reaction conditions, but instead gave 4-furyl-2-butanone as a major product. As this was reasoned to be generated by over-reaction of the initially formed Diels–Alder product, the reaction conditions were screened to reduce the Lewis acidity of HfCl₄. It was found that the Diels–Alder product was obtained in 65 % yield with moderate *endo*/*exo* selectivity (67/33) when a catalytic amount of HfCl₄ was employed at low temperature (−78 °C) for 17 h in Et₂O [Eq. (3)].



This HfCl₄-mediated Diels–Alder reaction was further applied to the diastereoselective reaction of a chiral dienophile, since the chiral 7-oxabicyclo[2.2.1]hept-5-ene derivatives obtained are important chiral building blocks for natural product synthesis.^[9] There are few successful examples of this kind of reaction, however, because of the easy reversibility of the reaction. For example, (1*R*,2*S*,5*R*)-8-phenylmenthyl acrylate,^[10] which is a widely used chiral dienophile in the carbo-Diels–Alder reaction, reacts at 25 °C over 24 h with furan in the presence of a catalyst of TiCl₄ supported on silica gel to afford the cycloadduct in 79 % yield with low to moderate selectivity (*endo*/*exo* = 33/67, *endo* = 33 % *de*, *exo* = 70 % *de*).^[9b] We applied our HfCl₄-mediated Diels–Alder reaction to the (−)-(1*R*,2*R*)-2-(naphthalene-2-sulfonyl)cyclohexyl acrylate developed by Sarakinos and Corey^[11] expecting to achieve a high diastereomeric excess because the high activity of HfCl₄ enables the reaction to proceed at low temperature under kinetic control. As expected, the Diels–Alder reaction [Eq. (4)] proceeds at low temperature (−45 °C) to afford the cycloadduct in good yield (83 %) with

high diastereomeric excess (*endo*/*exo* = 68/32, *endo* = 87 % *de*, *exo* = 91 % *de*). The absolute stereochemistry of the *en-*



do isomer was determined by comparison of its optical rotation with the literature value after conversion into the corresponding iodolactone.^[12] This highly diastereoselective Diels–Alder reaction is synthetically useful and practical, as demonstrated by our recent total synthesis of epoxyquinolins A and B from the *endo* isomer in high optical purity.^[13]

In summary the Diels–Alder reaction of furan is efficiently promoted by a catalytic amount of HfCl₄ to give cycloadducts in good yield with high *endo* selectivity. As HfCl₄ is an active Lewis acid catalyst, even in the presence of an excess amount of furan, the reaction proceeds at low temperature and prevents the usual *endo*/*exo* isomerization and gives high *endo* selectivity. This is a unique feature of HfCl₄ compared with the other Lewis acids,^[5] the Lewis acidity of which are reduced by the coordination with furan to give low yields and low *endo* selectivity. A wide range of reactive α,β -unsaturated esters and methyl vinyl ketone can be successfully employed as dienophiles in the HfCl₄-mediated reactions, and not only furan but substituted furans can also be employed as dienes, again with high *endo* selectivity, this not having been achieved by previous methods mediated by Lewis acids. The highly diastereoselective Diels–Alder reaction of a chiral acrylate has also been achieved.

Experimental Section

Typical procedure (Table 1, entry 4): Dimethyl maleate (80 μ L, 0.64 mmol) and freshly distilled furan (0.93 mL, 12.8 mmol) were added successively at 0 °C to a suspension of HfCl₄ (40.8 mg, 0.13 mmol) in CH₂Cl₂ (0.5 mL). After stirring the reaction mixture for 20 h at the same temperature, aqueous NaHCO₃ was added. After filtration of the inorganic materials, the organic materials were extracted with CHCl₃ ($\times$ 3) and the combined organic phase was dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel (ethyl

acetate/hexane = 1/10–1/1) gave 105.6 mg (78%) of the *endo* isomer and 13.1 mg (10%) of the *exo* isomer.

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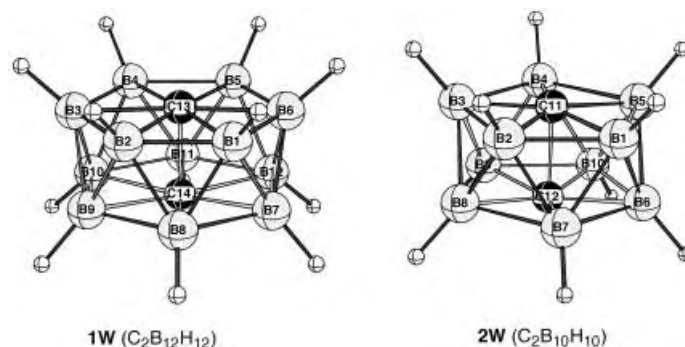
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Planar Hypercoordinate Carbons Joined: Wheel-Shaped Molecules with C–C Axles**

Zhi-Xiang Wang and Paul von Ragué Schleyer*

After two centuries of organic chemistry and the characterization of over 14 million carbon compounds with conventional bonding, our recent computational predictions of molecules with planar hexacoordinate^[1] and pentacoordinate carbon atoms^[2] has demonstrated that the bonding capabilities of this central element have not been exhausted. We now show computationally^[3] that the coordination of carbon can be raised to seven (or six) by the perpendicular extension of two planar hexacoordinate (or pentacoordinate) carbon atoms to form wheel-shaped (**W**) molecules (e.g. **1W** and **2W**, respectively).

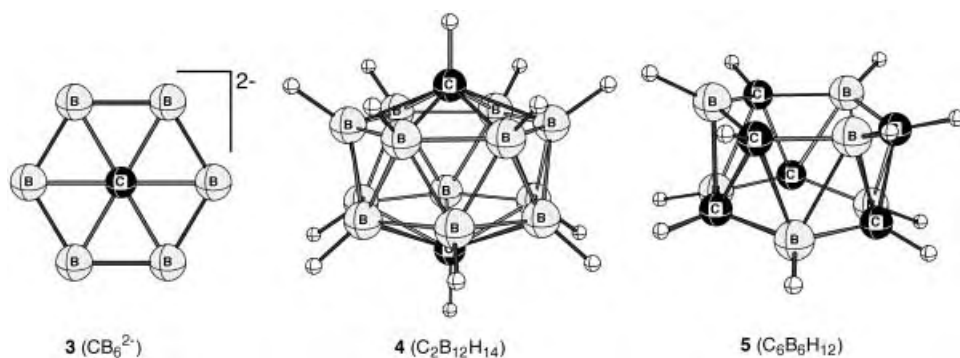


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There is an experimental precedent for our findings, but not involving carbon. The highly unusual geometry of the “nanowheel” $[\text{Al}_{14}(\text{NSiMe}_3)_2]_6\text{Li}(\text{OEt}_2)_2\text{Li}(\text{OEt}_2)_4\text{toluene}$ reported by Schnöckel et al.^[4] resembles **1W** structurally in having a “collapsed” polyhedron with “approximately Al-centered Al_6 rings”. This molecule and **1W** contain structural features found in species we have reported previously: the computed planar hexacoordinate carbon prototype, CB_6^{2-} (**3**, D_{6h}),^[1] the predicted but experimentally unknown *closo*- $\text{C}_2\text{B}_{12}\text{H}_{14}$ (**4**, D_{6d}),^[5] and the drum-shaped hexacarba-*arachno*-dodecarborane, $\text{C}_6\text{B}_6\text{H}_{12}$ (**5**, D_{3d}).^[6]



If the two hydrogen atoms linked to the apical carbons in **4** are removed, the two electrons remaining can form an extra axial bond inside the cages. This results in the “collapse” of the spherical structure of **4** and leads to **1W**. While lacking the C–C “axle” of **1W**, **5** has the same staggered skeletal structure. The 14-vertex $\text{C}_2\text{B}_{12}\text{H}_{12}$ (**1W**) can be viewed as a hydrogenated dimer of **3**; a C–C single bond joins two $\text{C}(\text{BH})_6$ moieties each of which possesses nearly planar hexacoordinate carbons. Within the $\text{C}(\text{BH})_6$ moieties of **1W**, the out-of-plane deviation angle, α (the C13–B1–B2–B3 dihedral angle, Table 1) is only 2.2° , and the C–B bond lengths are $1.817 \text{ \AA}$. The internal axial bond in **1W** is characterized by a short C–C separation ($1.597 \text{ \AA}$), which corresponds to a Wiberg C–C bond index (WBI)^[7] of 0.98 (compared to 1.04 for ethane), and by the nature of the HOMO (Figure 1). Similarly, removal of the two apical hydrogen atoms from *closo*-1,12- $\text{C}_2\text{B}_{10}\text{H}_{12}$ results in $\text{C}_2\text{B}_{10}\text{H}_{10}$ (**2W**), which possesses D_{5d} symmetry. In this structure, two nearly planar pentacoordinate carbons are joined. The angle, α , is 3.9° ; the C–B and C–C separations are $1.634 \text{ \AA}$ and $1.661 \text{ \AA}$, respectively, and the C–C WBI is 0.94 (Table 1). Excluding the electron pair required for axial C–C bonding, **1W** and **2W** have the same skeletal electron pair count as the regular fourteen and twelve vertex *closo* boranes and carboranes. Hence, Wade’s “*closo*” rule^[8] is still followed.

If, after removal of the two hydrogen atoms in **4**, the two electrons remain located on the carbon atoms (at least formally), the cages retain the regular polyhedral (**P**) shapes in the singlet biradical (**PS**) or in the triplet (**PT**) states. Both **1PS** and **2PS** are minima with long C–C separations, small WBIs (Table 1), and have nonbonding HOMOs (Figure 1). They do not follow Wade’s *closo* rule if the two diradical electrons are added to the skeletal electron pair count.

The less favorable electronic structures of **1PS** and **2PS**, when compared with **1W** and **2W**, are also characterized by smaller HOMO–LUMO gaps (in eV): 3.7 for **1PS** and 4.0 for **2PS** versus 6.2 for **1W** and 7.1 for **2W**. The triplets are discussed below.

The C–C axial bonding in **1W** and **2W** favors the wheel-shaped forms, but also leads to an increase in strain because of cage expansion and planarization of the carbon arrangements. The competition between the stabilizing axial bonding and destabilizing strain effects determines whether a **W** or a **P** isomer is favored. While **1W** is $18.2 \text{ kcal mol}^{-1}$ more stable

than **1PS**, **2W** is $61.0 \text{ kcal mol}^{-1}$ less stable than **2PS**. Electronegative substituents can increase the relative stability of **W** over **P** isomers decisively. Highly σ -electron-withdrawing fluorine atoms weaken the cage bonding of the perfluorinated **W** forms and thus decrease the cage deformation strain. Indeed, the 14-vertex $\text{C}_2\text{B}_{12}\text{F}_{12}$ only has a wheel-shaped minimum, **8W**. In complete contrast to $\text{C}_2\text{B}_{10}\text{H}_{10}$ (**2W** and **2P**), the 12-vertex $\text{C}_2\text{B}_{10}\text{F}_{10}$ (**9W**) is ac-

Table 1. Interatomic distances R [$\text{\AA}$] between apical atoms and their deviation angles (see text for definition) out of the face planes α [$^\circ$], number of imaginary (NIMG) frequencies, energy differences between wheel-shaped (**W**), polyhedral singlet (**PS**), and triplet (**PT**) isomers ΔE [kcal mol^{-1}], and Wiberg bond indexes (WBIs) between apical atoms.

		R ^[a]	α	NIMG ^[b]	ΔE ^[c]	WBI
$\text{C}_2\text{B}_{12}\text{H}_{12}$	1W ^[d]	1.597	2.2	0(119)	0.0	0.98
	1PS	2.709	21.7	0(95)	18.2	0.01
	1PT	2.670	21.2	0(112)	17.1	
$\text{C}_2\text{B}_{10}\text{H}_{10}$	2W	1.661	3.9	0(352)	0.0	0.94
	2PS	2.916	29.5	0(398)	−61.0	0.17
	2PT	2.859	28.7	0(431)	−50.9	
$\text{C}_2\text{Al}_{12}\text{H}_{12}$	6W	1.421	−9.7	8(231i)		1.47
	7W	1.568	−9.2	0(44)	0.0	1.09
	7PT	3.464	16.6	2(61i)	93.5	
$\text{C}_2\text{B}_{12}\text{F}_{12}$	8W	1.576	2.5	0(28)	0.0	0.96
	8PT	2.603	28.3	0(46)	46.3	
$\text{C}_2\text{B}_{10}\text{F}_{10}$	9W	1.667	5.0	0(118)	0.0	0.87
	9PS	2.833	27.9	0(138)	3.6	0.02
	9PT	2.829	27.8	0(118)	25.0	
$\text{B}_{14}\text{H}_{12}^{2-}$	10W	1.902	7.3	0(326)	0.0	0.81
	10PS	3.055	26.8	0(302)	−12.9	0.03
	10PT	3.008	26.1	0(315)	−12.8	
$\text{Al}_{14}\text{H}_{12}^{2-}$	11W	2.708	5.0	0(114)	0.0	0.75
	11PS	4.929	29.1	0(90)	10.2	0.17
	11PT	4.376	24.1	0(108)	12.7	
$\text{Si}_2\text{Al}_{12}\text{H}_{12}$	12W	2.420	2.2	0(85)	0.0	0.95
	12PT	3.798	18.3	2(67i)	34.4	
$\text{Ge}_2\text{Al}_{12}\text{H}_{12}$	13W	2.559	4.1	0(76)	0.0	0.94
	13PT	3.962	20.4	2(42)	25.1	
$\text{B}_{14}\text{F}_{12}^{2-}$	14W	1.990	9.1	0(123)	0.0	0.65
	14PT	2.893	25.4	0(129)	18.1	
$\text{Al}_{14}\text{F}_{12}^{2-}$	15W	2.801	6.0	0(68)	0.0	0.65
	15PT	4.227	21.9	0(40)	20.8	

[a] At $\text{R}(\text{U})\text{B3LYP}/6\text{-}311 + \text{G}^{**}$. [b] At $\text{R}(\text{U})\text{B3LYP}/6\text{-}31\text{G}^{**}$; the magnitudes of the of smallest frequencies are in parentheses. [c] At $\text{R}(\text{U})\text{B3LYP}/6\text{-}311 + \text{G}^{**} + \text{ZPE}$ ($\text{R}(\text{U})\text{B3LYP}/6\text{-}31\text{G}^{**}$). [d] All 14-vertex molecules have D_{6d} symmetry and 12-vertex systems have D_{3d} symmetry except for **5PT** (D_{2d}).

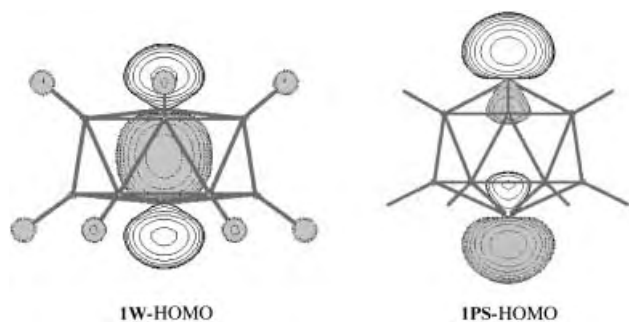


Figure 1. Comparison of the HOMOs of **1W** and **1PS**. Note the C–C bonding character of **1W**-HOMO and the biradical character of the **1PS**-HOMO.

tually 3.6 kcal mol^{−1} more stable than **9P**. The competition between central-atom bonding and cage strain is reflected in their isoelectronic analogues. While carbon atoms are “too small” to fit into an Al₆ ring (the 14-vertex **6W** has eight imaginary frequencies), the 12-vertex **7W** is a minimum containing concave hypercoordinate carbon atoms. Optimization starting with a polyhedral geometry of C₂Al₁₀H₁₀ collapsed into **7W**.

In the planar hexa- and pentacoordinate carbon molecules (for example, **3**), the carbon p_π orbital interacts with the ring π orbitals.^[1,2] The corresponding p_π orbitals of the central atoms of the wheel dimers interact with their counterparts on opposite faces. The central carbon atoms in **1W**, **2W**, **8W**, and **9W** have nearly planar hexa- or pentacoordination in addition to the additional axial bond perpendicular to the plane. This bond, together with the cage binding, stabilizes the unusual structures. The isolated ring fragments lacking such cage interactions, for example, C(BH)₆^{0,+2,-2} (*D*_{6h}), C(BF)₆^{0,+2,-2} (*D*_{6h}), C(BH)₅^{0,+2,-2} (*D*_{5h}), and C(BF)₅^{0,+2,-2} (*D*_{5h}) are higher order saddle points.

The removal of two hydrogen atoms from carboranes (for example, from **4**) leading to the **W** or **P** forms (which may be considered to be “bond-stretch isomers”) is similar to the 1,4-dehydrogenation of benzene that may lead to either butadiene (corresponding to our **W** forms) or to *p*-benzyne (corresponding to our **P** forms). The through-bond coupling^[9] interaction in *p*-benzyne also is present in **P** isomers. *p*-Benzyne and its derivatives, which are intermediates in the Bergman cyclization,^[10] are well known anti-tumor agents.^[11] Hydrogen abstraction by *p*-benzyne derivatives, generated from ene-diyne cyclizations, leads to the cleavage of DNA strands and to the death of tumor cells. The less stable polyhedral C₂B₁₂H₁₂ isomer (**1PS**, and its derivatives) of the more stable **1W** form, should behave similarly. The abstraction of a hydrogen atom from H₂ (as a computational model) by *p*-benzyne is exothermic by 4.0 kcal mol^{−1}. Hydrogen atom abstraction from H₂ by C₂B₁₂H₁₂ (**1PS**) is exothermic by 2.3 kcal mol^{−1}.^[12] Furthermore, the eventual hydrogen abstraction product (C₂B₁₂H₁₄) also has potential as a boron neutron capture therapy (BNCT) agent, of which polyhedral carborane or borane-based compounds are examples.^[13] Thus, derivatives might afford a two-pronged attack on malignant cells.

The same principles can be used to achieve planar hypercoordination for the B[−], Al[−], Si, and Ge analogues of carbon.

Considering the optimum central atom–ring “fit”, we located favorable congeners of **1** and **2** involving group 13 and heavier group 14 elements; Table 1 includes some examples, **10–15W** and **10–15PS**. Similar to the **PS** and **W** isomers of **1** and **2**, the two rings in both the **PS** and **W** isomers of **10–15** are more favorably bonded in staggered antiprismatic conformations. The electronic structures of **10–15W** also are similar and feature axial bonding between apical atoms, a short distance between the apical atoms, and WBIs in the 0.75–0.95 range (Table 1). As for **1** and **2**, the relative stability of **W** versus **PS** forms depends on the sizes of the apical atoms (that is, their covalent radii) in relation to the wheel radii. While **10W** is 12.9 kcal mol^{−1} less stable than **10PS**, **11W** is 10.2 kcal mol^{−1} more stable than **11PS**. On optimization, singlet **PS** starting geometries of Si₂Al₁₂H₁₂ and Ge₂Al₁₂H₁₂ collapsed into the wheel-shaped minima, **12W** and **13W**. As with **8W** and **9W**, electron-withdrawing substituents enhance the stability of the **W** forms over the **PS** forms. The **PS** starting geometries of B₁₄F₁₂^{2−} and Al₁₄F₁₂^{2−} collapsed into **W** isomers (**14W** and **15W**, respectively). Because B and Al atoms are too large to be incorporated into (BH)₅ and (AlH)₅ five-membered rings, respectively, the 12-vertex B₁₂H₁₀^{2−} and Al₁₂H₁₀^{2−} (both *D*_{5d}) only have **P** minima (not included in Table 1). Schnöckel’s [Al₁₄{(NSiMe₃)₂}₆I₆Li(OEt)₂][−][Li(OEt)₂]₄⁺·toluene nano-wheel^[4] is a derivative of **11W**, Al₁₄H₁₄^{2−}.

As mentioned above, the removal of two apical hydrogen atoms may result in a polyhedral biradical triplet (**PT**). For the species that have no **PS** minima (that is, **7** and **11–15**), **PT** triplets can be optimized in polyhedral geometries but are higher in energy than the corresponding **W** singlets (Table 1). For C₂B₁₂H₁₂ (**1**) and Al₁₄H₁₂^{2−} (**11**), the **PT** triplets and the **PS** singlets have nearly the same energies; all are less stable than the **W** forms (Table 1). The C₂B₁₀F₁₀ triplet, **9PT**, is 25.0 kcal mol^{−1} higher in energy than **9PS**. The triplets of B₁₄H₁₂^{2−} (**10PT**) and C₂B₁₀H₁₀ (**2PT**) are less stable than the **P** singlets but are more favorable than the singlet **W** forms.

We conclude that a family of “collapsed” polyhedral molecules is possible. These can contain hypercoordinated carbon atoms and other main group elements in unusual environments. Because cage substituents can help determine whether wheel-shaped or “bond-stretched” polyhedral isomers are more stable, it should be possible to control the properties of these species, for example, to adjust their “Bergman *p*-benzyne-like” capabilities.

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Rational Synthesis of Tetranuclear Ruthenium Polyhydride Clusters and Their Mixed-Ligand Analogues**

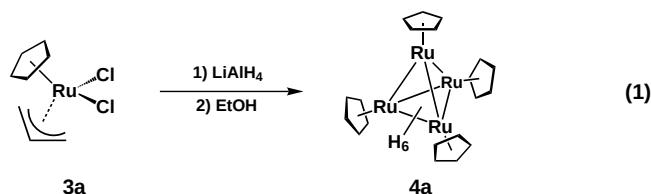
Yasuhiro Ohki, Naoki Uehara, and Hiroharu Suzuki*

The reactivity of transition-metal cluster complexes has recently been attracted considerable attention because of their potential applicability to organic synthesis.^[1] There have been a number of examples of unique reaction modes, such as successive cleavage of the carbon–hydrogen bond of alkanes,^[2] the cleavage of the carbon–carbon double bond of 1,1'-

disubstituted alkenes,^[3] and the catalytic hydrogenation of aromatic compounds in aqueous media,^[4] originating from the cooperative action of the metal centers. The advantageous properties of a multimetallic system over a monometallic one in the substrate activation step are its ability to *multiply coordinate* the substrate and the *multielectron transfer* between the substrate and the cluster. Such unique reactivity of the cluster likely comes from these two remarkable properties. The reactivity is most probably affected by the nuclearity of the cluster because the reactivity strongly depends on the number of transferable electrons: the more nuclei in the cluster, the more effectively electrons are transferred.^[5] It is well established for mononuclear transition-metal complexes that the auxiliary ligand allows control over the reactivity of the complex through electronic and steric perturbation of the reaction site. Thus, the development of a rational method for the synthesis of clusters with higher nuclearity and a variety of auxiliary ligands seems to be essential for the application of such clusters to organic synthesis.

Recently, we have established the high and unique reactivity of the di- and trinuclear ruthenium polyhydride complexes $[(\eta^5-C_5Me_5)Ru]_2(\mu-H)_4$ (**1**) and $[(\eta^5-C_5Me_5)Ru]_3(\mu-H)_3(\mu_3-H)_2$ (**2**).^[6] As an extension of the chemistry of “trimetallic activation”, we tackled the development of a rational method for the synthesis of a tetranuclear ruthenium polyhydride cluster. We report herein, to the best of our knowledge, the first example of a rational synthesis of a series of tetranuclear polyhydride complexes having several combinations of the auxiliary cyclopentadienyl ligands.

Treatment of $[CpRuCl_2(\eta^3-C_3H_5)]$ (**3a**)^[7] ($Cp = \eta^5-C_5H_5$) with $LiAlH_4$ in tetrahydrofuran followed by workup with ethanol [Eq. (1)] gave a new complex which was identified as the tetranuclear ruthenium hexahydride $[(CpRu)_4H_6]$ (**4a**) by ^1H and ^{13}C NMR spectroscopy and an X-ray diffraction study. In a similar manner, tetranuclear clusters $[(\eta^5-C_5H_4Me)Ru]_4H_6$ (**4b**) and $[(\eta^5-1,3-Me_2C_5H_3)Ru]_4H_6$ (**4c**) were derived from the corresponding Ru^{IV} precursors, $[(\eta^5-C_5H_4Me)RuCl_2(\eta^3-C_3H_5)]$ (**3b**) and $[(\eta^5-1,3-Me_2-C_5H_3)RuCl_2(\eta^3-C_3H_5)]$ (**3c**),^[8] respectively. Although the yields of **4a** and **4c** were not high (ca. 40%), the ^1H NMR spectra of the crude products obtained after removal of the aluminum salt showed that the tetranuclear hydride complexes **4a** and **4c** were formed exclusively. In the reaction of **3b** with $LiAlH_4$, however, the formation of **4b** was accompanied by a significant amount (ca. 40%) of the corresponding pentanuclear hydride complex, which was readily separated by column chromatography on alumina.



The ^1H NMR spectrum of the cluster **4a** exhibited two resonance signals assignable to Cp and hydride ligands at $\delta = 4.45$ ppm (20H) and $\delta = -8.59$ ppm (6H), respectively. The

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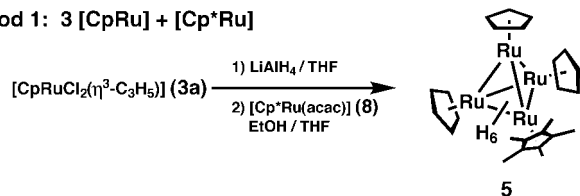
Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

inversion-recovery (T_1) measurement for the hydride resonance signal was performed at 400 MHz at various temperatures. The observed T_1 value of 319 ms at -80°C is deemed to be sufficient to characterize the complex as a classical metal hydride with no bonding interaction between the hydrogen atoms.^[9] This contrasts with the related hexahydride tetaruthenium cluster $[\text{H}_6\text{Ru}_4(\text{C}_6\text{H}_6)_4]^{2+}$, which has been identified to contain nonclassical hydride ligands on the basis of spectroscopic, crystallographic, and theoretical investigations.^[10] A significant upfield shift of the hydride signal is observed for **4a–c**; the signal moves further upfield as the number of methyl groups on the cyclopentadienyl ligand increases and is most probably due to the associated increase in the electron density at the metal center.

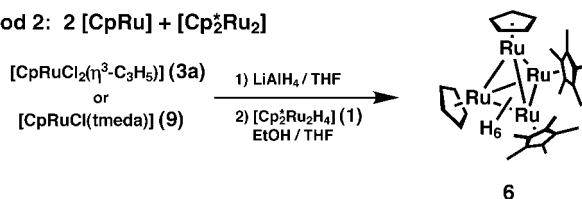
A series of tetranuclear ruthenium hexahydride complexes having several different combinations of the Cp (C_5H_5) and Cp* (C_5Me_5) ligands, were systematically synthesized as shown in Scheme 1.

When the LiAlH_4 adduct of **3a** was quenched with ethanol in the presence of 1/3 molar equivalent of the coordinatively unsaturated mononuclear complex **8**,^[11] the [3:1] mixed-ligand cluster $[\text{Cp}_3\text{Cp}^*\text{Ru}_4\text{H}_6]$ (**5**) was formed (Method 1, Scheme 1).

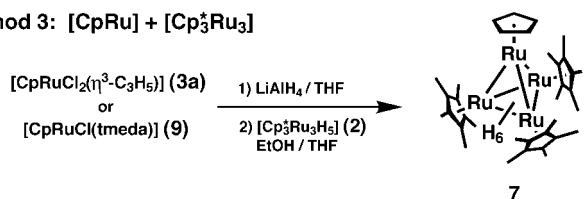
Method 1: 3 [CpRu] + [Cp*Ru]



Method 2: 2 [CpRu] + [Cp*₂Ru₂]



Method 3: [CpRu] + [Cp*₃Ru₃]



Scheme 1. Methods for synthesizing mixed-ligand complexes **5–7**.

The most important criterion for the synthesis of the mixed-ligand clusters is the stoichiometry of the precursors. The [2:2] mixed-ligand cluster that has two Cp and two Cp* ligands, $[\text{Cp}_2\text{Cp}^*\text{Ru}_4\text{H}_6]$ (**6**), was prepared by the reaction of two molar equivalents of the precursor of the “CpRu” fragment with **1** (Method 2, Scheme 1). Both **3a** and $[\text{CpRuCl}(\text{tmeda})]$ (**9**; tmeda = tetramethylethylenediamine)^[12] are applicable as the precursor of the “CpRu” fragment. In a similar manner the [1:3] mixed-ligand cluster was selectively synthesized by the reaction of the LiAlH_4 adduct of **3a** or **9** with an equimolar amount of **2** (Method 3, Scheme 1). The mixed-ligand clusters **5–7** were identified on the basis of the ^1H and ^{13}C NMR spectral data. The ^1H NMR spectra revealed the hydride ligands in **5–7** were equivalent in each complex, as observed for **4a–c**; this is probably due to the rapid exchange of their coordination sites. There is significant correlation between the chemical shifts for the hydride ligands in clusters **4–7** and the number of the methyl groups on the cyclopentadienyl ligands, $\delta = -8.59$ for **4a**, -8.69 for **4b**, -8.75 for **5**, -8.90 for **4c**, -8.94 for **6**, and -9.84 ppm for **7**. Thus, the electron density at the metal centers of the tetranuclear cluster complex is most probably controllable by changing the number of methyl groups on the C_5 rings.

The molecular structures of **4a–c**, **6**, and **7** were determined by X-ray diffraction studies (Figure 1).^[13] All of the clusters **4a–c**, **6**, and **7** adopt a pseudo-tetrahedral structure and the corresponding bond lengths within each of the clusters are similar. The six Ru–Ru bonds in **4a** are classified into two groups, namely, four long bonds (2.8952(4)–2.938(1) Å) and two short bonds (2.683(2), 2.6897(4) Å). The two short bonds Ru1–Ru2 and Ru3–Ru4 skew each other. The low-temperature analyses of **4a–c** allowed us to determine and refine the positions of the metal-bound hydrogen atoms. Four of the six hydride ligands triply bridge each of the Ru_3 faces; the other two hydride ligands bridge the two short Ru–Ru bonds (Figure 2). The presence of the bridging hydride ligands is likely responsible for the shortening of the two

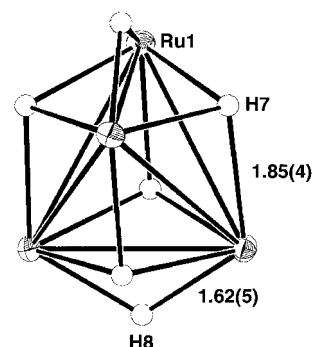


Figure 2. The Ru_4H_6 core of **4b**. $\text{C}_5\text{H}_4\text{Me}$ groups are omitted for clarity.

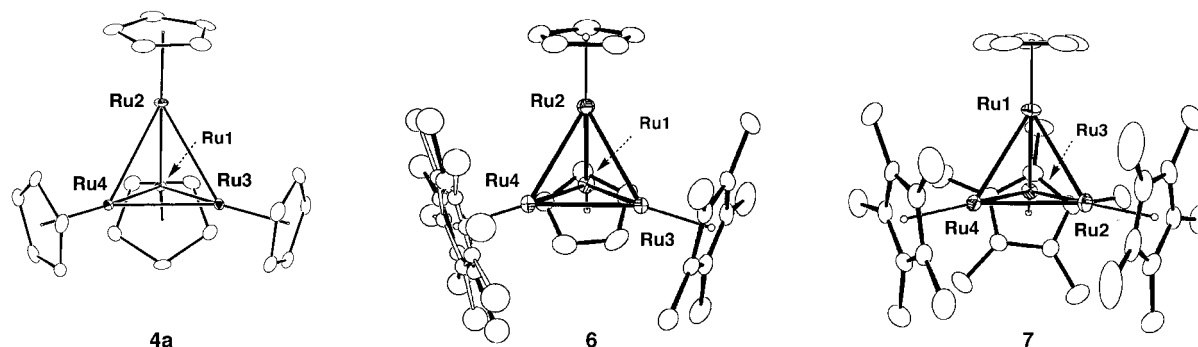


Figure 1. Molecular structures of **4a**, **6**, and **7**, with thermal ellipsoids at 30% probability level.

Ru–Ru bonds. Although the structural properties for **4a** are also common to the clusters **6** and **7**, the bond lengths of **6** and **7** are slightly elongated, probably due to the increased steric repulsion among the C₅R₅ (R = H or Me) ligands. The mean values of the distance between a ruthenium center and the centroid of the affiliated η⁵-C₅H₅ (Cp) ring are in the order of **4a** > **6** > **7**. This result suggests that the increase in electron density at the metal centers arising from the introduction of methyl groups into the Cp ring enhances the back donation from the ruthenium center to the Cp group.

We have developed the first rational synthesis of a series of tetranuclear polyhydride complexes containing several different combinations of auxiliary cyclopentadienyl ligands and demonstrated that the electron density at the metal centers and the size of the reaction site of the tetranuclear cluster complex is most probably controllable by changing the number of methyl groups on the C₅ rings.

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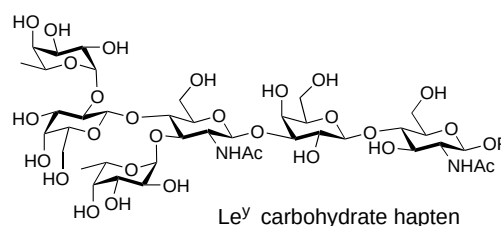
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crystal data: monoclinic, *P*₂₁/*n*, *a* = 18.217(5), *b* = 16.475(9), *c* = 9.772(6) Å, *β* = 90.87(3)°, *V* = 2932(3) Å³, *Z* = 4, *ρ*_{calcd} = 1.837 g cm^{–3}; 8976 reflections (6° ≤ 2θ ≤ 55°), 5691 observed with *F* > 2σ(*F*), 282 parameters; *R*₁ = 0.039, *wR*₂ = 0.108. X-ray structure analysis for **7**: Measurement performed on an AFC-7R four-circle diffractometer at –80°C; crystal data: monoclinic, *P*₂₁/*a*, *a* = 24.026(3), *b* = 16.699(2), *c* = 17.388(3) Å, *β* = 90.37(1)°, *V* = 6955(1) Å³, *Z* = 8, *ρ*_{calcd} = 1.683 g cm^{–3}; 16893 reflections (5° ≤ 2θ ≤ 60°), 10387 observed with *F* > 3σ(*F*), 703 parameters; *R* = 0.039, *R*_w = 0.043. CCDC-177793 (**4a**), CCDC-177794 (**4b**), CCDC-177795 (**4c**), CCDC-177796 (**6**), and CCDC-177797 (**7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Reactivity-Based One-Pot Synthesis of a Lewis Y Carbohydrate Hapten: A Colon–Rectal Cancer Antigen Determinant**

Kwok-Kong T. Mong and Chi-Huey Wong*

Lewis Y (Le^y) is part of a type 2 blood group antigen that carries a carbohydrate hapten containing two α-linked fucosyl moieties, one at the C-2 hydroxy group of the terminal galactose and the other at the C-3 hydroxy group of subterminal *N*-acetylglucosamine (Scheme 1).^[1] As a tumor-



Scheme 1. The structure of a Le^y carbohydrate hapten.

related glycoconjugate, it is expressed on the tumor cell surface in 96 % of colon–rectal adenocarcinoma and 46 % of hepatocellular carcinoma.^[2] Therefore, it is important to understand its pathological roles and to explore its antigenic properties to allow the development of cancer diagnostic and immunotherapeutic agents.^[3] Recently, the Le^y hapten has been synthesized by Danishefsky's group as part of a multi-antigenic glycopeptide to exploit its potential as a carbohydrate-based anticancer vaccine.^[4]

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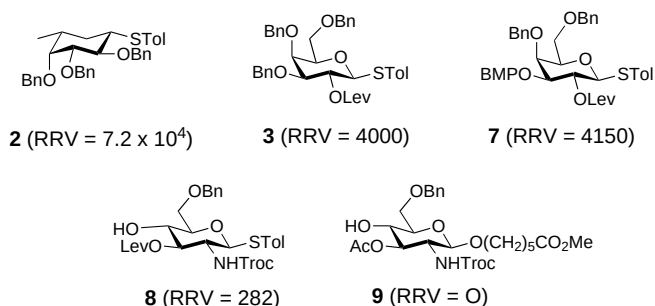
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The first synthesis of the Le^y hapten by Sinaÿ and Jacquinet involved the use of glycosyl orthoester and bromide donors.^[5] Schmidt et al. and Danishefsky et al. developed new syntheses using trichloroacetimidate and glycal methodologies.^[6] As part of our effort to develop automated programmable one-pot oligosaccharide synthesis without manipulation of protecting groups, we report here the design of building blocks with appropriate reactivity for use in the one-pot synthesis of the Le^y hapten.^[7,8] The special feature of this work lies in the integration of four glycosylation steps into one synthetic operation to furnish the target oligosaccharide in a few hours without any need for protecting group manipulation and intermediate isolation.

Reactivity-based one-pot synthesis is a newly developed strategy aimed at simplification of the complex synthetic procedures needed for oligosaccharide synthesis. It relies on the design, synthesis, and reactivity measurements of a large pool of thioglycoside building blocks to create a reactivity database. Based on this database and simple chemistry logic or computer software called "OptiMer",^[7] an appropriate combination of thioglycoside building blocks can be derived for any given oligosaccharide structure, and these building blocks can be used for the one-pot synthesis.

Retrosynthetic analysis of Le^y divided the hapten into three tentative units: a fucosyl, a dihydroxy bridging lactosaminyl, and a reducing end lactosaminyl unit (Scheme 2). To charge these units with different reactivity, different protecting groups were used based on the information derived from our current reactivity database.^[9] Simultaneously, orthogonal protection groups were required to provide potential acceptor sites for later glycosylation. Bearing this in mind, three functional building units **2**, **11**, and **13** were designed and synthesized. After consulting the reactivity database, a perbenzylated fucosyl thioglycoside was identified as our functional fucosyl donor **2** due to its high relative reactivity

value ($RRV = 7.2 \times 10^4$) and its preparation followed the literature procedure.^[7] The bridging lactosaminyl unit was prepared from the corresponding galactosyl unit **3** and glucosaminyl unit **8**, while the reducing end lactosaminyl units was synthesized from the galactosyl unit **7** and the glucosaminyl unit **9** (Scheme 3).

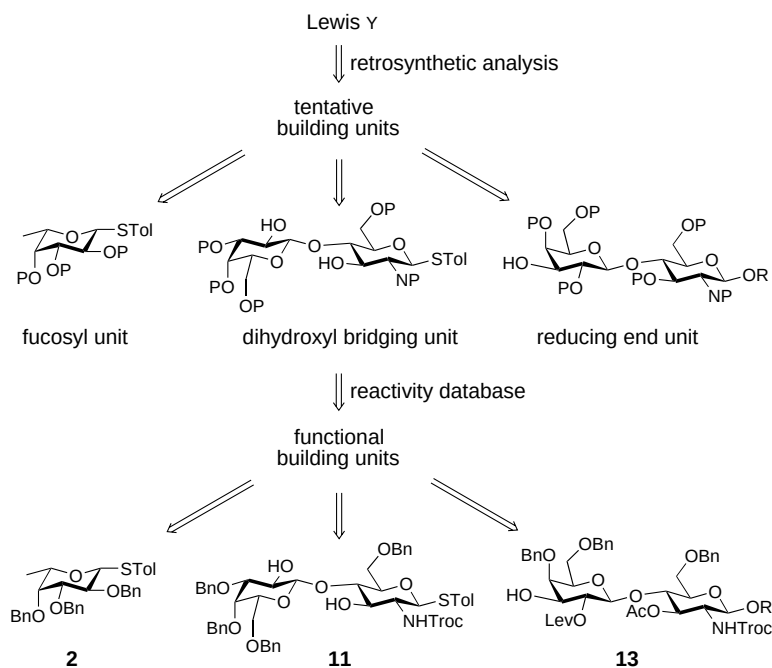


Scheme 3. Relative reactivity values (RRV) of functional building units **2**, **3**, and **7–9**.

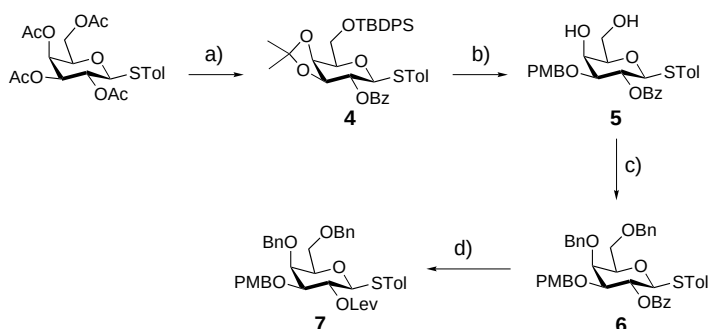
Building block **8** was chosen as the reducing end component of the bridging building block **11** because the reactivity of **11** was expected to be close to that of **8** based on the results of our previous study and should be an optimal building unit for coupling with the first donor **2** ($RRV = 7.2 \times 10^4$) in the planned one-pot operation.^[7] Galactosyl thioglycoside **3** was prepared according to the literature procedure reported by Sinaÿ and Jacquinet.^[4] Synthesis of galactosyl **7** began with the peracetylated β -galactosyl thioglycoside^[7] that was deacetylated under Zemplén conditions (Scheme 4). The resulting deacetylated product was silylated at the C-6 hydroxy group with *tert*-butyldiphenylsilyl chloride (TBDPSCI). Isopropylidenation with 2,2-dimethoxypropane masked the C-3 and C-4 hydroxy groups, and the remaining

C-2 hydroxy group was benzoylated with benzoyl chloride (BzCl) to furnish the fully protected compound **4**. The isopropylidene acetal function of **4** was removed with 70 % acetic acid at 80 °C, and the deprotected product was selectively benzylated with *p*-methoxybenzyl chloride (PMBCl) at the C-3 hydroxy group in the presence of dibutyltin(II) oxide. Removal of the TBDPS protecting group at the C-6 hydroxy group then furnished compound **5**. Subsequent benzylation of the C-4 and C-6 hydroxy groups with benzyl bromide (BnBr) gave compound **6**. Previous work showed that removal of benzoate group was sometimes problematic^[10] and so it was replaced with levulinoate to give **7** by consecutive debenzoylation and levulinoylation by using Zemplén deacylation and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) mediated levulinoylation, respectively. Syntheses of glucosaminyl units **8** and **9** were straightforward with standard operations.

With the prepared monosaccharide building blocks **2**, **3**, **7**, **8** and **9** in hand, their RRVs were obtained by HPLC analysis with the established competitive assay method (see Scheme 3).^[7] Under

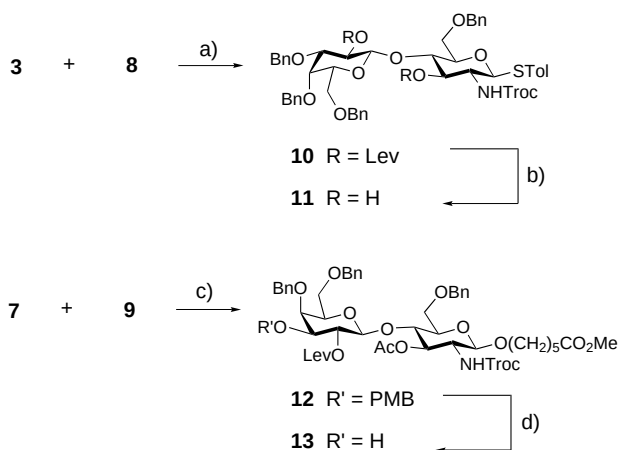


Scheme 2. Retrosynthetic analysis for one-pot synthesis of the Le^y hapten.



Scheme 4. Synthesis of galactosyl building unit **7**. a) 1) NaOMe, MeOH/CH₂Cl₂; 2) TBPSCl, imidazole, DMF; 3) 2,2-dimethoxypropane, cat. CSA, acetone; 4) BzCl, pyridine, CH₂Cl₂, 54% for four steps; b) 1) 70% AcOH in H₂O, 80°C; 2) Bu₂SnO, benzene/toluene, 120°C, 18 h; 3) *p*-methoxybenzyl chloride, cat. Bu₄NI, toluene, 90°C, 6 h; 4) TBAF, THF, 60% for four steps; c) BnBr, NaH, cat. Bu₄NI, DMF, 90%; d) 2) NaOMe, MeOH/CH₂Cl₂; 2) levulinic acid, EDC, DMAP, 90% for two steps. Lev = levulinoyl, Tol = *p*-methylphenyl, CSA = camphorsulfonic acid, DMAP = dimethylaminopyridine.

the guidance of these RRVs, the bridging and reducing end lactosaminyl building units were synthesized (Scheme 5). Galactosyl donor **3** (RRV = 4000) was glycosylated with

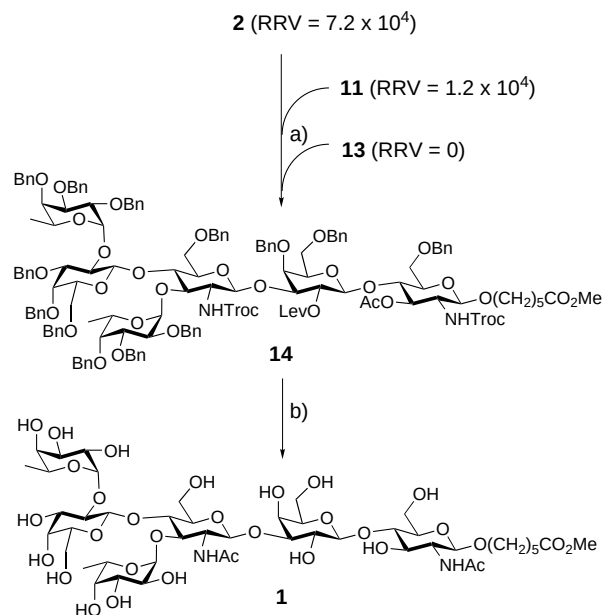


Scheme 5. Synthesis of lactosaminyl building units **10–13**. a) NIS, cat. TfOH, MS (AW300), –45°C, 40%; b) 4M NH₂NH₂·xH₂O in AcOH/pyridine, pyridine, 80%; c) NIS, cat. TfOH, MS (AW300), –45°C, 70%; d) DDQ, CH₂Cl₂/phosphate buffer, 70%. Troc = 2,2,2-trichloroethoxycarbonyl.

glucosaminyl acceptor **8** (RRV = 282) in the presence of *N*-iodosuccinimide/triflic acid (NIS/TfOH) to yield the precursor of the bridging lactosaminyl unit **10** in 40% yield.^[11] Deprotection of the two levulinoate groups with hydrazine hydrate in an acetic acid/pyridine (3:2) mixture converted **10** into the functional bridging unit **11** in 80% yield.^[12] The reducing end lactosaminyl unit precursor **12** was prepared in 70% yield by glycosylation of the galactosyl donor **7** with glucosaminyl acceptor **9** in the presence of NIS/TfOH. Cleavage of the PMB protecting group with dichlorodicyanoquinone (DDQ) furnished the functional reducing end lactosaminyl unit **13**. Unexpectedly, the RRV of **11** was determined to be 1.2×10^4 , which was 43-fold greater than its constituted glucosaminyl unit **8** (RRV = 282).^[7] The differ-

ence was probably due to the removal of two electron-withdrawing protecting groups (Lev) and hence increased the reactivity of the resulting thioglycoside building block. For the reducing end lactosaminyl unit **13**, a zero reactivity value was assigned.

The RRVs of all the functional building units, **2** (RRV = 7.2×10^4), **11** (RRV = 1.2×10^4), **13** (RRV = 0), presented an appropriate reactivity profile for one-pot synthesis. The one-pot synthetic operation was performed in the presence of the NIS/TfOH promotor system (Scheme 6). The first glycosylation between the fucosyl donor **2** and the functional bridging



Scheme 6. One-pot synthesis of the Le^y hapten **14** and its deprotected compound **1**. a) 1) NIS, cat. TfOH, MS (AW300), –70°C; 2) **13**, NIS, cat. TfOH, –25°C, 44%; b) 1) Zn dust, Ac₂O; 2) NaOMe, MeOH/CH₂Cl₂; 3) Pd-black, H₂, MeOH/AcOH, 25% for three steps. NHAc = *N*-acetamido.

lactosaminyl unit **11** was performed at –70°C, whereas the second glycosylation required higher temperature (–25°C). The lower temperature for the first glycosylation suppressed the formation of undesired succinimide by-product. In addition, low temperature favors the formation of the α -glycosidic linkage.^[13] The second glycosylation involves the coupling of two large sugar fragments for which a higher temperature was necessary for a practical reaction. The yield of fully protected determinant **14** was 44%, which was equivalent to 81% per glycosylation. Global deprotection of **14** was performed in three steps. Zinc dust in acetic anhydride removed the two trichloroethyl carbamate protecting functions (Troc) on **14** and reacylated the free amino groups simultaneously. The remaining levulinoate and acetyl protecting functions were cleaved by Zemplén deacylation. The final debenzylation was accomplished by way of a palladium-black catalyzed hydrogenation. Target Le^y hapten (**1**) was obtained in 25% yield from **14**. The characterization and anomeric purity of **1** were confirmed by HRMS and NMR analysis.

In conclusion, we have demonstrated the application of a reactivity-based one-pot strategy for the synthesis of the tumor-related oligosaccharide, Lewis Y hapten. The strategy

incorporates four glycosylation reactions into one synthetic operation, which significantly reduces the operation time to a few hours and improves the efficiency of the entire synthetic process. The building blocks (**3**, **7**, **8**, **11**) and their relative reactivity values have been proven to be useful for glycosylations as demonstrated in this study. These building blocks have been added to the OptiMer database (currently containing ~300 building blocks) and should find use in the programmable synthesis of Le^y and other oligosaccharides.

Experimental Section

Reactivity-based one-pot synthesis of the Le^y hapten **14**: Perbenzylated β -fucosyl thioglycoside donor **2** (0.31 g, 0.58 mmol), dihydroxyl lactosaminyl unit **11** (0.25 g, 0.25 mmol), and activated molecular sieves (AW300) were suspended in CH₂Cl₂ (6 mL) under argon and stirred for 1 h at room temperature. The reaction mixture was then cooled to -70 °C, and NIS (0.13 g, 0.58 mmol) and 0.5 M TfOH in diethyl ether (80 μ L, 0.04 mmol) were added. The reaction was monitored by thin layer chromatography (TLC) (hexane/CH₂Cl₂/EtOAc, 3:1:0.5). After complete consumption of **2**, reducing end lactosaminyl unit **13** (0.39 g, 0.37 mmol), a second portion of NIS (0.083 mg, 0.37 mmol), and 0.5 M TfOH in diethyl ether (40 μ L, 0.02 mmol) were added to the reaction mixture. The reaction temperature was raised to -25 °C and the reaction was monitored by TLC (hexane/EtOAc, 3:2). The reaction was quenched with addition of saturated sodium bicarbonate (sat. NaHCO₃) and solid sodium thiosulfate (Na₂S₂O₃). Molecular sieves were then filtered off and the filtrate was washed with saturated Na₂S₂O₃, saturated NaHCO₃, and brine, and dried (MgSO₄). The concentrate was purified with flash column chromatography (toluene/CH₂Cl₂/EtOAc, 4:1:1) to give **14** (0.3 g, 44%) as glassy white solid. ¹H NMR (600 MHz, CDCl₃, 20 °C): δ = 1.12 (d, *J* = 6.6 Hz, 3H; fucosyl-CH₃), 1.24 (d, *J* = 6.6 Hz, 3H; fucosyl-CH₃), 1.34 (t, *J* = 7.5 Hz, 2H; aglycon-CH₂), 1.54–1.60 (m, 4H; aglycon-CH₂), 1.85 (s, 3H; CH₃C=O), 2.09 (s, 3H; CH₃C=O), 2.28 (dt, *J* = 7.5, 2.2 Hz, 2H; aglycon-CH₂), 2.34 (d, *J* = 18 Hz, 1H; lev-CH₂), 2.43 (d, *J* = 19 Hz, 1H; lev-CH₂), 2.63 (br, 1H; lev-CH₂), 2.79 (dd, *J* = 18, 8.0 Hz, 1H; lev-CH₂), 3.15 (br, 1H), 3.31–3.34 (m, 2H), 3.41–3.52 (m, 5H), 3.55–3.60 (m, 3H), 3.65 (s, 3H), 3.67–3.71 (m, 6H), 3.81–3.93 (m, 7H), 3.97 (br, 2H), 4.04–4.10 (m, 3H), 4.17 (br, 1H), 4.28–4.81 (m, 34H), 4.94 (d, *J* = 11.4 Hz, 1H), 4.99–5.05 (m, 3H), 5.16 (d, *J* = 9.2 Hz, 1H), 5.22 (br, 1H; fucosyl-H¹), 5.68 (d, *J* = 3.9 Hz, 1H; fucosyl-H¹), 6.59 (br, 1H; carbamate-NH), 7.02 (d, *J* = 6.2 Hz, 2H; aromatic), 7.11–7.34 ppm (m, 63H; aromatic); ¹³C NMR (125 MHz, CDCl₃, 20 °C): δ = 16.35, 20.67, 67.88, 68.22, 68.33, 69.32, 70.88, 72.25, 72.37, 72.40, 72.48, 72.51, 72.56, 72.95, 73.21, 73.39, 73.50, 73.70, 74.06, 74.38, 74.47, 74.66, 74.75, 75.02, 75.28, 75.34, 75.45, 75.47, 75.60, 70.82, 78.64, 79.37, 79.42, 83.79, 95.56, 95.60, 97.63, 98.05, 100.10, 100.13, 101.14, 126.01, 126.94, 126.96, 127.12, 127.16, 127.20, 127.26, 127.36, 127.42, 127.56, 127.63, 127.69, 127.78, 127.84, 127.87, 127.94, 127.99, 128.08, 128.12, 128.14, 128.19, 128.26, 128.33, 128.36, 128.40, 128.42, 128.48, 128.56, 128.61, 137.62, 137.71, 138.00, 138.04, 138.14, 138.39, 138.57, 138.68, 138.77, 139.02, 139.22, 139.32, 154.13, 154.30, 170.66, 174.14 ppm; MS (ESI): *m/z* calcd for C₁₄₇H₁₆₄Cl₆N₂O₃₆Na [*M*+Na]⁺ 2766, found 2766.

Experimental details for compounds **1** and **4–13** are described in the Supporting Information.

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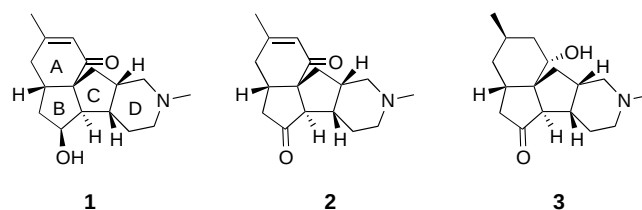
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Concise and Efficient Total Synthesis of *Lycopodium* Alkaloid Magellanine**

Chi-Feng Yen and Chun-Chen Liao*

An array of complex polycyclic alkaloids has been isolated from club mosses of the genus *Lycopodium* and these structures have posed a challenge for synthetic chemists.^[1] In the 1970s, the isolation and characterization of a group of closely related tetracyclic alkaloids, magellanine (**1**), magellaninone (**2**) (from *L. magellanicum*), and paniculatinone (**3**),



from *L. paniculatum* were reported by Castillo, MacLean, and co-workers.^[2] Owing to the intriguing structural features of these alkaloids, their synthesis remains a formidable challenge.

Magellanine (**1**), whose structure is characterized by a tetracyclic framework ABCD, contains two methyl groups, one carbonyl functionality, one double bond, and one hydroxy group on its periphery, and the piperidine ring D. Furthermore, this highly compact molecular architecture includes six contiguous stereogenic centers, one of which is a quaternary carbon atom. Not surprisingly, the structural novelty of the

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magellanine skeleton has evoked a great deal of attention from the synthetic community, and numerous studies have been directed at its total synthesis.^[3] So far, the total synthesis of **1** was successfully accomplished by Overman and co-workers^[4] (enantiomerically pure form) and Paquette et al.^[5] (racemic form). Herein, we describe an efficient total synthesis of **1** in its racemic form from commercially available acetovanillone (**4**).

Recent synthetic efforts in our laboratories directed at the utilization of masked *o*-benzoquinones resulted in the successful acquisition of bicyclo[2.2.2]octenones, oxatricycles, triquinanes, and bicyclo[4.2.2]decenones, which are pivotal subunits in the construction of several natural products.^[6] The present study highlights the efficacy of masked *o*-benzoquinone approach in the total synthesis of **1** via linear triquinane **9** (Scheme 1). We expected to complete the total synthesis of the title alkaloid by sequential elaboration of **9**, which contains the required BC rings with proper stereochemistry.

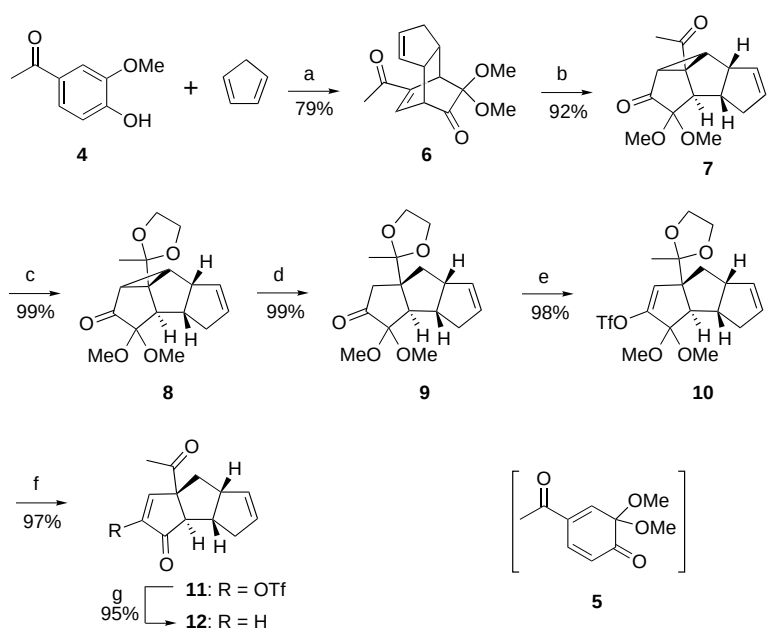
We planned to access the linear triquinane **9** by making use of a method that we recently developed^[7] which includes a Diels–Alder reaction of masked *o*-benzoquinone followed by the oxa-di- π -methane (ODPM) rearrangement (Scheme 1). Thus, acetovanillone (**4**) was treated with cyclopentadiene in the presence of DAIB in methanol. The masked *o*-benzoquinone **5**, transiently generated from **4**, was trapped smoothly with cyclopentadiene at ambient temperature to provide a single cycloadduct **6**, in which the four contiguous stereogenic centers are fixed by the regio- and stereocontrolled Diels–Alder reaction. Irradiation of **6** in acetone with fluorescent lamps (RUL-3000 Å) through Pyrex filters in a Rayonet reactor afforded tetracyclic diketone **7** through the ODPM

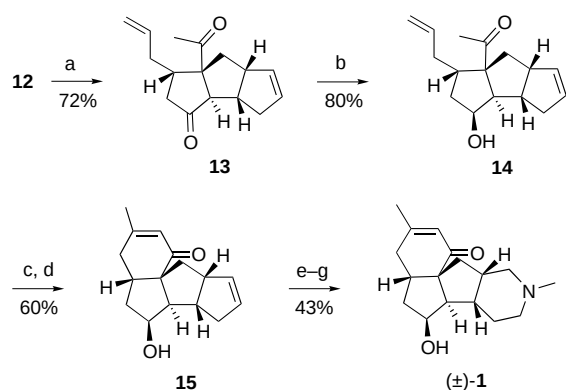
rearrangement^[8] in excellent yield. The success of this transformation is the result of an appropriately positioned electron-withdrawing acetyl group in **6**.^[7,9] The carbonyl group of the cyclopentane ring of **7** could serve both as an activating group for the opening of the cyclopropane ring and also to generate the required olefin. We foresee that the latent carbonyl functionality, present in the form of a dimethoxy acetal, is necessary for the Michael addition and for the further generation of an hydroxy group. At this stage, it was necessary to protect the carbonyl group of the aceto functionality in **7** for the selective opening of the cyclopropane ring. For this purpose, after considerable experimentation, the acetyl group was selectively protected under the conditions reported by Noyori and co-workers^[10] to deliver monoacetal **8** in quantitative yield. Opening of the strained cyclopropane ring of **8** with tributyltin hydride/AIBN^[11] led to the quantitative formation of linear triquinane **9**. Ketone **9** was then transformed into enol triflate **10** by using 2-pyridyltrifluoromethanesulfonimide.^[12] Triflate **10** was exposed to hydrochloric acid to yield diketone **11**, which in turn was readily converted into triquinane **12** in excellent yield by reductive cleavage of the triflate group.^[13]

With linear triquinane **12** secured, the stage was set for construction of the A ring. After several trials, it was possible to effect 1,4-addition of diallylcyanocuprate^[14] to **12** to afford **13** in good yield and with stereoselective delivery of the allyl group exclusively from the less hindered α face (Scheme 2). The stereochemistry of **13** was confirmed by X-ray diffraction analysis.^[15] Regioselective reduction of diketone **13** was effected by treatment with L-Selectride to generate β -alcohol **14**. This reduction is governed by the steric hindrance at the

concave face of **13**, thus leading to the attack of hydride from the α face. The silyl enol ether generated from alkenyl methyl ketone **14** was subjected to intramolecular cyclization with oxa- π -allylpalladium(II) intermediates^[16] to afford tetracyclic enone **15** in good yield.

Having successfully introduced the requisite six stereogenic centers and the ABC ring system, all that remained to complete the synthesis of the targeted molecule was to convert the cyclopentene ring of **15** into piperidine ring D. Toward that objective, **15** was subjected to sequential regiospecific oxidative cleavage of cyclopentene ring with osmium tetroxide/NMO and sodium periodate,^[17] and double reductive amination^[18] with methylamine hydrochloride to provide racemic magellanine (**1**). The NMR spectral data of ($\pm$)-**1** are in full consonance with those reported for the chiral molecule.^[4,19] Furthermore, the assignment was supported by its HETCOR spectrum (see Supporting Information). Thus, synthesis of the target molecule was completed over 14 steps in 9% overall yield (84% average yield per step), which is much higher than that of the earlier reported routes.^[4,5] Furthermore, unlike in the reported approaches, the starting materials used in the present study are commercially available and inexpensive.

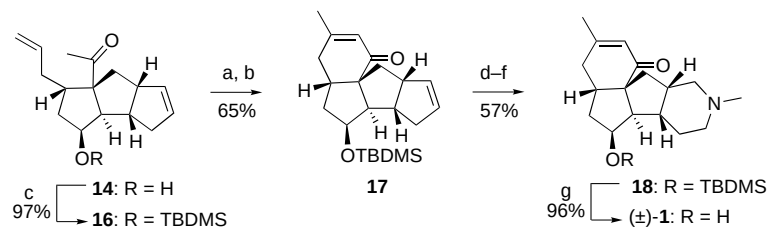




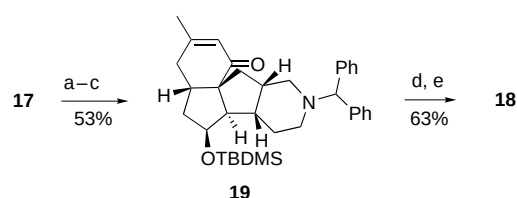
Scheme 2. Synthesis of magellanine (**1**): a) Allyltributyltin, *n*BuLi, CuCN, TMSCl, THF, $-78^{\circ}\text{C} \rightarrow \text{RT}$; b) L-Selectride, THF, $-78 \rightarrow -20^{\circ}\text{C}$; c) LDA, TMSCl, THF, $0^{\circ}\text{C} \rightarrow \text{RT}$; d) Pd(OAc)₂, MeCN, room temperature; e) OsO₄, NMO, *t*BuOH/THF/H₂O (2.5:5:1), room temperature; f) NaIO₄, H₂O/CH₂Cl₂, room temperature; g) CH₃NH₂Cl, NaBH₃CN, IPA, 4-Å molecular sieves, room temperature. LDA = lithium diisopropylamide, NMO = *N*-methylmorpholine *N*-oxide, IPA = 2-propanol.

In an effort to render the synthetic route more efficient, we elected to conduct the cyclization of TBDMS ether **16**, derived from **14**, instead of the free alcohol **14**. Accordingly, **14** was protected as its TBDMS ether **16** and subjected to intramolecular cyclization to afford tetracycle **17**, which in turn was transformed into *N*-methylpiperidine **18** (Scheme 3). Finally, the facile deprotection^[20] of TBDMS ether **18** afforded the target molecule. This new path allowed us to reach (±)-**1** in 16 steps in 12% overall yield (87% average yield per step). The stereochemistry of (±)-**1** was further confirmed by single-crystal X-ray structure analysis^[21] of its *O*- and *N*-protected derivative **19**, which was formed from **17** (Scheme 4). The azatetracycle **19** was transformed into **18** by selective hydrogenolysis^[22] followed by *N*-methylation.^[23]

In summary, we have completed an efficient total synthesis of racemic magellanine (**1**). It illustrates the power of the masked *o*-benzoquinone Diels–Alder protocol and serves to show how highly condensed molecular architectures can be synthesized from simple 2-methoxyphenols. It is noteworthy that all 13 carbon atoms of the tricyclic skeleton **6**, including the aceto functionality, served in its elaborate functionalization to the target molecule. The other salient features of the current synthesis include the photochemical ODPM rearrangement, intramolecular cyclization of an alkenyl ketone, and the selective oxidative cleavage and double reductive



Scheme 3. Alternative route to **1** from **14**. a) LDA, TMSCl, THF, $0^{\circ}\text{C} \rightarrow \text{RT}$; b) Pd(OAc)₂, MeCN, room temperature; c) imidazole, TBDMSCl, DMF, room temperature; d) OsO₄, NMO, *t*BuOH/THF/H₂O (2.5:5:1), room temperature; e) NaIO₄, H₂O/CH₂Cl₂, room temperature; f) CH₃NH₂Cl, NaBH₃CN, IPA, 4-Å MS, room temperature; g) TBAF, THF, room temperature. TBDMS = *tert*-butyldimethylsilyl, DMF = *N,N*-dimethylformamide, TBAF = tetrabutylammonium fluoride.



Scheme 4. Transformation of **17** into **18** via **19**. a) OsO₄, NMO, *t*BuOH/THF/H₂O (2.5:5:1), room temperature; b) NaIO₄, H₂O/CH₂Cl₂, room temperature; c) Ph₂CHNH₂Cl, NaBH₃CN, IPA, 4-Å molecular sieves, room temperature; d) 10% Pd/C, 1,4-cyclohexadiene, EtOH, room temperature; e) HCHO, NaBH₃CN, MeCN, room temperature.

amination. Although the present synthetic route leads to the racemic **1**, in principle, the enantiopure product can be obtained by means of kinetic resolution at different stages.

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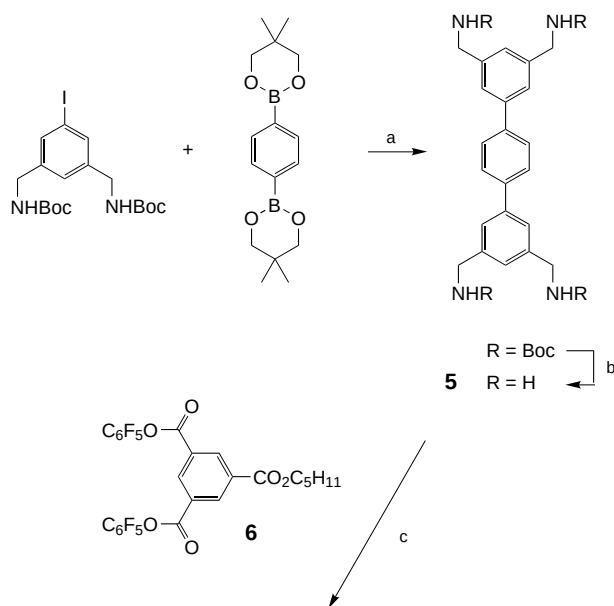
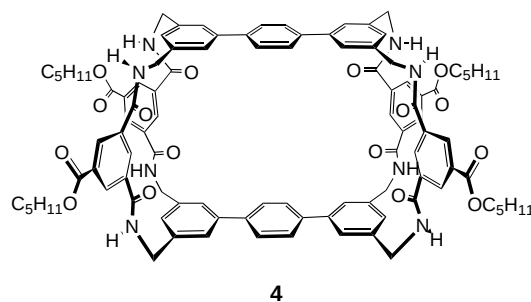
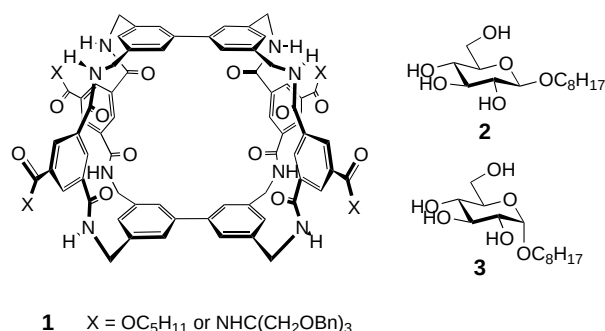
Highly Selective Disaccharide Recognition by a Tricyclic Octaamide Cage**

Grégory Lecollinet, Andrew P. Dominey, Trinidad Velasco, and Anthony P. Davis*

Carbohydrate recognition presents a continuing challenge to supramolecular chemistry,^[1] fuelled by the growing awareness of saccharide structures as mediators of biological events.^[2] However, while the biological interest is focussed largely on oligosaccharides, supramolecular chemists have concentrated mainly on monosaccharide substrates. A number of systems show preferential binding of di- versus monosaccharides,^[1c-e,3] but only a few boron-based receptors show good selectivity between disaccharides.^[1c,3a-3d] The latter employ covalent B–O bond formation, and are thus less relevant to biological carbohydrate recognition.

We recently described the tricyclic cage receptors **1**, which bind monosaccharide derivatives strongly and selectively even in the presence of a hydroxylic cosolvent.^[4] Receptor **1** proved remarkably selective for the all-equatorial β -glucoside **2** as against the α -anomer **3**. We now report the synthesis and binding properties of **4**, an “extended analogue” of **1** designed to accommodate disaccharide substrates. Compound **4** has proved to be the first receptor capable of distinguishing clearly between disaccharides through noncovalent interactions.

Receptor **4** was synthesized by two independent routes. In the first, the tetraaminoterphenyl **5** was prepared as shown in Scheme 1 and coupled under high dilution with bis(penta-



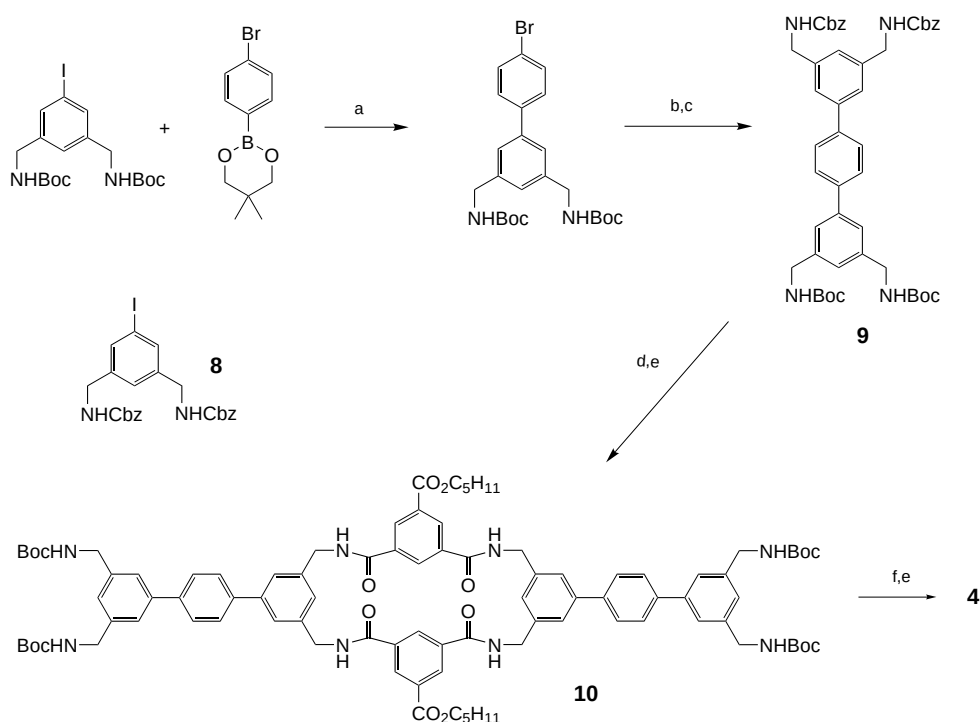
Scheme 1. Synthesis of **4** + **7**: a) [PdCl₂(dppf)], Na₂CO₃ aq. (2 M), DMF, 80 °C; b) trifluoroacetic acid (TFA), CH₂Cl₂; c) **6**, iPr₂NEt, THF/DMF, high dilution. dppf = diphenylphosphanylferrocene.

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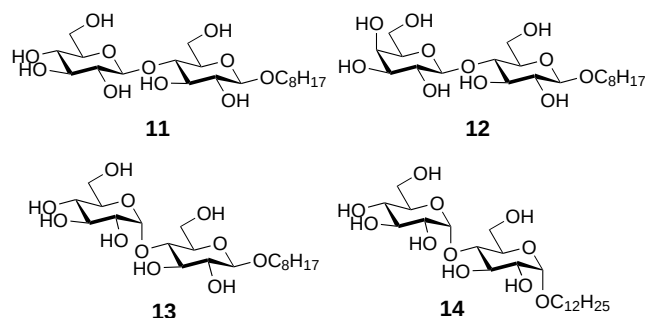
Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.



Scheme 2. Synthesis of **4**: a) $[\text{PdCl}_2(\text{dppf})]$, Na_2CO_3 aq. (2M), DMF, 80°C ; b) bis(pinacolato)diboron, $[\text{PdCl}_2(\text{dppf})]$, KOAc, DMF, 80°C ; c) **8**, $[\text{PdCl}_2(\text{dppf})]$, Na_2CO_3 aq. (2M), DMF, 80°C ; d) H_2 , 10% Pd/C, $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$; e) **6**, $i\text{Pr}_3\text{NEt}$, THF/DMF, high dilution; f) TFA, CH_2Cl_2 .

fluorophenyl) ester **6**. This direct route seemed viable as, for steric and geometric reasons, no [1+1] cyclization is possible between **5** and **6**. The smallest unstrained rings (favored at high dilution) result from [2+2] cyclizations, as required for **4**. However, a regioisomeric macrotricyclic **7** is also possible, and two cyclized products were indeed formed. Mass spectrometric and NMR spectroscopic data were consistent with a mixture of **4** + **7**, but unfortunately the two could not be separated. Pure **4** was therefore prepared by a longer but unambiguous sequence (Scheme 2) in which orthogonal protection in tetracarbamate **9** allowed sequential [2+2] cyclizations, leading specifically to **4** via **10**.

In common with receptor **1**, macrotricyclic **4** possesses extended, parallel apolar surfaces linked through spacers containing hydrogen-bond donor and acceptor groups. This geometry should be compatible with equatorially substituted carbohydrate derivatives.^[4a] Accordingly, the all-equatorial *n*-octyl- β -D-cellobioside **11**^[5,6] was employed for initial binding studies. In the first instance, **11** was added to the mixture of **4** and **7** in $\text{CDCl}_3/\text{CD}_3\text{OH}$ (92:8) (the solvent used for NMR



binding studies on **1**^[4]). As hoped, we observed changes in the ^1H NMR spectrum of just one of the macrotricycles (later identified as **4**). However, instead of signal movements with minor splittings (as observed for **1** + **2**^[4a]), the spectrum of **4** was replaced by a new set of resonance signals implying loss of all symmetry (see Figure S1 in the Supporting Information). Titration of **11** into pure **4** confirmed this result, revealing progressive loss of receptor and growth of the new spectrum (Figure 1), and clearly implying complex formation with slow exchange. Integration of bound versus uncomplexed receptor proved unworkable, but the growth of the new signals could be monitored by integration versus an internal standard. The data was consistent with 1:1 binding (Figure 2) with a binding constant (K_a) of

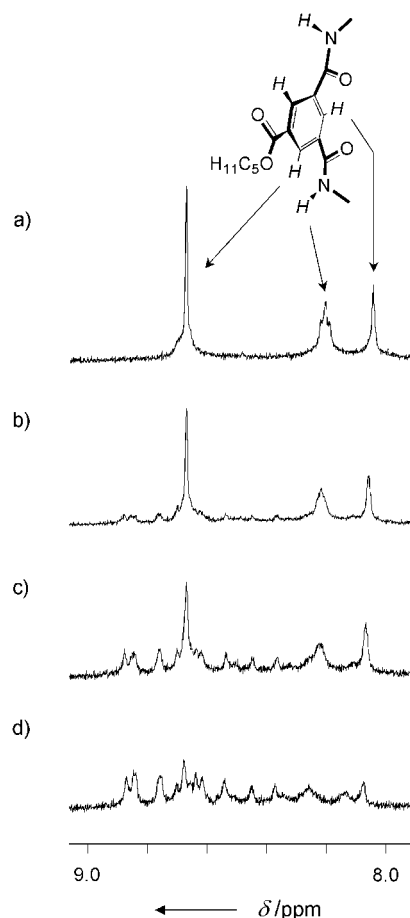


Figure 1. Partial ^1H NMR spectra in $\text{CDCl}_3/\text{CD}_3\text{OH}$ (92:8) of receptor **4** after addition of a) 0, b) 0.4, c) 1, and d) 5 equivalents of **11**.

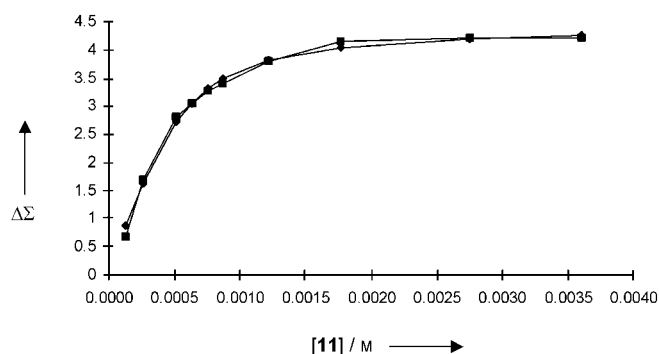


Figure 2. Experimental (■) and calculated (◆) values for the ^1H NMR binding study of **4** + **11** in $\text{CDCl}_3/\text{CD}_3\text{OH}$ (92:8). $[\textbf{4}] = 0.5 \text{ mM}$, $[\textbf{11}] = 0.13\text{--}3.6 \text{ mM}$. $T = 278 \text{ K}$. Experimental points were obtained by integration of the signal at $\delta = 8.8\text{--}8.9$ (see Figure 1) versus an internal standard (pentafluorobenzaldehyde, $\delta = 10.27$). The data were analyzed by using a nonlinear least-squares curve-fitting program implemented within Excel 2000.

7000 M^{-1} , slightly higher than the value of 980 M^{-1} measured for **1** + **2** under these conditions.^[4a] In a control experiment, glycoside **11** was added to macrocycle **10** under the same conditions; as expected, no change was observed in the spectrum of **10**. To investigate the selectivity of **4**, similar experiments were performed with octyl glucosides **2** and **3**, octyl β -D-lactoside **12**,^[6,7] octyl β -D-maltoside **13**,^[6,8] and dodecyl α -D-maltoside **14** as substrates. Remarkably, none of these compounds produced any detectable effect on the NMR spectrum of the receptor. Moreover, addition of **12** to (**4** + **11**) had no effect on the spectrum of the complex. The implied selectivity was confirmed by two further techniques. First, irradiation of **4** at $\lambda = 285 \text{ nm}$ caused fluorescence emission in the ranges $350\text{--}450 \text{ nm}$ and $650\text{--}750 \text{ nm}$. Addition of **11** caused substantial increases in the intensities of both bands (see Figure S2 in the Supporting Information). Analysis of the data supported a 1:1 binding model, with $K_a = 2500 \text{ M}^{-1}$ (Figure 3).^[9] In contrast, experiments with **2**, **3**, and **12–14** showed no sign of complex formation. In each case, addition of 10 equivalents of glycoside (to 0.3 mM) produced no effect on the fluorescence of **4**. The fluorescence titration of **4** versus **11** was repeated in a less competitive solvent system, $\text{CHCl}_3/\text{MeOH}$ (98:2), yielding a binding constant of 64000 M^{-1} (see

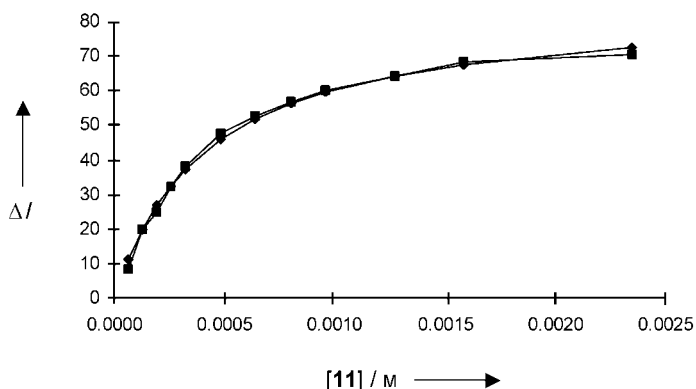


Figure 3. Experimental (■) and calculated (◆) values for the fluorescence binding study of **4** + **11** in $\text{CHCl}_3/\text{CH}_3\text{OH}$ (92:8). $[\textbf{4}] = 0.03 \text{ mM}$, $[\textbf{11}] = 0.065\text{--}2.3 \text{ mM}$.

Figures S3 and S4 in the Supporting Information). Even under these conditions, addition of lactoside **12** or β -maltoside **13** caused no change in emission (see Figure S5 in the Supporting Information). Second, weak but unambiguous induced circular dichroism was observed when **11** was added to **4** in $\text{CHCl}_3/\text{MeOH}$ (92:8) (see Figure S6 in the Supporting Information). The spectra were too noisy for quantitative analysis, but saturation was clearly observed with increasing $[\textbf{11}]$. Once again, negative results were obtained with **12** or **13**, the receptor remaining CD-silent.

In conclusion, these experiments seem to reveal an interaction of unusual specificity between a synthetic receptor **4** and a biomolecular substrate **11**. We cannot be absolutely certain that **4** does not bind the other glycosides, as complex formation might not induce a change in spectroscopic properties in these cases. However, the complete absence of any signal from any other substrate, on employing three quite different techniques, provides strong evidence for extreme selectivity. The substrates, moreover, are only subtly different from each other. For example, **11** and **12** are related by inversion at a single asymmetric center, at one end of the structure. Finally, the design strategy seems to have been validated. The geometry of **4** does indeed favor the “flat” all-equatorial substrate, supporting the notion that selective receptors for at least some complex biomolecules are accessible through rational design and synthesis.

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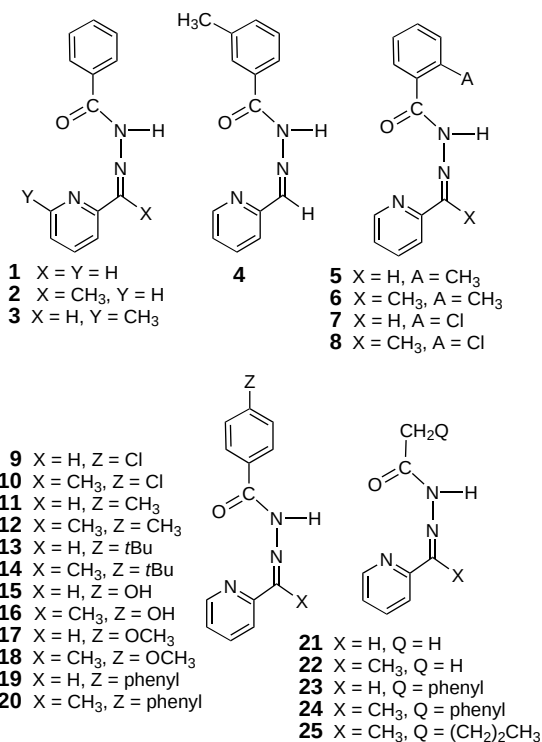
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Dynamic Acylhydrazone Metal Ion Complex Libraries: A Mixed-Ligand Approach to Increased Selectivity in Extraction**

Seema Choudhary and Janet R. Morrow*

Metal ion coordination chemistry is well suited to dynamic combinatorial chemistry approaches.^[1–3] Diverse metal ion complex libraries can be created simply by mixing a labile metal ion with different ligands.^[4] If ligand exchange is rapid, these metal ion complexes form the equilibrating components of a dynamic library. The equilibrium between complexes may be shifted upon addition of molecular targets. For example, small molecule or biopolymer targets perturb the equilibrium between metal ion complexes to increase the concentration of the metal ion complex that best binds the target.^[5–7] We previously reported on dynamic combinatorial libraries of metal ion Schiff-base complexes of limited diversity.^[8] Our selection protocol utilizes extraction of metal ion complex libraries from aqueous into organic solvent. In this method, the organic solvent is the ultimate target and complexes with the greatest stability and solubility in organic solvent versus aqueous solution are selected.^[9] Here we present studies using acylhydrazone ligand libraries and show that these libraries lead to improvements in efficiency and selectivity of metal ion extraction in comparison to single ligand systems.

Acylhydrazone ligands (Scheme 1) were chosen to explore the possibility of forming a double-orthogonal library^[4] by exchange at metal–ligand (M–L) and C=N bonds.^[10–13] Initial studies were carried out to establish the feasibility of using these exchange processes. Zn^{II} extracts into chloroform from a buffered aqueous solution in the presence of two equivalents of acylhydrazone ligand **1** (Table 1, Scheme 1). The predominant complex that extracts into chloroform is the neutral complex $[\text{Zn}(\text{1}^-)_2]$ as determined by comparison of ^1H NMR



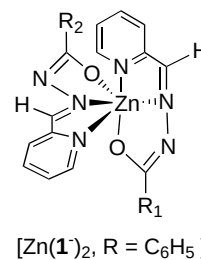
Scheme 1. Acylhydrazone ligands used in this study.

Table 1. Extraction of Zn^{2+} or Cd^{2+} into chloroform by acylhydrazone ligands.

Metal	Ligand	Extracted [%] ^[a]	Metal	Ligand	Extracted [%] ^[a]
Zn^{2+}	1	25	Zn^{2+}	2	62
Zn^{2+}	3	12	Zn^{2+}	4	26
Zn^{2+}	5	3.0	Zn^{2+}	6	28
Zn^{2+}	7	9.0	Zn^{2+}	8	43
Zn^{2+}	9	54	Zn^{2+}	10	62
Zn^{2+}	11	23	Zn^{2+}	12	56
Zn^{2+}	13	20	Zn^{2+}	14	54
Zn^{2+}	15	0	Zn^{2+}	16	0
Zn^{2+}	17	21	Zn^{2+}	18	54
Zn^{2+}	19	44	Zn^{2+}	20	64
Zn^{2+}	21	0	Zn^{2+}	22	1.2
Zn^{2+}	23	1.8	Zn^{2+}	24	2.0
Zn^{2+}	25	0	Cd^{2+}	1	15
Cd^{2+}	2	48	Cd^{2+}	5	2.1
Cd^{2+}	6	3.7	Cd^{2+}	7	4.0
Cd^{2+}	8	14	Cd^{2+}	13	13
Cd^{2+}	14	32			

[a] Extractions were carried out in 5.0 mM Mes buffer (10 mL), 0.100 M NaCl, and CHCl_3 (1 mL) at 23 °C at pH 5.50 for Zn^{II} (0.0500 mM) or pH 6.50 for Cd^{II} (0.0500 mM) with 0.100 mM ligand.

and mass spectral data to that of an authentic sample. After two hours, the extent of extraction of Zn^{II} from a water/chloroform mixture containing 0.0500 mM $[\text{Zn}(\text{1}^-)_2]$ is identical within experimental error to a second experiment containing 0.0500 mM $\text{Zn}(\text{NO}_3)_2$ and 0.100 mM **1**, confirming that our system is at equilibrium. Addition of a different acylhydrazone ligand (**13**) to either of the solutions above followed by stirring for 2 h increases the amount



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of extraction from 25 to 53 %, consistent with ligand exchange to form mixed–acylhydrazone complexes. Analysis of these mixtures by ^1H NMR spectroscopy and by electrospray ion mass spectrometry confirms the presence of mixed–acylhydrazone complexes. In contrast, exchange and formation of the $\text{C}=\text{N}$ bond is slow. Incubation of **1** with one equivalent of *o*-toluic acid hydrazide at pH 5.9, 23 °C, for 14 h leads to the formation of **5** (50 %) as determined by ^1H NMR spectroscopy. Incubation of **1**, *o*-toluic acid hydrazide, and $\text{Zn}(\text{NO}_3)_2$ in a 2:2:1 ratio fails to produce free or bound acylhydrazone (**5**) after several days. In addition, if 2-pyridinecarboxaldehyde and benzoic hydrazide are used in lieu of **1** for extraction of Zn^{II} , equilibrium is attained only after 80 h. All further extractions used acylhydrazone ligands under conditions where M–L exchange is dynamic but no $\text{C}=\text{N}$ exchange is anticipated.

A library of 25 different acylhydrazone ligands was studied for extraction of Zn^{II} and Cd^{II} . These d^{10} ions were chosen based on their flexible coordination geometries that can be readily distorted by ligand substituents.^[8] Such distortions in coordination geometry affect the stability and solubility of the complex. A variety of ligand substituents were chosen with the goal of varying the steric and electronic nature of the ligand (Table 1). A few important trends are discussed here. For both Zn^{II} and Cd^{II} , acylhydrazones derived from the ketone (compare **1** and **2**) extract metal ions better than do ligands derived from aldehydes, consistent with the extra methyl group forming a more hydrophobic metal ion complex with a higher molar volume. Ligands with benzyl substituents (**23**, **24**) extract little at pH 5.5, but efficiently at pH 8.5. This suggests that an aryl group is necessary to lower the pK_a of the acylhydrazone ligand for extraction at acidic pH. Acylhydrazones with substituents in the 2-position of the aryl ring (**5–8**) are less effective than analogous ligands substituted in the 4-position (**9–12**), likely due to steric interference of the substituent with binding. Ligands with methyl or *tert*-butyl groups on the aryl or pyridine rings (**3**, **4**, **11–14**) do not increase extraction over the unsubstituted derivatives (**1**, **2**), despite their higher molar volume.

Metal ion complex libraries are created by using two different ligands. In these experiments, ligand exchange leads to the formation of at least three different complexes in each experiment ($[\text{M}(\text{L}_1)_2]$, $[\text{M}(\text{L}_1)(\text{L}_2)]$, $[\text{M}(\text{L}_2)_2]$); the most stable and soluble combinations extract into chloroform. An increase in metal ion extraction by two different ligands compared to that by a single type of ligand is referred to as a ligand synergistic effect.^[14,15] Synergistic effects are detected here as deviations from calculated values for the extent of extraction (see Supporting Information). Positive deviations arise from the formation of mixed–acylhydrazone complexes with improved extraction properties. Mixed–ligand studies are carried out in three groups; the first contains ligands derived from ketones, the second contains ligands derived from aldehydes, and the third is a mixture of the two types of ligands.

No synergistic effects are observed for extraction of Zn^{II} by mixtures of two ligands derived from ketones. In addition, no ligand synergistic effects are observed for extraction of Cd^{II} by any ligand combination. However, ligands derived from

aldehydes show synergy in Zn^{II} extraction in a few cases including a 1.4-fold increase in extraction for **1** and **13** over that expected (53 % observed, 39 % calculated) and **1** and **7** (43 % observed, 31 % calculated). Larger effects are observed when the two classes of ligands are mixed. The percent extraction is nearly doubled for a mixture of **6** and **7** (61 % observed, 34 % calculated). Other combinations that show significant synergistic effects include a 1.6-fold increase for **7** and **8** (64 % observed, 47 % calculated), a 1.4-fold increase for **5** and **6** (47 % observed, 30 % calculated), and a 1.3-fold increase for **5** and **8** (58 % observed, 44 % calculated).

The largest synergistic effects are observed for Zn^{II} with ligands containing substituent variations in two positions (X and A in Scheme 1). The fact that there are no Cd^{II} ligand synergistic effects suggests that the size of the metal ion and thus steric considerations are important. It is also noteworthy that the substituent positions giving rise to synergistic effects are those that are most likely to influence the conformation and binding of the ligand through ligand steric effects. Methyl groups attached to the imine carbon atom influence the overall conformation of Schiff-base complexes^[16] by reducing the flexibility of the ligand. However, not just any combination is synergistic; acylhydrazones must have 2-aryl substituents for optimal results. Given that substituents at the 2-position decrease the ability of the ligand to bind to the metal ion, it is puzzling that these substituents increase the extent of synergy in extraction. Further studies are underway to determine the effect of these multiple ligand substituents on Zn^{II} complex structure.

An important goal in metal ion separations is to increase the selectivity of the ligand for a metal ion. Zn^{II} is normally more easily extracted than Cd^{II} due to its higher Lewis acidity; this is attested to by the negligible amount of Cd^{II} compared to Zn^{II} extracted at pH 5.5. In fact, selectivity for Zn^{II} versus Cd^{II} would be higher if the two metal ions were extracted at the same pH. Nonetheless, it is interesting that selectivity for Zn^{II} over Cd^{II} is enhanced for certain ligands and ligand mixtures. For example, a combination of **5** and **6** gives a selectivity of 12-fold for Zn^{II} versus Cd^{II} . Additional favorable combinations exhibiting higher selectivity include **6** and **7**, **7** and **8**, **5** and **8**, and **6** and **8** as shown in Figure 1. Four of the five involve combinations of ligands that are synergistic in the

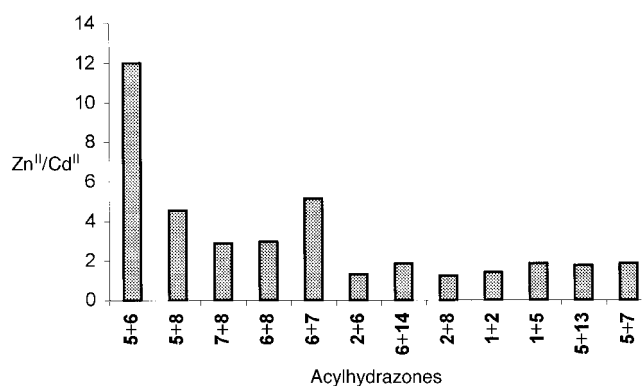


Figure 1. Comparison of percent extraction of Zn^{II} versus Cd^{II} by mixtures of acylhydrazone ligands. Extractions had 5.0 mM Mes buffer (10.00 mL), 0.100 M NaCl, CHCl_3 (1.00 mL) at 23 °C, at pH 5.50 for Zn^{II} (0.500 mM) or pH 6.50 for Cd^{II} (0.0500 mM) with 1.00 mM of each ligand.

extraction of Zn^{II} but not Cd^{II} . The highest selectivity with single ligands (Table 1) are 7.6-fold (**6**) and 3.1-fold (**8**). Interestingly both **6** and **8** are ketone-derived ligands with 2-aryl substituents, suggesting that this combination of substituents enhances extraction of Zn^{II} .

These studies demonstrate that dynamic combinatorial chemistry is a useful tool for the discovery of new metal ion complexes. Synergistic interactions of ligands are useful for building in selectivity for metal ions by using simple ligand substituent effects. This method has potential for practical applications given that the ligands are inexpensive and readily synthesized. However, there remains much to learn about the construction of an effective library of metal ion complexes. Future work will focus on exploring strategic positions for substituents on different types of ligands and on increasing the complexity of the library by using metal complexes that bind three ligands.

Experimental Section

Extraction solutions were stirred in foil-wrapped vials with teflon-lined crimp caps for 2 h and were analyzed for Zn^{II} or Cd^{II} by use of dithizone indicator.^[8] Standard deviations in measurements are 10% or less.

Acylhydrazone ligands were prepared by heating a solution of either 2-pyridinecarboxaldehyde (PCA) or 2-acetylpyridine in ethanol, a stoichiometric amount of the corresponding acylhydrazide, and a few drops of hydrochloric acid. Concentration of the solution and cooling followed by recrystallization from ethanol or ethanol/hexane yielded the ligand. In a typical preparation, benzoic hydrazide (0.272 g, 2.00 mmol) was added to a solution of PCA (0.190 mL, 2.00 mmol) in ethanol (20 mL) and a few drops of hydrochloric acid was added. The solution was gently heated and stirred for 0.25 h. Upon cooling, a white precipitate (**1**) formed, which was washed with ethanol, recrystallized, and dried in vacuo. ¹H NMR (400 MHz, [D₆]DMSO, 24 °C, TMS): δ = 12.0 (s, 1H; NH), 8.60 (d, ³J(H,H) = 4 Hz, 1H; H10), 8.46 (s, 1H; H6), 7.92 (m, 4H; H7, H8, H1, H5), 7.60 (t, ³J(H,H) = 4.2 Hz, 1H; H9), 7.53 (t, ³J(H,H) = 4.7 Hz, 2H; H2, H4), 7.40 ppm (t, ³J(H,H) = 5.6 Hz, 1H; H3) (see Supporting Information for ligand-numbering scheme); ESI-MS: *m/z* (%): 226(52) [PCA-BAH+H⁺], 248(100) [PCA-BAH+Na⁺].

[Zn(**1**)₂] was prepared by dissolving Zn(NO₃)₂ (0.788 g, 2.65 mmol) in hot ethanol (100 mL), followed by the addition of PCA (5.30 mmol), and benzoic hydrazide (0.721 g, 5.30 mol). Triethylamine (5.30 mmol) was added and the solution was heated to boiling for 0.25 h. Upon cooling, a bright yellow precipitate was recovered and recrystallized from ethanol. ¹H NMR (400 MHz, [D₂]chloroform, 25 °C, TMS): δ = 8.50 (s, 1H; H6), 8.21 (d, ³J(H,H) = 7.6 Hz, 2H; H1, H5), 8.06 (d, ³J(H,H) = 4.8 Hz, 1H; H10), 7.72 (t, ³J(H,H) = 7.6 Hz, 1H; H8), 7.38 (m, 4H; H9, H2, H4, H7), 7.14 ppm (t, ³J(H,H) = 5.2 Hz, 1H; H3); ESI-MS: *m/z* (%): 513(100), 514(32), 515(63), 516(29), 517(44), [Zn(PCA-BAH)₂+H⁺].

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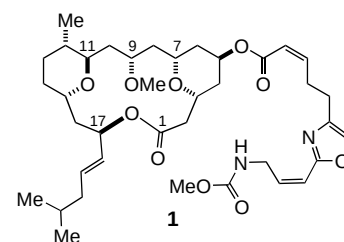
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Total Synthesis of Leucascandrolide A**

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Leucascandrolide A (**1**), a polyoxygenated marine macrocyclic of a new genus, was isolated in 1996 by Pietra and co-



workers from the calcareous sponge *Leucascandra caveolata* along the east coasts of New Caledonia.^[1] Despite subsequent intensive efforts, later expeditions failed to provide additional leucascandrolide A.^[2] Leucascandrolide A (**1**) displays strong cytotoxic activity in vitro on human KB and P388 cancer cell lines (IC₅₀ = 50 and 250 ng mL⁻¹, respectively) as well as powerful antifungal activity. An elegant total synthesis has been recently reported by Leighton and co-workers,^[3] and a formal synthesis has been documented by Rychnovsky and co-workers^[4] along with synthetic studies of the core by Crimmins et al.^[5] and Kozmin^[6] and a synthesis of the oxazole side chain by Wipf et al.^[7] The lack of availability of

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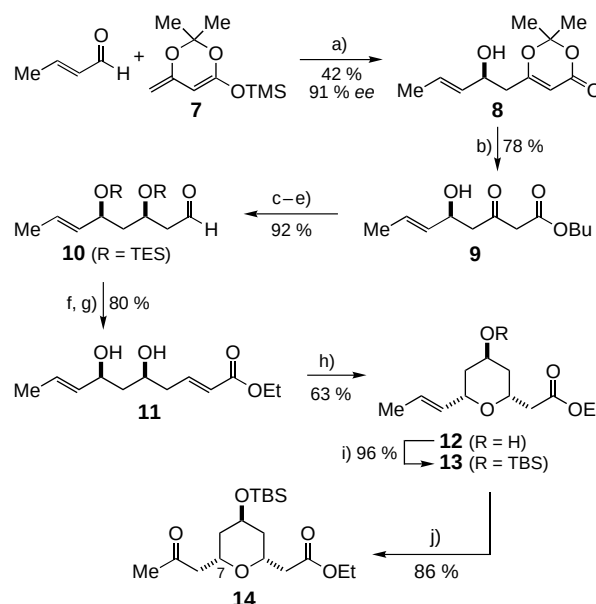
[**] We thank the ETH, SNF, Aventis, Eli Lilly, Merck, and Hoffmann-LaRoche for their generous support of our research program. We are grateful to Prof. Armido Studer (Marburg) for kindly supplying the silylated cyclohexadiene he has developed for tin-free radical reactions.

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Leucascandrolide A (**1**) from natural sources, its powerful biological activity as well as its unusual structure compelled us to embark on a program aimed at its total synthesis. Herein, we describe a concise, stereocontrolled, enantioselective total synthesis of the natural product which is realized through the application of modern enantio- and diastereoselective methods for asymmetric synthesis.

In our retrosynthetic strategy, we envisioned macrolactonization and late-stage introduction of the C17 side chain (Scheme 1). Additionally, the 2,6-*trans*-substituted tetrahydropyran would require a *trans*-selective intramolecular oxidative cyclization of a 6-hydroxy alkene. Cyclization retron **2** would be derived from methyl ketone **3** and aldehyde **4** by stereoselective aldol addition. The key building block **4** could be conveniently assembled by employing (*R*)-isopropylidene glyceraldehyde (**5**) and acetylene **6** by using a method we have described recently.^[8]

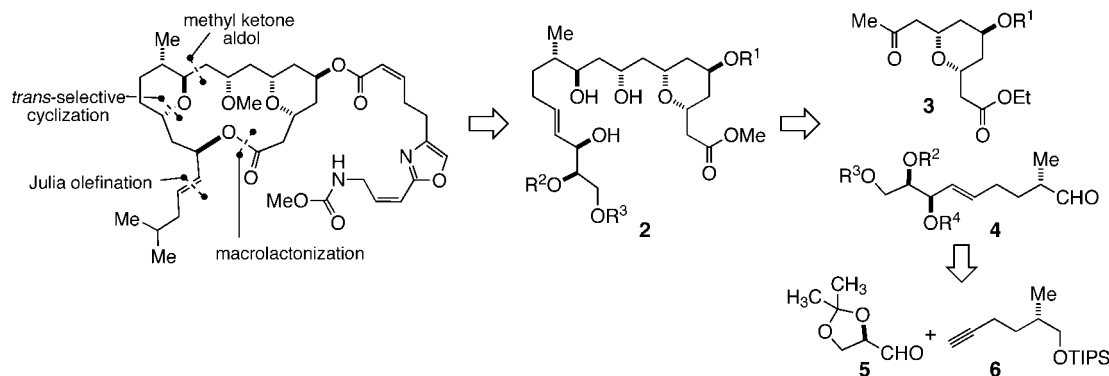
The synthesis of methyl ketone **14** commences with the enantioselective addition of trimethylsilyl dienolate **7** to crotonaldehyde catalyzed by our (*R*)-Tol-BINAP copper(I) fluoride complex (2 mol %) to give aldol adduct **8** in 42 % yield and 91 % *ee* (by HPLC) (Scheme 2).^[9] The C=O addition reactions of crotonaldehyde are typically executed only with some difficulty, because of its susceptibility towards polymerization; thus, formation of product **8** in high levels of enantioselectivity is noteworthy. When adduct **8** was heated at reflux in *n*-butanol, keto ester **9** was isolated (78 %), which, following *syn* reduction,^[10] protection of the corresponding diol, and semireduction of the butyl ester with DIBAL-H in toluene, furnished aldehyde **10** (92 % over 3 steps). Horner-Wadsworth-Emmons olefination under the conditions developed by Roush and Masamune^[11] followed by deprotection of the silyl ethers afforded **11** (80 % over 2 steps). This diol ester was observed to undergo cyclization readily upon treatment with catalytic amounts of *t*BuOK to give the thermodynamically favored 2,6-*syn*-disubstituted tetrahydropyran **12** in 63 % yield.^[12] The free secondary alcohol was then protected to furnish silyl ether **13** (96 %). Further elaboration of this intermediate to methyl ketone **14** necessitated the execution of a regioselective Wacker oxidation, which would need to proceed without jeopardizing the stereocenter at C7.^[13] We were pleased to discover that **13** participated in a high-yielding, highly regioselective Wacker oxidation reaction that gave access to the desired methyl ketone **14** in 86 % yield. It is worth noting that this advanced intermediate possesses one of



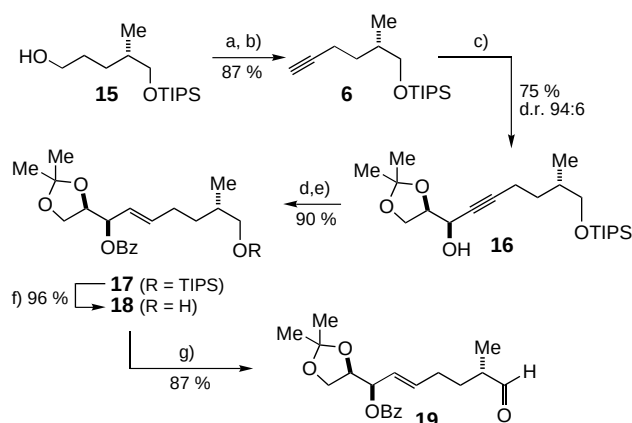
Scheme 2. a) (*R*)-Tol-BINAP (2.1 mol %), Cu(OTf)₂ (2.0 mol %), Bu₄NPh₃SiF₂ (4.0 mol %), THF, -78 °C, then **7** and crotonaldehyde, 4 h, then TFA, 42 %; b) *n*BuOH, reflux, 1 h, 78 %; c) NaBH₄, Et₃B, MeOH, THF, -78 °C, 5 h; d) TESCl, imid., DMAP, DMF, RT, 12 h; e) DIBAL-H, toluene, -78 °C, 30 min, 92 % (3 steps) (d.r. > 95:5); f) DBU, LiCl, (EtO)₂P(O)CH₂CO₂Et, CH₃CN, RT, 2 h; g) TBAF, THF, RT, 2 h, 80 % (2 steps); h) *t*BuOK (10 mol %), THF, 0 °C, 63 % (d.r. 10:1); i) TBSCl, imid., DMAP, DMF, RT, 96 %; j) PdCl₂ (20 mol %), CuCl, O₂, DMF/H₂O 7:1, RT, 86 %. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIBAL-H = diisobutylaluminum hydride, DMAP = 4-*N,N*-dimethylamino pyridine, imid. = imidazole, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TFA = trifluoroacetic acid, TMS = trimethylsilyl, (*R*)-Tol-BINAP = (*R*)-2,2'-Bis(di-*p*-tolyl-phosphino)-[1,1']-binaphthyl.

the tetrahydropyran rings found in the natural product with attendant stereocenters and, importantly, is accessed in nine steps and 30 % overall yield from **8**.

The next key intermediate, aldehyde **19**, was conveniently prepared starting from known alcohol **15** (Scheme 3).^[14] Oxidation of **15** to the corresponding aldehyde (TEMPO/bleach) was followed by conversion to terminal alkyne **6** in 87 % yield according to the Bestmann-Roth protocol.^[15] The addition of **6** to (*R*)-isopropylidene glyceraldehyde (**5**)^[16] was effected employing the method we have recently developed for the *in situ* generation of Zn-alkynylides under mild conditions. In the context of this project we aimed to establish



Scheme 1. Retrosynthetic Analysis. TIPS = triisopropylsilyl.

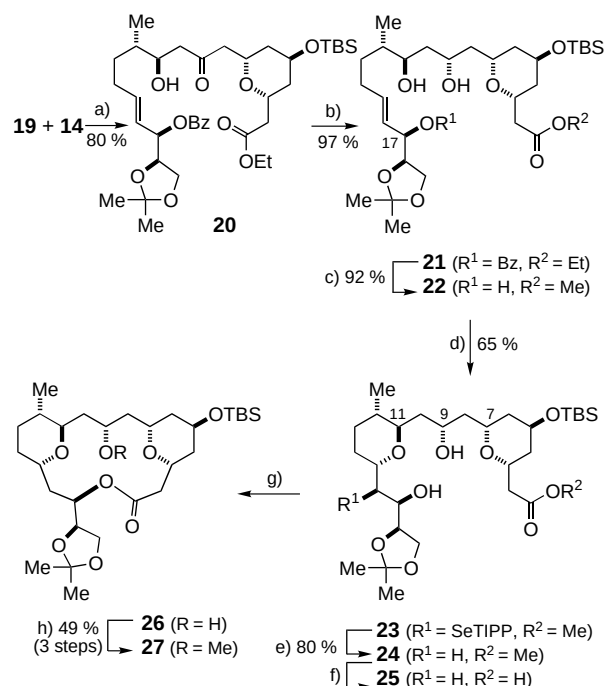


Scheme 3. a) TEMPO, bleach, KBr, CH₂Cl₂, pH 8.6 buffer, RT, 15 min; b) (MeO)₂P(O)CN₂CO₂CH₃, K₂CO₃, MeOH, 16 h, RT, 87 % (2 steps); c) Zn(OTf)₂, (–)-*N*-methylephedrine, Et₃N, toluene, then **5**, RT, 48 h, 75 % (d.r. 94:6); d) LiAlH₄, THF, RT, 5 h; e) BzCl, Et₃N, DMAP, CH₂Cl₂, RT, 15 h, 90 % (2 steps); f) TBAF, THF, 0 °C → RT, 24 h, 96 %; g) TPAP, NMO, CH₂Cl₂, RT, 30 min, 87 %. Bz = benzoyl, NMO = *N*-methyl morpholine *N*-oxide, TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl, TPAP = tetrapropylammonium perruthenate.

whether the reaction could be executed in a reagent-controlled manner with a chiral aldehyde possessing a stereogenic center at C_α.^[17] In this respect, we were delighted to find that **6**, upon treatment with Zn(OTf)₂, (–)-*N*-methylephedrine, and Et₃N in toluene, cleanly adds to **5** to give propargylic alcohol **16** in 75 % yield and 94:6 diastereoselectivity. Adduct **16** was converted to allylic benzoate (*E*)-**17** by reduction with lithium aluminum hydride followed by benzylation (90 % over two steps). Desilylation of **17** with TBAF gave **18** (96 %) and subsequent Ley oxidation^[18] led to aldehyde **19** (87 %) in seven steps and 49 % overall yield from **15**.

With the two key fragments in hand, we next turned to the critical, convergent coupling step. We were pleased to observe that **14** and **19** participated in an aldol addition reaction with Bu₂BOTf/Hünig's base to give β-hydroxy ketone **20** in excellent yield (80 %) as a single diastereomer (by ¹H NMR) possessing the requisite 1,5-*anti* configuration (Scheme 4).^[19] Unfortunately, **20** failed to undergo reduction under Tishchenko conditions.^[20] Alternatively, *anti* diol **21** was obtained from **20** by using Me₄NBH(OAc)₃^[21] (97 %, d.r. > 95:5 by ¹H NMR). Cleavage of the C17 benzoate (K₂CO₃, MeOH) gave access to key intermediate **22** (92 %).

The second tetrahydropyran ring was installed by an electrophile-mediated cyclization of the C11 hydroxy group onto the C=C double bond.^[22] A number of electrophiles, including I₂, IBBr,^[23] and Hg(OAc)₂ were screened, albeit all gave disappointing levels of diastereoselectivity (1:1). We subsequently decided to investigate selenium electrophiles, and promising results with phenylselenenyl chloride (d.r. 3:1, *anti:syn*) prompted us to examine bulkier, substituted phenylselenenyl halides.^[24] In this respect, 2,4,6-triisopropylphenylselenenyl bromide was the reagent of choice: Indeed **22** underwent clean cyclization in CH₂Cl₂ to the desired 2,6-*trans*-substituted tetrahydropyran **23** (74 %, d.r. 88:12 by ¹H NMR). To the best of our knowledge, the stereoselective formation of 2,6-substituted *trans* tetrahydropyrans mediated by 2,4,6-triisopropylphenylselenenyl bromide is unprecedented.



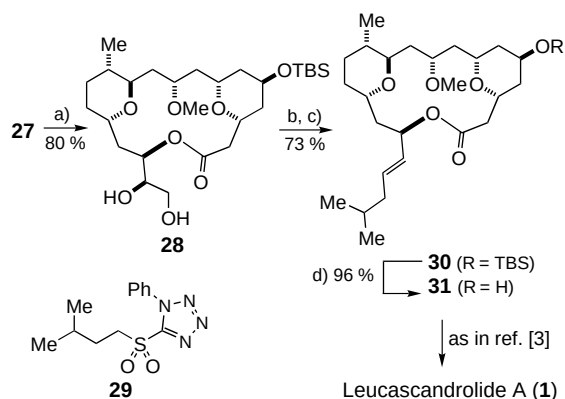
Scheme 4. a) Bu₂BOTf, Et₃Pr₂N, Et₂O, –78 °C, then **19**, 5 h, 80 % (d.r. > 95:5); b) TABH, AcOH, CH₃CN, –40 °C, 70 h, 97 % (d.r. > 95:5); c) K₂CO₃, MeOH, RT, 40 h, 92 %; d) TIPPSeBr, 2,6-di-*tert*-butyl-4-methylpyridine, CH₂Cl₂, –78 °C, 74 % (d.r. 88:12); e) 2,4-dimethoxy-3-methyl-3-*tert*-butyldimethylsilylcyclohexa-1,4-diene, AIBN, *n*-hexane, reflux, 1 h, 80 %; f) TMSOK, Et₂O, RT, 24 h; g) 2,4,6-trichlorobenzoylchloride, Et₃N, DMAP, DMF, RT; h) Me₃OBf₄, proton sponge, 4 Å M.S., CH₂Cl₂, RT, 49 % (3 steps). AIBN = 2,2'-azoisobutyronitrile, M.S. = molecular sieves, proton sponge = *N,N,N',N'*-tetramethyl-1,8-diaminonaphthalene, TABH = tetramethylammonium triacetoxyl borohydride, TIPP = 2,4,6-triisopropylphenyl.

propylphenylselenenyl bromide is unprecedented. Reductive deselenylation of **23** to **24** (80 %) was achieved under tin-free conditions with the silylated 1,4-cyclohexadiene reagent recently developed by Studer and Amrein.^[25] Following ester hydrolysis with TMSOK, *seco* acid **25** was obtained. Our objective at this point in the synthesis was to differentiate the two secondary hydroxy groups at C9 and C17 through a regioselective macrolactonization reaction.^[26] To our surprise, however, lactonization of the *seco* acid under the standard Yamaguchi conditions with various solvents (benzene, toluene, xylene, THF) failed to give any product. Instead a complex mixture of oligomers was obtained.

In earlier feasibility studies in our laboratory, we had observed that macrolactonization proceeded smoothly under Yamaguchi conditions from the precursor incorporating a C9 methyl ether.^[27] We hypothesized that the structure possessing a hydrogen-bonded network involving the C9 hydroxy group preorganizes the C7–C11 backbone in an arrangement that places the C9 oxygen atom between the tetrahydropyrans thus precluding cyclization.^[28] Consequently, we speculated that conducting the lactonization in a polar solvent able to disrupt hydrogen bonds would help the system adopt the necessary conformation for cyclization. Indeed, the use of DMF as solvent cleanly leads to macrocycle **26**, which, after O-methylation of the C9 alcohol with Me₃OBf₄^[29] in the

presence of proton sponge, furnished **27** (49% over 3 steps from **24**).

Hydrolysis of the acetonide present in **27** gave diol **28** (80%) without cleavage of the silyl ether; subsequent oxidative cleavage of the glycol furnished the corresponding aldehyde, setting the stage for the introduction of the C17 side chain (Scheme 5). Towards this aim, we used the Kocienski modification of the Julia–Lythgoe olefination^[30] with sulfone



Scheme 5. a) AcOH/THF/H₂O 2:1:1, 45°C, 5 h, 80%; b) Pb(OAc)₄, EtOAc, 0°C, 15 min; c) **29**, KHMDS, DME, −78°C→0°C, 73% (2 steps) (*E*:*Z* > 95:5); d) TBAF, THF, 0°C→RT, 7 h, 96%. DME = 1,2-dimethoxy ethane, KHMDS = potassium hexamethyldisilazide.

29^[31] to provide olefin (*E*)-**30** as a single isomer (by ¹H NMR) (73% over 2 steps). Deprotection of the secondary silyl ether furnished macrolide **31**, which was identical in all respects (¹H NMR, ¹³C NMR, IR, HRMS, [α]_D) with the intermediate reported previously.^[1,3,4] With a formal synthesis of **1** in hand, we proceeded to complete the total synthesis following the Leighton strategy to give fully synthetic leucascandrolide A.^[3]

In summary, we have reported an expedient, stereocontrolled total synthesis of leucascandrolide A (23 steps longest linear sequence, 2% overall yield). The salient methodological features of the approach include: 1) the use of a reagent-controlled zinc alkynylide addition to isopropylidene glycerinaldehyde; 2) catalytic, enantioselective dienolate aldol addition to crotonaldehyde; 3) the use of a selenium-mediated cyclization reaction for the formation of a *trans*-substituted tetrahydropyran. Moreover, interesting observations concerning hydrogen-bonding effects and conformational flexibility were made in the context of the macrocyclization reaction that may be applicable to other systems.

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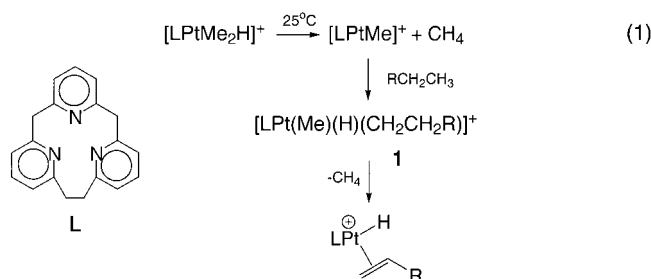
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Control of H–C(sp³) Bond Cleavage Stoichiometry: Clean Reversible Alkyl Ligand Exchange with Alkane in [LPt(Alk)(H)₂]⁺ (L = [2.1.1]-(2,6)-Pyridinophane)**

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The ability of platinum compounds to activate methane catalytically in aqueous solution was first described more than 30 years ago.^[1] Determining the mechanism of the Shilov reaction, which was considered to be an oxidative addition of an alkane to a platinum(II) center, remained challenging for over 25 years. First, increasingly persistent alkylhydridoplatinum(IV) complexes have been discovered,^[2] and then the ability of platinum(II) species to add hydrocarbons to produce very stable platinum(IV) alkyl hydrides was demonstrated.^[3]

Recent work^[4] has shown that the transient [LPtCH₃]⁺, where L is a ligand that cannot structurally accommodate the square-planar geometry preferred by four-coordinate Pt^{II} species and only modestly stabilizes the related octahedral alkane oxidative addition products, cleaves alkane C–H bonds. Here L is [2.1.1]-(2,6)-pyridinophane, and the transient is available according to Equation (1) in Scheme 1. This transient cleaves one substrate C–H bond, but methane is eliminated easily from the Pt^{IV} intermediate **1**; β-H elimination from the derived Pt^{II} alkyl compound then leads to net conversion of alkane to (coordinated) olefin, thus accomplishing a second substrate C–H bond cleavage.



Scheme 1. Synthesis of [LPtMe]⁺ and reaction to give **1**.

To obtain alkane activation products different from the hydrido *olefin* complexes, we suggest here a modification of the starting dialkylhydridoplatinum(IV) complex to allow only an alkane *single* C–H bond activation event. For this we

needed a species with a *single* alkyl ligand attached to a platinum(IV) center which will leave one hydride in the transient [LPtX]⁺ (X = H) species. As a synthetic source of this transient, we initially considered whether [LPtMe(H)₂]⁺ would selectively eliminate methane rather than H₂. The same question has been addressed recently for the complex TpPtMeH₂.^[5] The free energies for methane and for H₂ elimination from [LPtMe(H)₂]⁺ were calculated (DFT, PBE functional,^[6] SBK basis set,^[7] and program package Priroda^[8]; Figure 1) and show that methane elimination is favored, both thermodynamically and kinetically,^[9] by more than 13 kcal mol^{−1} relative to H₂ elimination. Due to the macrocycle constraints, Pt^{II} cannot achieve a planar four-coordinate geometry in [LPtH]⁺ (Figure 1), and the best geometry is

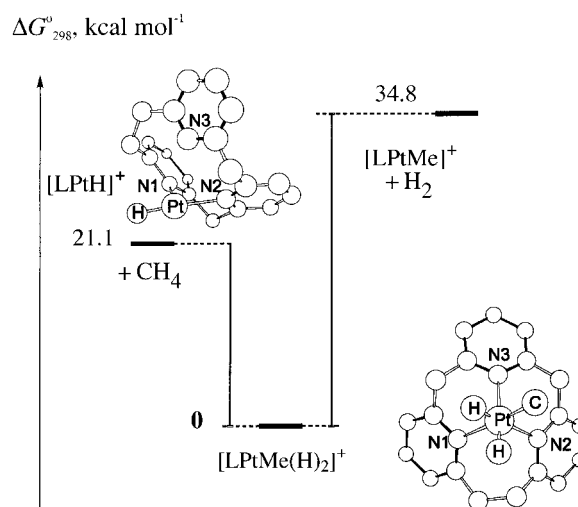
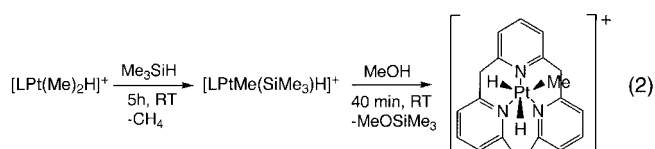


Figure 1. DFT-calculated Gibbs free energy [kcal mol^{−1}] of methane elimination from [LPtMe(H)₂]⁺. Selected bond lengths [Å]: [LPtH]⁺: Pt–N1 1.991, Pt–N2 2.173, Pt–N3 2.985; [LPtMe(H)₂]⁺: Pt–N1 2.243, Pt–N2 2.243, Pt–N3 2.222.

three-coordinate T-shaped, with only 14 valence electrons. The out-of-plane pendant N3 atom interacts negligibly with the Pt^{II} center, and the longer distance of Pt to N2 than to N1 shows the *trans* influence of hydride.^[10] Based on the energies in Figure 1, we expected to develop reversible alkane single C–H bond activation chemistry with a [LPtH]⁺ transient; this is unprecedented for Pt^{II}.

The synthesis of [LPtMe(H)₂]⁺,^[11] as its [BAR₄^F][−] salt (Ar^F = 3,5-(CF₃)₂C₆H₃), is summarized in Equation (2) (> 98 % yield based on NMR data, relative to signal for BAR₄^F; yield of isolated product 85 %). The new dihydridoplatinum(IV) com-



plex is air- and water-stable and can be recrystallized from a warm water–methanol mixture. No decomposition of this complex as a solid is observed at room temperature for at least two months. According to ¹H and ¹³C NMR data, the

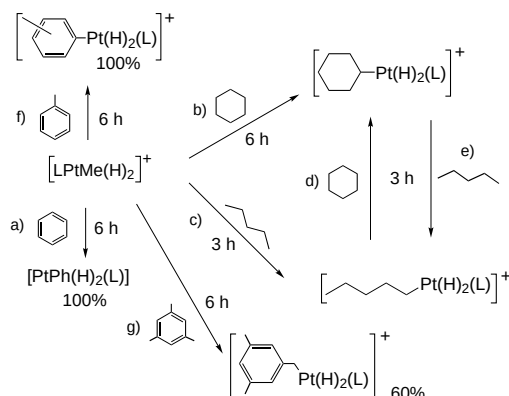
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[LPtMe(H)₂]⁺ ion is unsymmetrical. The ¹H NMR spectrum shows two separate resonance signals for nonequivalent hydrido ligands at $\delta = -20.37$ (s, ¹J_{Pt,H} = 1318 Hz) and -19.32 ppm (s, ¹J_{Pt,H} = 1276 Hz) (CD₂Cl₂, 21 °C), two sets of signals with an AX pattern for the ligand methylene bridges, three triplets for *para* protons of pyridine residues in a 1:1:1 ratio, and six doublets for the corresponding *meta* protons of equal intensity.

When [LPtMe(H)₂]⁺ was heated in a solution of dichloromethane containing benzene (50 vol %) in a sealed NMR tube at 86 °C, the NMR signals of the methyl ligand and both hydride ligands of the starting complex gradually disappear and two new hydride resonance signals appear at $\delta = -19.24$ (s, ¹J_{Pt,H} = 1349 Hz) and -18.13 ppm (s, ¹J_{Pt,H} = 1307 Hz) (CD₂Cl₂, 21 °C). Over 6 h, the starting complex transforms almost quantitatively into the dihydridophenylplatinum(IV) complex of the same low symmetry as its methyl predecessor (Scheme 2a) (> 98 % yield based on NMR data, relative to signal for BA₄^F; yield of isolated product 80 %).



Scheme 2. Reactions of [LPtMe(H)₂]⁺. See text for details.

Thermolysis of [LPtMe(H)₂]⁺ in 1:1 mixtures of cyclohexane or *n*-pentane (Scheme 2b and c, respectively) and CD₂Cl₂ used as a solvent also cleaved C–H bonds. After [LPtMe(H)₂]⁺ had been heated for 3–6 h at 86 °C, new dihydrido alkyl complexes [LPt(Alk)(H)₂]⁺ were obtained in 80 % (Alk = cyclohexyl; Cy) yield (based on NMR data, relative to signal for BA₄^F) or 70 % (Alk = *n*-amyl; *n*-Am) yield (based on NMR data, relative to signal for BA₄^F). The less than quantitative yield is due to side reactions with dichloromethane. In each case, two new hydride resonance signals appeared together with characteristic multiplets of methylene and methine protons in the α -position to the platinum center, along with their corresponding platinum satellites (see Supporting Information). No significant amounts of dihydrido *sec*-pentyl isomers were observed in the case of *n*-pentane even after longer time (20 h at 86 °C), thus indicating the high thermodynamic (see below) selectivity of the transient [LPtH]⁺ species towards primary alkane C–H bonds. Both cyclohexyl and *n*-pentyl dihydrides have been isolated, recrystallized from a warm water–methanol mixture, and further characterized by ¹³C NMR spectroscopy.

Why do these reactions stop at Pt^{IV} alkyl compounds, rather than proceeding to the Pt^{II} hydrido olefin products

(Scheme 1) produced when the reactive transient is [LPtMe]⁺? The reason is precisely the same as why [LPtMe(H)₂]⁺ loses methane, not H₂: the strong energetic preference against H₂ loss shown in Figure 1.

Figure 1, together with the electronic similarity of [LPtR(H)₂]⁺ when R = methyl, amyl, or cyclohexyl, suggests that the alkane cleavage shown in Scheme 2 should be reversible, to regenerate [LPtH]⁺. The reversibility of alkyl ligand exchange at a platinum(IV) center at 86 °C has been shown by two experiments in which either *n*-amyl- or cyclohexyldihydridoplatinum(IV) complexes were heated at this temperature with a 1:1 mixture of the other related hydrocarbon and CD₂Cl₂. In the case of [LPt(*n*-Am)(H)₂]⁺ the conversion was complete in 3 h with 60 % yield of [LPtCy(H)₂]⁺ (Scheme 2d). Free *n*-pentane was detected in the course of this reaction. Some of the starting compound decomposed to form unidentified products presumably derived from reaction with CD₂Cl₂. Similarly, [LPtCy(H)₂]⁺ reacted completely with *n*-pentane in 3 h to form [LPt(*n*-Am)(H)₂]⁺ in 50 % yield (Scheme 2e). Since these hydrocarbyl exchange reactions of secondary (Cy) and primary alkyl compounds are complete within 3 h we can conclude that this time is sufficient to bring *n*-pentane to equilibrium with corresponding isomeric primary and secondary pentyl dihydrides. Therefore, the observed selectivity of *n*-pentane C–H bond cleavage (see above) reflects thermodynamic, not kinetic selectivity of transient [LPtH]⁺.

To learn more about the regioselectivity of transient [LPtH]⁺ we studied the reactivity of [LPtMe(H)₂]⁺ towards toluene and mesitylene, two other aromatic hydrocarbons that offered both saturated and aromatic C–H bonds. Both react cleanly in the course of 3–6 h at 86 °C in 1:1 hydrocarbon–CD₂Cl₂ mixtures with [LPtMe(H)₂]⁺ to produce new platinum(IV) hydrocarbyl dihydrides (Scheme 2f and g, respectively). Toluene traps the transient efficiently and gives rise to two distinct products in a 2:1 ratio. Their hydrides resonate at $\delta = -19.28$ (s, ¹J_{Pt,H} = 1350 Hz) and -18.17 ppm (s, ¹J_{Pt,H} = 1310 Hz) for the major isomer and $\delta = -19.30$ (s, ¹J_{Pt,H} = 1351 Hz) and -18.19 ppm (s, ¹J_{Pt,H} = 1308 Hz) for the minor isomer. Two distinct methyl groups of the tolyl ligands integrate as 3H each relative to their hydride resonance signals. According to the pattern of aryl resonance signals, the major product is the *meta*-tolyl isomer, [LPt(*m*-Tol)(H)₂]⁺. The minor product is assigned as the *para*-tolyl isomer. Neither an *ortho* isomer nor a product of methyl C–H bond cleavage is observed. It is usual^[12] that aromatic C–H bonds are preferred in oxidative addition to a metal center. Mesitylene, however, gives a single reaction product which is obtained in poorer yield (60 %, based on NMR data, relative to the signal for BA₄^F) than alkanes (Scheme 2g). In this case new hydride resonance signals appear at $\delta = -20.13$ (s, ¹J_{Pt,H} = 1334 Hz) and -19.20 ppm (s, ¹J_{Pt,H} = 1290 Hz). Aromatic protons show two broadened singlets, $\delta = 6.62$ (br s, 1H; *para*-CH) and 6.73 ppm (br s, 2H; *ortho*-CH); two singlets integrate as two equivalent methyl groups (2.16; s, 6H) and as a platinum-bound methylene group with characteristic platinum satellites at $\delta = 3.46$ ppm (apparent s, ¹J_{Pt,H} = 110 Hz, 2H). These data are consistent with the formulation of the reaction product as [LPt(CH₂-3,5-Me₂C₆H₃)(H)₂]⁺.

Thus, 1,3,5-trimethylbenzene fails to react with sterically inaccessible aromatic C–H bonds but prefers activation of less hindered saturated C–H bonds. The only precedent for such selectivity of mesitylene oxidative addition to a platinum atom is the d^{10} transient $[\text{Pt}(\text{Cy}_2\text{PC}_2\text{H}_4\text{PCy}_2)]$.^[13,14] At the same time, formation of mixtures of isomeric aryl- and benzylplatinum(II) complexes as products of methylarene activation with platinum(II) complexes is known.^[15]

Thus, the influence of $\text{X}=\text{H}$ versus $\text{X}=\text{Me}$ in transient $[\text{LPtX}]^+$ is controlled by both the thermodynamics and kinetics of the reductive elimination of the resulting $[\text{LPtH(R)X}]^+$. When $\text{X}=\text{Me}$, methane elimination is accessible, but when $\text{X}=\text{H}$, H_2 elimination is energetically inaccessible, resulting in a Pt^{IV} product and only a single alkane C–H bond cleaved. In short, the number of methyl groups in the $[\text{LPt}(\text{Me})_n\text{H}_{3-n}]^+$ precursor dictates the number of alkane substrate C–H bonds that can be altered. This controllable production of alkane-derived $[\text{Pt}^{\text{IV}}(\text{alkyl})]$ or $[\text{Pt}^{\text{II}}(\text{olefin})]$ complexes may prove valuable in subsequent efforts to derivatize and effect net production of functionalized organic products from alkanes.

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Directing Otherwise Incompatible Reactions in a Single Solution by Using DNA-Templated Organic Synthesis**

Christopher T. Calderone, James W. Puckett, Zev J. Gartner, and David R. Liu*

General methods for translating amplifiable information carriers such as DNA into synthetic molecules may enable the evolution of non-natural molecules through iterated cycles of translation, selection, and amplification that are currently available only to proteins and nucleic acids. During the process of developing such a method, we recently discovered that DNA templates can sequence-specifically direct a broad range of chemical reactions without any apparent structural requirements.^[1,2] The generality of DNA-templated synthesis together with appropriate linker and purification strategies enabled the first multistep small-molecule syntheses programmed by DNA templates,^[3] which raised the possibility of using this approach to generate synthetic small-molecule libraries of useful complexity.

DNA-templated synthesis^[4–24] can generate products individually linked to oligonucleotides that both encode and direct their syntheses.^[1–3] This feature may enable reaction modes useful for library construction that are not available through current synthetic approaches. Present synthesis methodology, for example, cannot differentiate functional groups of similar reactivity on different molecules within the same solution even though such differentiation would enable diversification to take place without the effort or constraints associated with spatial separation. Here we report that DNA oligonucleotides can simultaneously direct several different types of synthetic reactions within the same solution, even though the reactants involved would be cross-reactive and therefore incompatible under traditional synthesis conditions. Our findings represent a new mode of reaction made possible by DNA-templated synthesis and may enable the one-pot diversification of synthetic library precursors into products of multiple reaction types.

The ability of DNA templates to mediate diversification by using different types of reaction without spatial separation was first tested by preparing three oligonucleotide templates of different DNA sequences (**1a–3a**) functionalized at their 5'-ends with maleimide groups and three oligonucleotide reagents (**4a–6a**) functionalized at their 3'-ends with an amine, thiol, or nitroalkane group, respectively. The DNA sequences of the three reagents each contained a different 10-base annealing region that was complementary to ten bases

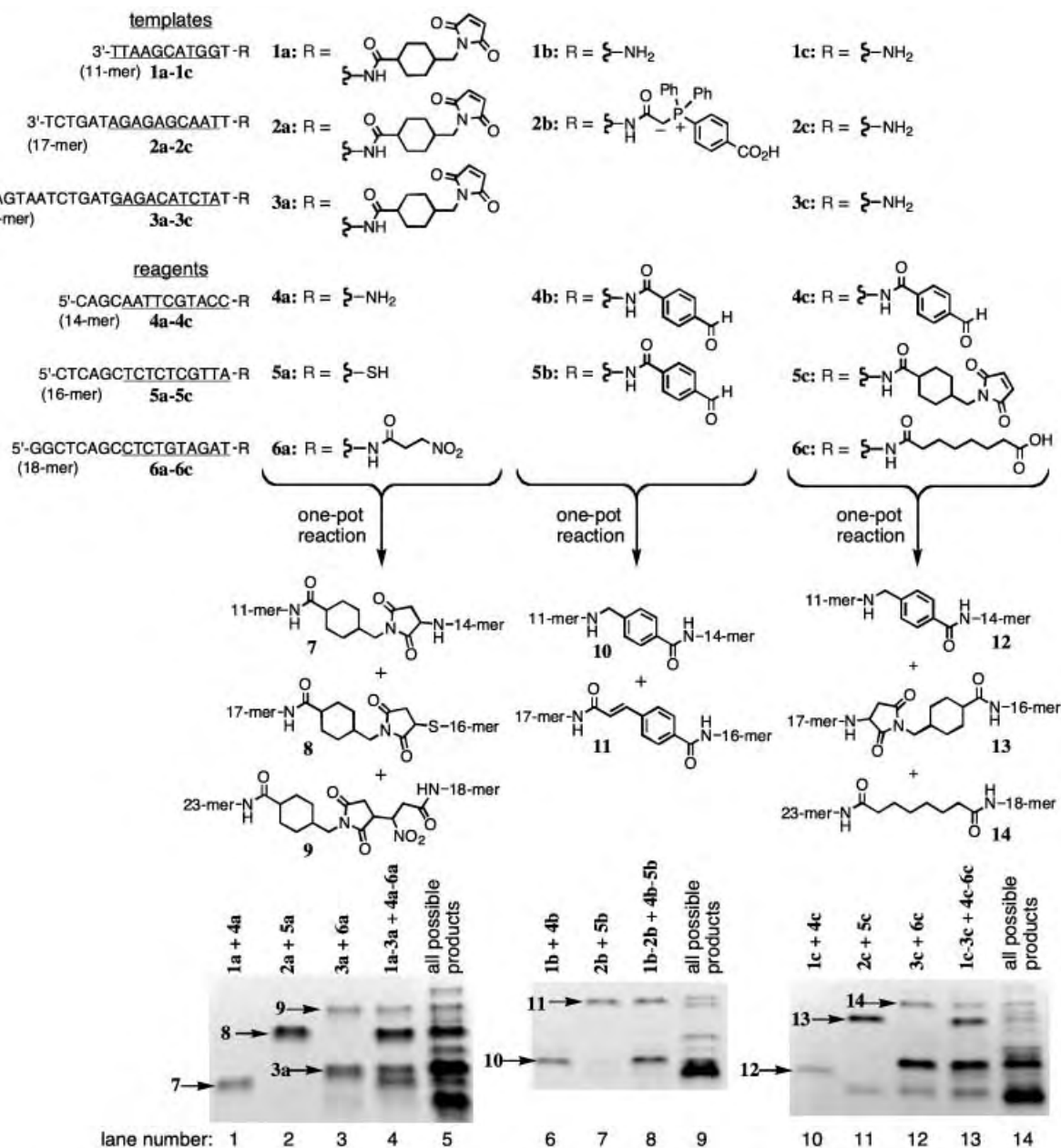
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near the 5'-end of each of the templates. Combining **1a** with **4a**, **2a** with **5a**, or **3a** with **6a** in three separate vessels at pH 8.0 resulted in the expected^[1,2] DNA-templated amine conjugate addition, thiol conjugate addition, or nitro-Michael addition products **7–9** (Scheme 1).

To distinguish the nine possible reaction products that could be generated upon combining **1a–6a**, we varied the lengths of the template oligonucleotides as 11, 17, or 23 bases and the lengths of the reagent oligonucleotides as 14, 16, or 18 bases in length. Differences in oligonucleotide length were achieved using extensions distal from the reactive groups and did not significantly affect the efficiency of the DNA-templated reactions. This design enabled all nine possible

reaction products (linked to 25, 27, 29, 31, 33, 35, 37, 39, or 41 bases of DNA) to be distinguished by denaturing polyacrylamide gel electrophoresis. A solution containing all three templates (**1a–3a**) was combined with a solution containing all three reagents (**4a–6a**) at pH 8.0. The resulting reaction exclusively generated the three desired products **7**, **8**, and **9** with lengths of 25, 33, and 41 bases, respectively, and indicates that only the three reactions corresponding to the complementary template–reagent pairs took place (Scheme 1). Formation of the other six possible reaction products was not detected by densitometry (<5% reaction). In contrast, individually reacting templates and reagents containing the same, rather than different, 10-base annealing regions enabled



Scheme 1. Subjecting maleimides, aldehydes, or amines to multiple DNA-templated reaction types in a single solution. The reactants shown were combined either pairwise (lanes 1–3, 6–7, or 10–12) or in one pot (lanes 4, 8, and 13) under the conditions described in the text and the resulting products were analyzed by denaturing gel electrophoresis. Annealing regions of oligonucleotides are underlined. To generate all the possible products (lanes 5, 9, and 14), which mimics a traditional reaction mode, templates and reagents analogous to those shown in the scheme but containing DNA sequences capable of annealing to any reagent or template, respectively, were reacted in pairs and combined.

the formation of all possible products (Scheme 1, lane 5). This result demonstrates the ability of DNA-templated synthesis to direct the selective one-pot transformation of a single functional group into three distinct types of products (in this example, maleimide into secondary amine, thioether, or α -branched nitroalkane).

To test the ability of this diversification mode to support one-pot reactions requiring non-DNA-linked accessory reagents, we conducted an analogous experiment with two aldehyde-linked reagents of either 14 or 16 bases in length (**4b** or **5b**, respectively) and a complementary 11-base amine-linked template (**1b**) or a 17-base phosphorane-linked template (**2b**). Combining **1b** and **4b** at pH 8.0 in the presence of 3 mM NaBH₃CN resulted in the DNA-templated reductive amination product **10**, while **2b** and **5b** under the same conditions generated Wittig olefination product **11** (Scheme 1). Mixing all four reactants together in one pot resulted in an identical product distribution as the combined individual Wittig olefination or reductive amination reactions (Scheme 1). No reaction between amine **1b** and aldehyde **5b** or between phosphorane **2b** and aldehyde **4b** was detected (Scheme 1, lane 8 versus 9).

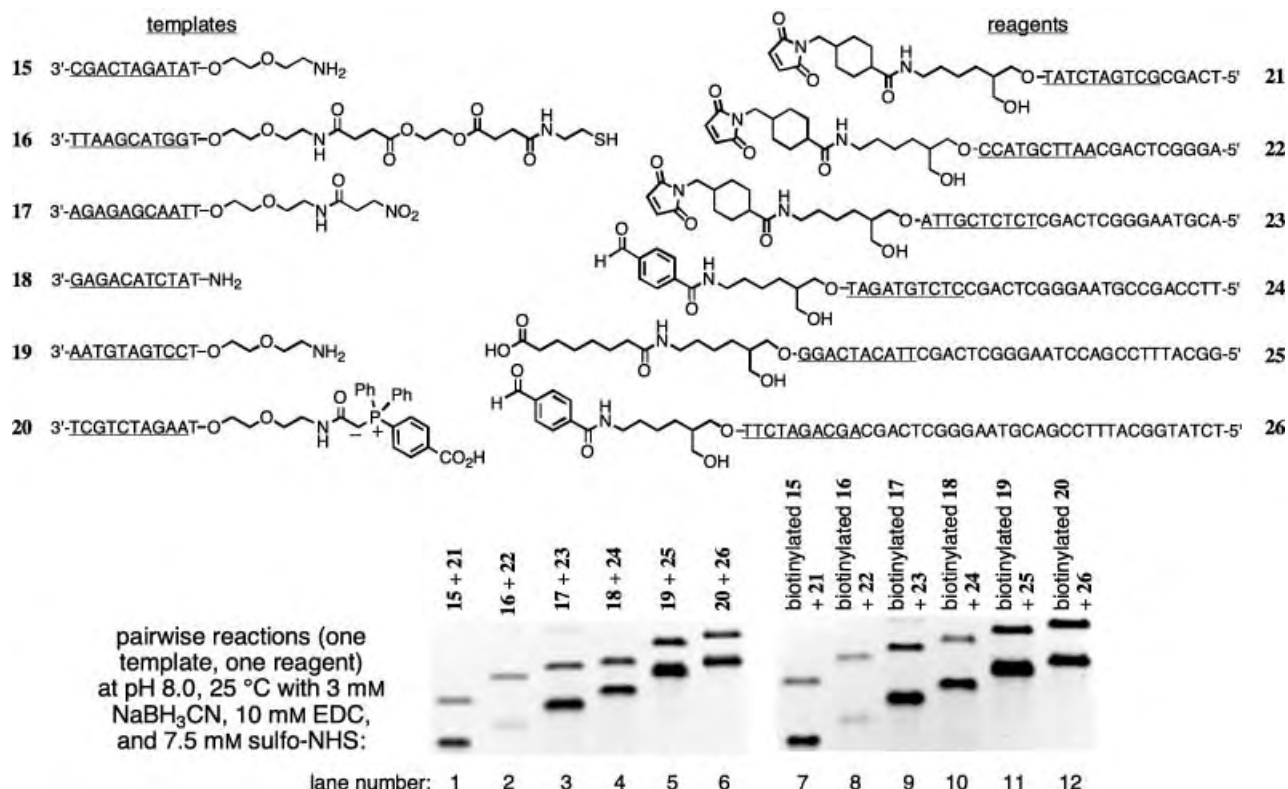
We further explored the generality of this approach by including multiple reaction types that required different accessory reagents. Three amine-linked templates (**1c–3c**) of length 11, 17, or 23 bases were combined with a reagent linked to an aldehyde, carboxylic acid, or maleimide group (**4c–6c**) 14, 16, or 18 bases in length, respectively, at pH 8.0 in the presence of 3 mM NaBH₃CN, 10 mM 1-(3-dimethyl-amino-propyl)-3-ethylcarbodiimide (EDC), and 7.5 mM *N*-hydroxysulfosuccinimide (sulfo-NHS). The reactions containing all six reactants afforded the same three reductive amination, amine acylation, and conjugate addition products (**12–14**) that were generated from the individual reactions containing one template and one reagent and did not produce detectable quantities of the six possible undesired products arising from non-DNA-templated reactions (Scheme 1, lanes 10–14). Collectively, these results indicate that DNA-templated synthesis can direct simultaneous reactions between several mutually cross-reactive groups in a single pot to yield only the sequence-programmed subset of many possible products.

The above three examples each diversified a single functional group (maleimide, aldehyde, or amine) into products of different reaction types. A more general format for the one-pot diversification of a DNA-templated synthetic library into products of multiple reaction types would involve the simultaneous reaction of different functional groups linked to both reagents and templates. To examine this possibility we prepared six DNA-linked nucleophile templates (**15–20**) and six DNA-linked electrophile reagents (**21–25**) collectively encompassing all of the functional groups used in the above three examples (amine, aldehyde, maleimide, carboxylic acid, nitroalkane, phosphorane, and thiol). These twelve DNA-linked reactants could, in theory, undergo simultaneous amine conjugate addition, thiol conjugate addition, nitro-Michael addition, reductive amination, amine acylation, and Wittig olefination in the same pot, although the apparent second-order rate constants of these six reactions vary more than tenfold.^[1,2]

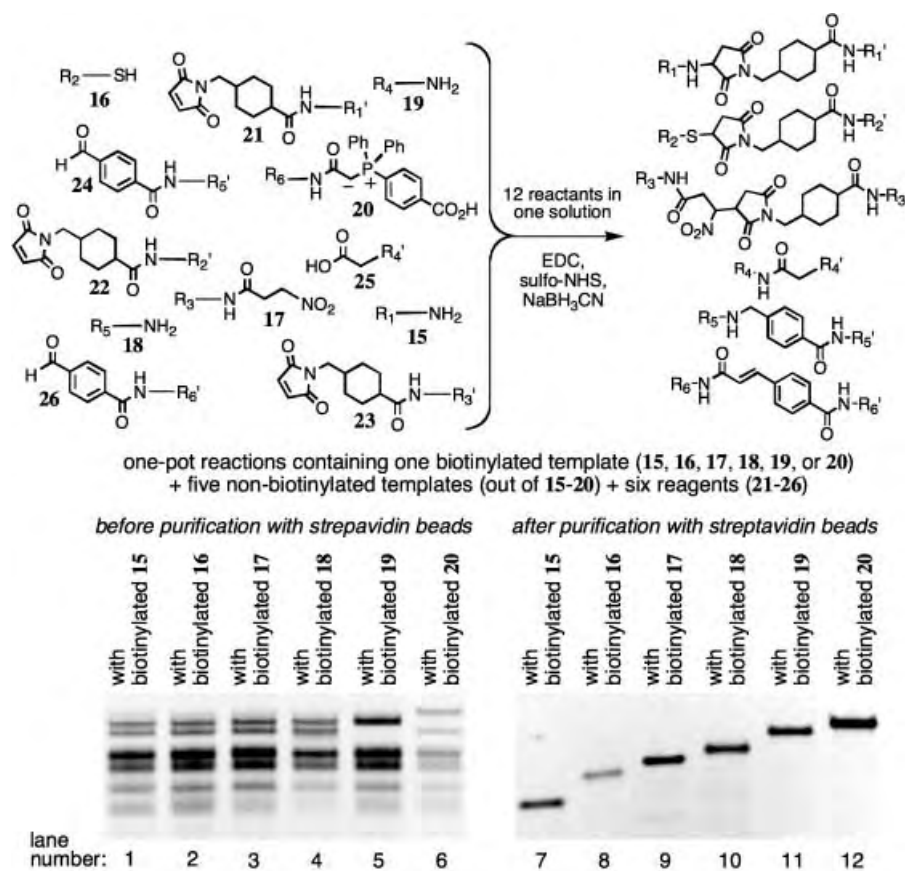
Determining the outcome of combining all twelve reagents and templates in a single pot by using oligonucleotides of varying lengths is difficult because of the large number (at least 28) of possible products that could be generated. Instead, we varied the length of the reagents as 15, 20, 25, 30, 35, or 40 bases but fixed the length of the templates at 11 bases (Scheme 2). Each of the six complementary template–reagent pairs when treated separately at pH 8.0 in the presence of 3 mM NaBH₃CN, 10 mM EDC, and 7.5 mM sulfo-NHS generated the expected amine conjugate addition, thiol conjugate addition, nitro-Michael addition, reductive amination, amine acylation, or Wittig olefination products (Scheme 2). Reaction yields were at least half of those previously reported^[1,2] for the corresponding individual reactions, despite having to compromise between differing optimal reaction conditions. Templates **15–20** were also prepared in a 3'-biotinylated form. The biotinylated templates demonstrated reactivities indistinguishable from those of their non-biotinylated counterparts (Scheme 2).

Six separate reactions each containing twelve reactants were then performed at pH 8.0 in the presence of 3 mM NaBH₃CN, 10 mM EDC, and 7.5 mM sulfo-NHS (Scheme 3). Each reaction contained a different biotinylated template (biotinylated **15–20**) together with five non-biotinylated templates (from **15–20**) and six reagents (**21–25**). These reactions were initiated by combining a solution containing six templates with a solution containing six reagents. The products that arose from each biotinylated template were captured with streptavidin-coated magnetic beads and identified by denaturing gel electrophoresis. Since the six reagents in each reaction contained oligonucleotides of unique lengths, the formation of any reaction products involving the biotinylated templates and any of the reagents could be detected. In all six cases, the biotinylated template formed only the single product programmed by its DNA sequence (Scheme 3) despite the possibility of forming up to five other products in each reaction. Taken together, these findings indicate that reactions of significantly different rates requiring a variety of non-DNA-linked accessory reagents can be directed by DNA-templated synthesis in the same solution, even when both templates and reagents contain several different cross-reactive functional groups. The ability of DNA templates to direct multiple reactions at concentrations that exclude nontemplated reactions from proceeding at appreciable rates mimics, in a single solution, a spatially separated set of reactions.

Compared to the use of traditional synthetic methods, the generation of libraries of small molecules by DNA-templated synthesis is limited by several factors including the need to prepare DNA-linked reagents; the restriction of aqueous, DNA-compatible chemistries; and the reliance on characterization methods such as mass spectrometry and electrophoresis that are appropriate for reactions performed on a molecular biology scale (pg to μ g). On the other hand, DNA-templated synthesis allows the direct *in vitro* selection (as opposed to screening) and amplification of synthetic molecules with desired properties, may enable the preparation of synthetic libraries of unprecedented diversity, and requires only minute quantities of material for selection and identification of active library members.^[1] In addition, the above



Scheme 2. Templates and reagents used in pairwise and 12-reactant one-pot DNA-templated reactions. Templates **15–20** were prepared in either a non-biotinylated form or a 3'-biotinylated form. Lanes 1–6: denaturing gel electrophoresis of pairwise DNA-templated reactions of non-biotinylated templates **15–20** with complementary reagents **21–26**, respectively. Lanes 7–12: denaturing gel electrophoresis of pairwise DNA-templated reactions of biotinylated **15–20** with **21–26**, respectively. In all lanes the product band appears above the reagent band and the 11-base templates are not visible.



Scheme 3. A one-pot DNA-templated reaction containing 12 reactants and at least 7 possible reaction types generates only 6 sequence-programmed products out of at least 28 possible products. Templates **15–20**, one of which was biotinylated, were combined with reagents **21–26**. Lanes 1–6: denaturing gel electrophoresis of crude reactions. Products arising from each biotinylated template were isolated using streptavidin-coated magnetic beads and analyzed by denaturing gel electrophoresis in lanes 7–12. R, R' = linkers and DNA oligonucleotides shown in Scheme 2.

work demonstrates that potentially useful modes of reactivity not possible using current synthetic methods can be achieved in a DNA-templated format. In this case, we have shown that six different types of reactions can be performed simultaneously in one solution, provided that the required non-DNA-linked accessory reagents are compatible (in the above work, NaBH_3CN , EDC, and sulfo-NHS). This reaction mode may enable the diversification of synthetic small-molecule libraries using different reaction types^[25–29] in a single solution in addition to the more common diversification approach of using different building blocks in a given reaction. The use of this and other novel modes of reactivity enabled by DNA-templated synthesis is the subject of ongoing studies in our laboratory.

Experimental Section

Oligonucleotides were synthesized by using standard automated solid-phase techniques. Modified phosphoramidites and controlled-pore glass supports were obtained from Glen Research (Sterling, VA, USA). Unless otherwise noted, functionalized templates and reagents were synthesized by treating 5'- $\text{H}_2\text{N}(\text{CH}_2\text{O})_2$ -terminated oligonucleotides (for templates) or 3'- $\text{OPO}_3\text{-CH}_2\text{CH}(\text{CH}_2\text{OH})(\text{CH}_2)_4\text{NH}_2$ -terminated oligonucleotides (for reagents) in a 9:1 mixture of aqueous 200 mM pH 7.2 sodium phosphate buffer and DMF containing the appropriate *N*-hydroxysuccinimide ester (2 mg mL⁻¹, Pierce, Rockford, IL, USA) at 25°C. For the aldehyde and nitroalkane-linked oligonucleotides (**4b**, **4c**, **5b**, **6a**, **17**, **24**, and **26**) the NHS esters were generated by combining the appropriate carboxylic acid (900 mM in DMF) with equal volumes of dicyclohexylcarbodiimide (900 mM in DMF) and NHS (900 mM in DMF) for 90 min. Phosphorane-linked oligonucleotides (**2b** and **20**) were prepared by reaction of the appropriate amino-terminated oligonucleotide with a DMF solution (20 mg mL⁻¹, 0.1 volumes) of the NHS ester of iodoacetic acid (SIA, Pierce) in pH 7.2 buffer for 90 min as above, followed by addition of a solution (20 mg mL⁻¹, 0.1 volumes) of 4-diphenylphosphanylbenzoic acid in DMF. Thiol-linked template **16** was synthesized by treating the appropriate oligonucleotide with ethylene glycol bis(succinimidylsuccinate) (EGS, Pierce) for 15 minutes, followed by addition of 2-aminoethanethiol (300 mM, 0.1 volumes). Reagent **5a** was synthesized using 3'- $\text{OPO}_3\text{-(CH}_2)_3\text{SS}(\text{CH}_2)_3\text{ODMT}$ -functionalized controlled-pore glass (CPG) support and reduced prior to use according to the manufacturer's protocol. Linkers between DNA oligonucleotides and the functional groups in **1a–6c** are as follows: **1b** and **1c**: DNA-5'- NH_2 ; **1a**, **2a–2c**, **3a**, and **3c**: DNA-5'- $\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{-NH-}$; **5a**: DNA-3'- $\text{O}(\text{CH}_2)_3\text{SH}$; **4a–4c**, **5b**, **5c**, **6a**, and **6c**: DNA-3'- $\text{O-CH}_2\text{CH}(\text{CH}_2\text{OH})(\text{CH}_2)_4\text{NH-}$. The oligonucleotide sequences used to generate all possible products in Scheme 1 (lanes 5, 9, and 14), with annealing regions underlined, are: R-TATCTACAGAG-3' (**1a–1c**); R-TATCTACAGAGTAGTCT-3' (**2a–2c**); R-TATCTACAGAGTAGTCTAATGAC-3' (**3a–3c**); 5'-CAGCCTCTGTAGAT-R (**4a–4c**); 5'-CTCAGCCTCTGTAGAT-R (**5a–5c**); 5'-GGCTCAGCCTCTGTAGAT-R (**6a–6c**). Functionalized templates and reagents were purified by gel filtration (Sephadex G-25) followed by reverse-phase HPLC (0.1M triethylammonium acetate/acetonitrile gradient). Representative functionalized templates and reagents were further characterized by MALDI mass spectrometry.

3'-biotinylated oligonucleotides were prepared by using biotin-TEG CPG (Glen Research). Products arising from the biotinylated templates were purified by mixing with streptavidin-linked magnetic beads (1.05 equiv, Roche), washing twice with 4M guanidinium hydrochloride, and eluting with aqueous 10 mM tris(hydroxymethyl)aminomethane (Tris) pH 7.6 with 1 mM biotin at 80°C.

All reactions were performed by dissolving reagents and templates in separate vessels in pure water before combining them into a solution of 50 mM aqueous *N*-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid (TAPS buffer), pH 8.0, 250 mM NaCl at 25°C for 16 h with DNA-linked reactants at 60 nM (Scheme 1) or at 12.5 nM (Scheme 2 and Scheme 3). NaBH_3CN , EDC, and sulfo-NHS were present when appropriate as described in the text. Products were analyzed by denaturing

polyacrylamide gel electrophoresis using ethidium bromide staining and UV transillumination. Differences in charge states, attached functional groups, and partial secondary structure resulted in modest variations in gel mobility for different functionalized oligonucleotides of the same length (see Schemes 1, 2, and 3).

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Framework Topology of ERS-10 Zeolite**

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Carlo Perego, and Roberto Millini*

*Dedicated to Professor Jens Weitkamp
on the occasion of his 60th birthday*

Zeolites are crystalline microporous aluminosilicates with frameworks based on a three-dimensional (3D) network of corner-sharing TO_4 ($\text{T} = \text{Si}, \text{Al}$) tetrahedra. A zeolite framework can be described as a regular assembly of finite (secondary building units, SBUs) or infinite building units (periodic building units, PerBUs). These PerBUs are layers or chains that stack in one or two directions according to given symmetry operations and/or simple lateral translations to build a regular 3D structure. However, when two or more stacking modes are possible, the same PerBU gives rise to different regular 3D structures, as well as to disordered intermediates arising from deviation of the stacking sequence from the periodic ordering. Ordered 3D structures (known as end-members) and disordered intermediates built with the same PerBU belong to the same family of structure types; the most notable examples are ZSM-11 and Beta zeolites. ZSM-11 is an intergrowth of MFI and MEL end-members of the pentasil family, which can be built by applying different symmetry operations to the same pentasil (PerBU) layer: inversion (*i*) in the case of MFI and reflection (*m*) in the case of MEL.^[1]

Analogously, the structure of zeolite Beta can be described as an intergrowth of polymorphs stacked along the *c* direction.^[2,3] The stacking faults are manifested by anisotropic broadening of a selected class of reflection peaks in powder diffraction patterns. According to Newsam et al.,^[2] "The diffraction intensity from faulted complex materials can be computed by exploiting the recursive properties of faulting sequences in crystals". This approach was implemented in their program DIFFaX,^[4] which is based on a recursion algorithm and allows simulation of X-ray diffraction patterns (XRD) from faulted materials.

Recently, Carluccio et al.^[5] reported the synthesis of the new zeolite ERS-10 by using 6-azonia-spiro-[5,5]-undecane hydroxide as a structure-directing agent (SDA); the XRD pattern of ERS-10 is characterized by the features typical of an intergrowth material, namely the contemporaneous presence of sharp and broad reflections (Figure 1). These features

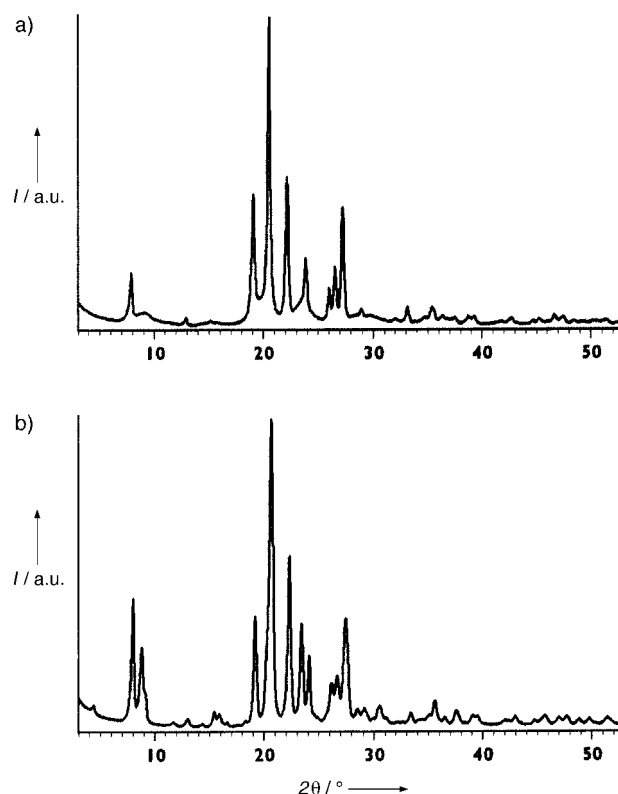


Figure 1. XRD patterns of a) as-synthesized ERS-10 and b) EUO.

make a structural characterization of this zeolite very difficult, requiring extensive model building of the stacking sequences and comparison of the DIFFaX computed patterns with the experimental one.

Preliminary structural characterization^[6] indicated that the XRD pattern of ERS-10 is closely related to that of EU-1^[7] (IZA code EUO) (Figure 1).

According to Marler and Gies,^[8] EUO is in turn structurally related to two other zeolites: nonasil^[8] (IZA code NON) and NU-87^[9] (IZA code NES). Inspection of the unit cell parameters of these zeolites indicated that parameters *a* and *b* are very similar, while *c* varies in a regular way from NON to NES (Table 1). In fact, all these structures can be built from the same pseudo-hexagonal sheet defined by Briscoe et al. for EUO.^[7] In all cases, the sheets regularly stack along the *c* axis and are interconnected by O atoms only in the case of NON; otherwise they are interconnected by O atoms and -O-Si-O-Si-O- bridges in EUO, and by -O-Si-O-Si-O- bridges in NES.^[9] In the case of ERS-10, the sharp reflections present in the XRD pattern were indexed according to an orthorhombic unit cell with the following parameters: *a* = 13.704(2), *b* = 22.329(3) and *c* = 5.0682(8) Å.^[6] Moreover, parameters *a* and *b* are identical to those of NON, EUO, and NES, while

Table 1. Unit cell parameters for NON, EUO, NES, and ERS-10.

Zeolite	<i>a</i> [Å]	<i>b</i> [Å]	<i>c</i> [Å]
NON ^[a]	13.627	22.323	15.058
EUO	13.695	22.326	20.178
NES ^[b]	13.698	22.660	25.213
ERS-10	13.704	22.329	5.068

[a] matrix: (010, 001, 100). [b] matrix: (100, 001, 010).

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c is $1/4$ that of EUO, that is the thickness of the above-mentioned pseudo-hexagonal sheet. This was considered a strong indication that ERS-10 is closely related to these zeolites. Furthermore, the presence of broad reflections supported the hypothesis that ERS-10 is a disordered member of this zeolite family.

This hypothesis was further confirmed by the discovery of NU-85, recognized as an EUO/NES intergrowth.^[10] The reflections that appear broad in the XRD pattern of ERS-10 are still sharp in the case of NU-85, but their relative intensity depends on the extent of the intergrowth phenomena.^[10] It is therefore clear that ERS-10 and NU-85 are two disordered members of the same family of zeolites. However, instead of treating ERS-10 as an intergrowth of EUO and NES alone, we considered the possibility of including also NON. The first step of the procedure was to identify the PerBUs present in the ordered structures. We focused our attention on gottardiite, the natural counterpart of NU-87, mainly for two reasons: 1) the framework topology of this zeolite allows each PerBU to be easily isolated; 2) an accurate structural model refined from single-crystal X-ray diffraction data is available for this material.^[11]

Figure 2 shows the projection of the gottardiite framework along the [100] direction; the PerBUs identified in this

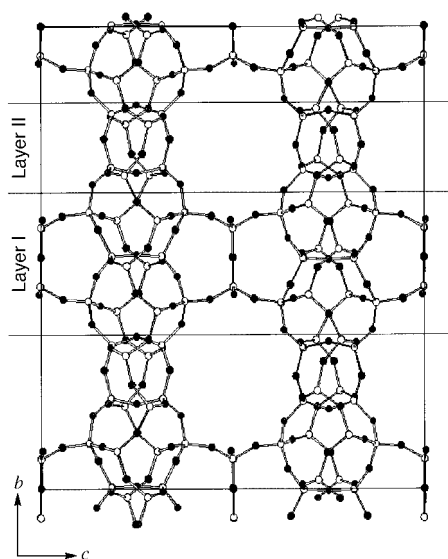


Figure 2. Framework topology of zeolite gottardiite (NES); layers I and II are also shown.

structure, defined as layer I and layer II respectively, are also shown. Figure 3 shows the building scheme that allows the three framework types, NON, EUO, and NES, to be built from these layers. The DIFFaX simulations were carried out using the connection modes reported in Table 2. Several trials were performed in which different layer-to-layer stacking probabilities were adopted, and the results of each trial were evaluated by comparing the powder pattern calculated with DIFFaX with that of calcined ERS-10. A third layer (see Table 2) structurally identical to layer I was introduced to account for fault clustering. This implies that the “I to I” stacking sequence forms thick domains instead of being

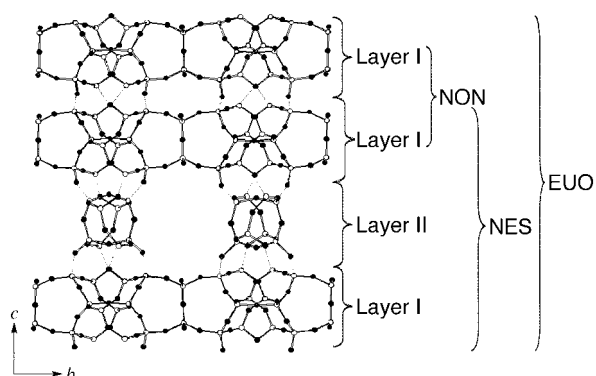


Figure 3. Building scheme of NON, EUO, and NES, starting from layers I and II (DIFFaX setting).

Table 2. Layer–layer transition adopted.

From layer	To layer	Translations	Probability first step [%]	Probability second step [%]
I	I	$0.5a$	34	34
I	I ^[a]	$0.5a$	33	33
I	II	none	33	33
I ^[a]	I	$0.5a$	25	25
I ^[a]	I ^[a]	$0.5a$	55	55
I ^[a]	II	none	20	20
II	I	$0.5a$	50	40
II	I ^[a]	$0.5a$	50	40
II	II	none	0	20

[a] Layer I' structurally identical to layer I.

randomly dispersed throughout the crystals. For further details on the meaning of this fault clustering see the paper by Treacy et al.^[4] The best agreement was found when the probabilities listed in Table 2 (first step) were used, leading to a satisfactory reproduction of the basic features of the calcined ERS-10 synchrotron powder diffraction pattern (SXPd, Figure 4). However, some minor differences between the two patterns still persist because DIFFaX is not a refinement program.

The structural model obtained so far is based on a random distribution, perpendicular to the stacking vector (the crystallographic b axis in the gottardiite setting, corresponding to the c axis in the DIFFaX setting), of straight channels with 6–

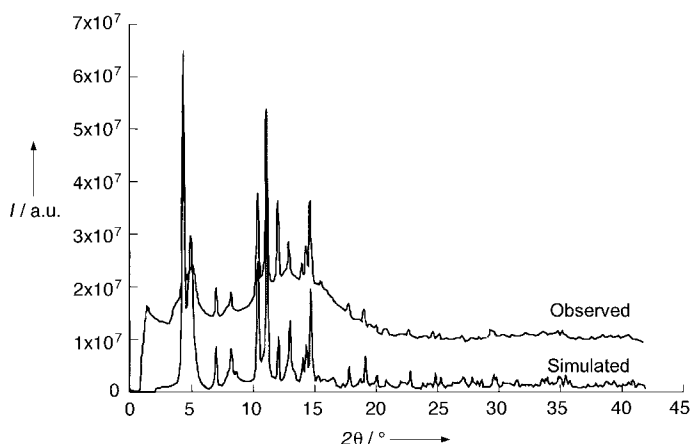


Figure 4. Comparison between the observed and the simulated SXPd patterns of ERS-10 (stacking probabilities as in Table 2, step 1).

and 10-ring openings (Figure 5). Moreover, adjacent one-dimensional channels are linked by short 12-ring channels or side pockets whose dimensions depend on the stacking faults; in any case the access to these bridging sections is possible only through 10-ring windows.

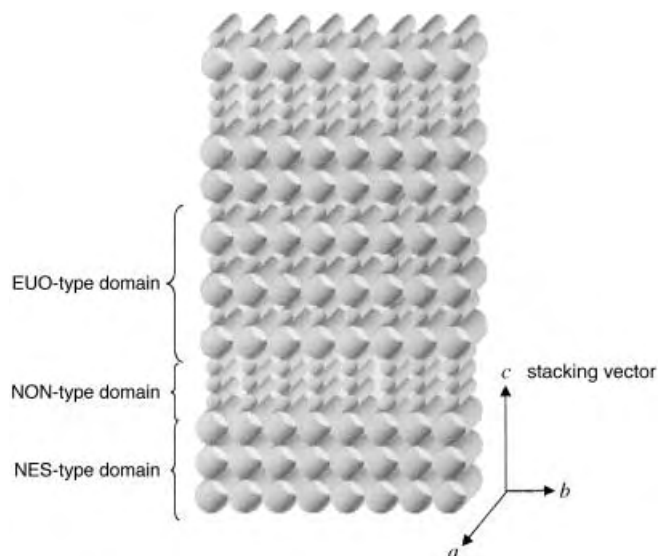


Figure 5. Roll stacking disordered model of zeolite ERS-10 (DIFFaX setting), is possible to show the random sequence of the straight 10-ring channels (large cylinders) and 6-ring ones (small cylinders).

This result is somewhat in contrast with the catalytic performances of zeolite ERS-10.^[12] In particular, for ERS-10 a spaciousness index (SI)^[13] of 5.3 apparently indicates a pore width close to that of offretite, a zeolite characterized by a monodimensional linear channel system with 12-ring openings.^[12] Actually, an SI of 5 was reported also for the medium-pore EUO zeolite and this anomalous value was explained with the presence of the large 12-ring cavities in its porous structure.^[14] Since the SI alone is not sufficient for defining the pore width of ERS-10, other test reactions, that is the ethylbenzene disproportionation and the liquid-phase alkylation of benzene with propylene, were considered, leading to the conclusion that the effective ERS-10 pore width is in the intermediate range between those of medium- and large-pore zeolites.^[12]

There are two possible explanations for this. The first one implies the existence on the crystal surface of cups with 12-ring openings, corresponding to the side pockets mentioned above: a situation similar to that observed for ERB-1 (IZA code MWW).^[15] This material belongs to the class of medium-pore zeolites, being characterized by the presence of two noninterconnected channel systems both with 10-ring openings; however, it displays outstanding catalytic properties typical of large-pore zeolites.^[15] These features were attributed to the fact that the reaction takes place in the 12-ring cups present on the [001] crystal surface.^[15]

The second possible explanation concerns the existence of very large channels with egg-shaped 14-ring openings, which can be generated when a layer II–layer II interconnection occurs (Figure 6). This situation, not considered in the first model, led to an improvement of agreement between the

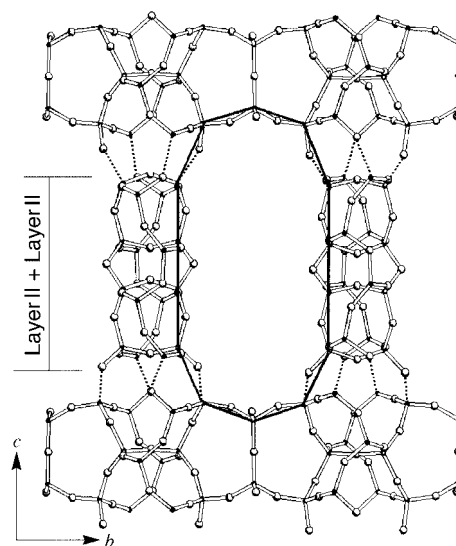


Figure 6. Egg-shaped 14-ring openings generated by the layer II–layer II interconnection (DIFFaX setting).

simulated and the experimental diffraction pattern, due to the reduced intensity of the broad reflection located at $\approx 4^\circ 2\theta$ (Figure 7). The best results were obtained when the layer II–layer II stacking probability was set to 20 % (Table 2, second step).

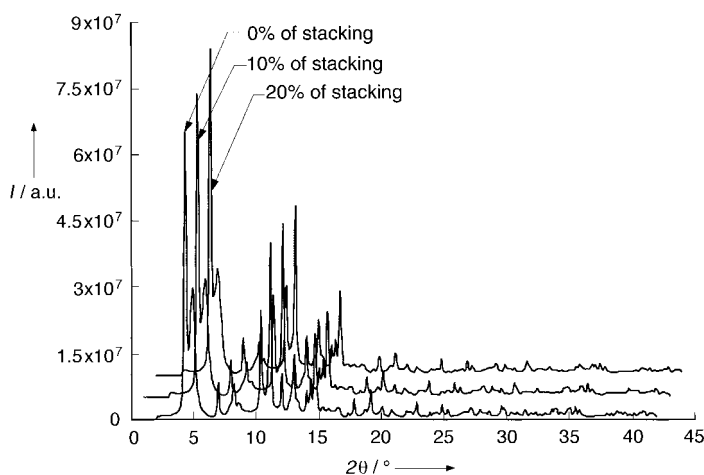


Figure 7. Simulated diffraction pattern with increasing layer II–layer II stacking probabilities.

Although the existence of 14-ring channels in ERS-10 structure remains to be confirmed by other techniques (e.g. by HREM^[16]), it is clear that their presence accounts well for the catalytic performances of this zeolite.

In any case, what emerges from this work is that ERS-10 is really an intergrowth of zeolites NON, EUO, and NES, a conclusion supported by the fairly good agreement between the simulated and the experimental SXP patterns.

Experimental Section

Synthesis: ERS-10 zeolite was synthesized according to the method reported in reference [6]. NaOH, aluminum isopropylate, and 6-azonia-spiro[5,5]undecane hydroxide were dissolved in demineralized water and

the resulting solution was heated at 353 K. The silica source (tetraethylorthosilicate, TEOS) was added gradually under vigorous stirring, then the resulting mixture was aged for 4 h, cooled to room temperature, charged in an oscillating stainless-steel autoclave and heated at 443 K for 336 h. After crystallization the autoclave was cooled to room temperature with cold water. The solid product was collected by filtration, repeatedly washed with demineralized water, and finally dried overnight at 423 K. A fraction of the solid was calcined at 823 K for 4 h to remove the organic molecules trapped in the ERS-10 pores.

Powder data collection: X-ray powder diffraction (XRD) patterns were obtained with a Philips X'PERT diffractometer equipped with a pulse-height analyzer and a secondary curved graphite crystal monochromator. Data were collected stepwise over $3 \leq 2\theta \leq 53^\circ$, with a step size of $0.02^\circ 2\theta$ and an accumulation time of 20 s per step, using $\text{Cu K}\alpha$ radiation ($\lambda = 1.54178 \text{ \AA}$).

Synchrotron X-ray powder diffraction data were collected at room temperature on a sample loaded in a glass capillary mounted in Debye–Scherrer geometry at BM08, GILDA beamline (ESRF, Grenoble) during the experiment 08-02-174. The beamline was set to deliver a wavelength of $\lambda = 0.82714 \text{ \AA}$, and the data was collected on a Fuji Image Plate located at 204.83 mm from the sample and perpendicular to the incident beam; the exposure time was 3 min. Elaboration of the scanned digital images (Fuji BAS2000 scanner) was carried out using the Fit2d software package.^[17]

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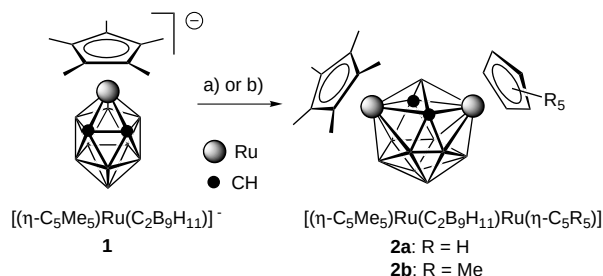
Direct Electrophilic Insertion into a Twelve-Vertex Metallocarborane**

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In memory of Margarita I. Rybinskaya

Direct insertion of metal-complex fragments into *closo*-carboranes and metallocarboranes to give polyhedral expansion products is one of the most interesting reactions in metallocarborane chemistry.^[1] The nucleophilic insertion into the cage molecules has been well studied.^[2] Herein we report the first direct electrophilic insertion^[3] into a 12-vertex metallocarborane.

We studied the reaction of ruthenacarborane anion **1** with $[(\eta\text{-C}_5\text{R}_5)\text{Ru}(\text{MeCN})_3]^+$ ($\text{R} = \text{H}, \text{Me}$) (Scheme 1). The electrophilic attack of the fragments $[(\eta\text{-C}_5\text{R}_5)\text{Ru}]^+$ was expected



Scheme 1. Electrophilic insertion into **1** to give **2a,b**. Reagents and conditions: a) $[(\eta\text{-C}_5\text{R}_5)\text{Ru}(\text{MeCN})_3]\text{X}$ ($\text{X} = \text{PF}_6$ or CF_3SO_3), CH_3NO_2 , 100°C , 4 h, about 50% yield; b) $[(\eta\text{-C}_5\text{Me}_5)\text{RuCl}_4]$, THF, 20°C or even -78°C , 74% yield.

to proceed at the C_5Me_5 ring to give triple-decker complexes $[(\eta\text{-C}_5\text{R}_5)\text{Ru}(\mu\text{-}\eta\text{-C}_5\text{Me}_5)\text{Ru}(\text{C}_2\text{B}_9\text{H}_{11})]$, similar to the formation of $[(\eta\text{-C}_5\text{R}_5)\text{Ru}(\mu\text{-}\eta\text{-C}_5\text{Me}_5)\text{Ru}(\eta\text{-C}_5\text{Me}_5)]^+$ by reaction of the same fragments with $[(\eta\text{-C}_5\text{Me}_5)_2\text{Ru}]$.^[4] However, electrophilic insertion into the ruthenacarborane cage occurs instead to give 13-vertex diruthenacarboranes **2a,b**.

It should be emphasized that the electrophilic insertion reactions were previously unknown. Parent *ortho*-carborane $\text{C}_2\text{B}_{10}\text{H}_{12}$ as well as neutral metallocarboranes $[(\eta\text{-C}_5\text{H}_5)\text{Co}(\text{C}_2\text{B}_9\text{H}_{11})]$ and $[(\eta\text{-C}_5\text{Me}_5)\text{Rh}(\text{C}_2\text{B}_9\text{H}_{11})]$ were proved to be unreactive towards $[(\eta\text{-C}_5\text{R}_5)\text{Ru}]^+$. In contrast, in the case of **1** the insertion can be carried out even at -78°C by reaction of **1** with $[(\eta\text{-C}_5\text{Me}_5)\text{RuCl}_4]$ (**3**) in THF. The high reactivity of anion **1** is evidently connected with its greater nucleophilicity.

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The precursor salt **TI-1** was obtained by reaction of **3** with the thallium derivative of the dicarbollide anion $\text{Ti}[\text{Ti}(\text{C}_2\text{B}_9\text{H}_{11})]$. Since **TI-1** reacts with **3** to give the symmetrical compound **2b**, the latter can be prepared by direct reaction of $\text{Ti}[\text{Ti}(\text{C}_2\text{B}_9\text{H}_{11})]$ with two equivalents of **3**.

All the compounds were characterized by ^1H and ^{11}B NMR spectroscopy and elemental analysis. The ^1H NMR spectra of **2a** and **2b** display narrow signals for the C_5H_5 and C_5Me_5 ligands which supports the diamagnetism of the compounds. It should be mentioned that the cage CH protons appear as a broad singlet at $\delta = -0.67$ ppm (**2a**) or -1.27 ppm (**2b**), dramatically up-field shifted in comparison with the corresponding signals of the precursor anion **1** ($\delta = 2.72$ ppm). The ^{11}B NMR spectra show down-field signals at $\delta = 95.10$ ppm (**2a**) or 97.03 ppm (**2b**), characteristic for the presence of a low-coordinate boron atom adjacent to metal atoms.^[5] These spectral data are in good agreement with that reported by Hawthorne and Salentine for the 13-vertex diferracarborane $[(\eta\text{-C}_5\text{H}_5)_2\text{Fe}_2\text{C}_2\text{B}_9\text{H}_{11}]$,^[6] proposed to have a structure similar to **2a,b**.

The structures of **PPN-1** ($\text{PPN} = (\text{Ph}_3\text{P})_2\text{N}$) (Figure 1) and **2b** (Figure 2) were determined by X-ray structure analysis.^[7] The anion **1** has a sandwich geometry with almost parallel C_5 and C_2B_3 rings in staggered conformation. One of the carbon atoms in the cage is disordered leading to the superposition of

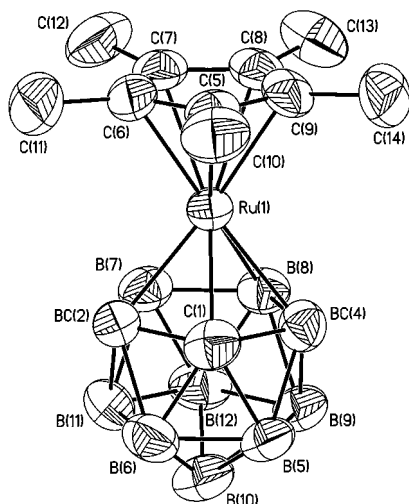


Figure 1. Structure of anion **1**. Atoms are represented as 50% probability ellipsoids. Hydrogen atoms are omitted for clarity. The disordered carbon atoms are signed as BC(2) and BC(4).

the C(2) and B(2) or B(4) atoms. The $\text{Ru}\cdots\text{C}_5\text{Me}_5$ plane distance ($1.82 \text{ \AA}$) is almost the same as the corresponding distance in $[(\eta\text{-C}_5\text{Me}_5)_2\text{Ru}]$ ($1.81 \text{ \AA}$).^[8]

Compound **2b** possesses nearly ideal C_{2v} symmetry for a 13-vertex dimetallacarborane cage (Figure 2). The $\text{Ru}\cdots\text{C}_5\text{Me}_5$ plane distance ($1.88 \text{ \AA}$) is considerably longer than that in anion **1**. Both ruthenium atoms are bonded to C_2B_4 faces with a common C_2B frame in the bridging position. The distances from the Ru atoms to the bridging boron atom B(1) ($2.070(3)$

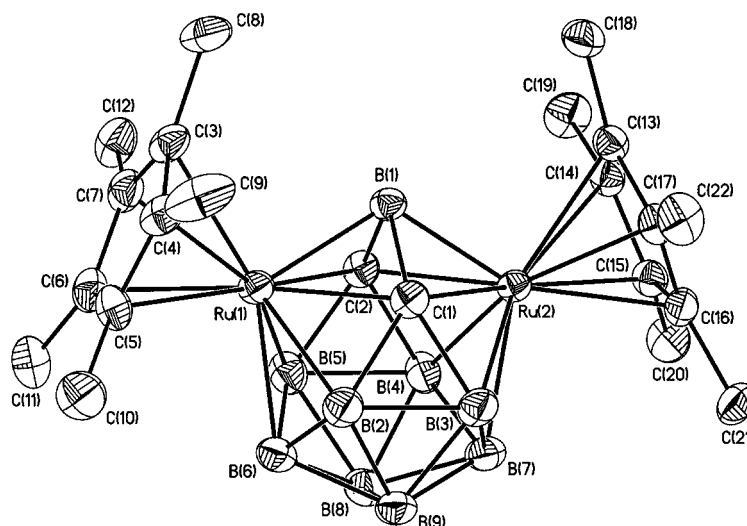


Figure 2. Structure of **2b**. Atoms are represented as 50% probability ellipsoids. Hydrogen atoms are omitted for clarity.

and $2.063(3) \text{ \AA}$, av $2.07 \text{ \AA}$) are much shorter than other $\text{Ru}\cdots\text{B}$ distances ($2.191(4)\text{--}2.213(3) \text{ \AA}$, av $2.20 \text{ \AA}$). The distance $\text{Ru}(1)\cdots\text{Ru}(2)$ ($3.5307(5) \text{ \AA}$) suggests that there is no direct interaction between the ruthenium atoms.

Compounds **2a,b** belong to $2n$ skeletal electron (*hypercloso*)^[9] systems (where n is the number of vertexes) which violate Wade's rules.^[10] Nevertheless, they are stable over 200°C even in air. To explain this violation, one might suggest that the ruthenium atoms are in the oxidation state III, but diamagnetism of the compounds rules out this speculation. According to the extended Hückel calculations by Fowler,^[11] neutral $\text{B}_{13}\text{H}_{13}$ (C_{2v} symmetry, $2n$ -electron system) has a nearly nonbonding LUMO, suggesting that $\text{B}_{13}\text{H}_{13}$ and $[\text{B}_{13}\text{H}_{13}]^{2-}$ should be almost equally stable. Analogously, two series of stable 13-vertex dimetallacarboranes, having $2n$ and $2n + 2$ skeletal electrons, could be suggested, exemplified by **2a,b** and $[(\eta\text{-C}_5\text{H}_5)_2\text{Co}_2\text{C}_2\text{B}_9\text{H}_{11}]$,^[4b] respectively.

The reactions presented here illustrate a novel approach to the synthesis of dimetallacarboranes. We are currently studying applicability limits of this method.

Experimental Section

All the reactions were carried out under an argon atmosphere, whereas isolation of products was conducted in air.

Ti $[(\eta\text{-C}_5\text{Me}_5)\text{Ru}(\text{C}_2\text{B}_9\text{H}_{11})]$ (TI-1**):** Acetonitrile (8 mL) was added to a mixture of $[(\eta\text{-C}_5\text{Me}_5)\text{RuCl}]_4$ (109 mg, 0.1 mmol) and $\text{Ti}[\text{Ti}(\text{C}_2\text{B}_9\text{H}_{11})]$ (227 mg, 0.42 mmol) and the resulting suspension was stirred for 72 h. The reaction mixture was diluted with acetone (10 mL), filtered, and evaporated to dryness in vacuo. The residue was redissolved in THF and reprecipitated by addition of diethyl ether to give **TI-1** (182 mg, 79%) as a white air-stable solid. ^1H NMR (400.13 MHz, $[\text{D}_6]\text{acetone}$, 25°C): $\delta = 1.89$ (s, 15 H; C_5Me_5), 2.72 ppm (bs, 2 H; cage CH); $^{11}\text{B}\{^1\text{H}\}$ NMR (128.38 MHz, $[\text{D}_6]\text{acetone}$, 25°C): $\delta = -28.12$ (1 B), -24.65 (2 B), -15.41 (2 B), -9.96 (1 B), -8.87 (2 B), -1.48 ppm (1 B); elemental analysis (%) calcd: C 25.15, H 4.57, B 16.98; found: C 24.94, H 4.66, B 17.04.

$[(\eta\text{-C}_5\text{Me}_5)\text{Ru}(\text{C}_2\text{B}_9\text{H}_{11})\text{Ru}(\eta\text{-C}_5\text{H}_5)]$ (2a**):** Nitromethane (5 mL) was added to a mixture of $[(\eta\text{-C}_5\text{H}_5)\text{Ru}(\text{MeCN})_3]\text{PF}_6$ (65 mg, 0.15 mmol) and **TI-1** (86 mg, 0.15 mmol). The solution was stirred under reflux for 4 h leading to a color change from yellow to bright red. The mixture was evaporated to dryness; the residue was dissolved in CH_2Cl_2 and filtered through a thin

layer (3 cm) of Al_2O_3 . The solution was concentrated to 2 mL and hexane (20 mL) was added to precipitate the product as an orange-red air-stable solid. Yield 38 mg (47 %). ^1H NMR (400.13 MHz, $[\text{D}_1]\text{chloroform}$, 25 °C): $\delta = -0.69$ (bs, 2H; cage CH), 1.60 (s, 15H; C_5Me_5), 5.22 ppm (s, 5H; C_5H_5); $^{11}\text{B}\{^1\text{H}\}$ NMR (128.38 MHz, $[\text{D}_1]\text{chloroform}$, 25 °C): $\delta = -5.26$ (2B), 16.24 (2B), 17.92 (2B), 31.94 (1B), 38.31 (1B), 95.10 ppm (1B); elemental analysis (%) calcd: C 38.17, H 5.84, B 18.19; found: C 38.16, H 5.89, B 18.11.

$[(\eta\text{-C}_5\text{Me}_5)\text{Ru}(\text{C}_2\text{B}_9\text{H}_{11})\text{Ru}(\eta\text{-C}_5\text{Me}_5)]$ (**2b**): THF (4 mL) was added to a mixture of $[(\eta\text{-C}_5\text{Me}_5)\text{RuCl}]_4$ (41 mg, 0.038 mmol) and **TI-1** (86 mg, 0.15 mmol). The reaction mixture was stirred for 4 h and filtered through a thin layer (3 cm) of Al_2O_3 . The solution was concentrated to 2 mL and hexane (20 mL) was added to precipitate the product as a red air-stable solid. Yield 67 mg (74 %). ^1H NMR (400.13 MHz, $[\text{D}_1]\text{chloroform}$, 25 °C): $\delta = -1.27$ (bs, 2H; cage CH), 1.59 ppm (s, 30H; C_5Me_5); $^{11}\text{B}\{^1\text{H}\}$ NMR (128.38 MHz, $[\text{D}_1]\text{chloroform}$, 25 °C): $\delta = -5.62$ (2B), 17.78 (4B), 36.37 (2B), 97.03 ppm (1B); elemental analysis (%) calcd: C 43.68, H 6.83, B 16.08; found: C 43.65, H 6.78, B 15.98.

Analogously, direct reaction of $[(\eta\text{-C}_5\text{Me}_5)\text{RuCl}]_4$ (82 mg, 0.075 mmol) and $\text{Ti}[\text{Ti}(\text{C}_2\text{B}_9\text{H}_{11})]$ (81 mg, 0.15 mmol) in THF or Me_2CO gave **2b** (64 mg, 70 %).

Complex **2b** was also prepared in 55 % yield starting from $[(\eta\text{-C}_5\text{Me}_5)\text{-Ru}(\text{MeCN})_3]\text{CF}_3\text{SO}_3$, similar to preparation of **2a**.

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were performed using SHELXTL 5.1. CCDC-188268 (PPN-1) and CCDC-188269 (**2b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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Conformation-Dependent Ionization Energies of L-Phenylalanine**

Kang Taek Lee, Jiha Sung, Kwang Jun Lee, Young Dong Park, and Seong Keun Kim*

In recent years there has been an outburst of research interest in small biological molecules in the gas phase.^[1] By placing these molecules on the “transparent cover glass” of an isolated environment, one can unravel intrinsic properties usually hidden in the complex medium of a real biological system. The need for such gas-phase studies arises from the anticipation that many biological phenomena can be traced to the fundamental properties of the molecular constituents. Both laser spectroscopy and theoretical methods have made great contributions to elucidating the structures and dynamics of nonrigid biomolecules and their solvated complexes in the gas phase.^[2]

Amino acids are known to exist in various conformations resulting from the flexibility of their structures, which comprise a backbone and a side chain or residue. The conformational variety of amino acids plays a crucial role in determining the three-dimensional structure of proteins and controlling their dynamics.^[3] The energy barrier that separates different conformers is typically rather small so that thermal energy at room temperature enables the molecule to freely change from one conformation to another. Therefore, it is not generally feasible to isolate a specific conformer experimentally at room temperature. By employing a supersonic expansion, however, one can cool down the molecule to a temperature low enough to isolate it in various frozen forms, in other words, as individual conformers. Numerous exper-

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- [7] Crystallographic data for PPN-1: at 295 K crystals of $\text{C}_{48}\text{H}_{56}\text{B}_9\text{NP}_2\text{Ru}$ are monoclinic, space group $P2_1/c$, $Z = 4$, $a = 16.800(3)$, $b = 16.044(3)$, $c = 18.490(4)$ Å, $\beta = 109.152(5)^\circ$, $V = 4707.7(15)$ Å³, $\mu(\text{MoK}\alpha) = 4.36 \text{ cm}^{-1}$. Intensities of 26827 reflections were measured with a Smart 1000 CCD diffractometer at 295 K ($\lambda(\text{MoK}\alpha) = 0.71073$ Å, $2\theta < 50^\circ$), and 8271 independent reflections ($R_{\text{int}} = 0.0603$) were used in further refinement. One of the two carbon atoms in the cage was assumed to be disordered and occupied positions adjacent to either side of C(1). In the subsequent refinements each of the disordered atoms was assigned the scattering power of an atom that was half boron and half carbon. The refinement converged to $wR_2 = 0.0973$ and $GOF = 0.992$ for all independent reflections ($R1 = 0.0487$ was calculated against F for 4518 observed reflections with $I > 2\sigma(I)$). Crystallographic data for **2b**: at 140 K crystals of $\text{C}_{72}\text{H}_{44}\text{B}_9\text{Ru}_2$ are monoclinic, space group $P2_1/n$, $Z = 4$, $a = 8.3431(13)$, $b = 15.782(3)$, $c = 20.446(3)$ Å, $\beta = 101.483(3)^\circ$, $V = 2638.4(7)$ Å³, $\mu(\text{MoK}\alpha) = 11.55 \text{ cm}^{-1}$. Intensities of 30997 reflections were measured with a Smart 1000 CCD diffractometer at 140 K ($\lambda(\text{MoK}\alpha) = 0.71073$ Å, $2\theta < 60^\circ$), and 7647 independent reflections ($R_{\text{int}} = 0.0325$) were used in further refinement. The refinement converged to $wR_2 = 0.0981$ and $GOF = 1.040$ for all independent reflections ($R1 = 0.0414$ was calculated against F for 6443 observed reflections with $I > 2\sigma(I)$). All calculations

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imental studies have dealt with amino acids and their conformers in the gas phase.^[4–15]

Another interesting subject involves amino acids that carry a whole ionic charge since electrostatic interactions are ubiquitous in many proteins and affect their structures and functions. Many gas-phase studies on ionic amino acids, peptides, and proteins have focused on protonated cations or metal ion complexes, but to our knowledge, an unadulterated ionic amino acid has not yet been studied, presumably because of the difficulties in producing an intact ion in the gas phase.

Here we report a study on the photoionization of the aromatic amino acid phenylalanine (Phe) generated by supersonic expansion. We measured the ionization energies (IEs) of all low-energy conformers by resonant two-photon ionization (R2PI). This revealed strikingly different IE values that range from 8.80 to 9.15 eV. We found that a very strong correlation exists between the IE of a given conformer and how its backbone interacts with the side chain.

Figure 1 depicts the six lowest energy conformational structures of Phe as determined by Simons and co-workers; they are shown here for expedient reference.^[13] They can be divided into two subgroups according to the intramolecular

structure of the conformers in the first subgroup. In the other subgroup (subgroup II), which includes the conformers A, C, and D, the direction of the hydrogen bonding is reversed between the amino and the carboxy group, that is, $\text{NH}_2 \rightarrow \text{COOH}$, whether it involves only a single or both hydrogen atoms of the amino group. In these conformers the carboxy hydrogen atom remains free and does not interact with the phenyl ring. This means that there is little interaction between the residue and the backbone through either the carboxy group or the amino group.

In a recent paper^[15] we pointed out that this grouping of Phe conformers may be incorrect with regard to conformer E. We proposed that conformer E should be included in subgroup II rather than subgroup I, with hydrogen bonding from the amino to the carboxy group, based on our observation that conformer E binds water just as efficiently as members of subgroup II and much more efficiently than those of subgroup I. Theoretical calculations predict that all conformers of subgroup II interact more strongly with water than those of subgroup I because water tends to make a hydrogen bond with the free carboxy hydrogen atom. As will be discussed later, this proposition is further corroborated by new findings in the present study. Our regrouping of the conformers would classify A, C, D, and E as subgroup II and X and B as subgroup I.

Figure 2a shows a one-color R2PI excitation spectrum of Phe in the S_1 origin region. The six peaks are the band origins of the corresponding six lowest energy conformers shown in Figure 1, with the structure of conformer E undetermined as described above. The adiabatic IE of Phe is known to be 8.5 eV,^[16] but its vertical IE is not yet known. Since the one-color two-photon energy (~ 9.4 eV) could be well above the vertical IE, we employed two-color R2PI to reduce the excess energy above the ionization threshold. Figure 2b displays a two-color R2PI excitation spectrum obtained at conditions similar to those given in Figure 2a but with the ionization laser fixed at 285.5 nm. Strikingly, the bands B and X are totally missing in this spectrum, while all other bands are observed with nearly the same intensity ratio as in the one-color spectrum. We note that the band E behaves more like those of subgroup II than of subgroup I. The peak at 37646 cm^{-1} in Figure 2a, which is known to be a low-frequency vibration of X,^[13] also disappears in Figure 2b.

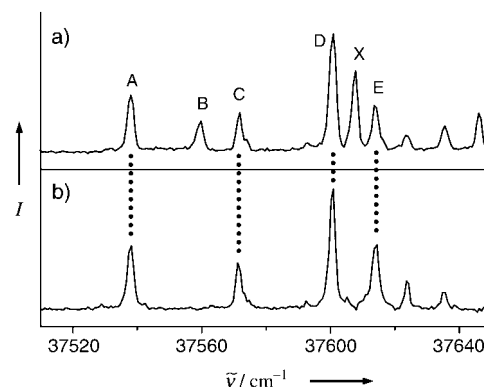


Figure 2. Mass-resolved R2PI excitation spectra of jet-cooled Phe obtained by a) one-color and b) two-color ionization. The wavelength of the ionization laser was fixed at 285.5 nm in (b).

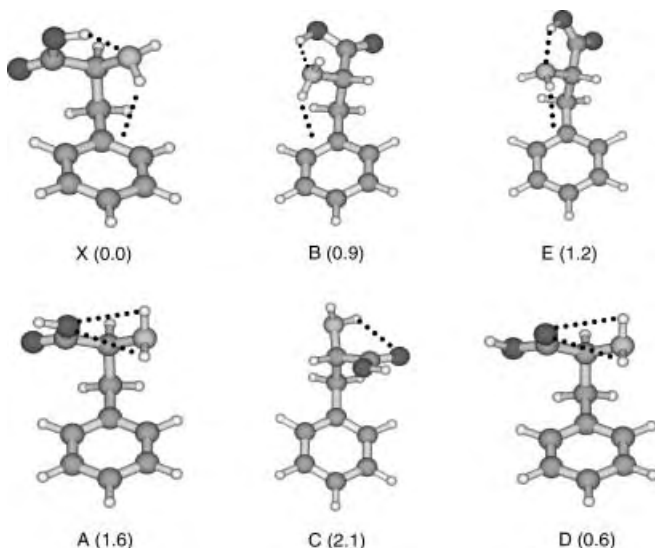


Figure 1. Geometries of the six most stable Phe conformers optimized at the B3LYP/6-31 + G(d) level. The labels are adopted from reference [13]. In parentheses are shown the relative energies (in kcal mol^{-1}) calculated at the MP2/6-311G(d,p) level with the zero-point energy corrections (B3LYP/6-31 + G(d)).

hydrogen-bonding scheme. In the first subgroup (subgroup I) consisting of the conformers X, B, and E, the carboxy hydrogen atom forms a hydrogen bond with the nonbonding electrons of the amino group. Additionally, an amino hydrogen atom interacts with the phenyl ring in what appears to be a π -hydrogen bond, thereby forming a complete sequence of hydrogen bonds, $\text{COOH} \rightarrow \text{NH}_2 \rightarrow \pi$. The strength of the latter hydrogen bond, $\text{NH}_2 \rightarrow \pi$ should be enhanced by the former hydrogen bond, $\text{COOH} \rightarrow \text{NH}_2$, which endows the amino hydrogen atom with a stronger positive charge.^[13] Thus these two hydrogen bonds act cooperatively in determining the

The absence of the bands associated with the two conformers B and X, in contrast to the presence of the bands for A, C, D, and E in Figure 2b, must mean that the two-photon energy here (~ 9.0 eV) is smaller than the IEs of the conformers B and X but still larger than those of the other four conformers.

To further confirm this observation we obtained the photoionization efficiency (PIE) curves for all six conformers (Figure 3). For each curve the wavelength of the excitation laser was fixed at the S_1 band origin of the corresponding conformer, thus the selection of the species being ionized is

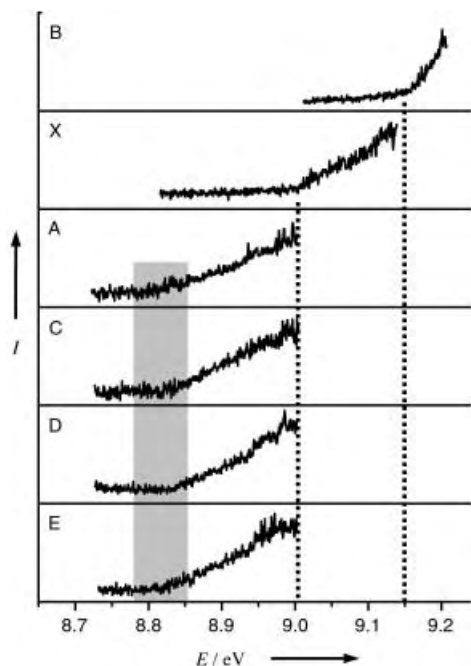


Figure 3. PIE curves of the Phe conformers. Each curve was obtained by scanning the wavelength of the ionization laser across the IE while fixing the wavelength of the excitation laser at the S_1 band origin of the labeled conformer.

achieved in the first excitation step. Here, too, band E behaves like a member of subgroup II along with the bands A, C, and D. All the PIE curves are seen to have a very gradual increase in the ion signal and a poorly defined ionization threshold. This feature can be explained by a poor Franck–Condon factor for ionization, as in similar cases of 2-phenylethylamine (PEA),^[17] benzyl and salicyl alcohol,^[18] and *p*-methoxyphenethylamine.^[19] It has been recognized for such molecules that the minima of the neutral and the cationic potential energy surfaces (PES) are much displaced from each other. A cation is thus produced at a repulsive part of the PES, where the density of states is very high at a considerable internal energy which leads to a broad and structureless band profile in the photoion or photoelectron spectra.

Conformers B and X of subgroup I have IEs of 9.15 and 9.00 eV, respectively, much larger than the nearly identical IEs of ~ 8.8 eV for all the conformers of subgroup II. That is indeed the reason for the absence of the bands B and X in the two-color R2PI excitation spectrum in Figure 2b. If we classified the conformers into two different subgroups only on the basis of the magnitude of IE, we would have two

subgroups, (A, C, D, E) vs. (B, X). It is very interesting that this classification by IE gives the same result as our earlier classification of the Phe conformers on the basis of the propensity of Phe toward hydration. Hydration was found to take place only with A, C, D, and E but not with B and X,^[15] which was suggested to result from the different hydrogen-bonding schemes resulting from the different geometries between the two subgroups. Likewise, the higher IEs of B and X should also reflect the structural difference between the two subgroups.

As already mentioned with regard to Figure 1, there is an additional hydrogen bond for B and X between the amino group and the phenyl ring in addition to, and enhanced by, the hydrogen bond between the carboxy and amino groups. When B and X are ionized by two-photon ionization via the $\pi\pi^*$ resonance state (S_1), the phenyl ring would attain a positive charge, at least partially, which will turn the attractive interaction between the amino hydrogen atom and the phenyl ring into a repulsive one. In contrast conformers A, C, D, and E would be little influenced by the positive charge on the phenyl ring since the interaction between the backbone and the phenyl ring is much weaker for these conformers in the first place in their neutral state. Therefore, the nascent cations of B and X are expected to be higher in energy than the other conformers because of their repulsive backbone– π interaction, which also leads to the higher IEs.

The conformer-dependent IEs have been observed recently for molecules such as 1-iodopropane,^[20] 9-ethylfluorene,^[21] *p*-methoxyphenethylamine,^[19] and formanilide.^[22] However, the difference between the IEs of different conformers is generally small for these molecules, mostly below ~ 300 cm^{-1} . By comparison, the difference of up to 0.35 eV (~ 2800 cm^{-1} or 8 kcal mol^{-1}) in the IEs of the two subgroups of Phe conformers is remarkably large—an order of magnitude greater than all the known cases.

In summary, we employed the technique of supersonic jet cooling for Phe to freeze out its various conformational structures and used R2PI to measure the IE for specific conformations. We found that the IE is very much conformation-dependent, ranging from 8.80 to 9.15 eV. The magnitude of the differences in the IEs exceeds the largest value reported to date for a conformation-dependent IE of any molecule by an order of magnitude. Two distinct subgroups were proposed for the six lowest energy conformers of Phe on the basis of the magnitude of IE, which turned out to give the same classification as that derived from the conformation-dependent propensity toward hydration. The culprit for the large variances in the IEs as well as the propensities for hydration was the drastically different nature of hydrogen bonding between the two subgroups of conformers. It reflects the large conformational change upon ionization, the effect of which is maximized in the present case of Phe because of the characteristically strong intramolecular hydrogen bonds typically found in amino acids.

Experimental Section

The experimental setup used in this study has been described in detail.^[15] Phe powder was vaporized by heating the oven to 180 °C and expanded through a pulsed nozzle with a 0.8-mm hole by using neon carrier gas at

1 atm. The Phe sample was purchased from Aldrich Chemical Company and used without further purification.

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Fluorous Biphasic Esterification Directed towards Ultimate Atom Efficiency**

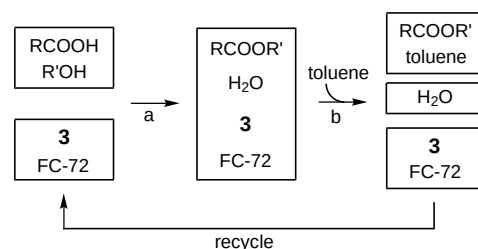
Jiannan Xiang, Akihiro Orita, and Junzo Otera*

Esterification technology is currently undergoing intensive innovation to meet the rapidly increasing demands for sustainable chemistry.^[1] Since the direct reaction between a carboxylic acid and an alcohol is innately an equilibrium process, high atom efficiency^[2] is not easy to achieve: either of the reactants must be used in excess and/or the water formed

must be removed constantly during the reaction to bias the equilibrium to the product side. In particular, the direct condensation between carboxylic acids and alcohols with a strict 1:1 stoichiometry by use of a simple catalyst system is very difficult to complete, although activation of the carboxylic acid component with a stoichiometric amount of promoter such as DCC^[3] or DEAD^[4] is another possible but uneconomical choice. In this context, graphite bisulfate was reported to catalyze esterification between equimolar reactants.^[5] Later, microwave irradiation coupled with *p*-toluene-sulfonic acid catalyst was reported.^[6] Recently, a few more related catalysts have appeared. Although the Soxhlet technique must be invoked, NaHSO₄·H₂O^[7] and HfCl₂·2 THF^[8] were found to work well as a catalyst. On the other hand, Ph₂NH₂⁺OTf⁻ served for the present purpose without recourse to any dehydration reagents or apparatus.^[9] The yields of all of these reactions were high (mostly > 85 %) but, unfortunately, not perfectly quantitative, except for two cases in the HfCl₂·2 THF protocol (> 99 %). This is somewhat problematic, not only in view of atom efficiency but also of practical operation. The 1:1 stoichiometry is truly effective only if 100 % conversion is reached. In this case, the product ester constitutes a sole organic component in the reaction mixture, but otherwise separation of the remaining carboxylic acid and alcohol from the product mixture is unavoidable. As a consequence, an ideal goal of esterification would be 100 % yield by use of equimolar reactants without recourse to any dehydration technique.

Recently, we disclosed that the fluorous biphasic transesterification by use of fluoroalkyldistannoxane catalysts gave rise to virtually 100 % yields with ester and alcohol reactants in a 1:1 ratio.^[10] It was suggested in this protocol that liberation of a lighter alcohol from the equilibrium system as a result of its lower solubility in fluorocarbon solvents facilitated the conversion in favor of the esters with a higher alcohol component. Since water is much less fluorophilic than alcohols, we postulated that the condensation between carboxylic acids and alcohols should proceed more efficiently. We report herein the first fluorous biphasic esterification that achieves the above-mentioned goal. Furthermore, facile separation of the catalyst is another notable advantage that results from the fluorous biphasic technology.

As shown in Scheme 1, an equimolar mixture of RCOOH (1) and R'OH (2) together with [Cl(C₆F₁₃C₂H₄)₂SnOSn(C₂H₄C₆F₁₃)₂Cl]₂ (3)^[11] (5 mol %) in FC-72 (perfluorohexanes) was heated at 150 °C. After being cooled to room temperature, toluene was added to the



Scheme 1. Esterification in a biphasic system. Reagents and conditions: a) acid (2.0 mmol), alcohol (2.0 mmol), 3 (0.1 mmol), FC-72 (5 mL), 150 °C, 16 h; b) extraction with toluene (5 mL and 2 × 2 mL).

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mixture. The organic layer was separated from the fluororous layer and analyzed by GLC. The results are summarized in Table 1. With less sterically demanding reactants, no sign of the reactant alcohol was detected in the reaction mixture and only a single peak attributable to the ester was observed, indicative of virtually perfect conversions (Table 1, entries 1–13). It is safe to assume that the GLC results are normally accurate to within $\pm 1\%$ and thus the yields are $>99\%$. Notwithstanding, a higher level of precision was pursued by calibrating our GLC machine with some representative esters (Table 1, entries 1, 8–14). It was shown that the detection limit was actually less than 0.1% and thus the yields could be considered as $>99.9\%$. The yields of isolated products were also consistently quantitative.^[12] Furthermore, this protocol is tolerant of various functional groups (Table 1, entries 3–7).

The catalyst was recovered from the FC-72 layer without weight loss, but not in pure form. A portion of the catalyst was converted into unidentifiable species, which were presumably organotin carboxylate derivatives. Nonetheless, the recovered material exhibited similar catalytic activity to that of the original, and thus the FC-72 solution that contained the organotin species could be recycled for repeated use (see below).

In the above procedure, toluene was added to the reaction mixture to recover the ester from the FC-72 solution, simply because the small-scale reaction did not mechanically allow the quantitative separation of the product (3 mmol). On the other hand, when larger amounts of reactants were used

(10 mmol) the product could be pipetted from the surface of the fluororous layer, although a small amount of the ester might have remained. This, however, is not problematic when the same reaction is repeated [Eq. (1)]. In fact, as shown in Table 2, quantitative yields were attained in ten runs with a single catalyst. Notably, only little catalyst loss occurred: the modified catalyst (491 mg) was recovered from 517 mg of the original after the 10th run. Thus, this esterification process does not require the use of conventional organic solvents.

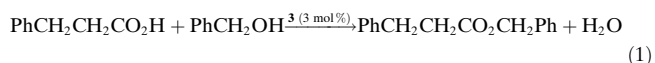
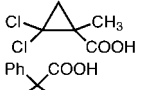
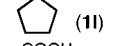
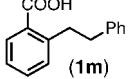


Table 2. Esterification using recycled fluororous tin catalyst **3** [Eq. (1)].^[a]

Run	Yield [%]	
	Isolated	GC
1	99.8	99.9
2	99.6	99.8
3	99.6	99.9
4	100.0	100.1
5	99.6	99.9
6	99.8	100.0
7	99.8	99.9
8	99.7	99.8
9	99.5	99.7
10 ^[b]	99.6	99.9

[a] Reagents and conditions: acid (10.0 mmol), alcohol (10.0 mmol), **3** (0.3 mmol), FC-72 (50 mL), 150 °C, 20 h. [b] After 10th run, 95% (491 mg) of the catalyst was recovered.

Table 1. Fluororous biphasic esterification.^[a]

Entry	RCOOH	R'OH	Yield (RCOOR') [%]	
			GLC	Isolated
1	Ph(CH ₂) ₂ COOH (1a)	PhCH ₂ OH (2a)	> 99.9	100
2	1a	C ₈ H ₁₇ OH (2b)	> 99	100
3	1a	TBSO(CH ₂) ₈ OH	> 99	98
4	1a	THPO(CH ₂) ₈ OH	> 99	98
5	1a	geraniol	> 99	100
6	1a	PhCH=CHCH ₂ OH	> 99	99
7	1a	PhC≡CCH ₂ OH	> 99	99
8	Ph(CH ₂) ₃ COOH (1b)	2a	> 99.9	100
9	C ₇ H ₁₅ COOH (1c)	2a	> 99.9	99
10	<i>p</i> -NO ₂ C ₆ H ₄ COOH (1d)	2a	> 99.9	100
11	C ₆ F ₃ COOH (1e)	2a	> 99.9	99
12	<i>p</i> -CF ₃ C ₆ H ₄ COOH (1f)	2a	> 99.9	99
13 ^[b]	CH ₂ =CH(CH ₂) ₈ COOH (1g)	2a	> 99.9	98
14 ^[b]	(4-ClC ₆ H ₄ O)C(CH ₃) ₂ COOH (1h)	2a	> 99.9	98
15 ^[b]	1a	menthol	45	44
16 ^[b]	1a	borneol	65	63
17 ^[b]	Ph ₂ C(CH ₃)COOH (1i)	2a	3.5	
18 ^[b]	1-adamantanecarboxylic acid (1j)	2a	14	
19 ^[b]	 (1k)	2a	13	
20 ^[b]	 (1l)	2a	16	
21 ^[b]	 (1m)	2a	4	
22 ^[b]	C ₆ H ₅ COOH (1n)	2a	22	
23 ^[b]	<i>p</i> -CH ₃ C ₆ H ₄ COOH (1o)	2a	26	
24 ^[b]	PhCH=CHCOOH (1p)	2a	32	

[a] Reaction conditions: acid (2.0 mmol), alcohol (2.0 mmol), **3** (0.10 mmol), FC-72 (5.0 mL), 150 °C, 10 h.

[b] Reaction time: 16 h.

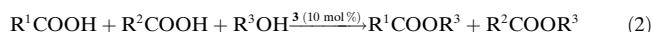
As is apparent from Table 1, the reaction is sensitive to the steric bulk of the reactants (Table 1, entries 15–21). Secondary alcohols as well as carboxylic acids with a bulky group at the α position (except for one case, Table 1, entry 14) did not give satisfactory yields. Neither simple aromatic carboxylic acids nor α,β -unsaturated carboxylic acids gave good yields (Table 1, entries 22–24), whereas electron-deficient aromatic derivatives reacted smoothly (Table 1, entries 10–12). Such differences in reactivity led us to carry out competition reactions between carboxylic acids and either octanol or benzyl alcohol [Eq. (2)]. As summarized in Table 3, equimolar amounts of two carboxylic acids of different reactivity were exposed to one equivalent of the alcohol. Remarkably, complete bias was observed: the ester (R¹COOR³) derived from the reactive carboxylic acid was produced in $\approx 100\%$ yield whereas none of the competing ester (R²COOR³) from the less reactive carboxylic acid was detected. The yield of the esters was

Table 3. Competition between carboxylic acids in fluorous biphasic esterification [Eq. (2)].^[a]

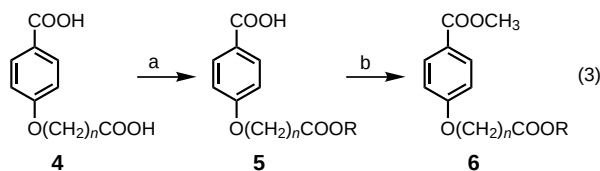
Entry	R ¹ COOH	R ² COOH ^[b]	R ³ OH	Yield [%]		
				R ¹ COOR ² GLC	Isolated	R ¹ COOR ³ GLC
1	1a	1i	2b	> 99.9	98	< 0.1
2	1a	1j	2b	> 99.9	98	< 0.1
3	1a	1k	2a	> 99.9	99	< 0.1
4	1a	1k	2b	> 99.9	100	< 0.1
5	1a	1l	2b	> 99.9	100	< 0.1
6	1a	1m	2b	> 99.9	99	< 0.1
7	1b	1i	2b	> 99.9	99	< 0.1
8	1b	1j	2b	> 99.9	98	< 0.1
9	1b	1k	2b	> 99.9	100	< 0.1
10	1b	1l	2b	> 99.9	99	< 0.1
11	1b	1m	2b	> 99.9	98	< 0.1
12	1c	1i	2b	> 99.9	97	< 0.1
13	1c	1m	2b	> 99.9	99	< 0.1
14	1c	1n	2b	> 99.9	97	< 0.1
15	1f	1k	2b	> 99.9	99	< 0.1
16	1f	1j	2b	> 99.9	100	< 0.1
17	1f	1k	2a	> 99.9	98	< 0.1
18	1f	1l	2b	> 99.9	100	< 0.1
19	1f	1m	2b	> 99.9	99	< 0.1

[a] Reaction conditions: R¹COOH (1.0 mmol), R²COOH (1.0 mmol), alcohol (1.0 mmol), **3** (0.10 mmol), FC-72 (5.0 mL), 150 °C, 16 h. [b] Unreacted R²COOH was quantitatively converted into the methyl ester (see text).

confirmed to be > 99.9% on the basis of GLC, which was carefully calibrated as described already. Furthermore, the organic layer was separated from the reaction mixture and treated with trimethylsilyldiazomethane (1.5 equiv) to convert the unreacted carboxylic acids into the methyl esters, the yield of which was found to be more than 99.9%.^[13] Notably, such perfect discrimination is rather surprising because reaction of the less reactive carboxylic acids actually takes place, though to a lesser extent, under noncompetitive conditions, which is suggestive of the involvement of some unique kinetic effects.



The differentiation between aliphatic and aromatic carboxylic acids was highlighted with substrates **4** [Eq. (3); Table 4].



Exposure of these substrates to an alcohol resulted in the exclusive esterification of the aliphatic alcohol to furnish the single products **5** in quantitative yields. The complete discrimination of the two carboxylic acid functions was further confirmed by transformation of **5** into methyl benzoate derivatives **6**. GLC analysis revealed quantitative formation of the methyl ester without contamination by any other products.^[14]

Table 4. Selective esterification of dicarboxylic acid [Eq. (3)].

Entry	n	R	Yield (5) [%] ^[c]	Yield (6) [%] ^[d]
1	1	PhCH ₂ CH ₂	100	99.9
2	1	cyclo-C ₆ H ₁₁ CH ₂ CH ₂	100	99.7
3	4	C ₈ H ₁₇	100	99.8

[a] Reaction conditions: **4** (1.0 mmol), ROH (1.0 mmol), **3** (0.10 mmol), FC-72 (5.0 mL), 150 °C, 16 h. [b] Reaction conditions: **5** (1.0 mmol), Me₃SiCHN₂ (1.5 mmol, 2 M solution in hexane, 0.75 mL), toluene (10 mL), MeOH (5 mL), room temperature, 3 h. [c] Yield of isolated product (column chromatography). [d] GLC yield.

In summary, almost complete atom efficiency has been realized in the fluoroalkyldistannoxane-catalyzed fluorous biphasic esterification. This atom efficiency, in conjunction with the facile recovery of the catalyst, holds great promise for developing a green esterification process. The nearly perfect stoichiometry as well as discrimination between carboxylic acids discovered herein may pave the way to elucidate characteristic features of kinetics in the fluorous biphasic system. Further studies are in progress in our laboratories.

Experimental Section

Typical procedure (Table 1, entry 1): A 50-mL test tube was charged with 3-phenylpropanoic acid (**1a**; 300 mg, 2.0 mmol), benzyl alcohol (**2a**; 216 mg, 2.0 mmol), **3** (172 mg, 0.10 mmol, 5 mol %), and FC-72 (5.0 mL). The test tube was placed in a stainless pressure bottle and heated at 150 °C for 10 h. After the pressure bottle had been cooled, toluene (5.0 mL) was added to the reaction mixture. The toluene and FC-72 layers were separated, and the latter was extracted with toluene (2 × 2.0 mL). GC analysis of the combined organic layer showed a quantitative yield of benzyl 3-phenylpropanoate.

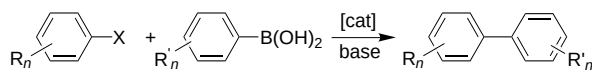
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Simple Mixed Tricyclohexylphosphane–Triarylphosphite Complexes as Extremely High-Activity Catalysts for the Suzuki Coupling of Aryl Chlorides**

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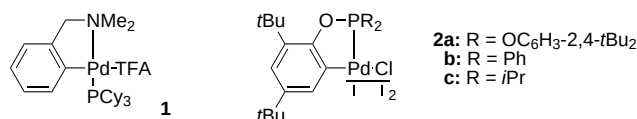
The coupling of aryl halides with aryl boronic acids, the Suzuki reaction (Scheme 1), is one of the most powerful and versatile methods for the synthesis of biaryls.^[1] There has



Scheme 1. The Suzuki coupling of aryl halides.

recently been considerable interest in the development of new catalysts that can couple aryl chlorides because of the lower cost and greater availability of these substrates compared with their bromide or iodide counterparts.^[2] Unfortunately the comparatively high C–Cl bond strength makes aryl chlorides difficult to activate. Consequently most catalysts that are able to catalyze aryl chloride coupling reactions still need to be used in relatively high loadings. Therefore the advantages associated with the use of aryl chlorides may be negated by the high cost of the catalyst systems.

We recently reported that complex **1**, based on the comparatively inexpensive ligands *N,N*-dimethylbenzylamine and tricyclohexylphosphane, shows very high activities in Suzuki coupling reactions of aryl chlorides at low catalyst loadings.^[2c] Previously we had shown that the orthopalladated



complex **2a**, which is easily prepared from the very inexpensive ligand tris(2,4-di-*tert*-butylphenyl)phosphite (**3**)^[3] shows good activity in the Suzuki coupling of aryl bromide substrates.^[4] This latter complex shows no propensity to couple even electronically activated aryl chlorides such as 4-chloroacetophenone. Therefore we were highly surprised to find that mixed PCy₃–P(OAr)₃ complexes either formed in situ or preformed show, to the best of our knowledge, the highest activity reported to date in aryl chloride coupling reactions. Preliminary findings of this study are reported below.

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The initial coupling studied was that of the deactivated substrate 4-chloroanisole with phenylboronic acid using the catalyst formed in situ from PCy₃ and the dimeric complex **2a**. As can be seen from the results summarized in Table 1, good to excellent conversions are obtained at 0.01 mol% Pd loadings with K₃PO₄, K₂CO₃, KF, or a mixture of K₃PO₄/KF acting as base (Table 1, entries 2–5, respectively). When cesium carbonate is used then even higher activity results. Under these conditions astonishingly high turnover numbers (TONs) of up to 34 000 are seen (Table 1, entries 7 and 8). By comparison, the previous highest reported TONs observed in this reaction were 8000, which was obtained under the same conditions using complex **1** as catalyst, and 12 800 when the highly sterically encumbered ligand PBu(Ad)₂ (Ad = adamantyl) was employed.^[2c,e] Increasing the PCy₃·Pd ratio from 1:1 to 2:1 led to a decrease in catalyst performance. When the orthopalladated phosphite precursor **2a** was replaced by the analogous phosphinite-containing complexes **2b** and then **c**^[5] a slight decrease in activity was observed with decreasing π -acidity of the orthopalladated ligand (Table 1, entries 11 and 12).

These results clearly demonstrate that complexes of the simple, inexpensive, easily handled PCy₃ ligand can show excellent activity, providing that the correct choice of palladium precursor is made.^[2c,f] “Classical” palladium precursors such as palladium acetate or palladium dibenzylideneacetone are generally very poor in this regard.^[2f] Indeed we find that when the coupling is performed with an equimolar mixture of palladium acetate, ligand **3**, and PCy₃, substantially lower activity results (Table 1, entry 13). The use of the preformed complex **4**, which is readily synthesized by reaction of **2a** with an excess of PCy₃ (Scheme 2),^[6] gave no advantage over the catalyst formed in situ.

The catalyst formed from **2a** and PCy₃ shows an order of magnitude higher activity than catalysts formed in situ from palladium acetate and either PCy₂(*o*-biphenyl) or P*t*Bu₃ (Table 1, entries 15 and 16), both of which have previously been shown to be excellent catalysts for the Suzuki coupling of aryl chlorides.^[2h,d] In addition catalysts formed in situ from **2a** and these phosphanes were not as active as that formed from PCy₃ although they were substantially better than those formed in situ from palladium acetate.

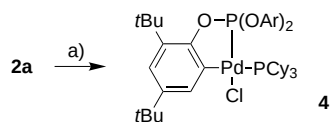
It may be anticipated that a catalyst formed in situ from complex **1** and one equivalent of ligand **3** would show essentially identical activity to that formed from **2a** and PCy₃. Indeed an increase in conversion at 17 h is observed compared to that of **1**, but it is not as high as that observed when the phosphite complex **2a** is used as the palladium precursor. Interestingly, it seems as if the added phosphite ligand *decreases* the rate of conversion, as exemplified by the results after two hours compared with those with **1**, but increases the catalyst longevity (Table 1, entries 19–22)—catalyst **1** shows essentially no further activity after 2 h.

Next we investigated the couplings of electronically non-activated and activated aryl chlorides (Table 1, entries 23–29) and found that extremely high TONs of up to 1 000 000 were observed. By contrast, to the best of our knowledge, the highest TONs reported for any Suzuki, or indeed any coupling reaction with an aryl chloride substrate is 100 000, obtained with complex **1**.^[2c]

Table 1. Suzuki coupling of aryl chloride substrates.^[a]

Entry	ArCl	ArB(OH) ₂	Catalyst (mol %)	Base	Conv. [%] ^[b]	TON mol product per mol Pd
1	C ₆ H ₄ -4-OMe	Ph	2a (0.5) + PCy ₃ (1.0)	K ₃ PO ₄	100	100
2	C ₆ H ₄ -4-OMe	Ph	2a (0.005) + PCy ₃ (0.01)	K ₃ PO ₄	91	9100
3	C ₆ H ₄ -4-OMe	Ph	2a (0.005) + PCy ₃ (0.01)	K ₂ CO ₃	82	8200
4	C ₆ H ₄ -4-OMe	Ph	2a (0.005) + PCy ₃ (0.01)	KF	51	5100
5	C ₆ H ₄ -4-OMe	Ph	2a (0.005) + PCy ₃ (0.01)	K ₃ PO ₄ /KF (1:1)	72	7200
6	C ₆ H ₄ -4-OMe	Ph	2a (0.005) + PCy ₃ (0.01)	Cs ₂ CO ₃	100	10000
7	C ₆ H ₄ -4-OMe	Ph	2a (0.0005) + PCy ₃ (0.001)	Cs ₂ CO ₃	34	34000
8	C ₆ H ₄ -4-OMe	Ph	2a (0.001) + PCy ₃ (0.002)	Cs ₂ CO ₃	68	34000
9	C ₆ H ₄ -4-OMe	Ph	2a (0.0015) + PCy ₃ (0.003)	Cs ₂ CO ₃	99	33000
10	C ₆ H ₄ -4-OMe	Ph	2a (0.001) + PCy ₃ (0.004)	Cs ₂ CO ₃	37	18500
11	C ₆ H ₄ -4-OMe	Ph	2b (0.0005) + PCy ₃ (0.001)	Cs ₂ CO ₃	29	29000
12	C ₆ H ₄ -4-OMe	Ph	2c (0.0005) + PCy ₃ (0.001)	Cs ₂ CO ₃	26	26000
13	C ₆ H ₄ -4-OMe	Ph	Pd(OAc) ₂ (0.1) + 3 (0.1) + PCy ₃ (0.1)	Cs ₂ CO ₃	12	120
14	C ₆ H ₄ -4-OMe	Ph	4 (0.001)	Cs ₂ CO ₃	28	28000
15	C ₆ H ₄ -4-OMe	Ph	Pd(OAc) ₂ (0.001) + PCy ₂ (<i>o</i> -biphenyl) (0.002)	Cs ₂ CO ₃	4	4000
16	C ₆ H ₄ -4-OMe	Ph	Pd(OAc) ₂ (0.001) + <i>Pr</i> Bu ₃ (0.002)	Cs ₂ CO ₃	3	3000
17	C ₆ H ₄ -4-OMe	Ph	2a (0.0005) + PCy ₂ (<i>o</i> -biphenyl) (0.001)	Cs ₂ CO ₃	8	8000
18	C ₆ H ₄ -4-OMe	Ph	2a (0.0005) + <i>Pr</i> Bu ₃ (0.001)	Cs ₂ CO ₃	11.5	11500
19	C ₆ H ₄ -4-OMe	Ph	1 (0.001)	Cs ₂ CO ₃	6 ^[c]	6000
20	C ₆ H ₄ -4-OMe	Ph	1 (0.001)	Cs ₂ CO ₃	6	6000
21	C ₆ H ₄ -4-OMe	Ph	1 (0.001) + 3 (0.001)	Cs ₂ CO ₃	3 ^[c]	3000
22	C ₆ H ₄ -4-OMe	Ph	1 (0.001) + 3 (0.001)	Cs ₂ CO ₃	20	20000
23	C ₆ H ₄ -2-Me	Ph	2a (0.00005) + PCy ₃ (0.0001)	Cs ₂ CO ₃	10	100000
24	C ₆ H ₄ -2-Me	Ph	2a (0.0005) + PCy ₃ (0.001)	Cs ₂ CO ₃	82	82000
25	C ₆ H ₄ -4-Me	Ph	2a (0.00005) + PCy ₃ (0.0001)	Cs ₂ CO ₃	48	480000
26	C ₆ H ₄ -4-COMe	Ph	2a (0.00005) + PCy ₃ (0.0001)	Cs ₂ CO ₃	88	880000
27	C ₆ H ₄ -4-NO ₂	Ph	2a (0.00005) + PCy ₃ (0.0001)	Cs ₂ CO ₃	92	920000
28	C ₆ H ₄ -4-COMe	C ₆ H ₄ -4-Me	2a (0.00005) + PCy ₃ (0.0001)	Cs ₂ CO ₃	100	1000000
29	C ₆ H ₄ -4-NO ₂	C ₆ H ₄ -4-Me	2a (0.00005) + PCy ₃ (0.0001)	Cs ₂ CO ₃	100	1000000

[a] Reaction conditions: ArCl (10 mmol), ArB(OH)₂ (15 mmol), base (20 mmol), 1,4-dioxane (30 mL), 100 °C, N₂, 17 h. [b] Conversion to Suzuki product, based on aryl chloride determined by GC (hexadecane standard). [c] Reaction time = 2 h.

Scheme 2. a) PCy₃, 2 equiv per Pd, CH₂Cl₂, reflux 18 h.

Regardless of conditions, the mixed PCy₃-P(OAr)₃ systems show higher activity than complex **1**. Given that the rate-determining step in the Suzuki coupling of aryl chloride substrates is generally accepted to be oxidative addition, it is not surprising that catalysts that usually show good activity tend to have strongly electron-donating ligands that maximize electron density on the palladium center.^[7] Thus it seems counter-intuitive that the inclusion of a π -acidic triarylphosphite ligand, which shows little or no tendency to facilitate the coupling of even activated aryl chlorides,^[8] should enhance activity. Plots of conversion against time in the coupling of 4-chloroanisole with phenylboronic acid catalyzed by **1** and the catalyst formed in situ from **2a** and PCy₃ are shown in Figure 1. It is immediately apparent that the inclusion of the triarylphosphite ligand does not increase the rate, it may even lead to a slight decrease, instead it leads to greatly increased catalyst longevity compared with complex **1**. What is the basis of this increased longevity? If it is assumed that the rate-determining step is oxidative addition, then the catalyst spends most of its time “resting” in a zerovalent state.^[9] This “resting” state will be stabilized both thermodynamically and

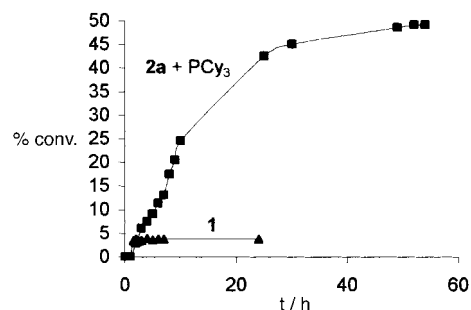


Figure 1. Plots of conversion [%] versus time (*t*) in the coupling of 4-chloroanisole (10 mmol) with phenylboronic acid (15 mmol) catalyzed by **1** (▲) and 0.5 **2a** + PCy₃ (■) (both at 0.001 mol % Pd). Reaction conditions: Cs₂CO₃ (20 mmol), 1,4-dioxane (27 mL), hexadecane internal standard (3.0 mL, 0.034 M in 1,4-dioxane), 100 °C, N₂. Conversions determined by GC.

kinetically by the reversible coordination of the π -acidic triarylphosphite ligand. Decoordination of the phosphite ligand would give a low-coordinate, electron-rich complex readily able to oxidatively add the aryl chloride substrate and thus enter the catalytic manifold.

In summary, catalysts formed from mixtures of the readily available, easily handled and inexpensive ligands **3** and PCy₃ show by far the highest activity yet reported in the Suzuki coupling of aryl chlorides.

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- [7] Fu and co-workers have recently reported that highly sterically hindered triarylphosphanes can catalyze couplings of electronically deactivated aryl chlorides (see ref. [2b]), indicating that more subtle effects than brute donor-strength can play an important role.
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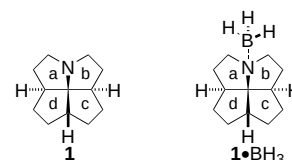
Synthesis of *cis,cis,cis,cis*-[5.5.5.5]-1-Azafenestrane**

Scott E. Denmark,* Laurenz A. Kramps, and Justin I. Montgomery

The structural theory of organic chemistry is one of the most highly evolved constructs in natural science. The ability to explain and correctly predict the detailed molecular structure of millions of compounds naturally inspires research to test the limits of the theory. One important subset of this field of investigation probes the extent to which a tetracoordinate carbon atom (bearing all carbon substituents) can deviate from the van't Hoff/Le Bel tetrahedral geometry. The interesting family of compounds called fenestranes^[1] com-

prises molecules with planarizing distortion of the central carbon atom. The magnitude of the distortion is dependent on the size and configuration of the fused rings. Because the parent, unsubstituted fenestranes are low molecular weight hydrocarbons, they are not amenable to X-ray crystallographic analysis. The few X-ray structures on record are of substituted and functionalized derivatives.^[2]

We were intrigued by the possibility of replacing one of the ring-fusion carbon atoms with a nitrogen atom to facilitate salt formation and provide an opportunity for X-ray analysis of an unsubstituted fenestrane. In addition to establishing the full molecular structure and the extent of the central carbon planarization, the pyramidal distortion of the nitrogen atom would also be of interest; to our knowledge, no monoazafenestranes have been prepared. An unusual tetraamino [5.5.5.5]fenestrane is known and it exists as an equilibrium mixture of (degenerate) open and closed forms when protonated.^[3] We describe herein the first synthesis of an unsubstituted 1-azafenestrane **1** along with the synthesis and X-ray crystallographic analysis of the borane adduct **1**·BH₃.



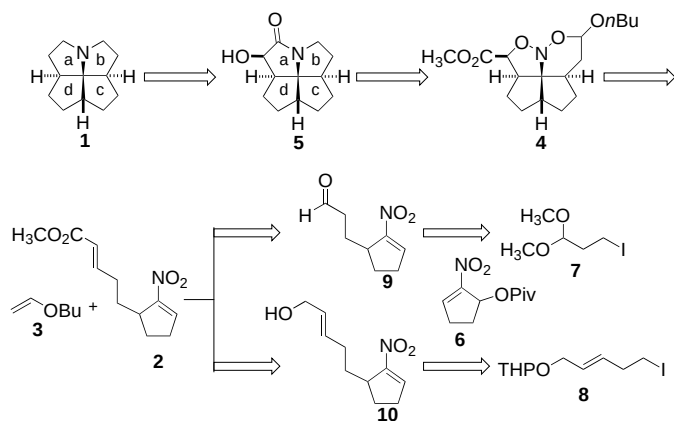
Analysis of the tetracyclic ring structure of **1** reveals that it contains an embedded pyrrolizidine unit fused to a bicyclo[3.3.0]octane system. In recent years, a large number of pyrrolizidine-based alkaloid natural products in the necine, alexine and australine families have been synthesized in these laboratories.^[4] The key strategic operation in all of these syntheses is the tandem [4+2]/[3+2] cycloaddition of nitroalkenes.^[5] This process allows for the facile and stereocontrolled construction of highly functionalized nitroso acetals that serve as precursors for pyrrolizidines upon catalytic hydrogenolysis.

The application of the tandem cycloaddition strategy to the synthesis of **1** is outlined in Scheme 1. Constructing the core of **1** requires the creation of one of the four rings in the tandem [4+2]/[3+2] process by cycloaddition of a C₂ dienophile (butyl vinyl ether (**3**)) with a cyclopentenyl nitro diene **2** (ring C) bearing the suitable dipolarophilic tether. The tetracyclic nitroso acetal **4** is then poised for hydrogenolytic unmasking to a tricyclic pyrrolizidine (third ring, c) which should undergo spontaneous lactam formation (→**5**; fourth ring, d) from the appended carboxylic ester. Thus, three of the four rings of [5.5.5.5]-1-azafenestrane can be assembled in two chemical manipulations. Two-stage reduction of the α-hydroxy lactam **5** leads to the target azafenestrane **1**. This approach allows for a modular synthesis of fenestranes containing rings of different size at various positions. With regard to the configuration at the ring fusions, only one relationship was expected to be variable. In the [4+2] process, the approach of the dienophile can take place on the two diastereotopic faces of the nitroalkene to create *cis* and *trans* isomers. The [3+2] process is formally in the spiro mode family^[6] and thus is expected to

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

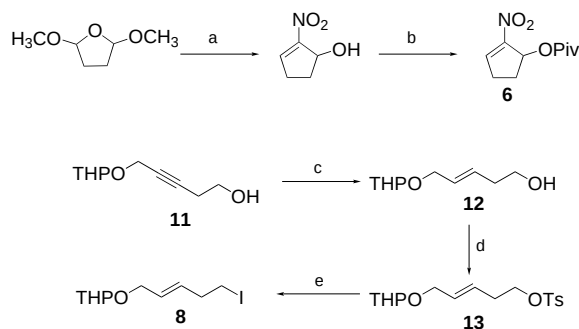


Scheme 1. Retrosynthetic strategy for the construction of azafenestrane **1** by tandem [4+2]/[3+2] cycloaddition. Piv = pivaloyl, THP = tetrahydropyranyl.

proceed via an *exo*-mode pathway to create a *cis* ring fusion independent of the tether length.

The side chain of nitroalkene **2** (that creates ring d) could be introduced by nucleophilic addition to the nitro allylation reagent **6**.^[7] The required nucleophiles (alkyllithium reagents) could be obtained by halogen–metal exchange from the corresponding iodides **7** and **8**. Each side chain precursor requires a different sequence to complete the construction of the desired α,β -unsaturated ester: 1) Horner–Wadsworth–Emmons (HWE) or Wittig reaction with aldehyde **9** and 2) oxidation of an allyl alcohol **10** to the acid followed by esterification. Both approaches were pursued in view of the unknown sensitivity of the nitroalkene to these agents.

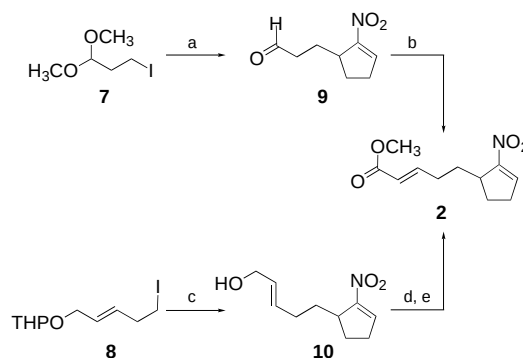
The synthesis began by preparation of the key subunits (Scheme 2). Pivalate **6** was prepared by modification of procedures for the synthesis of the analogous cyclohexene



Scheme 2. a) 1. HCl, 80 °C; 2. NaOH, MeNO₂, H₂O, MeOH, RT; 3. Al₂O₃, 40 °C; b) pivalic anhydride, H₂SO₄, 9 % (four steps); c) LiAlH₄, Et₂O, reflux, 70 %; d) TsCl, Et₃N, CH₂Cl₂ 0 °C, 90 %; e) NaI, acetone, reflux, 99 %. Ts = tosyl.

derivative.^[7] Unfortunately, the cyclopentenyl case could not be optimized above 9 %, but the reactions could be scaled up by using inexpensive starting materials. The iodo acetal **7**^[8] and THP-protected iodide **8**^[9] were prepared directly and by adaptation of literature procedures, respectively.

The nitro allylating agent **6** behaved similarly toward the two organolithium nucleophiles derived from **7** and **8** by iodine–lithium exchange with *tert*-butyl lithium^[10] (Scheme 3).



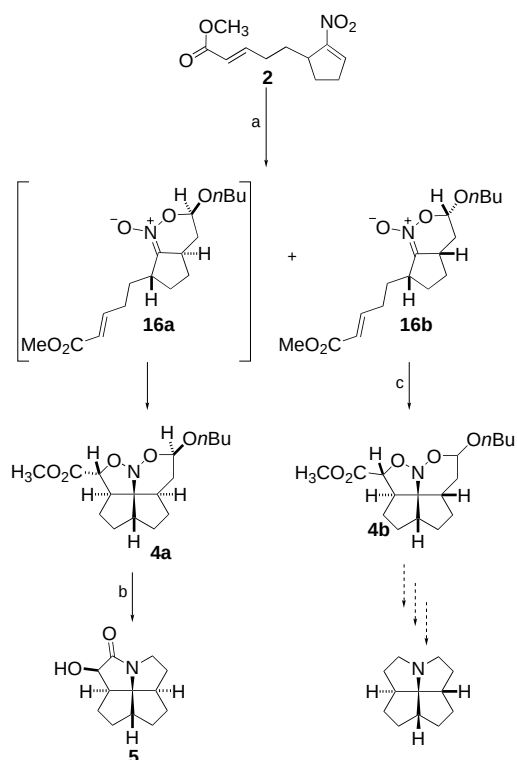
Scheme 3. a) 1. *t*-BuLi, THF/hexane/Et₂O, –100 °C; 2. **6**, –50 °C, TsOH, aq. acetone, 61 %; b) trimethylphosphonoacetate, *n*-BuLi, THF, –70 °C, 22 %; c) 1. *t*-BuLi, THF/hexane/Et₂O, –100 °C; 2. **6**, –50 °C, TsOH, MeOH, 67 %; d) Dess–Martin reagent, CH₂Cl₂, 89 %; e) 1. [(H₂bipy)Cl₅CrO], CH₂Cl₂, 2. MeOH, 3. CH₂N₂, 36 % (three steps).

Both the aldehyde **9** and the primary alcohol **10** were obtained in comparable, synthetically viable yields after hydrolysis of the protective groups. Homologation of **9** by using either methyl (triphenylphosphoranylidene)acetate or trimethylphosphonoacetate (with *n*-BuLi) afforded low (15–22 %) yields of **2**. The oxidation of alcohol **10** could be effected with the Jones reagent, but low yields were obtained and the purification of the product proved to be difficult. Better results were obtained when [(H₂bipy)Cl₅CrO]^[11] in CH₂Cl₂ was used. This chromium(v) complex afforded a mixture of acid and acid chloride, which could be converted to the desired ester **2** simply by treatment with MeOH. The remaining carboxylic acid could be converted to **2** with diazomethane.

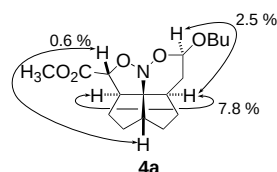
The [4+2] cycloaddition of nitroalkene **2** and butyl vinyl ether (**3**) afforded two diastereomers of nitronate **13**. Only one of these diastereomers underwent spontaneous [3+2] cycloaddition to give nitroso acetal **4a** (Scheme 4). Nuclear Overhauser NMR spectroscopic investigations of **4a** confirmed the relative configuration of this compound (Scheme 5).

The reaction has not been optimized to control the diastereoselectivity by the use of different Lewis-acids. Increasing the selectivity of the reaction would improve the yield of nitroso acetal **13a**. Nitronate **13b** is also a useful compound and the separation from the nitroso acetal **4a** was easy because of the high polarity of **13b** compared to that of **4a**. Preliminary investigations indicated that the nitronate **13b** can undergo [4+2] cycloaddition at elevated temperature (NaHCO₃, toluene, 97 °C) to give the diastereomeric nitroso acetal **4b**, which can potentially be transformed to diastereomeric fenestrane **1b** (Scheme 4).

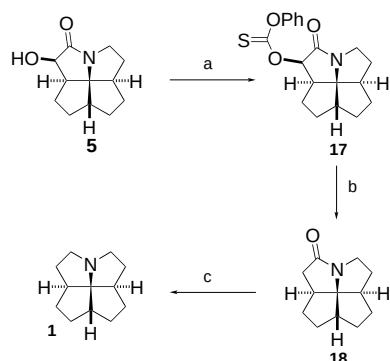
Hydrogenation of nitroso acetal **4a** afforded hydroxy 1-azafenestrane **5** in 72 % yield. The yield of **5** from nitroalkene **2** is 48 %—remarkable for the formation of a fenestrane skeleton. Completion of the synthesis required two deoxygenation steps (Scheme 6). First, the hydroxy group was removed by conversion to the phenyl thionocarbonate **12**, which was reduced with *n*-Bu₃SnH/AIBN by a method originally described by Barton and McCombie.^[12] The resulting lactam **13** was reduced with LiAlH₄ to give the target *cis,cis,cis,cis*-[5.5.5.5]-1-azafenestrane (**1**).



Scheme 4. a) **3**, Me₃Al, toluene, -70°C, **4a** (67%) and **16b** (27%); b) Raney nickel, H₂ (1100 kPa, 160 psi), MeOH 72%; c) benzene, K₂CO₃, 80°C, 70%.



Scheme 5. nOe analysis of nitroso acetal **4a**.



Scheme 6. a) Phenyl thionochloroformate, pyridine, DMAP, 77%; b) nBu₃SnH, AIBN, benzene, reflux, 98%; c) LiAlH₄, THF, reflux, 83%.

The spectroscopic data for **1** clearly support the structure and C₁ symmetry of the molecule (seven ¹³C NMR signals).^[13] To secure the detailed molecular structure, we surveyed the formation of crystalline salts and found that treatment of **1** with a solution of borane in THF formed an adduct (as judged by ¹H NMR analysis) which could be recrystallized from

diethyl ether to afford **1**·BH₃ as colorless needles. X-ray crystallographic analysis^[14] of **1**·BH₃ (Figure 1) confirms the gross molecular structure but also reveals that the compound

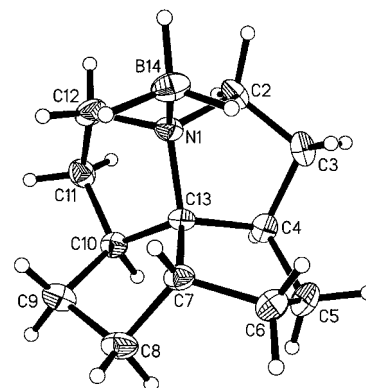


Figure 1. SHELXTL plot of **1**·BH₃ from X-ray analysis (35% thermal ellipsoids).

crystallizes in a chiral space group (*P*₂₁) because of the twist of the five-membered rings (dihedral angle B-N(1)-C(13)-C(7) = 11.6°).^[15] The planarization of the central carbon atom (C(13)) is only modest as defined by the two orthogonal bond angles: N-C(13)-C(7) = 116.1° and C(4)-C(13)-C(10) = 116.6°. This was not unexpected as these angles in the *all-cis* stereoisomer of the parent [5.5.5]fenestrane hydrocarbon are calculated to be 113°.^[1]

In summary, we have demonstrated the feasibility of a tandem cycloaddition approach to 1-azafenestranes and the ability to obtain crystalline adducts suitable for X-ray analysis. The preparation of more strained and flattened congeners is underway and will be reported in due course.

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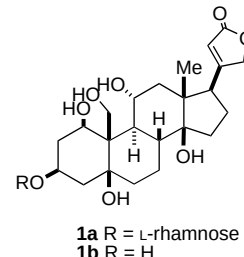
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- [13] Data for **1**: b.p.: 40 °C (0.1 Torr); ¹H NMR (500 MHz, CHCl₃, TMS): δ = 1.33 (m, 4H, HC(5), HC(4)), 1.46 (m, 2H; HC(2)), 1.78 (m, 4H; HC(5), HC(4)), 1.89 (m, 2H; HC(2)), 2.02 (m, 1H; HC(6)), 2.18 (m, 2H; HC(3)), 2.70 (dt, *J* = 10.5, 6.2 Hz, 2H; HC(1)), 2.92 ppm (dt, *J* = 10.5, 6.4 Hz, 2H; HC(1)); ¹³C NMR (126 MHz, CHCl₃): δ = 29.6, 30.3, 30.5 (C(2), C(4), C(5)), 50.9 (C(3)), 51.9 (C(6)), 52.4 (C(1)), 93.1 ppm (C(7)); IR (CH₂Cl₂): ν̄ = 2945 (s), 2864 (m), 1454 (w), 1269 (vw), 1173 (vw), 1119 (vw); MS (FAB): *m/z* (%): 178 (*M*⁺+1, 100) (vw); TLC (CHCl₃/MeOH 20:1, Al₂O₃): *R*_f = 0.64; C, H, N analysis (%): calcd for C₁₂H₁₉N: C 81.30, H 10.80, N 7.90; found: C 81.02, H 10.95, N 7.97.
- [14] X-ray crystal structure analysis of **1**·BH₃. A single crystal deposited from Et₂O solution at –25 °C: formula C₁₂H₂₂BN. *M*_r = 191.12, crystal size 0.2 × 0.2 × 0.02 mm³, *a* = 6.2685(13) Å, *b* = 12.773(3) Å, *c* = 7.5043(15) Å, β = 111.517(4)°, *V* = 558.93(19) Å³, ρ_{calcd} = 1.136 g cm^{–3}, μ = 0.064 mm^{–1}, absorption correction by integration, *Z* = 2, monoclinic space group *P*2₁, Siemens 3-circle platform diffractometer with a molybdenum (*K*_α = 0.71073 Å) X-ray source and CCD area detector, *T* = 193(2) K, 5835 measured reflections (±*h*, ±*k*, ±*l*), 1074 independent and 722 observed reflections with *I* > 2σ(*I*), *R* = 0.0423, *wR* = 0.0494 (against |*F*²|), residual electron density 0.12 e Å^{–3}; programs used: SHELXTL V6. CCDC-189803 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
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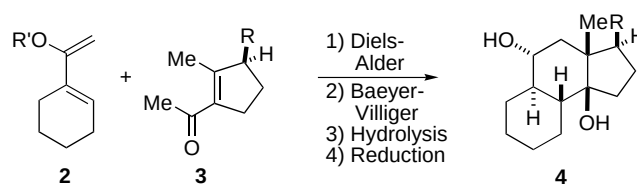
Efficient Synthesis of a Tricyclic BCD Analogue of Ouabain: Lewis Acid Catalyzed Diels–Alder Reactions of Sterically Hindered Systems**

Michael E. Jung* and Pablo Davidov

The naturally occurring cardenolide ouabain (**1a**) and its aglycone ouabagenin (**1b**) are members of a class of highly oxygenated cardiotonic steroids (digitalis glycosides) used in the treatment of congestive heart failure.^[1] Ouabain has been synthesized starting from other natural steroids,^[2] however, no total synthesis^[3] has been reported to date although an excellent synthetic route has been described.^[4] We have reported some preliminary results on an approach to the bicyclic CD ring system of ouabain in which we attempted to use an anionic [1,3] sigmatropic shift of a 7-alkenylbicyclo[3.2.1]heptane-1,7-diol, which afforded products from an unusual anion-accelerated retroene reaction.^[5] We report here a completely different route that allowed us to prepare a tricyclic BCD ring system analogue of ouabain in a very efficient manner. In this route we have developed a novel Diels–Alder reaction of sterically hindered enones and dienes to afford heavily substituted cyclohexene systems extremely easily.



Initially, we decided to investigate a possible Diels–Alder approach for the synthesis of the CD ring system of ouabain. Cycloaddition of a 1-(alkoxyvinyl)cyclohexene **2** with the enone **3** followed by conversion of the ketone to an acetate by a Baeyer–Villiger oxidation and final hydrolysis and reduction of the cyclic ketone would give the diol **4**, which has the required five contiguous asymmetric centers of the BCD ring system of ouabain (Scheme 1). The anticipated difficulty of carrying out a Diels–Alder reaction with a hindered dienophile such as **3** made us first investigate a simpler model system. All attempts at effecting the cycloaddition of 2-trimethylsilyloxybutadiene (**5**) with the known dienophile **6**



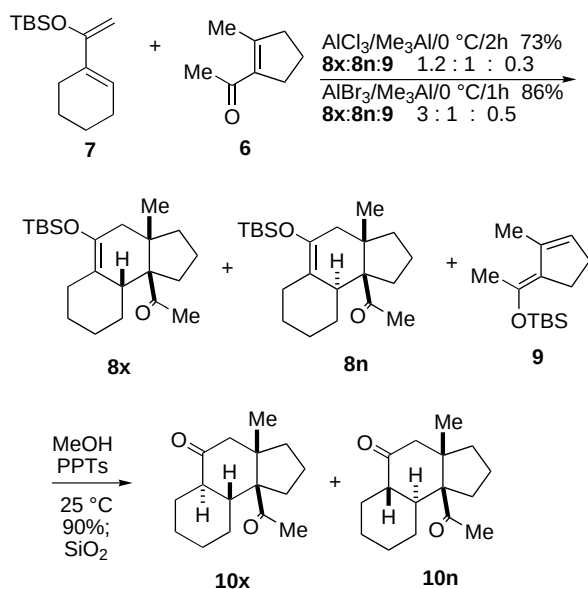
Scheme 1. Diels–Alder approach to the diol **4**, which contains the BCD ring system of ouabain (**1a**).

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(see Scheme 2; prepared in one step from cyclohexane)^[6] were unsuccessful; thermal conditions (toluene, 110 °C) returned the starting materials, and Lewis acid catalysis (AlCl₃ or TiCl₄) resulted in decomposition of the diene.^[7] Even the highly reactive Danishefsky's diene (*trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene) did not give the expected product with the enone **6**, either at 23 °C for seven days or at 110 °C for several hours, thus implicating the unreactivity of the dienophile **6**.

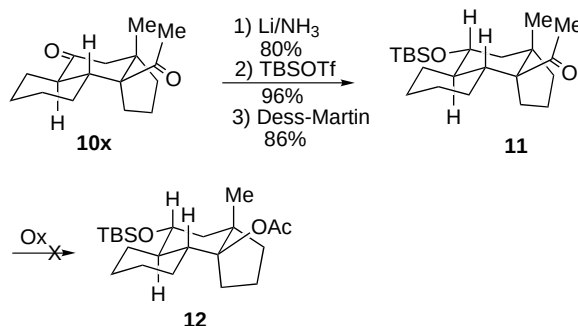
Since the trimethylsilyl enol ether did not withstand the Lewis acidic conditions, we decided to study the more stable diene **7** (see Scheme 2). We have shown that this diene is quite useful in various cycloadditions.^[8] Again thermal conditions (110 °C/48 h) did not effect cycloaddition and starting materials were returned. However, use of mixed Lewis acid systems afforded a mixture containing the desired product in good yield. Thus treatment of **7** and **6** in toluene with 50 mol % of a 10:1 AlCl₃ and AlMe₃ mixture at 0 °C for 2 h furnished a 1.2:1:0.3 mixture of the desired *exo* isomer **8x**, the *endo* isomer **8n**, and an unknown impurity tentatively assigned structure **9**^[9] in 73% yield (Scheme 2).^[10–12] However, we



Scheme 2. Reaction between the dienophile **6** and hindered diene **7** in the presence of the mixed Lewis acid system 10:1 AlCl₃/AlMe₃. TBS = *tert*-butyldimethylsilyl, PPTs = pridinium *p*-toluenesulfonate.

found that AlBr₃ is much easier to work with^[13] than AlCl₃ and was thus preferable as a catalyst. Use of 50 mol % of a 10:1 mixture of AlBr₃/AlMe₃ in a toluene/dichloromethane mixture at 0 °C for 1 h afforded the same three products **8x**, **8n**, and **9** in 86% yield in a 3:1:0.5 ratio. We propose that the small amount of AlMe₃ eliminates any trace of HX in the medium thereby extending the stability of the silyloxy diene. The two diastereomeric products were inseparable by column chromatography but conversion of the silyl enol ethers proceeded in excellent yield under mildly acidic conditions^[14] to give the two diastereomeric ketones, **10x** and **10n**, which were separable by simple column chromatography. The structures of these ketones were assigned by NOE NMR

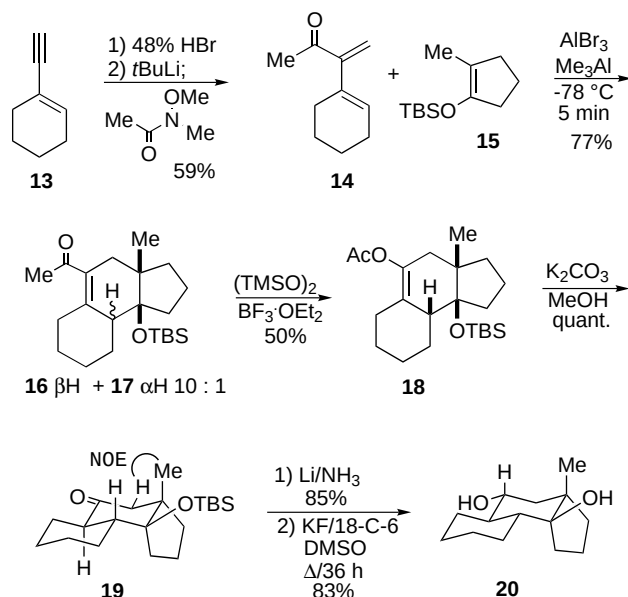
experiments; the undesired minor isomer **10n** was highly crystalline and was characterized by X-ray crystal structure analysis.^[15] The last stereocenter was introduced by Li/NH₃ reduction of the cyclic ketone **10x**, which yielded the expected equatorial alcohol and a 1:1 diastereomeric mixture of secondary alcohols from the acetyl group (Scheme 3). The



Scheme 3. Conversion of **10x** to the silyl ether ketone **11** as a proposed route to **12**.

two alcohols were easily differentiated by selective protection of the equatorial alcohol with a *tert*-butyldimethylsilyl (TBS) group. The acetyl moiety was regenerated in quantitative yield by exposure to the Dess–Martin periodinane to give the silyl ether ketone **11**. At this point we were ready to attempt the second key step of the route, the Baeyer–Villiger oxidation. Unfortunately, the acetyl moiety is so sterically hindered that all attempts to effect this oxidation failed to yield any of the desired product **12**.^[16] This result seemed to doom this attempt at the preparation of a tricyclic BCD ring system analogue of ouabain by this route.

Thus, we decided to try to effect an inverse electron demand in the key cycloaddition, namely the coupling of an electron-poor diene with an electron-rich dienophile (Scheme 4). The desired 2-acetyl-1,3-diene **14** was prepared



Scheme 4. Synthesis of the desired ketone **19** and its conversion to the diol **20**, a BCD ring system analogue of ouabain (**1a**). 18-C-6 = [18]crown-6.

from ethynylcyclohexene (**13**) in two steps (addition of $\text{HBr}^{[17]}$ and coupling of the derived organometallic compound with the Weinreb amide).^[18] This enone was then treated with the TBS-protected enol ether **15** under the same conditions as before—50 mol % of a 10:1 mixture of AlBr_3 and AlMe_3 in toluene/dichloromethane at -78°C for 5 min—to afford a 10:1 diastereomeric mixture of the desired *exo* adduct **16** and the *endo* adduct **17** in 77 % yield, which were easily separable by chromatography, affording **16** in 72 % yield. Baeyer–Villiger oxidation of this mixture of enones was effected by using bis(trimethylsilyl) peroxide and $\text{BF}_3\cdot\text{OEt}_2$ to furnish the desired acetate **18** in 50 % yield. This enol acetate was hydrolyzed in quantitative yield under mildly basic conditions to yield the desired ketone **19**. The structure of this ketone was assigned based on a strong NOE between the quaternary methyl group and the equatorial proton α to the ketone group (Scheme 4). Reduction of the ketone **19** with Li/NH_3 yielded the desired equatorial alcohol in 85 % yield. Finally deprotection of the TBS group required forcing conditions,^[19] namely heating with KF in DMSO for 36 h, to cleanly remove the protecting group and yield the desired diol **20** in 83 % yield along with 15 % of the recovered hydroxy silyl ether. The structure of **20** was confirmed by a single-crystal X-ray structure analysis (Figure 1).^[16]

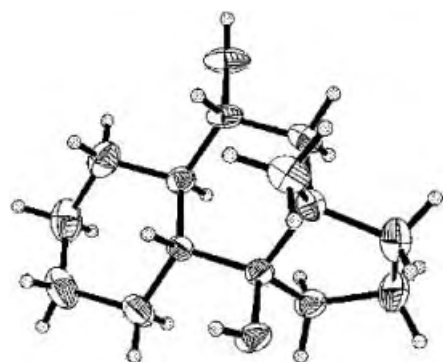
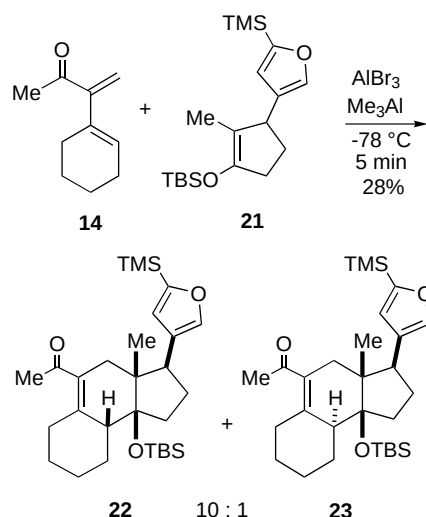


Figure 1. X-ray structure analysis of diol **20**.

Finally, we have some preliminary results that indicate that more functionalized silyl enol ethers can be used as ring D precursors in this process (Scheme 5). A racemic mixture of the silylfuran **21** was synthesized by using a modified version of the procedure developed by Kim and Park.^[20] Treatment of the diene **14** and the dienophile **21** with 0.5 equivalents of AlBr_3 and 0.05 equivalents of AlMe_3 at -78°C for 5 min furnished a 10:1 mixture of the *exo* adduct **22** and the *endo* adduct **23** in 28 % yield. The structures were assigned based on our previous results (for the *exolendo* stereocenter) and NOE experiments which displayed a through-space interaction between the protons of the quaternary methyl group and a proton from the furyl group, thus implying that the two groups were *syn* to each other. Although this unoptimized reaction provided low yields of the desired *exo* adduct **22**, it demonstrated the feasibility of this approach to obtain advanced tricyclic adducts containing four correct contiguous stereocenters plus a butenolide-equivalent moiety.



Scheme 5. Synthesis of **22** and **23** by using the highly functionalized silyl enol ether **21** as ring D precursor.

In summary, we have been able to prepare the diol **20**, a tricyclic BCD ring system analogue of the steroid ouabain **1a**, by an efficient route that highlights a new procedure for the formation of hindered cyclohexyl systems through the use of a mixed Lewis acid medium for effecting cycloadditions of hindered systems bearing acid-sensitive functionalities. Further studies on this reaction and the synthesis of ouabain **1a** are currently in progress.

Experimental Section

Diels–Alder adducts 8x and 8n: The enone **6** (1.5 g, 12 mmol) was dissolved in a solution of toluene (20 mL) and dichloromethane (7 mL), and the mixture was cooled to -8°C . Trimethylaluminum (0.3 mL of a 2.0 M solution in toluene, 0.6 mmol) was slowly added to the solution, followed after 15 min by aluminum bromide (6 mL of a 1.0 M solution in dibromomethane, 6 mmol). The mixture was stirred 15 min and the silyl enol ether **7** (3.8 g, 16 mmol) in dichloromethane (5 mL) was slowly added to the mixture. The reaction was warmed to 0°C over 1 h and quenched with pyridine (20 mL) and the mixture warmed to 23°C . The suspension was filtered over a small pad of silica gel, and the solvent removed in vacuo. The product was purified by column chromatography over silica gel (94:6 hexanes/ethyl acetate) to yield the desired compound (3.724 g, 10.3 mmol, 86 %) as a 3:1 mixture of the diastereomers **8x** and **8n**. The diastereomers were inseparable by column chromatography. **8x:** ^1H NMR (500 MHz, CDCl_3): δ = 2.92 (bd, 1H), 2.73 (bd, 1H), 2.19 (s, 3H), 1.99 (m, 1H), 1.55–1.81 (m, 8H), 1.03–1.48 (m, 6H), 1.00 (s, 3H), 0.93 (s, 9H), 0.10 (s, 3H), 0.09 ppm (s, 3H); ^{13}C NMR (125.75 MHz, CDCl_3): δ = 214.8, 138.2, 113.3, 64.1, 44.2, 42.1, 40.0, 38.6, 31.5, 30.7, 30.1, 29.5, 25.9, 25.6, 22.6, 20.1, 18.2, 14.1, -3.8 , -3.9 ppm. **8n:** ^1H NMR (500 MHz, CDCl_3): δ = 2.98 (bd, 1H), 2.12 (s, 3H), 1.55–1.81 (m, 8H), 1.03–1.48 (m, 8H), 0.95 (s, 9H), 0.90 (s, 3H), 0.13 (s, 3H), 0.11 ppm (s, 3H); ^{13}C NMR (125.75 MHz, CDCl_3): δ = 214.1, 140.0, 113.9, 63.8, 43.2, 41.2, 39.3, 38.8, 31.7, 30.9, 30.2, 29.3, 25.8, 25.7, 22.7, 20.0, 18.4, 14.3, -3.7 , -4.0 ppm; IR of mixture (thin film on NaCl): $\tilde{\nu}$: 2955 (s), 2930 (s), 2857 (m), 1696 (s), 1471 (m), 1361 (m), 1251 (m), 1179 (m), 851 (s), 777 cm^{-1} (m); MS of mixture (m/z): 362.29 [M^+], 319.26, 239.20, 182.12.

Diels–Alder adducts 16: The dienone **14** (0.793 g, 5.27 mmol) was dissolved in a solution of toluene (7 mL) and dichloromethane (3.5 mL) and the mixture was cooled to -78°C . Trimethylaluminum (0.125 mL of a 2.0 M solution in toluene, 0.25 mmol) was added as a chemical dessicant. Shortly afterwards (5 min), aluminum bromide (2.5 mL of a 1.0 M solution in dibromomethane, 2.5 mmol) was added dropwise followed immediately by the silyl enol ether **15** (1.27 g, 6 mmol) neat. After 5 min the reaction was quenched by adding pyridine (10 mL) at -78°C and warming the mixture to 23°C . The suspension was filtered through a small pad of silica and the

filtrate was concentrated in vacuo. ^1H NMR spectroscopy of the crude product reveals a 10:1 mixture of diastereomers **16** and **17** in favor of the desired *exo* adduct. The residue was purified by column chromatography on silica gel (95:5 hexanes/ethyl acetate) to yield the desired isomer **16** (1.46 g, 4.03 mmol, 76.5%). ^1H NMR (500 MHz, CDCl_3): δ = 2.77 (bd, 1H), 2.19 (s, 3H), 2.12 (m, 1H), 2.05 (m, 2H), 1.89 (bd, 1H), 1.72–1.85 (m, 4H), 1.65 (m, 3H), 1.40 (m, 2H), 1.23 (m, 2H), 1.15 (m, 1H), 0.92 (s, 3H), 0.86 (s, 9H), 0.11 (s, 3H), 0.10 ppm (s, 3H); ^{13}C NMR (125.75 MHz, CDCl_3): δ = 205.8, 140.8, 129.8, 87.3, 46.1, 44.7, 38.6, 37.0, 33.4, 30.8, 29.9, 29.4, 27.0, 26.1, 25.9, 18.9, 18.3, 18.1, –2.3, –2.8; IR (thin film on NaCl): $\tilde{\nu}$ = 2953 (s), 2928 (s), 2855 (s), 1690 (s), 1471 (m), 1350 (m), 1251 (s), 1226 (m), 1124 (s), 1062 (s), 1005 (m), 833 (s), 770 cm^{-1} (s); high-resolution MS (m/z) [$M+\text{H}$] $^+$ 362.2616, calcd for $\text{C}_{22}\text{H}_{38}\text{O}_2\text{Si}$ 362.2641.

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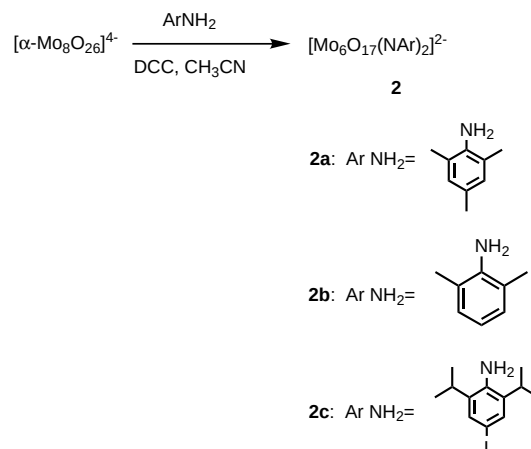
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- [13] Aluminum tribromide (AlBr_3) is commercially available as a 1M solution in dibromomethane, while aluminum trichloride (AlCl_3) is supplied as a 1M solution in nitrobenzene. The lower boiling point and lack of a chromophore makes the use of the former preferable. All of the solutions of AlBr_3 and AlMe_3 were prepared by mixing the commercially available solutions (a 2M solution of AlMe_3 in toluene was used).
- [14] Hydrolysis of the silyl enol ether with tetrabutylammonium fluoride (TBAF) gave poor yields, presumably due to retro-Michael reactions.
- [15] We thank Dr. Saeed Khan for obtaining the X-ray crystal structures. CCDC-194419 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Centre, 12 Union Road, Cambridge CB21EZ, UK; Fax: (+44) 1223-336033; or deposit@ccdc.cam.ac.uk).
- [16] For example, oxidation with *meta*-chloroperoxybenzoic acid (MCPBA) (alone or in the presence of a radical inhibitor at elevated temperatures), trifluoroperacetic acid, 3,5-dinitroperbenzoic acid, hydrogen peroxide, and bis(trimethylsilyl)peroxide in the presence of trimethylsilyl triflate gave only starting material or desilylated starting material under all conditions tried. The addition of several other nucleophiles to this very hindered ketone was also unsuccessful.
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Towards Main-Chain-Polyoxometalate-Containing Hybrid Polymers: A Highly Efficient Approach to Bifunctionalized Organoimido Derivatives of Hexamolybdates**

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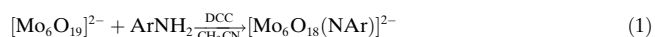
There have been increasing efforts towards making multifunctional hybrid materials by using covalently linked polyoxometalates (POMs) and organic polymers.^[1–5] The motivation lies not only in the combination of the so-called value-adding properties,^[6,7] but also in the exploration of possible synergistic effects.^[8,9] For example, the covalent grafting of electron-accepting POMs into an organic conjugated polymer may result in highly photoconductive materials with photochromic effects. Judeinstein reported the first POM–polymer hybrid ten years ago where a lacunary Keggin POM cluster was covalently linked to a polystyrene or polymethacrylate backbone through Si–O bonds.^[1] This approach has been expanded recently by Lalot and co-workers to prepare polymer–POM cross-linked networks^[2] and by Stein and co-workers to generate macroporous silica materials functionalized with POM clusters.^[3,4] A polymer–POM hybrid has also been reported recently by Maatta and co-workers.^[5] While these works are exemplary, they all involve insulating non-conjugated polymers and the POMs are all introduced as polymer pendants. To our knowledge, there has been no report of covalently embedding POMs in the main chain of a conjugated polymer or any organic polymer. This might be because of the critical challenges associated with preparing pure bifunctionalized POMs in sufficient quantity (that is, in gram amounts). Although the bifunctionalization of hexamolybdates with organoimido ligands has been demonstrated,^[10] the reaction always results in a mixture of various multiple functionalized products, which makes the isolation of large amounts of the desired bifunctionalized product tedious and impractical, if not impossible. This situation is expected since POMs usually have numerous equally reactive sites. Selective functionalization other than mono or exhaustive functionalization is thus hard to achieve.^[11] Herein we report an unusual transformation which allows the selective synthesis of bifunctionalized hexamolybdates in high yields. The reaction is clean and the purification is simple, which paves the way for the synthesis of main-chain-POM-containing

polymers. A bifunctionalized cluster (compound **2c**, see scheme 1) with two iodo functional groups has been synthesized and successfully applied as a monomer for the synthesis of the first POM–conjugated-polymer hybrid.



Scheme 1. Synthesis of bifunctionalized hexamolybdates.

We have previously reported an efficient method for the direct functionalization of the hexamolybdate ion [Eq. (1)], where DCC = *N,N'*-dicyclohexyl methanediimine.^[12] Attempting to use the same approach but with higher amine loading ratios failed to generate the bifunctionalized product in high yields. Instead, a mixture of various polyfunctionalized products are formed and thus repeated recrystallization is needed for product purification. When the tetrabutylammonium salt of the α -octamolybdate ion, $[\alpha\text{-Mo}_8\text{O}_{26}]^{4-}$, is subjected to the same reaction conditions, however, bifunctionalized hexamolybdate products are selectively synthesized (Scheme 1). Yields of over 60% are readily obtained.



We carried out the reaction of the $[\alpha\text{-Mo}_8\text{O}_{26}]^{4-}$ ion with TMA in deuterated acetonitrile and monitored the reaction mixture directly by ¹H NMR spectroscopy. The same reaction but with the $[\text{Mo}_6\text{O}_{19}]^{2-}$ cluster was also carried out for comparison. TMA has one single resonance signal for the aromatic protons in its ¹H NMR spectrum, as do the functionalized products, which makes monitoring of the reaction convenient. It is found that with an POM:amine:DCC ratio of 1:2:2, both reactions are completed in 12 h. As shown by the NMR spectra in Figure 1, the $[\text{Mo}_8\text{O}_{26}]^{4-}$ cluster gives overwhelmingly the bifunctionalized products, whereas $[\text{Mo}_6\text{O}_{19}]^{2-}$ gives mixtures of both mono- and bifunctionalized products. The resonance signal at 6.88 ppm corresponds to the monofunctionalized product, while the one at 6.86 ppm corresponds to the *cis* bifunctionalized product. Notice that there is another signal at 6.87 ppm, which is attributable to the bifunctionalized product in a *trans* conformation.

To shed some light on the possible reaction mechanism, we studied the effect of the reactant ratios on product distributions. With the $[\alpha\text{-Mo}_8\text{O}_{26}]^{4-}$ ion as the reactant, the dominant

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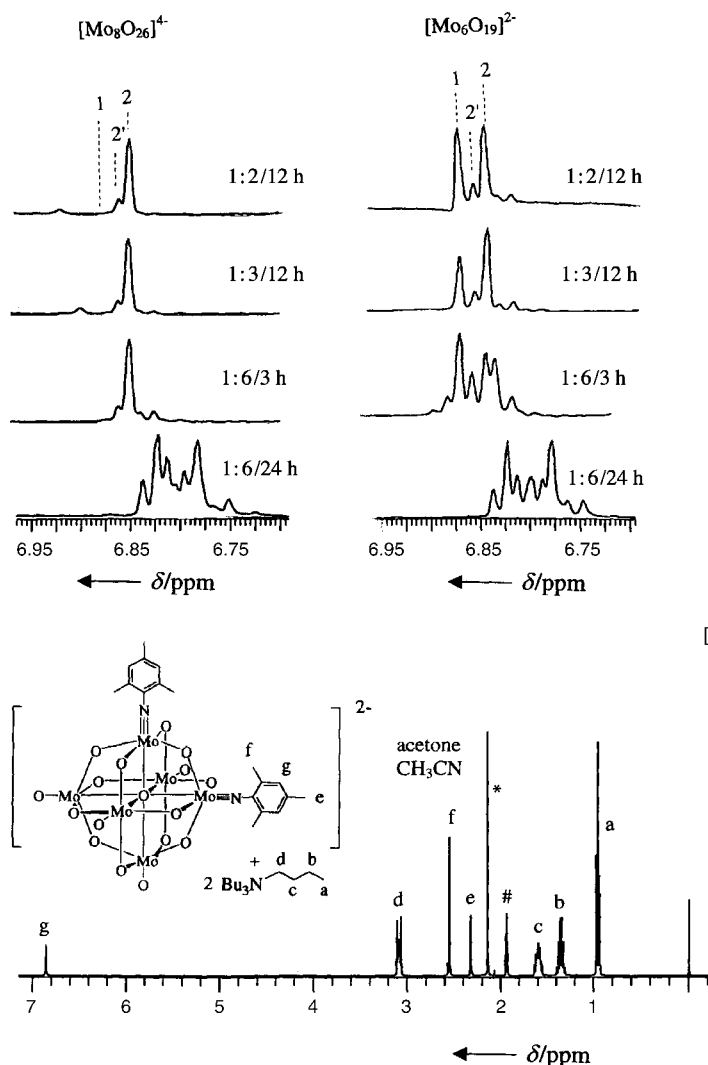


Figure 1. ^1H NMR spectra of the reaction mixtures of $[\alpha\text{-Mo}_8\text{O}_{26}]^{4-}$ (left) or $[\text{Mo}_6\text{O}_{19}]^{2-}$ (right) with 2,4,6-trimethylaniline (TMA) and DCC in $[\text{D}_3]\text{MeCN}$. The POM:amine ratios and reaction times are shown next to the spectra; 1 = monofunctionalized product, 2 = *cis* bifunctionalized product, 2' = *trans* bifunctionalized product. The bottom spectrum is the ^1H NMR spectrum of the purified product **2a**.

product after 12 h of reaction is the bifunctionalized cluster, whether the cluster:amine ratio is 2:1, 1:1, 1:2, or 1:3. Longer reaction time does not change the product distribution. Even with a cluster:amine ratio of 1:6, the bifunctionalized cluster is still the major product after 3 h of reaction, although unlike the reactions with lower amine:POM ratios, letting the reaction go longer results in a mixture of products (Figure 1). This result is because of further reactions of the bifunctionalized product with excess amine. In contrast, direction functionalization of the $[\text{Mo}_6\text{O}_{19}]^{2-}$ ion with two or more equivalents of amine always led to a mixture of products. Similar product distributions are obtained for the two reactions when excess amine is used and the reaction time is sufficiently long.

While more studies, including reaction kinetics and spectroscopic studies, are needed to elucidate the detailed reaction mechanism, our results did provide some clues for the transition from the $[\alpha\text{-Mo}_8\text{O}_{26}]^{4-}$ cluster to the functionalized

hexamolybdate product. Since the cluster skeleton has changed during the reaction, cluster disassembly and reassembly must be involved in the reaction process. It is known that the $[\text{Mo}_8\text{O}_{26}]^{4-}$ cluster can disassemble to the $[\text{Mo}_2\text{O}_7]^{2-}$ cluster in the presence of base.^[13,14] It is likely that the octamolybdate ion is first decomposed to the dimolybdate ion. This proposal is further supported by our observation that the reaction of the dimolybdate ion with two equivalents of TMA gives similar product distributions to that of the octamolybdate ion with TMA. Since the bifunctionalized product is predominantly formed, it is possible that the dimolybdate ion forms an intermediate complex with two equivalents of amine, which then assembles with two other dimolybdate ions to form the bifunctionalized hexamolybdate product (solid-line path in Figure 2). The majority of the

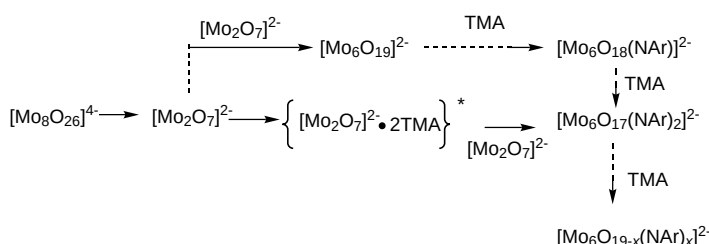


Figure 2. Proposed reaction mechanism for the formation of bi- and polyfunctionalized clusters. For details see the main text.

functionalization (imido formation) appears to occur before the hexamolybdate cluster formation, although further functionalization on hexamolybdate ions are possible, particularly when the amine is in excess (dashed-line path in Figure 2).

We have synthesized three bifunctionalized hexamolybdates (Scheme 1). Compounds **2a–2c** are all soluble in common organic solvents, their ^1H NMR spectra (see Experimental Section and Figure 1) show clearly resolved signals, which can all be unambiguously assigned. The structures of Compounds **2b** and **2c** are also characterized by single-crystal X-ray diffraction.^[15] Both Compounds **2b** and **2c** crystallize in the triclinic space group $P\bar{1}$. Consistent with previous reports, the two organoimido ligands occupy two terminal positions in a *cis* conformation.^[10] While compounds **2b** and **2c** show very similar molecular structures, their crystal-packing motifs are rather different. Within the lattice of $(\text{Bu}_4\text{N})_2\text{2c}$, the cluster ions are organized into dimers where the iodine atom of one cluster is brought into close proximity to a μ_2 -oxygen atom of another cluster (Figure 3). The I–O separation observed is 3.20 Å, which is 0.3 Å shorter than the sum of their van der Waals radius, which indicates the presence of a weak van der Waals interaction between them. It is known that among all the oxygen atoms in a $[\text{Mo}_6\text{O}_{19}]^{2-}$ ion, the μ_2 oxygen atoms have the highest negative charge density.^[16] The charge density on the μ_2 oxygen atom can be further increased by the electron-donating effect of the two organoimido ligands,^[8] which should facilitate the interaction of the μ_2 oxygen atom with the highly polarizable iodine atom. The “dimerization” is also boosted by the π – π stacking of the two near parallel phenyl rings. The existence of the π – π interactions is

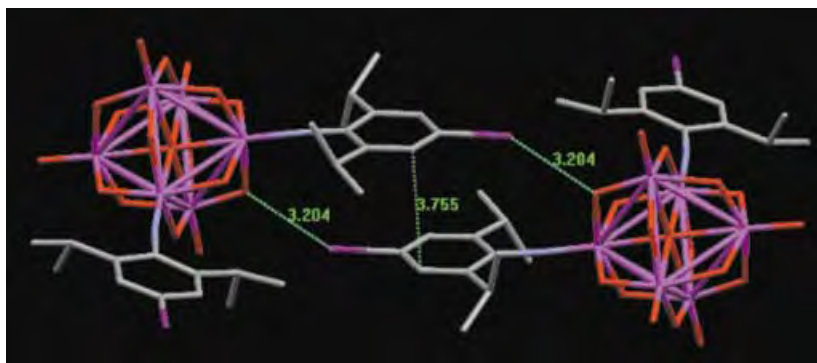
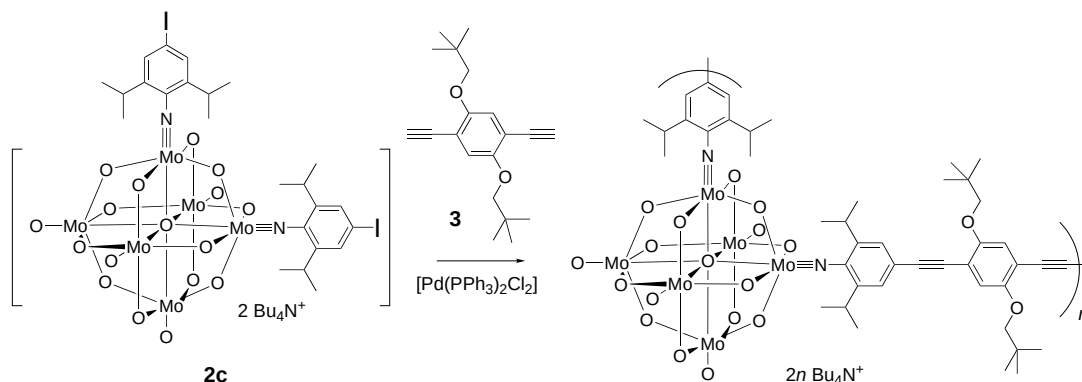


Figure 3. Dimer formation of the anions **2c** in the lattice of $(\text{Bu}_4\text{N})_2\mathbf{2c}$. Highlighted numbers indicate the interatomic distances [Å].

clearly indicated by their short vertical separation of 3.755 Å. The “dimerization” is not observed in the crystal structure of **2b**.

Compound **2c** has two iodo groups, which makes it an excellent monomer from which a main-chain-POM-containing conjugated polymer (or oligomer) can be synthesized through Palladium-catalyzed coupling reactions.^[17] As shown in Scheme 2, we have carried out the Pd-catalyzed coupling of **2c** with 2,5-di(2,2-dimethylpropoxy-1,4-diethynylbenzene). The reaction went smoothly in DMF at room temperature and the polymer can be readily separated by pouring the reaction mixture into methanol. The ¹H NMR spectra of the polymer are consistent with the proposed structure.^[18] Based on the end group analysis, the number of repeating units in the polymer is estimated to be about 18.^[19] While the molecular weights of the polymer appear not to be very high,^[19] nonetheless, good quality films can be readily prepared by spin-coating or casting, which allows the physical properties of the polymers to be studied. The detailed structural and physical property characterizations of this unique main-chain-POM-containing hybrid polymer are in progress and will be reported in a separate paper shortly.

In conclusion, we have discovered an unusual and highly efficient approach for the selective synthesis of bifunctionalized organoimido hexamolybdates. This approach allows the facile introduction of two functional groups to a hexamolybdate cluster, and thus paves the way for the synthesis of main-chain-POM-containing hybrid polymers.



Scheme 2. Synthesis of main-chain-POM-containing conjugated polymers.

Experimental Section

$(\text{Bu}_4\text{N})_2[\text{Mo}_6\text{O}_{19}]$ and $(\text{Bu}_4\text{N})_2[\text{Mo}_6\text{O}_7]$ were prepared by literature methods.^[13] $(\text{Bu}_4\text{N})_4[\alpha\text{-Mo}_8\text{O}_{26}]$ was conveniently prepared by the addition of NBu_4Br to an aqueous solution of $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$ (purchased from Acros), from which the product immediately precipitates. The structure of $(\text{Bu}_4\text{N})_4[\alpha\text{-Mo}_8\text{O}_{26}]$ was confirmed by elemental analysis and X-ray single-crystal structure determination.^[20]

A typical synthesis for compounds **2a–2c** is exemplified by the synthesis of **2a**: A mixture of TMA (0.14 g, 1.0 mmol), *N,N'*-dicyclohexylcarbodiimide (0.21 g, 1.0 mmol), and $(\text{Bu}_4\text{N})_4[\alpha\text{-Mo}_8\text{O}_{26}]$ (1.08 g, 0.46 mmol) was refluxed in anhydrous acetonitrile (8 mL) under nitrogen for about 24 h. After being cooled to room temperature, filtration of the resulting dark-red solution removed the white precipitates. The product precipitates from the filtrate as orange crystals. The product was

collected by filtration, washed successively with EtOH and Et₂O several times, and then recrystallized twice from acetone to yield 0.52 g of **2a** (yield based on Mo: 65 %). Elemental analysis (%) calcd for $\text{C}_{50}\text{H}_{94}\text{N}_4\text{O}_{17}\text{Mo}_6$: C 37.56, H 5.92, N 3.50; found: C 37.18, H 5.74, N 3.54; ¹H NMR (400 MHz, $[\text{D}_3]\text{MeCN}$, 25 °C, TMS): δ = 6.86 (m, ArH, 4H), 3.10 (t, J = 8.50 Hz, NCH_2 , 16H), 2.56 (s, (Ar-)Me₂, 12H), 2.33 (s, (Ar-)Me, 6H), 1.60 (q, J = 8.50 Hz, CH_2 , 16H), 1.35 (H, J = 8.50 Hz, CH_2 , 16H), 0.96 ppm (t, J = 7.25 Hz, CH_3 , 24H). UV/Vis (MeCN): λ (ϵ) = 206 (8.9×10^{-4}), 242 (6.3×10^{-4}), 360 nm (3.2×10^{-4}).

2b (yield, 62 %): Elemental analysis (%) calcd for $\text{C}_{48}\text{H}_{88}\text{N}_4\text{O}_{17}\text{Mo}_6$: C 36.70, H 5.77, N 3.57; found: C 36.56, H 5.74, N 3.53; ¹H NMR (400 MHz, $[\text{D}_3]\text{MeCN}$, 25 °C, TMS): δ = 7.03 (m, ArH, 4H), 6.88 (m, ArH, 2H), 3.10 (t, J = 8.50 Hz, NCH_2 , 16H), 2.60 (s, (Ar-)Me₂, 12H), 1.60 (q, J = 8.50 Hz, CH_2 , 16H), 1.35 (H, J = 8.50 Hz, CH_2 , 16H), 0.96 ppm (t, J = 7.25 Hz, CH_3 , 24H). UV/Vis (MeCN): λ (ϵ) = 208 (6.5×10^{-4}), 244 (5.1×10^{-4}), 356 ppm (2.8×10^{-4}). Crystals suitable for single-crystal X-ray analysis were grown by diffusion of Et₂O into an acetonitrile solution at room temperature.

2c (yield, 63 %): Elemental analysis (%) calcd for $\text{C}_{56}\text{H}_{104}\text{N}_4\text{O}_{17}\text{Mo}_6\text{I}_2$: C 34.76, H 5.42, N 2.90; found: C 34.60, H 4.61, N 2.83; ¹H NMR (400 MHz, $[\text{D}_3]\text{MeCN}$, 25 °C, TMS): δ = 7.47 (s, ArH, 4H), 3.81 (m, J = 7.50 Hz, CH, 4H), 3.10 (t, J = 8.50 Hz, NCH_2 , 16H), 1.60 (q, J = 8.50 Hz, CH_2 , 16H), 1.35 (H, J = 8.50 Hz, CH_2 , 16H), 1.25 (d, J = 6.25 Hz, (Ar-)CHMe₂, 24H), 0.96 (t, J = 7.25 Hz, CH_3 , 24H). UV/Vis (MeCN): λ (ϵ) = 206 (8.7×10^{-4}), 250 (7.2×10^{-4}), 366 (6.2×10^{-4}). Crystals suitable for single-crystal X-ray analysis were grown from acetonitrile at room temperature.

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 [15] Crystal structure data for **2b**: $C_{48}H_{90}Mo_6N_4O_{17}$, $M_r = 1570.88$, triclinic, $P\bar{1}$, $a = 12.4970(5)$, $b = 12.6163(5)$, $c = 20.5340(9)$ Å, $\alpha = 81.523(2)$, $\beta = 76.693(2)$, $\gamma = 76.237(2)^\circ$, $V = 3045.4(2)$ Å³, $Z = 2$, $Z' = 1$, $\rho_{\text{calc}} = 1.713$ g cm⁻³, $T = 100(2)$ K, $R1 = 0.0395$, and $wR2 = 0.1083$. GOF (F^2) = 1.062. Crystal structure data for **2c**: $C_{56}H_{104}I_2Mo_6N_4O_{17}$, $M_r = 1394.87$, triclinic, $P\bar{1}$, $a = 16.3470(6)$, $b = 19.4509(7)$, $c = 22.6548(8)$ Å, $\alpha = 98.023(2)$, $\beta = 96.859(2)$, $\gamma = 90.465(2)^\circ$, $V = 7079.6(4)$ Å³, $Z = 4$, $Z' = 2$, $\rho_{\text{calc}} = 1.815$ g cm⁻³, $T = 100(2)$ K, $R1 = 0.0369$, and $wR2 = 0.0964$. GOF (F^2) = 1.027. CCDC-187412 and -187413 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/contents/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit @ccdc.cam.ac.uk).
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 [18] ¹H NMR spectrum of the polymer: (400 MHz, [D₆]acetone, 25°C): $\delta = 7.32$ (b, ArH, 4H), 7.10 (b, ArH, 2H), 4.04 (b, CH, 4H), 3.79 (b, OCH₂, 4H), 3.45 (t, $J = 6.25$ Hz, NCH₂, 16H), 1.81 (b, CH₂, 16H), 1.44 (m, CH₂, 16H), 1.34 (d, $J = 7.50$ Hz, (Ar)-CHMe₂, 24H), 1.17 (s, 18H, CH₃ in alkoxy chains), 0.97 ppm (t, $J = 7.37$ Hz, CH₃, 24H). UV/Vis (MeCN): $\lambda_{\text{max}} = 440$ nm.
 [19] A small peak at 7.47 ppm in the ¹H NMR spectrum of the polymer is identified as arising from the end-group protons associated with the aromatic terminus. The integration of the peak at 7.47 ppm versus that at 7.32 ppm is 1:18. Assuming both ends of the polymer are capped by the iodo end group (as no acetylene proton resonance is observed in the NMR spectrum), this integration ratio gives the number of repeating units at 18.
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A Three-Phase Emulsion/Solid-Heterogenization Method for Transport and Catalysis**

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We describe a method for the heterogenization of (catalytic) reactions, which eliminates the need for organic solvents. The method relies on a novel multiphase transport concept, namely on the transport of hydrophobic substrates to an entrapped catalyst, and the transport of the resulting product from the catalyst-entrapping environment back into the bulk. The general idea is as follows: A catalyst is entrapped inside a hydrophobically modified porous sol-gel matrix; the hydrophobic substrate for that catalyst forms an emulsion in water in the presence of a suitable surfactant; and the powdered catalytic sol-gel material is dispersed in that emulsion. Upon contact of the surfactant with the hydrophobic interface of the sol-gel matrix, it reorients and spills the substrate into the pores of the matrix, where the catalyst is entrapped. The catalytic process takes place there, and the product is extracted out by the same transport vehicle, namely by the emulsifying surfactant; then the emulsion is broken, and the product separated.

We term this whole process the EST (emulsion–solid transport) process, and have demonstrated it (following a detailed search for optimal conditions) with the $[CH_3(C_8H_{17})_3N]^+[RhCl_4]^-$ catalyzed hydrogenation of chalcone and *cis*-stilbene, in which the solid is a partially alkylated SiO₂ sol-gel matrix within which the catalyst is entrapped, and where the emulsifying surfactant is cetyl(trimethylammonium) *p*-toluenesulfonate.

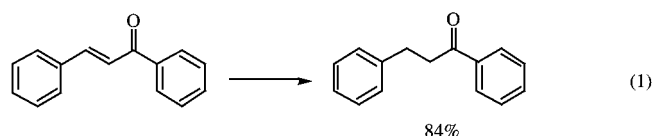
Heterogenization of homogeneous catalytic procedures has been of central interest in the field of catalysis. Several heterogenization methods have been developed^[1] which can be classified into the following categories: Covalent-bond immobilization of the catalyst on supports such as inorganic matrices,^[2] organic-polymer solids,^[3] organic–inorganic composites,^[4] and recently also on dendrimers^[5] and liquid–liquid biphasic systems^[6] in which the catalyst is in one phase and the product is in the other. Recent examples of such systems are fluorinated biphasic catalytic systems^[7] and ionic liquids.^[8] Other methods include supported liquid-phase catalysis (SLPC), which is based on immobilizing the catalyst within a thin liquid film on a high surface area support^[9] and physical immobilization of the catalysts within porous supports, which requires no covalent bonding and which retains the homogeneous catalyst in its native structure. Sol-gel catalysis has been

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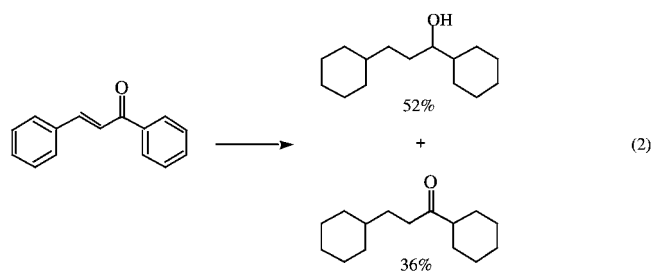
[**] We gratefully acknowledge support from the Ministry of Science, Art, and Sport through the Tashtiot project, as well as from the Israel Science Foundation through Grant No. 143/00–12.0.

a prominent example of this approach, and is used in this study.^[10] As we shall see below, the EST not only eliminates the need for organic solvents, but also opens up a new way of controlling the selectivity of catalysts.

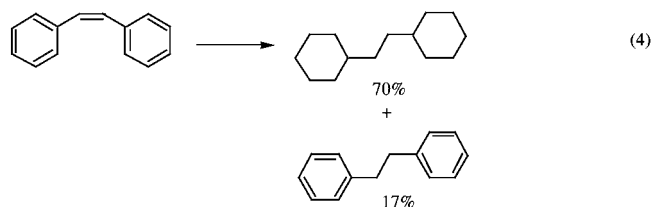
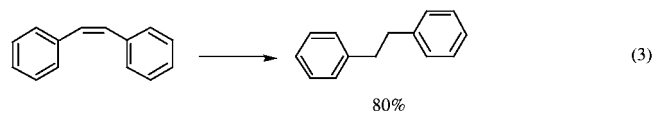
Under the conditions described in the Experimental Section, emulsified chalcone was hydrogenated by the ethyl-derivatized, porous, solid catalytic material **1** (preparation and composition of all catalysts is described in the Experimental Section), to form the saturated ketone shown in 84% yield [Eq. (1)]. As suggested above, the emulsion acted as a vehicle for carrying the hydrophobic substrate to the alkylated solid, releasing its “cargo” there, and for carrying the product from the catalyst into the bulk solution within the same emulsion.



Interestingly, the catalytic activity was modified and enhanced by just changing the length of the alkyl chain of the alkyltrialkoxysilane. Thus, the octyl-derivatized catalyst **2** afforded 52% of the fully saturated 1,3-dicyclohexylpropan-1-ol accompanied by 36% of the 1,3-dicyclohexylpropan-1-one [Eq. (2)].



The alkyl-chain effect was also observed for the hydrogenation of *cis*-stilbene. While the short-chained **1** successfully hydrogenated the emulsified substrate to form 1,2-diphenylethane in 80% yield [Eq. (3)], the use of catalyst **2** resulted in 70% of the fully hydrogenated 1,1'-(1,2-ethanediyl)dicyclohexane [Eq. (4)].



Blank experiments were carried out to demonstrate that the successful transport of the substrate from the solution to the catalyst and of the product back into solution requires all the

components of the EST system. Thus, with the non-alkylated catalyst **3** no product could be observed upon attempted hydrogenation of the emulsified *cis*-stilbene. In another blank experiment, in which catalyst **2** was used but without the emulsifying surfactant, catalysis did occur resulting in 43% 1,1'-(1,2-ethanediyl)dicyclohexane and 21% 1,2-diphenylethane, but without the convenience of the transport: The organic material was adsorbed into the hydrophobic sol-gel matrix (eventually poisoning the catalyst) and the product could be obtained only by organic-solvent extraction of the porous material.

The proposed mechanism of the EST process is best interpreted in terms of the well-studied behavior of adsorbed micelles.^[11,12] Thus, several reversible processes (and one irreversible process) take place simultaneously (see Figure 1; S = substrate, P = product):

1. emulsified substrate + catalyst $\rightleftharpoons$ adsorbed surfactant + released/adsorbed substrate
2. adsorbed substrate $\rightarrow$ adsorbed product
3. adsorbed product + adsorbed surfactant $\rightleftharpoons$ emulsified product + solid

These equilibria are the key to the “communication” between the two phases: The first equilibrium is shifted by the catalytic reaction according to the Le Chatelier principle, while the third one is driven by the available adsorbed surfactant molecules.

An important feature of the EST is the possibility it opens up to change and affect the selectivity of the catalyst. The key is a careful control of the hydrophilic–lipophilic balance (HLB) of the solid itself. Thus, when the more hydrophobic catalyst **2** was used, the aromatic bonds in the substrates were reduced as well as the olefinic bond, while in the presence of the less hydrophobic catalyst **1**, only the olefinic bonds were

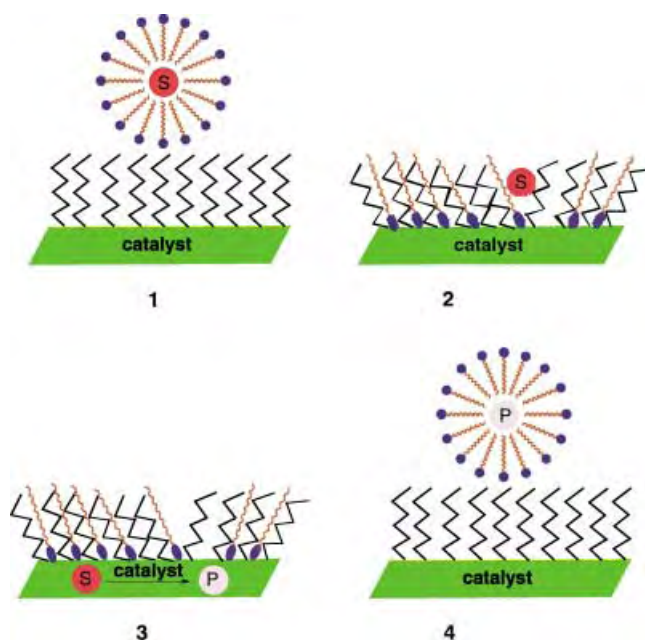


Figure 1. Illustration of the transport, reaction, and adsorption/desorption steps of the EST process. The emulsion which contains the substrate (**1**) spills its content into the catalyst material (**2**), the catalytic process takes place (**3**), and then the adsorbed surfactant carries the product back to the solution (**4**).

reduced. This different performance can be explained in terms of the proposed mechanism of EST. Thus, using the more hydrophobic interface facilitates the adsorption process of the hydrophobic substrate, leaving it in the vicinity of the entrapped catalyst longer, for fuller reduction.

Various degrees of alkylation of the matrix were tested, and the low ratio of alkylsilane:TMOS = 1:20 (tetramethylorthosilicate) gave the best results: Both higher and lower hydrophobicities gave inferior results; higher ratios caused the hydrophobic product to remain in the matrix, while lower ratios did not cause the emulsion to spill its content into the matrix. That so many silanols are still needed at the interface for the optimal EST process points to the possibility that the breaking of the micellar structures occurs mainly through adsorption of the ammonium head and, to a lesser degree, through interaction of the hydrophobic chain of the surfactant with the hydrophobic moieties on the surface. Indeed, the ethyl groups of **1** may be too short for such an interaction.

In conclusion, we have developed a new approach of heterogenization of catalysts, which is based on an aqueous three-phase system. Taking into account the intensive interest of replacing organic solvents with water even for hydrophobic reactants,^[13] our EST process offers a new solution to that problem as well. Furthermore, in some recent papers^[14] we have shown that sol-gel materials can be used, with the aid of surfactants, for tailoring a wide spectrum of reactivities of a single compound; here we provide a second example, in which the HLB of the sol-gel matrix can be used for that purpose as well. Finally, we believe that the EST approach will find applications beyond catalysis, because the concept demonstrated in Figure 1, coupled with chemical reactivity, is general.

Experimental Section

Preparation of the modified sol-gel entrapped catalysts 1 and 2: A solution of ethyltriethoxyorthosilicate (0.36 mL, 1.68 mmol; ETOS) in EtOH (2.0 mL) was hydrolyzed by vigorous stirring with triply distilled water (0.12 mL; TDW) and hydrochloric acid (0.018 mL; 1M) at 60°C for 20 h. The resulting solution was added to (5.0 mL, 33.6 mmol) of tetramethylorthosilicate ([ETOS]:[TMOS] = 1:20) that was prehydrolyzed with TDW (4.0 mL) at 25°C for 2 h. Methyltriethylammonium chloride (65 mg, 0.16 mmol; Aliquat 336) and RhCl₃·3H₂O (43 mg, 0.16 mmol) in MeOH (5.0 mL) was added to the combined solutions. Gelation occurred within 1–2 days and the resulting material was dried at 0.5 mm Hg for 24 h at 25°C and for an additional 12 h at 78°C. The xerogel formed was heated under reflux for 30 min with CH₂Cl₂ (20 mL), dried at 0.5 mm for 3 h, sonicated with the same solvent for 30 min, and dried again (3 h), which yielded the final ceramic catalyst **1** (2.64 g).

By a similar procedure, a homogeneous solution of TMOS (5.0 mL, 33.6 mmol) in TDW (4.0 mL; obtained by vigorous stirring of the mixture) and octyltrichlorosilane (0.39 mL, 1.68 mmol; OTS) was added to a solution of Aliquat 336 (65 mg, 0.16 mmol) and RhCl₃·3H₂O (43 mg, 0.16 mmol) in MeOH (5 mL). The mixture was stirred until gelation occurred (3–4 days), and the gel treated as above, which resulted in **2** (2.7 g).

For control-experiment comparison, the non-alkylated sol-gel catalyst **3** was prepared, as follows: A solution of TMOS (5.0 mL, 33.6 mmol) was stirred with TDW (4.0 mL) for 2 h until homogenous, and then Aliquat 366 (65 mg, 0.16 mmol) and RhCl₃·3H₂O (43 mg, 0.16 mmol) dissolved in MeOH (5.0 mL) were added, and the solution stirred until gelation occurred (1–2 days). The resulting gel was treated as described above, to yield 2.38 g of ceramic material.

Emulsion experiments: The oil-in-water (O/W) emulsion was prepared by adding the oil phase (chalcone (1.0 g, 4.8 mmol) or *cis*-stilbene (1.0 mL, 5.6 mmol) both dissolved in 2.0 mL heptane) dropwise to a vigorously

stirred solution of surfactant (2% w/w) in water (15.0 mL). Vigorous stirring was continued for 5 min and resulted in a stable emulsion when cetyl(trimethylammonium) *p*-toluenesulfonate was used. Other surfactants which were tested (cetyl(trimethylammonium) bromide, sodium dodecylsulfate, Tween 80, and Tween 20) were inferior either for the emulsification or for the catalytic process.

After the catalytic reaction was stopped, the filtered emulsion of the products and the unreacted starting material was broken by adding of 5% sodium sulfate (10.0 mL) and heating the mixture in a closed vial at 80°C for 24 h, (until full separation of the two phases). Occasionally it was necessary to add another salt (NaCl) to obtain complete separation. If the surfactant was used in excess of 2% w/w, the resulting emulsions were difficult to break. Finally, it should be noted that we could extract the organic material from the emulsions with organic solvents, but our efforts were mainly directed toward methods which avoid these solvents.

The catalytic reactions: The above emulsion containing either chalcone or *cis*-stilbene and catalytic material (0.9 g) was placed in a 50-mL glass-lined stainless-steel autoclave. After sealing the reaction vessel, it was purged with hydrogen three times, pressurized to 200 psi of H₂ and heated at 80°C for 20 h with magnetic stirring. The autoclave was cooled to room temperature and the hydrogen was released. The catalyst was then separated from the emulsion by filtration and the emulsion broken as described above. The products—all known—were characterized by GC, GC-MS, and NMR spectroscopy.

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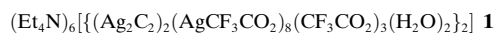
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Facile Construction of Anionic Silver(I) Aggregates with Embedded Acetylide and Cyanide Ions**

Quan-Ming Wang and Thomas C. W. Mak*

In memory of Richard K. McMullan

We have shown that the combination of Ag_2C_2 with other kinds of silver salts leads to the formation of a series of double,^[1] triple,^[2] and quadruple^[3] salts that contain neutral or cationic silver cluster units. In addition, we have carried out exploratory studies on structural control by introducing ancillary ligands to direct the assembly process.^[4] Recently, we established the generality of generating an anionic silver aggregate in a mixed-valent $\text{Ag}^{\text{I/II}}$ complex by disproportionation of silver(I) in the presence of a tetraaza macrocycle.^[5] This prompted us to conduct further studies on structural diversity by incorporating hydrophobic organic cations into silver acetylide systems, thus favoring the formation of anionic silver aggregates through the attainment of overall charge balance. Proceeding on this premise, we have successfully employed a quaternary ammonium cation as the mediating agent to obtain the high-nuclearity silver complexes **1** and **2**, the latter featuring co-intercalation of cyanide and acetylide ions within a novel anionic silver column.



Compound **1** was prepared by dissolving Ag_2C_2 in an aqueous solution of $\text{CF}_3\text{CO}_2\text{Ag}$ and AgBF_4 followed by the addition of Et_4NBF_4 . X-ray structural analysis indicated that complex **1** consists of a discrete high-nuclearity cluster anion $[(\text{Ag}_2\text{C}_2)_2(\text{AgCF}_3\text{CO}_2)_8(\text{CF}_3\text{CO}_2)_3(\text{H}_2\text{O})_2]_2^{6-}$, which is composed of two kinds of polyhedral units, a bicapped trigonal prism (cage A; Figure 1) and a triangulated dodecahedron (cage B).

For cage A, three edges $\text{Ag1}\cdots\text{Ag2}$, $\text{Ag3}\cdots\text{Ag4}$, and $\text{Ag5}\cdots\text{Ag6}$ constitute the vertical sides of a trigonal prism, and Ag7 and Ag8 each caps a rectangular face. The mean deviation of the atoms constituting the three rectangular faces of the trigonal prism lies in the range 0.008–0.012 Å. A C_2^{2-} species is accommodated in this cage and lies closer to the uncapped rectangular face $\text{Ag3}\cdots\text{Ag4}\cdots\text{Ag5}\cdots\text{Ag6}$.

Cage B is analogous to that found in $[\text{Ag}_6^{\text{I}}(\text{C}_2)(\text{CF}_3\text{CO}_2)_5(\text{H}_2\text{O})_\infty]^{1-}$,^[5a] being composed of two atom sets $\text{Ag9}\cdots\text{Ag1}\cdots\text{Ag2}\cdots\text{Ag10}$ and $\text{Ag8}\cdots\text{Ag12}\cdots\text{Ag12a}\cdots\text{Ag11}$, which are each coplanar within 0.019 and 0.016 Å, respectively, making a dihedral angle of 89.7°. This cage also encloses a C_2^{2-} ion, which

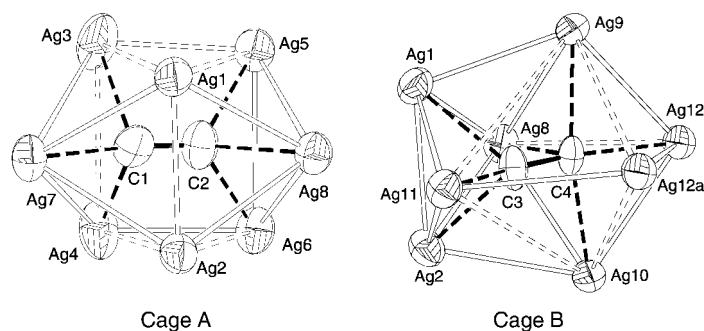


Figure 1. Cage A and cage B in **1** (35% ellipsoids shown). $\text{Ag}\cdots\text{Ag}$ distances longer than 3.4 Å (twice the van der Waals radius of silver) are represented by broken open lines. Selected bond lengths [Å]: C1–C2 1.21(2), C3–C4 1.18(1), C1–Ag3 2.23(1), C1–Ag(4) 2.24(2), C1–Ag7 2.11(2), C2–Ag5 2.13(2), C2–Ag6 2.16(2), C2–Ag8 2.39(2); C3–Ag1 2.34(1), C3–Ag2 2.30(1), C3–Ag11 2.23(1), C4–Ag8 2.59(1), C4–Ag9 2.32(1), C4–Ag10 2.34(1), C4–Ag12 2.12(1). Symmetry code: a: $-x, -y+1, -z$.

displays an asymmetric coordination mode with C3 bound to three but C4 to four silver centers.

Cages A and B share a triangular face $\text{Ag1}\cdots\text{Ag2}\cdots\text{Ag8}$ to form a double cage, and two such double cages share an edge to generate a centrosymmetric quadruple cage comprising twenty-four silver atoms and four encapsulated acetylide ions (Figure 2). This discrete anionic cluster $[(\text{Ag}_2\text{C}_2)_2(\text{AgCF}_3\text{CO}_2)_8(\text{CF}_3\text{CO}_2)_3(\text{H}_2\text{O})_2]_2^{6-}$ exhibits pseudosymmetry *m* with a plane passing through $\text{Ag7}\cdots\text{Ag8}\cdots\text{Ag11}\cdots\text{Ag12}\cdots\text{C1}\cdots\text{C2}\cdots\text{C3}\cdots\text{C4}$. While single cages occur commonly and several double cages are known, this Ag_{24} quadruple cage is found for the first time and is so far the largest known cluster in the silver acetylide system.

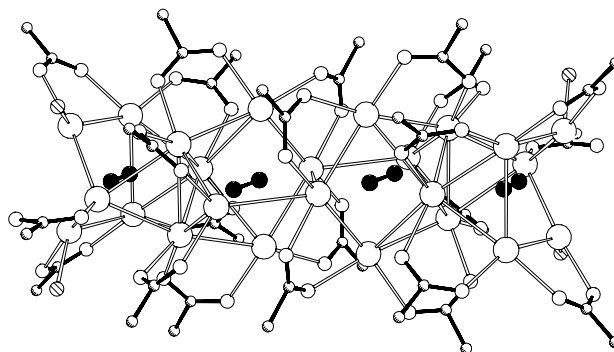


Figure 2. The centrosymmetric high-nuclearity Ag_{24} cluster (quadruple cage) in **1** generated by edge-sharing of Ag_{13} double cages with four embedded C_2^{2-} species. F atoms have been omitted for clarity, and only short $\text{Ag}\cdots\text{Ag}$ distances are shown. Large circles, silver; medium circles, oxygen; hatched medium circles, aqua ligands; black dumbbells, C_2^{2-} species; side-hatched small circle, carbon.

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The aqua ligands are terminally coordinated to silver atoms of type Ag3 and Ag4 , and the trifluoroacetate ligands each bridges an $\text{Ag}\cdots\text{Ag}$ edge except the one that has a monodentate carboxylate group. The rodlike clusters pack in a head-to-tail pattern along the *b* direction, and the Et_4N^+ counterions fill the space around them.

Complex **2** was synthesized in a similar manner to **1** except that AgCN was introduced as an additional component. It is a

novel silver complex containing three kinds of anions: trifluoroacetate, acetylide, and cyanide.

The basic structural unit of **2** is a silver(I) double cage of symmetry 2, one half of which taking the shape of a triangulated dodecahedron that encapsulates a C_2^{2-} ion (Figure 3a). Two such polyhedra share an edge $Ag1 \cdots Ag1a$ and have an additional vertex-to-vertex connection to generate the double cage, such that a twofold axis passes through the midpoints of $Ag1 \cdots Ag1a$ and $Ag7 \cdots Ag7a$. Two pendant silver atoms of type $Ag8$ are each attached to a vertex of the double cage, yielding the $[(C_2)_2@Ag_{14}]Ag_2$ unit.

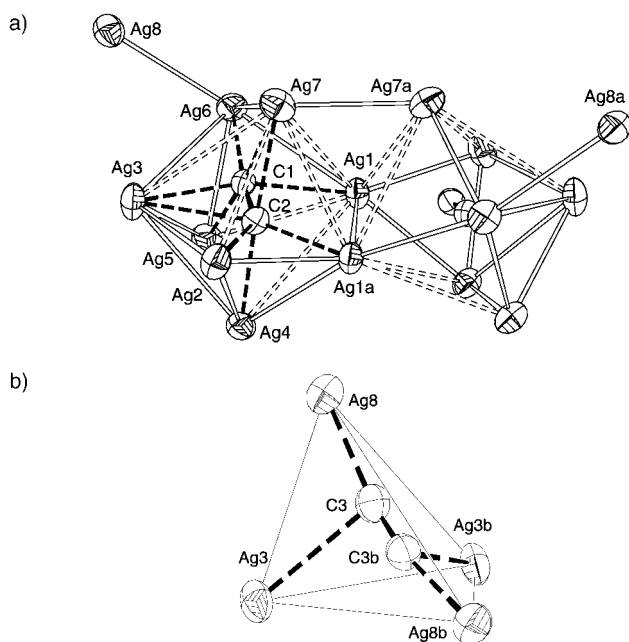


Figure 3. a) Ag_{14} double cage with two embedded C_2^{2-} species and a pair of pendant silver atoms in **2** (35% ellipsoids shown). $Ag \cdots Ag$ distances longer than 3.4 Å (twice the van der Waals radius of silver) are represented by broken open lines. The C–Ag bonds are only shown in the left half for clarity. b) Distorted Ag_4 tetrahedron with an intercalated CN^- , which is disordered over a site of symmetry 2 ($C3 = \frac{1}{2}C + \frac{1}{2}N$). Selected bond lengths [Å]: C1–C2 1.221(9), C1–Ag1 2.569(6), C1–Ag3 2.392(6), C1–Ag5 2.339(6), C1–Ag6 2.106(6), C1–Ag7 2.433(6), C2–Ag1a 2.274(6), C2–Ag2 2.211(6), C2–Ag3 2.592(6), C2–Ag4 2.308(7), C2–Ag7 2.554(6), C3–C3b 1.11(1), C3–Ag3 2.643(7), C3–Ag8 2.137(7). Symmetry codes: a: $x, -y + \frac{1}{2}, -z + \frac{1}{2}$; b: $-x + \frac{1}{2}, -y, z$.

An interesting structural feature is found in **2**, where the cyanide ion is located in a distorted tetrahedral $Ag3$ – $Ag8$ – $Ag3b$ – $Ag8b$ environment (Figure 3b). This type of coordination mode of a cyanide ligand is unprecedented, as thus far all reported μ_4 -CN moieties are bound to metal centers in a nearly planar rectangular environment. The silver(I) double cages and tetrahedra link up alternately to generate an infinite anionic silver(I) column $\{[(Ag_2C_2)_2(AgCN)(AgCF_3CO_2)_{11}(CF_3CO_2)_3(H_2O)_6]^{3-}\}_\infty$ along the b direction (Figure 4). The presence of the CN^- ion is confirmed by the band at 2139 cm^{-1} in the IR spectrum, and also on the basis of its coordination mode. The acetylide ion is normally encapsulated in a cage comprising six or more silver atoms, while the largest ligation number of cyanide is four.

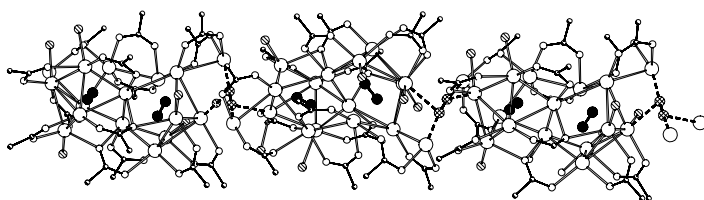


Figure 4. Infinite silver(I) column running along the b direction in **2** derived from linkage of silver cages with co-intercalation of cyanide and acetylide ions. F atoms have been omitted for clarity, and only short $Ag \cdots Ag$ distances are shown. Large circles, silver; medium circles, oxygen; hatched medium circles, aqua ligands; black dumbbells, C_2^{2-} species; cross-hatched dumbbells, CN^- ions; side-hatched small circle, carbon.

In **2**, the aqua ligands also act as terminal coordination groups. The trifluoroacetate ligands function as μ_2 bridges across $Ag \cdots Ag$ edges except one in the μ_3 mode. The silver(I) columns pack parallel to one another with Et_4N^+ ions located between them.

Under the induction of argentophilicity,^[6] namely the d^{10} – d^{10} closed-shell attraction^[7] between silver(I) ions, Ag_2C_2 readily dissolves in a concentrated aqueous solution of a silver salt to generate polynuclear $[Ag_n(C_2)]^{(n-2)+}$ moieties, the assembly of which may be affected by coexisting ions and solvent molecules to afford novel crystal structures that exhibit unprecedented geometries of silver polyhedra each enclosing a C_2^{2-} species. Further study on the synthesis of a variety of anionic silver acetylide aggregates by variation of quaternary ammonium counterions and coexisting halide/pseudohalide is in progress.

Experimental Section

Ag_2C_2 was prepared as described previously.^[1] **Caution:** thoroughly dried Ag_2C_2 detonates easily upon mechanical shock or heating, and only a small quantity should be used in any chemical reaction.

1: Ag_2C_2 was added to 1 mL of a concentrated aqueous solution of $AgCF_3CO_2$ (0.442 g, 2 mmol) and $AgBF_4$ (0.195 g, 1 mmol) in a plastic beaker with stirring until saturated. The excess amount of Ag_2C_2 was filtered off, and Et_4NBF_4 (0.108 g) was added to the filtrate. The colorless solution was placed in a desiccator charged with P_2O_5 , and colorless platelike crystals of **1** were deposited in about 32% yield (based on Et_4NBF_4) after a few hours. Elemental analysis (%): calcd: C 19.94, H 2.14, N 1.39; found: C 19.80, H 1.90, N 1.21.

2: Excess $AgCN$ was added to 1 mL of a concentrated aqueous solution of $AgCF_3CO_2$ (0.442 g, 2 mmol) and $AgBF_4$ (1.17 g, 6 mmol) in a plastic beaker with stirring until saturated. Then Ag_2C_2 was added and stirred until equilibrium was reached. The undissolved amount of Ag_2C_2 and $AgCN$ was filtered off, and Et_4NBF_4 (0.108 g) was added to the filtrate. The resulting clear solution was placed in a desiccator charged with P_2O_5 . Colorless prismatic crystals of **2** were obtained in about 30% yield. Elemental analysis (%): calcd: C 17.64, H 1.87, N 1.44; found: C 17.82, H 1.62, N 1.21. Both compounds **1** and **2** readily decompose in common solvents such as water and ethanol. Complexes **1** and **2** are unstable to heat; **1** decomposes to a black residue at about 145°C and **2** melts at 105°C .

Crystal data for **1**: $C_{100}H_{128}Ag_{24}F_{66}N_6O_{48}$, $M_r = 6024.96$, $P\bar{1}$ (no. 2), $a = 17.0844(5)$, $b = 19.6091(6)$, $c = 27.3695(8)$ Å, $\alpha = 79.490(1)$, $\beta = 81.743(1)$, $\gamma = 74.041(1)^\circ$, $V = 8625.3(4)$ Å³, $Z = 2$, $\lambda = 0.71073$ Å, $\rho_{\text{calcd}} = 2.320\text{ g cm}^{-3}$, $\mu(\text{MoK}\alpha) = 2.795\text{ mm}^{-1}$, $R1 = 0.0740$, $wR2 = 0.1749$ for 13 663 observed reflections ($I > 2\sigma(I)$). Crystal data for **2**: $C_{57}H_{72}Ag_{16}F_{42}N_4O_{34}$, $M_r = 3881.11$, $Pnma$ (no. 52), $a = 15.0738(7)$, $b = 25.747(1)$, $c = 27.088(1)$ Å, $V = 10 514.4(9)$ Å³, $Z = 4$, $\lambda = 0.71073$ Å, $\rho_{\text{calcd}} = 2.452\text{ g cm}^{-3}$, $\mu(\text{MoK}\alpha) = 3.051\text{ mm}^{-1}$, $R1 = 0.0460$, $wR2 = 0.1304$ for 7909 observed reflections ($I > 2\sigma(I)$). Data collection was performed at 20°C on a Bruker SMART 1000 CCD diffractometer using frames of oscillation range 0.3° , $1 < \theta < 28^\circ$. The

structures were solved by direct methods and refined by full-matrix least-squares on F^2 . The cyanide group in **2** is disordered over a site of symmetry 2, and the independent carbon atom is represented by $\frac{1}{2}C + \frac{1}{2}N$.

CCDC-184663 (**1**) and CCDC-184664 (**2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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Cobalt-Catalyzed Coupling Reaction of Alkyl Halides with Allylic Grignard Reagents**

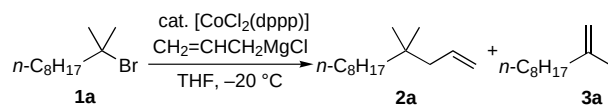
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Nickel- and palladium-catalyzed cross-coupling reactions of organic halides with organometallic reagents is one of the most versatile carbon–carbon bond-forming reactions in organic synthesis.^[1] In most cases, aryl and vinyl halides are employed as organic halides, yielding sp^2 – sp , sp^2 – sp^2 , and sp^2 – sp^3 linkages. The connection of two sp^3 carbon atoms under transition metal catalysis is also important, and a variety of retrosynthetic analyses are conceivable in which an arbitrary carbon–carbon bond in an alkyl chain is cleaved. However, coupling with alkyl halides is difficult for two main reasons: 1) Oxidative addition of alkyl halides is much slower than that of

aryl and vinyl halides. 2) β -Hydride elimination of the alkylpalladium and -nickel compound is problematic. Thus, novel and efficient methods for alkyl–alkyl coupling are currently under intense investigation.^[2,3]

We are interested in cobalt-catalyzed reactions^[4,5] and report herein the cobalt-catalyzed cross-coupling reaction of alkyl halides with allylic Grignard reagents. Allylation of various alkyl halides proceeds smoothly, and even quaternary carbon atoms have become readily accessible by transition-metal-catalyzed coupling reactions.

Allylmagnesium chloride (1.0 M solution in THF, 1.5 mmol) was added to a solution of 2-bromo-2-methyldecane (**1a**; 0.50 mmol) in THF in the presence of $[CoCl_2(dppp)]$ (0.05 mmol) at $-20^\circ C$ (Scheme 1; $dppp = 1,3$ -bis(diphenylphosphanyl)propane). Stirring for 2 h at $-20^\circ C$ provided the



Scheme 1. Cobalt-catalyzed cross-coupling reaction of alkyl halide **1a** with allylmagnesium chloride.

allylated product **2a**, which contains a quaternary carbon center (90 % yield), and **3a** (8 %). No allylated product was obtained when the $[CoCl_2(dppp)]$ catalyst was omitted. The yield of **2a** was lower when 1,4-bis(diphenylphosphanyl)butane (DPPB), 1,2-bis(diphenylphosphanyl)ethane (DPPE), and bis(diphenylphosphanyl)methane (DPPM) were employed in place of DPPP. Reaction at $-40^\circ C$ led to recovery of **1a**, whereas reaction at $0^\circ C$ resulted in a lower ratio of **2a**/**3a** (82:18).

Allylation of a variety of alkyl halides proceeded smoothly, although tuning of reaction conditions was necessary for the different substrates (Table 1). Benzylic allylation of **1d** required DPPE in place of DPPP to attain a satisfactory result. Primary and secondary bromides were less reactive. Instead, use of alkyl iodides such as **1g–i** led to high yields at $-40^\circ C$. It is worth noting that halides **1h**, **1h-I**, and **1i-I**, which have alkoxy groups at the β position to the halide atom, participated in the allylation.

Other allylic Grignard reagents were available for this reaction (Scheme 2). Regioselective coupling was observed to yield methyl-branched product **5b** upon treatment of **1g-I** with crotyl Grignard reagent. Unfortunately, reaction of prenyl Grignard reagent was unsuccessful.

Substrates having proper carbon–carbon double bonds were then subjected to the cobalt-catalyzed allylation (Scheme 3). Consequently, tandem cyclization/allylation occurred, thereby affording 3-butenyl-substituted lactones after Jones oxidation of the cyclic acetals. For example, iodoacetal **7c** was converted to lactone **9c** bearing a quaternary center, and cyclization of **7d** provided the *trans* isomer **9d** exclusively.

Interestingly, treatment of **7e** with the allyl Grignard reagent $CH_2=CHCH_2MgCl$ in the presence of $[CoCl_2(dppp)]$ furnished the ring-opening product **9e** (Scheme 4). Given that intramolecular carbocobaltation proceeds to yield cyclopropylmethylcobalt species, β -carbon elimination would provide a route to **9e**. However, β -carbon elimination seems unlikely

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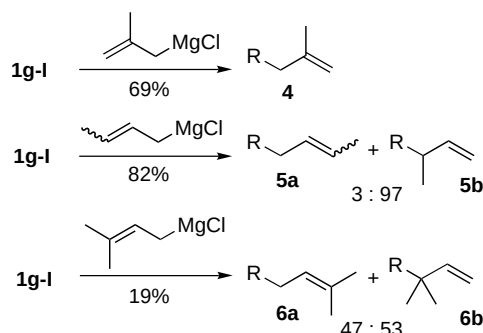
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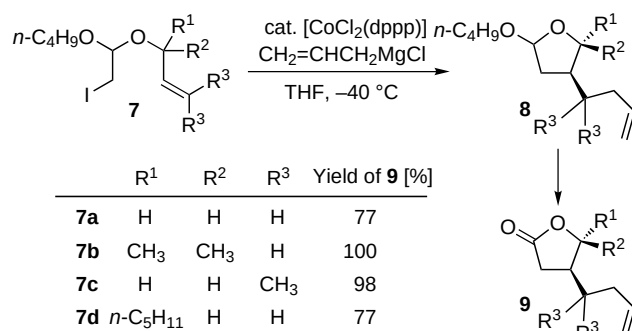
Table 1. Cobalt-catalyzed allylation of alkyl halides.

1	1	Temperature [°C]	Yield of 2 [%]
	1b	−20	83
	1c ^[a]	0	76 ^[b]
	1d	−20	73 ^[c]
	1e	0	57
	1f	−20	84
	1g	0	30
	1g-I	−40	82
	1a-Cl	20	31
	1h	0	49
	1h-I	−40	82
	1i-I	−40	76 ^[d]

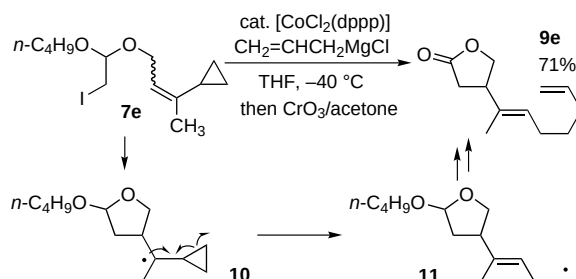
[a] *trans/cis* = 87/13. [b] *trans/cis* = 82/18. [c] DPPE was used. [d] *trans/cis* = 86/14.



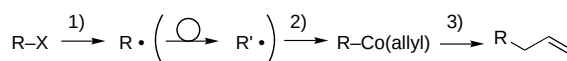
Scheme 2. R = Ph(CH₂)₃. Conditions: cat. [CoCl₂(dppp)], THF, −40 °C.



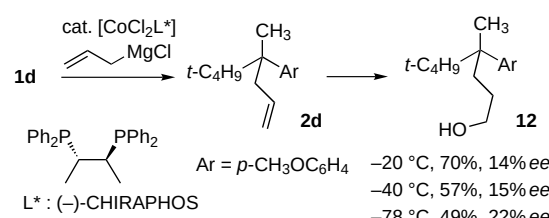
Scheme 3. Cobalt-catalyzed reaction of iodoacetals **7** to give lactones **9**.



Scheme 4. Cobalt-catalyzed reaction of **7e** with CH₂=CHCH₂MgCl to give the ring-opening product **9e**.



Scheme 5. Proposed mechanism for the catalytic reaction: 1) single-electron transfer from cobalt complex; 2) recombination of alkyl radical and cobalt complex; 3) reductive elimination.



Scheme 6. Cobalt-catalyzed asymmetric allylation of **1d**.

because β -hydride and β -alkoxy eliminations were minor processes in the reactions of **1**. Alternatively, the existence of radical intermediates **10** and **11** can account for the ring opening.^[6]

Scheme 5 shows schematically a proposed mechanism for the catalytic reaction in analogy with the results of previous reports.^[4] Namely, the oxidative addition proceeds via a single-electron transfer from an electron-rich allylcobalt complex to the alkyl halide. π -Allyl ligands may prevent the formation of the vacant coordination sites necessary for β -elimination, which enables allylation of tertiary and secondary alkyl halides and alkyl halides having β -alkoxy groups.

Finally, asymmetric allylation was investigated (Scheme 6).^[7,8] Treatment of **1d** with allylmagnesium chloride in the presence of [CoCl₂{(−)-chiraphos}] at −20 °C afforded **2d**. Hydroboration of **2d** followed by usual oxidation provided **12** in 70% yield and 14% *ee*. When the reaction was carried out at a lower temperature (−78 °C), the enantiomeric excess increased to 22%. The cobalt-catalyzed asymmetric allylation provides a novel utility of transition-metal-catalyzed radical reactions.

In summary, [CoCl₂(dppp)] effectively catalyzes the cross-coupling reaction of alkyl halides with allylic Grignard reagents. Not only primary alkyl halides but also secondary and tertiary alkyl halides undergo allylation, in the latter case to give quaternary carbon centers.

Experimental Section

Anhydrous cobalt(II) chloride (7.0 mg, 0.050 mmol) was placed in a 20 mL flask and was heated with a hair dryer in vacuo for 2 min. After the color of



the cobalt salt became blue, DPPP (25 mg, 0.060 mmol) and anhydrous THF (1.0 mL) were sequentially added under argon. The mixture was stirred for 10 min at room temperature. 2-Bromo-2-methyldecane (**1a**, 0.12 g, 0.50 mmol) and allylmagnesium chloride (1.0 M solution in THF, 1.5 mL, 1.5 mmol) were successively added dropwise to the reaction mixture at -20°C . While the Grignard reagent was being added, the mixture turned reddish-brown. After being stirred for 2 h at -20°C , the reaction mixture was poured into saturated NH_4Cl solution, and the products were extracted with ethyl acetate (20 mL $\times$ 2). The combined organic layer was dried over Na_2SO_4 and concentrated. Purification of the crude oil by silica gel column chromatography (hexane) provided 4,4-dimethyl-1-dodecene (**2a**) and 2-methyl-1-decene (**3a**) (94 mg, 90% and 8% yields, respectively, as determined by ^1H NMR spectroscopy).

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Distal Cu Ion Protects Synthetic Heme/Cu Analogues of Cytochrome Oxidase against Inhibition by CO and Cyanide**

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Cytochrome c oxidase (CcO) is the enzyme that makes aerobic metabolism possible by catalyzing the final step in the respiratory electron-transfer chain—a four-electron ($4e^-$), four-proton (4H^+) reduction of O_2 to water.^[1,2] Catalysis proceeds at the heterobimetallic heme/ Cu_B site (Figure 1).^[3] The Fe center is the site of O_2 binding, and reduction of O_2 is coupled to oxidation of $\text{Cu}_\text{B}^\text{I}$, at least under single-turnover conditions.^[4,5] One of the poorly understood questions regarding the structure–activity relationship at the heme/ Cu_B site is how the heme reactivity is affected by the closely positioned, positively charged Cu_B center. Such effects are expected to manifest themselves in an attenuated affinity of the Fe center for small molecules. Among these, CO and the ions CN^- and N_3^- , are of particular interest, because the cytotoxicity of the CN^- and N_3^- ions arises from the inhibition of CcO and resultant respiratory shutdown,^[7] and CO is an endogenous inhibitor of ferrohemes. The mode of CN^- ion binding to the heme/ Cu_B site and the effect(s) of Cu_B on such binding remain controversial.^[8] Likewise, contradictory results have been reported for differences in the CO affinities of the wild-type and Cu_B -free mutants of terminal oxidases.^[9,10]

Previously, we demonstrated that the biomimetic complexes shown in Figure 1b quantitatively reproduce the key reactivity of the heme/ Cu_B site^[6,11] and thus allow the study of questions that are not easily addressed by working with the enzyme itself. Herein we report that the steady-state reduc-

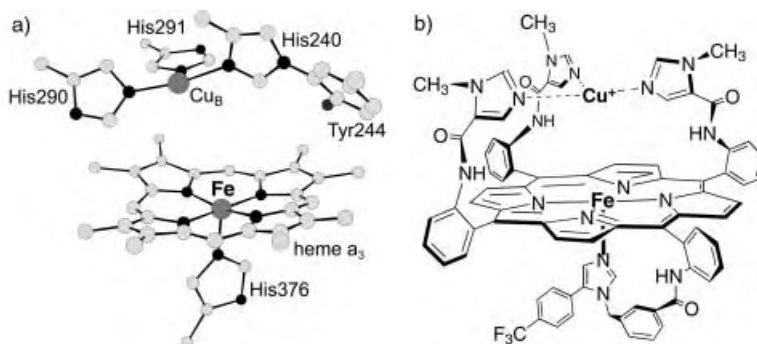


Figure 1. a) The heme/ Cu_B site of bovine cytochrome oxidase;^[3] the C atoms are light gray and the N and O atoms are black, b) a synthetic heme/ Cu_B analogue in the reduced form; exogenous ligands and counterion are omitted.^[6]

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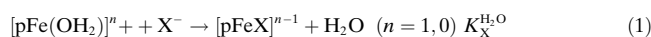
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tion of O₂ catalyzed by these biomimetic complexes is reversibly inhibited by both the CN[−] ion and CO, and the distal Cu center notably decreases the catalysts' susceptibility to inhibition. The possibility that Cu_B may protect against small-molecule inhibition has not been previously considered.

Inhibition was studied electrochemically in pH 7 buffered electrolytes with the water-insoluble catalysts deposited on the surface of an edge-plane graphite rotating-disk electrode to obtain rapid electron delivery from the electrode to the catalytic sites.^[13] Whereas the distal Cu center is critical for catalytic activity under diffusion-limited electron flux,^[12] the FeCu and Fe-only complexes catalyze O₂ reduction with identical kinetics, mechanism, and stability when electron flux is rapid.^[11] In this regime comparative voltammetry of the FeCu and Fe-only catalysts in the presence of the inhibitors yields data that are free of the ambiguities caused by the different catalytic behavior of the mono- and bimetallic catalysts.

Under anaerobic conditions, rapid equilibration among the [pFe^{III}(OH₂)]⁺, [pFe^{III}X], [pFe^{II}(OH₂)], and [pFe^{II}X][−] species (X = CN[−], N₃[−]; p represents the pentadentate porphyrin shown in Figure 1b) is observed by cyclic voltammetry of the Fe-only complex. Equilibrium constants for displacement of H₂O by X[−], K_X^{H₂O}, [Eq. (1), Table 1] have been derived from voltammetric titration experiments.^[13] The CN[−] ion has an appreciable affinity not only for Fe^{III} but also for Fe^{II} centers, whereas binding of the N₃[−] ion to Fe^{II} centers is only weakly favored over the coordination of H₂O. Anaerobic voltammetry of the FeCu complex in the presence of X[−] ions suggests the existence of more than four species and is complicated by the loss of Cu at [CN[−]] > 50 μM^[14,15] and at [N₃[−]] > 0.5 mM, which precluded quantitative characterization of this system.^[13]



Inhibition of O₂ reduction is more significant at higher potentials (Figure 2), at which CN[−] ions decrease the amount of the active catalyst both by directly binding to it (forming [pFe^{II}CN][−]) and by shifting the redox Fe^{III/II} equilibrium towards the ferric form, as [pFe^{III}CN] is a weaker oxidant than the [pFe^{III}(OH₂)]⁺ ion. This simple picture is sufficient to quantitatively model the catalytic half-wave potentials observed in a range of CN[−] concentrations.^[13]

At sufficiently reducing potentials the cyanide-ligated catalyst is so easily reduced that only a competition between O₂ and CN[−] ions for the Fe^{II} center determines the potential-

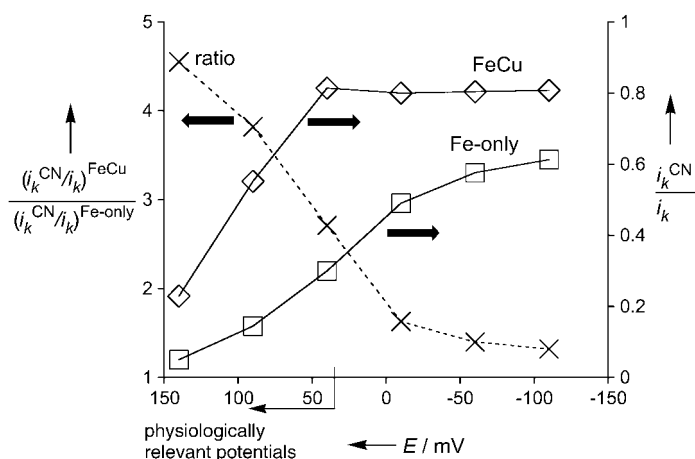
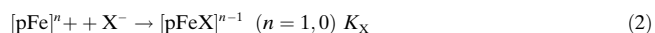


Figure 2. Susceptibility of the FeCu (◊) and Fe-only (◻) catalysts to inhibition by CN[−] ions (3.5 μM) at pH 7 as a function of potential *E* (vs. the normal hydrogen electrode (NHE)). Right scale: the fraction of the retained catalytic activity, i_k^{CN}/i_k (i_k^{CN} : kinetic current in the presence of CN[−]; i_k : kinetic current in the absence of CN[−] ions). Left scale: the retained fraction for the FeCu catalyst relative to that for the Fe-only analogue (×). The physiologically relevant potentials are those of cytochrome c and ubiquinol, the physiological reductants of CcO and the related ubiquinol oxidase.

independent residual catalytic activity (Figure 2, $E < -0$ V). In accord with inhibition enzymatic kinetics, the ratio of the lost ($i_k - i_k^{\text{CN}}$) to retained (i_k^{CN}) catalytic activity is proportional to [CN[−]] (Figure 3). The proportionality coefficient K_X is the equilibrium binding constant of CN[−] ions to five-coordinate Fe^{II} centers [Eq. (2), Table 1]. The $K_{\text{CN}}/K_{\text{CN}}^{\text{H}_2\text{O}}$ ratio, equal to the affinity of [pFe^{II}] for H₂O, indicates that during steady-state catalysis in the absence of CN[−] ions < 1 % of the ferrous complex is five coordinate.



The data in Figure 3 show that, depending on the potential, the susceptibility of the Fe-only catalyst to CN[−] ion inhibition is up to five times that of the FeCu analogue. Relative to the Fe-only complex, the CN[−] ion affinity of the FeCu analogue is 2.6 and approximately two-times lower in the reduced and oxidized states, respectively, and its Fe^{III/II} potential in the aqua form is ~20 mV more oxidizing. Because at physiologically relevant potentials reduction of Fe^{III}CN unit is unfavorable, the higher Fe^{III/II} potential and the lower CN[−] ion affinity of the oxidized FeCu complex increase the difference in susceptibility of the mono and bimetallic catalysts at $E > -0$ V.

Table 1. Equilibrium constants, K [M^{−1}] for CN[−], N₃[−] ion, and CO binding to the synthetic analogues and the heme/Cu_B site, and the CO and O₂ on-rates, k_{on} , which are listed in square parentheses.

Catalyst	Redox and ligation state of Fe	Constant	CN [−]	N ₃ [−]	CO [k_{on} , M ^{−1} s ^{−1}]	O ₂ [k_{on} , M ^{−1} s ^{−1}]
Fe-only	[pFe ^{III} (OH ₂)] ⁺	$K_X^{\text{H}_2\text{O}}$	7×10^5 ^[a]	2×10^2 ^[a]		
	[pFe ^{II} (OH ₂)]	$K_X^{\text{H}_2\text{O}}$	3×10^3 ^[a]	2.5 ^[a]		
	[pFe ^{II}]	K_X	4×10^5 ^[b]		1.9×10^6 [3.8×10^3]	$[1 \times 10^7]$ ^[11]
FeCu	pFe ^{II}	K_X	1.5×10^5 ^[b]		7.6×10^5 [3.3×10^3]	$[\sim 2.5 \times 10^7]$ ^[11]
CcO	Fe ^{III} (OH ₂)		1×10^6 ^[16] – 10^8 ^[17]	1×10^2 ^[18] – 10^4 ^[19]		
	Fe ^{II} _{a3}		1×10^3 – 10^4 ^[17]		1×10^6 – 10^7 ^[17] [7×10^4] ^[19,20]	$[1\text{--}3 \times 10^8]$ ^[2]

[a] From anaerobic cyclic voltammetry.^[13] [b] From the data in Figure 3.

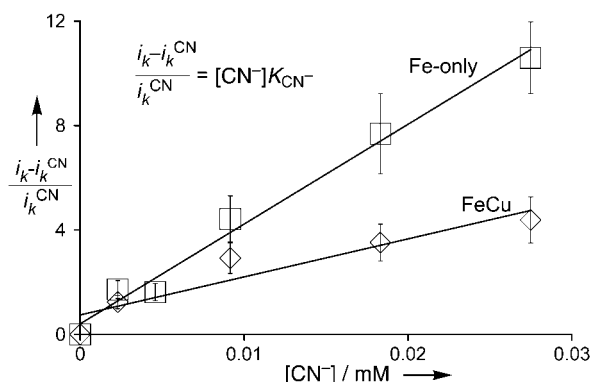


Figure 3. The ratio of the lost ($i_k - i_k^{\text{CN}}$) to retained (i_k^{CN}) catalytic activity at -100 mV (the potential-independent regime, see Figure 2) for the FeCu ($\diamond$) and Fe-only ($\square$) catalysts as a function of $[\text{CN}^-]$. The lines are the least-squares fits to the equation shown. The data were collected only at $[\text{CN}^-]$ where extraction of Cu was deemed to be insignificant, although a possibility of some Cu loss can not be excluded entirely.

Steric perturbations of CN^- ions within the more constrained binding pocket of the FeCu complex probably accounts for the lower CN^- ion affinity of this complex. The weaker CN^- ion binding to the oxidized FeCu catalyst relative to the Fe-only analogue is unexpected because the higher positive charge of the biometallic complex should favor anion binding. Possible CN^- ion binding to the Cu center, suggested by non-catalytic experiments,^[13] may compensate the extra charge and increase steric congestion around the Fe center. The weaker binding of CN^- ions particularly to the $\text{Fe}^{\text{III}}\text{Cu}^{\text{II}}$ catalyst is biologically significant because the tolerance of an organism to CN^- ion poisoning relates to the dissociative stability of the oxidized cyanide-ligated heme/ Cu_B site, which is not reducible by ferrocyanide c.

Because CO and the CN^- ion have similar stereoelectronic requirements as ligands, the steric origin of the weaker CN^- ion binding to the FeCu catalyst is supported by 2.5-fold lower affinity of the FeCu catalyst for CO. The effects of steric constraints on CO binding to heme units have been studied extensively and spectroscopic^[6] as well as structural^[3] evidence exists for Cu-induced perturbation of heme-bound CO in CO-ligated heme/ Cu_B site. The rates of CO binding to and dissociation off Fe centers (and hence K_{CO} , Table 1) in our heme/ Cu_B analogues were obtained by measuring the loss rate of catalytic O_2 reduction at a fixed potential in the presence of CO (Figure 4). A comparison of the FeCu and Fe-only catalysts reveals that Cu does not significantly affect the CO on-rate but accelerates the off-rate, which suggests Cu-induced destabilization of the CO adduct. In contrast to CN^- and N_3^- ions, equilibration between the free and CO-bound catalysts is slow. This situation results in cyclic voltammograms that display irreversible redox events from which relevant equilibrium constants, $K_{\text{CO}}^{\text{H}_2\text{O}}$, could not be determined.

Our biomimetic complexes reproduce the relative ligand affinities of the oxidized (o) and reduced (r) heme/ Cu_B site in CcO : $\text{CN}^-(\text{o}) \sim \text{CO}(\text{r}) > \text{CN}^-(\text{r}) > \text{N}_3^-(\text{o}) \geq \text{HCO}_2^-(\text{o})$.^[17] Quantitatively, the oxidized catalysts display lower and the reduced catalysts higher affinities for anionic ligands (CN^- , N_3^- , and formate^[13]) than the heme/ Cu_B site in the same redox

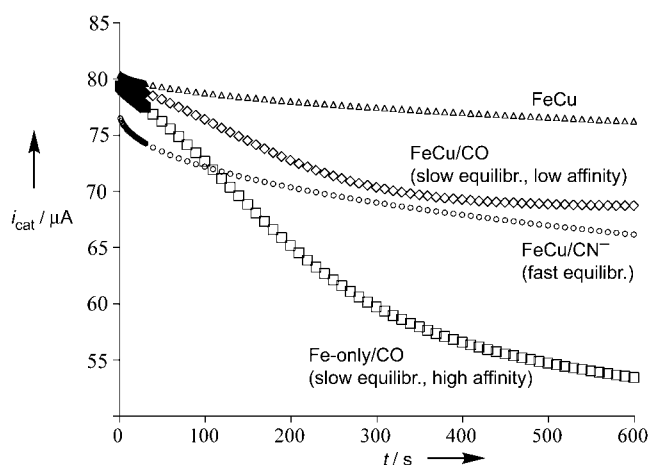


Figure 4. The catalytic current, i_{cat} , as a function of time, t , for O_2 reduction at -100 mV by the FeCu ($\diamond$) and Fe-only ($\square$) catalysts in the presence of CO (240 Pa) and, for comparison, by the FeCu catalyst in the absence of an inhibitor ($\triangle$) and in the presence of $10 \mu\text{M}$ CN^- ($\circ$).^[14] In air-saturated electrolytes at the electrode rotation frequency of 200 revolutions per minute. In the presence of CO, the rapid drop of i_{cat} at 100–300 s results from a slowly established equilibrium between the CO-bound and free catalysts. Least-square fits of the $i_{\text{cat}}(t)$ data^[13] yield the CO on- and off-rates.

state. This situation is consistent with more efficient charge stabilization (either $[\text{pFe}^{\text{III}}(\text{OH}_2)]^+$ or $[\text{pFe}^{\text{II}}\text{X}]^-$) in the biomimetic complexes in contact with an aqueous electrolyte relative to charge stabilization in the protein matrix.^[11] The rate of equilibration between CN^- (N_3^-) bound and free catalysts is rapid and qualitatively comparable to that of the “pulsed” oxidized cytochrome oxidase,^[21] but the on-rates of both CO and O_2 are approximately tenfold lower than those reported for the enzyme. The origin of this difference is uncertain.

In summary, we have observed that during the steady-state reduction of O_2 under physiologically relevant conditions Cu decreases the susceptibility of functional heme/ Cu_B analogues to inhibition by CN^- ions and CO. An up to fivefold-higher concentration of CN^- ions is required to inhibit the same fraction of the FeCu catalyst as the Fe-only analogue operating at physiologically relevant potentials. This results from a combination of weaker CN^- ion binding to both the $\text{Fe}^{\text{III}}\text{Cu}^{\text{II}}$ and $\text{Fe}^{\text{II}}\text{Cu}^{\text{I}}$ catalysts and an approximately 20 mV more oxidizing $\text{Fe}^{\text{III/II}}$ potential in the aqua FeCu complex.

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