

ANGEWANDTE CHEMIE

INTERNATIONAL EDITION

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40/1

Page 1–264

40 Years of *Angewandte Chemie* International Edition

The cover picture of this anniversary issue marks the start of the fortieth year of the International Edition of *Angewandte Chemie*. “Publishing is like mountaineering” was a thought I had when I first saw this picture. I probably thought more of the effort of the ascent than the joy one experiences on reaching the peak. However, just like the climber who finds contentment, if not actually enjoyment, at every step of the preparation and the climb, the same is also true for all those involved in the stages of publication of books and journals.

In 1961, the plan to produce an English version of a German scientific journal was farsighted and courageous. The project had, to use the imagery above, Himalayan dimensions, not least because at that time there was not inconsiderable opposition from German-speaking chemists. The plan was put forth and realized essentially by two former editors of the journal, Wilhelm Foerst and Helmut Gr  newald. In 1961 *Angewandte Chemie* appeared every two weeks and contained the sections: Reviews, Communications, Conference Reports, Literature Abstracts, and Book Reviews. With the exception of a few excellent Reviews from abroad, all the articles came from the German-speaking community. Even at this time the spectrum of topics covered was broad



and varied, something that is still one of the trademarks of the journal. What could be more topical today than the first review in issue 1 of the International Edition by G. Schramm et al. from T  bingen on the “Non-Enzymatic



Synthesis of Polysaccharides, Nucleosides and Nucleic Acids and the Origin of Self-Reproducing Systems”? Table 1 gives an overview of the reviews in the first year (1962). The list reflects the quality of the journal at the time in that many of the author’s names are very familiar and have even found their way into textbooks. Early in 2002 we are planning to publish a 40-year review index as a special issue of *Angewandte Chemie*.

Changes in the terrain and the weather require swift but considered reactions from the climber. Editors and publishers must react with similar speed and consideration to changes in the research landscape and the publishing business. *Angewandte Chemie* reacted resolutely at the start of the 1960s and since then, through a series of developments and innovations (Table 2) has contributed considerably to enhancing the visibility, attractiveness, and accessibility of excellent scientific content to a worldwide interdisciplinary readership. Two of the many changes were the introduction of an extended Table of Contents with graphical material 25 years ago and the Highlights section a decade ago.

Ten years of Highlights is also a small anniversary. These short articles which can range from a minireview to a detailed critical appraisal of just one particularly important research result (and everything in between), and which have in no way detracted from the importance of the longer traditional review articles, are used by readers to pinpoint key issues in chemis-



try. Many of the themes of the Highlights from 1991 (Table 3) have been dominant ones in the 1990s and are still of great importance today.

The year 2000 began with the “millennium issue”, the two reviews of which (from T. R. Cech and K. C. Nicolaou et al.) promptly entered the top ten articles most viewed electronically in Wiley InterScience; in addition this issue included the first article of a new section, Essays (about the early history of Ferrocene, written by P. Laszlo and R. Hoffmann). Essays provide a platform to address themes from every aspect of chemistry including the philosophy or history of science. Use of unpublished results from original research should be extremely limited. Primarily a known topic should be discussed illuminatingly and critically from a new vantage point.

The Essay in this issue aptly concerns *Angewandte Chemie* itself, and addresses an often controversially discussed topic, the impact factor. What do the Reviews contribute to the impact factor

of *Angewandte Chemie* and what do the Communications bring? Is the impact factor of *Angewandte Chemie* flawed through the publication of the

two editions? What are the results of a long-term citation analysis of individual articles? We are very grateful to the author, Werner Marx from the Max-Planck-Institut für Festkörperforschung, Stuttgart, Germany, that he has taken such a close look at the impact factor of the journal. To increase curiosity about the Essay, Figure 1 shows the development of the impact factor of *Angewandte Chemie* along with those of two other well known chemistry journals since the beginning of this measurement scale. Most surprising (and pleasing) is that the impact factor for *Angewandte Chemie* climbed significantly in the second half of the 1990s although in this time the number of Communications, which are supposedly less cited than Reviews, greatly increased (Figure 2).

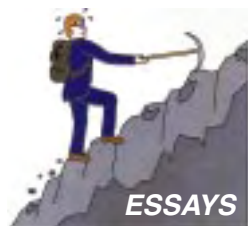


Table 1. Authors and Title of the Reviews in *Angewandte Chemie* in 1962.

Becke-Goehring, M., Fluck, E. Biemann, K.	Phosphonitrilic Chlorides from Phosphorus Pentachloride
Brill, R. Bunnett, J. F. Calvin, M. Criegee, R. Dachs, K., Schwartz, E.	The Application of Mass Spectrometry in Organic Chemistry: Determination of the Structure of Natural Products The Structure of Ice The Mechanism of Bimolecular β -Elimination Reactions The Path of Carbon in Photosynthesis (Nobel Lecture) Attempts to Synthesize Tetramethylcyclobutadiene Pyrrolidone, Capryllactam and Lauro lactam as new Monomers for Polyamide Fibers Recent Studies on Fluoroalkyls and Related Compounds Long Periods in Drawn Polyethylene
Emel�us, H. J. Fischer, E. W., Schmidt, G. F. Graf, R. et al. Harteck, P., Reeves, R. R. Heine, H. W. Helfferich, F. Hinrichs, H., Niedetzky, J. Hofmann, U. Holtschmidt, H. Holtschmidt, H., Oertel, G. Hund, F. H�nig, S. J�chle, W. Jones, R. A. Y., Katritzky, A. R. K�brich, G. Kresze, G. et al. Kr�hnke, F., Zecher, W. K�hle, E. Kunin, R., Winger, A. G. Meerwein, H. et al. Muxfeldt, H. Neeb, R.	β -Lactams, their Polymerization and Use as Raw Materials for Fibers Chemical Reactions in the Atmosphere The Isomerization of Aziridine Derivatives Theories of Ion-Exchange Column Performance: A Critical Study A New Type of Converter for Ammonia Synthesis The Chemical Basis of Ancient Greek Vase Painting High-Temperature Chlorination of Amines and Acylamines Isocyanates of Esters of Some Acids of Phosphorus and Silicon Mixed-Phase Pigments with Rutile Structures Heterocyclic Azo Dyes by Oxidative Coupling Biology and Biochemistry of Reproduction and Contraception Phosphorus Nuclear Magnetic Resonance Spectroscopy
Neumann, W., Fischer, P. Plesske, K.	Electrophilic Substitutions at Saturated Carbon Atoms Organic <i>N</i> -Sulfinyl Compounds Syntheses Using the Michael Addition of Pyridinium Salts Carbonic Acid Derivatives from Formamides Liquid Ion-Exchange Technology Ionic Hydrogenations and Dehydrogenations Syntheses in the Tetracycline Series Inverse Polarography and Voltammetry: New Methods for Trace Analysis
Plieninger, H. Randerath, K. Reichstein, T. Rinke, H. Rochlitz, F., Vilcsek, H. Smets, G. Smidt, J. et al. Smith, W. C. Sommer, L. H. Sprague, B. S. et al. Schlittler, E. et al. Schramm, G. et al.	The Preparation of Carbodiimides from Isocyanates Ring Substitutions and Secondary Reactions of Aromatic-Metal π -Complexes Prephenic Acid: Properties and the Present Status of its Synthesis Thin-Layer Chromatography of Nucleotides Special Properties of the Sugars in Cardioactive Glycosides Elastomeric Fibers Based on Polyurethanes β -Chloroethanephosphonic acid Dichloride: Its Synthesis and Use Chemical Reactions and Microtacticity of High Polymers The Oxidation of Olefins with Palladium Chloride Catalysts The Chemistry of Sulfur Tetrafluoride The Stereochemistry of Organosilicon Compounds Copolymers and Fibers from Vinylidenedicarbonyl Recent Developments in Non-Mercurial Diuretics Non-Enzymatic Synthesis of Polysaccharides, Nucleosides and Nucleic Acids and the Origin of Self-Reproducing Systems Automatic Activity Measurements during the Separation of Radioactive Compounds by Thin-Layer Chromatography Syntheses Using Heterocyclic Amides (Azolides) (New Methods of Preparative Organic Chemistry)
Schulze, P.-E., Wenzel, M.	Advances in the Chemistry of Organic Ring Systems with Adamantane Type Structures
Staab, H. A.	Nucleotide Intermediates in the Biosynthesis of Polysaccharides Conversion of Natural Substances by Microbial Enzymes
Stetter, H.	Reactivity of Dichloro- and Trichloropyrimidyl Dyes and the Sensitivity of their Dyeings to Hydrolysis
Strominger, J. L. Tamm, Ch. Thumm, O., Benz, J.	The α -Addition of Immonium Ions and Anions to Isonitriles Accompanied by Secondary Reactions (New Methods of Preparative Organic Chemistry)
Ugi, I.	The Synthesis of Nucleosides
Ulbricht, T. L. V. Vetter, K. J.	Problems in the Theoretical Treatment of Reactions Occurring at Easily Passivated Metal Anodes
Virtanen, A. I.	Some Organic Sulfur Compounds in Vegetables and Fodder Plants and their Significance in Human Nutrition
Voltz, J. Vossius, V. Walter, S. et al.	Dyeing of Poly(acrylonitrile) Fibers with Azatrimethinecyanines Patenting of Chemical Inventions in the Federal Republic of Germany Enrichment of Heavy Water by High Pressure Exchange between Hydrogen and an Aqueous Catalyst Suspension Aspects of Nucleophilic Carbene Chemistry
Wanzlick, H. W. Wieland, T., Pfeleiderer, G. Wittig, G. Zeil, W.	Isozymes and Heteroenzymes Small Rings with Carbon-Carbon Triple Bonds Mechanical and Dielectric Relaxation Phenomena and their Molecular-Physical Interpretation

Table 2. Changes and innovations at *Angewandte Chemie* over the last 25 years.

1976	Table of Contents with graphical abstract
1979	Changing cover picture, after around 1988 in color
1988	Founding of <i>Advanced Materials</i> in <i>Angewandte Chemie</i>
1991	Highlights
1992	Electronic journal editorial system
1995	Founding of <i>Chemistry - A European Journal</i> in <i>Angewandte Chemie</i> <i>Angewandte Chemie</i> Homepage: www.angewandte.com
1997	Full-page graphics for Reviews and Communications
1998	Regular press service
	Full-text on-line at www.interscience.wiley.com
1999	Simultaneous publication of the German and International Editions
2000	Founding of <i>ChemBioChem</i> and <i>ChemPhysChem</i> in <i>Angewandte Chemie</i> Essays; Web editor; EarlyView (that is, the electronic publication of the issue in Wiley InterScience before the printed version)
2001	Color Table of Contents Web site reviews New editorial office system with on-line submission and refereeing over the WWW

Strong growth in various aspects has characterized *Angewandte Chemie* in the last five years. Figures 2–4 show the increase in Communications submitted, the growth in the number of pages published, and the increase in the number of Communications submitted from outside Germany. Figure 5 shows the origin of the Communications submitted in more detail. Last year alone, *Angewandte Chemie* received approximately 250 (ca. 15%) more Communications than in 1999 and 160 (23%) more were published—this is roughly as many as were published in the whole first volume of the International Edition (often four of them could be printed on one page in 1962). An enormous effort from the editors and the publisher—350 more pages (ca. 10%) were published than were planned—made a significant reduction of the publication time possible. At the start of 2000 the average publication time was still over 160 days but by the end of the year has been reduced to around 135 days; however, again last year particularly important and competitive work was published in less than two months, and this will be the case in the future. Publication time has different meanings to different journals. Not least because we do not want to put our authors at a disadvantage in cases of priority conflicts, our publication times are not manipulated in any way. Only if there is a very valid reason is the received date of the original manuscript not given. The publication time is the time between the date of receipt of the original manuscript and the publication date of the issue (the complete issue is published electronically about seven days before the printed version).

This reduction of publication times was made possible by various means including the publication of English Communications in the German Edition. Of 859 Communications in the last year, 498 were published in English alone and 361 in German and English. This change coupled with an expansion of the editorial staff should result in a further reduction of publication times in 2001.

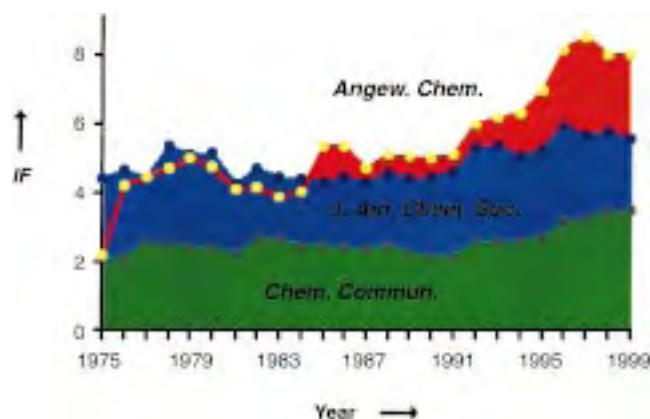


Figure 1. The development of the impact factor (IF) of *Chemical Communications*, the *Journal of the American Chemical Society*, and *Angewandte Chemie* since 1976.

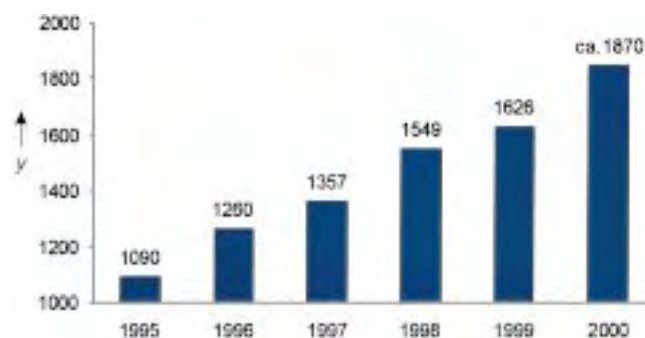


Figure 2. The increase in the number of Communications *y* submitted since 1995.

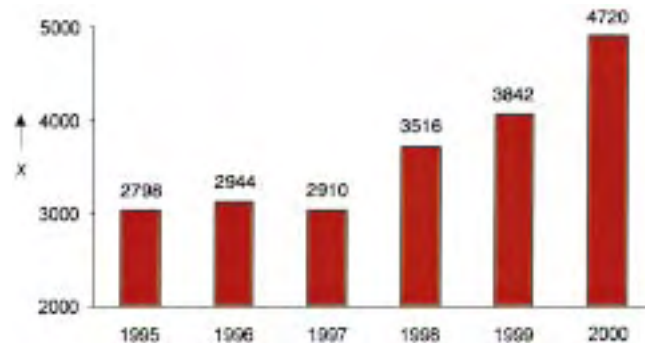


Figure 3. Increase in the number of pages published *x* of the German Edition of *Angewandte Chemie* since 1995. 4500 pages were planned for 2000 and 4900 were published; 5300 pages are planned for 2001.

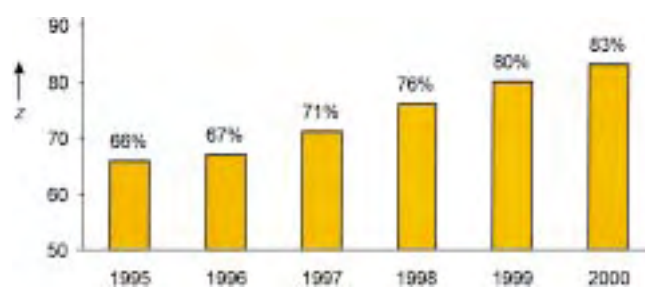


Figure 4. The number of Communications *z* submitted from outside Germany since 1995.

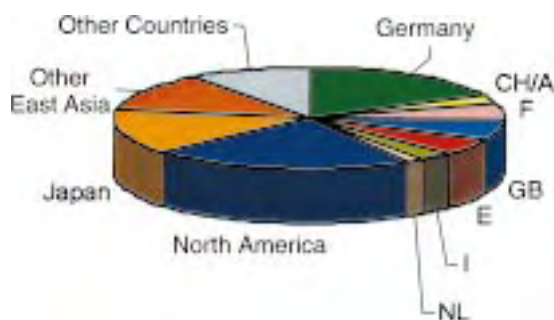


Figure 5. Origin of the Communications submitted to *Angewandte Chemie* 2000.

Color in the Table of Contents: Clarity, liveliness, and visibility will be further enhanced in *Angewandte's* Table of Contents from 2001 through the sensible use of color. Our Table of Contents—a model for many other journals—was the first in chemistry to present graphical material with explanatory text. This has served our readers well for almost 25 years. In an ever more colorful (and noisy) world it is essential that we in-



Table 3. Authors and title of the Highlights in *Angewandte Chemie* 1991.

Alt, H. G.	Designed Coupling of C_1 Ligands: Organometallic Model Reactions
Beck, W.	Highly Reduced Metal Carbonyls
Bolm, C.	Bis(4,5-dihydrooxazolyl) Derivatives in Asymmetric Catalysis
Bolm, C.	Catalytic Enantioselective Epoxidations of Simple Olefins
Chisholm, M. H.	Metallenes and Metallaynes – from Small Molecules to Infinite Polymers
Constable, E. C.	Helices, Supramolecular Chemistry, and Metal-directed Self-Assembly
Constable, E. C.	Sandwiches Bring a New Element to Molecular Recognition
Diederich, F., Whetten, R. L.	C_{60} : From Soot to Superconductors
Enkelmann, V.	Novel Building Blocks for the Synthesis of Organic Metals
Haarer, D., Kador, L.	Optical Detection of Single Molecules in a Solid A New Frontier in Optical Spectroscopy?
Heinze, J.	Ultramicroelectrodes – a New Dimension in Electrochemistry?
Herrmann, W. A.	Between Stars and Metals: Phosphorus Monoxide, PO
Hopf, H.	Incarcerated Atoms and Reactive Molecules
Kessler, H. et al.	Toward the Understanding of Immunosuppression
Kölle, U.	Energetic and Constitutional Hysteresis in Bistable Molecules
McBride, J. M., Carter, R. L.	Spontaneous Resolution by Stirred Crystallization
Mulzer, J.	Erythromycin Synthesis – A Never-ending Story?
Paetzold, P.	Monovalency of the Third Main-Group Elements: News from EX-Type Compounds
Plückthun, A., Ge, L.	The Rationality of Random Screening – Efficient Methods of Selection of Peptides and Oligonucleotide Ligands
Regitz, M.	Stable Carbenes – Illusion or Reality?
Ritter, H.	Novel Polymeric Materials from Monodisperse Copolypeptides by Biotechnological Methods
Schwarz, H.	Activation of Methane
Staunton, J.	The Extraordinary Enzymes Involved in Erythromycin Biosynthesis
Stoddart, J. F.	The Third Allotropic Form of Carbon
Süss-Fink, G.	Molecular Systems with Perfect Metal Structure
Vögtle, F., Knops, P.	Dyes for Visual Distinction between Enantiomers: Crown Ethers as Optical Sensors for Chiral Compounds
von Kiedrowski, G.	Light-Directed Parallel Synthesis of Up to 250 000 Different Oligopeptides and Oligonucleotides
Wachter, J.	New Discoveries in the Realm of Metal-Metal Multiple Bonds: $[\eta^5-C_5Me_5)_2Co_2]$, the First Organometallic Multiple-Bond Complex without Bridging Ligands
Waldmann, H.	$LiClO_4$ in Ether – an Unusual Solvent
Wendorff, J. H.	Piezoelectric Liquid-Crystalline Elastomers

Table 4. The departing and new members of the Editorial Board of *Angewandte Chemie*.

Departing:

Prof. Gerhard Ertl, Fritz-Haber-Institut der Max-Planck-Gesellschaft, Berlin
Prof. Arndt Simon, Max-Planck-Institut für Festkörperforschung, Stuttgart
Prof. Günter Wulff, Heinrich-Heine-Universität, Düsseldorf

New:

Prof. Reinhart Ahlrichs, Universität Karlsruhe
Prof. Martin Jansen, Max-Planck-Institut für Festkörperforschung, Stuttgart
Prof. Rolf Mülhaupt, Albert-Ludwigs-Universität, Freiburg
Prof. Martin Quack, Eidgenössische Technische Hochschule, Zürich
Dr. Peter Raddatz, Merck KGaA, Darmstadt
Prof. Bernd Wetzlar, Boehringer Ingelheim GmbH, Ingelheim am Rhein

crease the signal-to-noise ratio for the contributions we publish. We herewith encourage our authors to submit appropriate—not too large!—color graphical material that can be used in the Table of Contents. Reproduction will be free of charge in all cases where there is color in the article itself.

What else will 2001 bring? Many excellent and original manuscripts, naturally, that had not been published be it on preprint server or elsewhere. Three particularly attractive reviews stand at the beginning in this anniversary issue; the main authors were or are members of the Editorial Board or the International Advisory Board of *Angewandte Chemie*. It is the most important role of the members of these boards to mold the journal through excellent publications and thus demonstrate in which directions it should develop. The new and departing members of the Editorial Board are given in Table 4; there were no changes in the composition of the International Advisory Board.

Publishing on the “Web” these days is a matter of course; 40 years ago this was unimaginable. For subscribers, *Angewandte Chemie* is fully accessible electronically (www.interscience.wiley.com). In addition, our Homepage (www.angewandte.com) offers no end of interesting information (Hot Papers, Very Important Papers, Article Finder, Press Releases etc.). In the last few months, a Web editor has strengthened the editorial staff and has already made the Home-



page more attractive to viewers and will develop this further intensively. He will also oversee the new section "Web Sites" which can be found, for the very first time, at the end of this issue after the book reviews. Articles for this section are most welcome; prior contact with the editorial office is advisable (angewandte@wiley-vch.de). The reviewing of web sites should help readers to sift the wheat from the chaff in the web, no doubt there is already more trash than treasure out there!

In the previous 40 years, more than a few issues have left the readers, authors, and editors with the feeling that they have conquered another mountain, and the current issue is also no insignificant peak. We are already looking forward to the next ones (dispel thoughts of Sisyphus) and thus to your contribution, whether it is for one of the sections in the journal or comments on this issue and the development of *Angewandte Chemie* in general.



Dr. Peter Göllitz

PS: Last year we began the ascent of new peaks with the founding of *ChemBioChem* and *ChemPhysChem*, and thanks to the magnificent support of the Editorial Board Members, great heights have been reached already. The response of the authors has been excellent, the two journals have both received nearly two hundred manuscripts in the first shortened year of publication, and the interest of the readers has been great. The new issues of *ChemBioChem* and *ChemPhysChem* will appear alternately at the end of each issue of *Angewandte Chemie* throughout the year.



COVER PICTURE

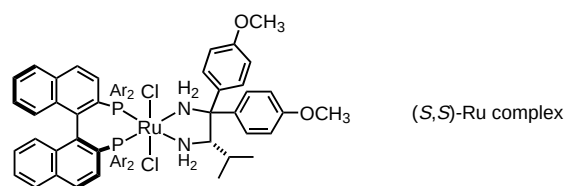
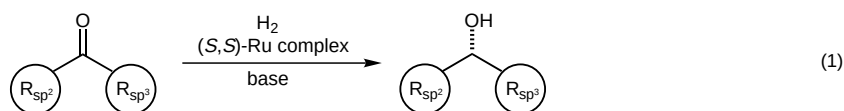
The cover picture shows a model of the “progenitor-TADDOLs” in front of a panorama of the Fünffingersstocks and the Wenden Glacier in the Titlisgebiet (Switzerland). The model is flanked by a stylized view of the general mechanistic model for the preferred stereochemical pathway of the Ti-TADDOLate-catalyzed reaction of chelating substrates (left) and a blackboard (right) showing formulae of compounds that can be prepared with high enantioselectivity by nucleophilic addition in the presence of titanium TADDOLates. From TADDOL, introduced in 1982, a genuine auxiliary system for the “introduction of chirality” (not only by reaction) has been developed, which, in the final sprint against the competition has a good chance of securing a place on the winning podium. The photograph of the mountain landscape was taken by Dr. J. Frackenpohl, the cover picture was generated by one of the authors (A.H.) of the comprehensive review of TADDOLs in this issue (p. 92 ff.) with the help of the program Povray.



REVIEWS

Contents

No interaction with the metal center is necessary for the rapid, productive, and stereoselective catalytic hydrogenation of simple ketones when these reactions are carried out in the presence of complexes of general form $[\text{RuCl}_2(\text{phosphane})_2(1,2\text{-diamine})]$. The combined use of a BINAP ligand and a chiral 1,2-diamine allows for asymmetric hydrogenation of a wide range of aromatic, heteroaromatic, and olefinic ketones to the corresponding chiral alcohols with high enantiomeric excess [Eq. (1)]. R_{sp^2} = aryl, heteroaryl, alkenyl; R_{sp^3} = alkyl; Ar = 3,5- $(\text{CH}_3)_2\text{C}_6\text{H}_3$.



Angew. Chem. **2001**, *113*, 41–75

R. Noyori,* T. Ohkuma 40–73

Asymmetric Catalysis by Architectural and Functional Molecular Engineering: Practical Chemo- and Stereoselective Hydrogenation of Ketones

Keywords: asymmetric hydrogenation • carbonyl hydrogenation • P ligands • ruthenium • synthetic methods

Mimicking nature: The encapsulation of an active site within a protein shell is a well-known structural motif in enzymology. During the last decade considerable advances have been made in using the unique architecture of a dendrimer to shield photo-, electro-, or catalytically active core moieties (see schematic representation). This area of research has led to many new discoveries spanning the design of biological mimics to the construction of optoelectronic devices.

Angew. Chem. **2001**, *113*, 76–94



S. Hecht, J. M. J. Fréchet* 74–91

Dendritic Encapsulation of Function: Applying Nature's Site Isolation Principle from Biomimetics to Materials Science

Keywords: dendrimers • materials science • molecular devices • structure–property relationships



Since their discovery nearly 20 years ago TADDOLs and their derivatives have revealed themselves to be true chiral auxiliary systems. Compounds of this type are accessible from tartaric acid with an almost unlimited degree of structural variety. They serve not only as homogeneous and solid phase bound chiral reagents and ligands for stoichiometric and catalytic applications, but also assist in creating cholesteric phases and host lattices capable of distinguishing between enantiomeric inclusions or facilitating enantioselective solid-phase reactions. The availability of over 120 crystal structures (see the overlays in the picture) makes it possible to discuss mechanistic models for courses of the various reactions.



Angew. Chem. **2001**, *113*, 96–142

D. Seebach,* A. K. Beck,
A. Heckel 92–138

TADDOLs, Their Derivatives, and
TADDOL Analogues: Versatile
Chiral Auxiliaries

Keywords: asymmetric catalysis •
asymmetric synthesis • enantiomer
separation • TADDOLs

ESSAY



The evaluation of the publications in *Angewandte Chemie* as well as the journal as a whole, in terms of the numbers of citations in the Science Citation Index (SCI) and the Journal Impact Factor (JIF), are studied with regard to errors resulting from the publication of two editions of the journal.

Angew. Chem. **2001**, *113*, 143–148

W. Marx* 139–143

Angewandte Chemie in Light of the
Science Citation Index

Keywords: impact factor • literature
searches • science citation index

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.com>

Scandium Carbide Endohedral Metallofullerenes (Sc_2C_2)@ C_{84}

C.-R. Wang, T. Kai,
T. Tomiyama, T. Yoshida,
Y. Kobayashi, E. Nishibori,
M. Takata, M. Sakata,
H. Shinohara*



Towards the Development of Antitumor Vaccines: A Synthetic Conjugate of a Tumor-Associated MUC1 Glycopeptide Antigen with the Tetanus Toxin Epitope

S. Keil, C. Claus, W. Dippold,
H. Kunz*

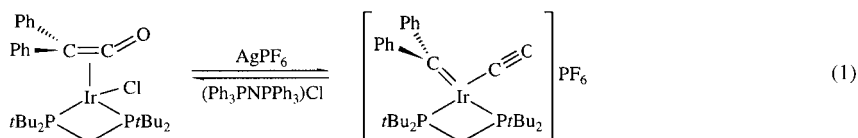


Synthesis and Structure of a $\text{Ga}_{84}\text{R}_{20}^{4-}$ Cluster. A link between Metalloid Clusters and Fullerenes?

A. Schnepf and H. Schnöckel*

HIGHLIGHTS

At a cationic ketene iridium(II) complex a fundamentally important reaction for organometallic chemistry, namely the metal-assisted reversible cleavage of a C–C double bond [Eq. (1)], has been illustrated for the first time. This study will probably initiate a reinvestigation of the elementary steps of the Fischer–Tropsch synthesis with the aim to find more appropriate catalysts for the selective generation of oxygen-containing products.



Angew. Chem. **2001**, *113*, 149–150

H. Werner,* E. Bleuel 145–147

Metal-Assisted Cleavage of a C–C Double Bond: Simple and Reversible

Keywords: carbene complexes • iridium • isomerization • ketene complexes • rhodium

A danger to cryptography is not yet present but theoretical concepts of quantum-information processing can be realized experimentally using the methods of NMR spectroscopy and these thereby usher in the quantum computer. The design and synthesis of compounds suitable to form the molecular basis of larger NMR quantum computers is an interesting, but far from trivial, challenge.

Angew. Chem. **2001**, *113*, 151–153

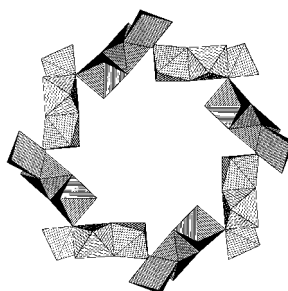
S. J. Glaser* 147–149

NMR Quantum Computing

Keywords: NMR spectroscopy • quantum computer • scalar coupling • through-bond interactions

COMMUNICATIONS

The highest nuclearity cyclic structure for the 3d metals is the Ni₂₄ cage reported. It can be described as an octamer of trinuclear units (shown schematically), held together by metal–ligand bonds and a large number of hydrogen bonds.



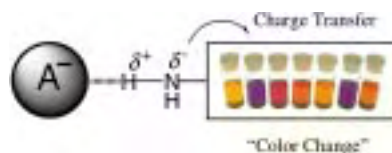
Angew. Chem. **2001**, *113*, 155–158

A. L. Dearden, S. Parsons, R. E. P. Winpenny* 151–154

Synthesis, Structure, and Preliminary Magnetic Studies of a Ni₂₄ Wheel

Keywords: hydrogen bonds • magnetic properties • nickel • N ligands • O ligands

 **No elaborate syntheses** are required to generate colorimetric anion sensors. Rather, many commercially available chromophores (dyes) with built-in hydrogen bond donor sites have been found to act as “off-the-shelf” anion indicators (see scheme). These species allow for the so-called naked eye detection of fluoride, chloride, and phosphate anions under a range of conditions.



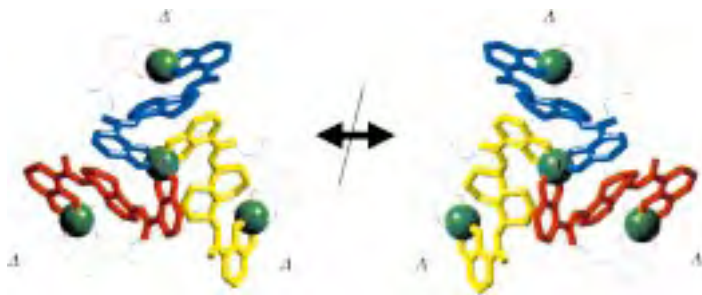
Angew. Chem. **2001**, *113*, 158–161

H. Miyaji, J. L. Sessler* 154–157

Off-the-Shelf Colorimetric Anion Sensors

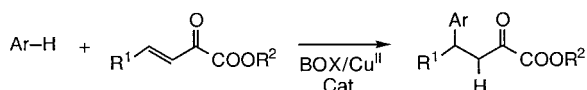
Keywords: anions • charge transfer • hydrogen bonds • indicators • sensors

Enough mechanical stiffness that the metal centers can no longer racemize is provided by the connection of four labile metal centers (Al^{III} , Ga^{III} , In^{III} , Fe^{III}) and six achiral bis-catecholate ligands in a rigid tetrahedral assembly (see picture). The resolution and unprecedented kinetic stability of such a chiral supramolecular assembly is reported here for the first time.



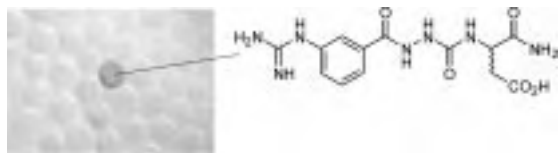
Angew. Chem. **2001**, *113*, 161–164

Useful catalytic BOXes: Chiral bisoxazoline (BOX)/Lewis acid complexes can catalyze highly enantioselective Friedel–Crafts alkylation reactions. The new reaction (see scheme) is successful with both aromatic and heteroaromatic compounds and with a wide range of β,γ -unsaturated α -ketoesters (R^1 = alkyl, aryl, or a protected alcohol). Products are formed with up to >99% *ee*.



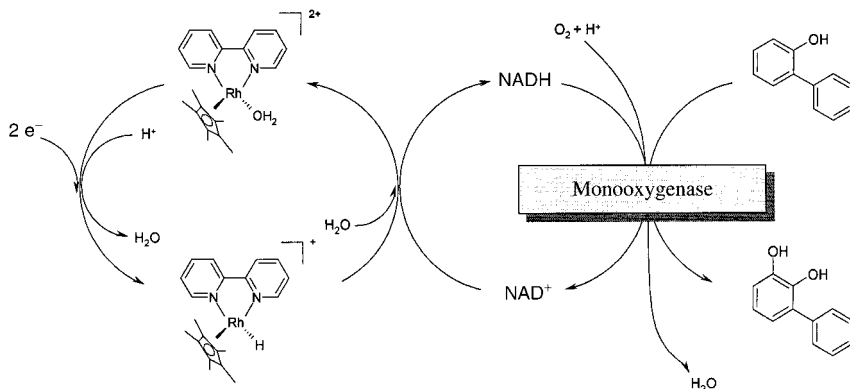
Angew. Chem. **2001**, *113*, 164–167

Libraries of low molecular weight aza-RGD mimetics were synthesized according to the split method and evaluated by on-bead screening with a soluble integrin receptor. No coding was required because the biologically active mimetics could be identified using MS^n after photochemical cleavage from the stained beads (see picture). New $\alpha_v\beta_3$ antagonists were found by this approach.



Angew. Chem. **2001**, *113*, 169–173

In oxygen-containing media the electrochemical regeneration of NADH is easier than expected, such that the regeneration procedure can even be applied to NAD(P)H-dependent monooxygenases (see scheme).



Angew. Chem. **2001**, *113*, 190–193

A. J. Terpin, M. Ziegler, D. W. Johnson, K. N. Raymond* 157–160

Resolution and Kinetic Stability of a Chiral Supramolecular Assembly Made of Labile Components

Keywords: chiral resolution • cluster compounds • host–guest chemistry • kinetic stability • supramolecular chemistry

K. B. Jensen, J. Thorhauge, R. G. Hazell, K. A. Jørgensen* 160–163

Catalytic Asymmetric Friedel–Crafts Alkylation of β,γ -Unsaturated α -Ketoesters: Enantioselective Addition of Aromatic C–H Bonds to Alkenes

Keywords: aromatic substitution • asymmetric catalysis • Friedel–Crafts alkylations • Lewis acids • synthetic methods

C. Gibson, G. A. G. Sulyok, D. Hahn, S. L. Goodman, G. Hölzemann, H. Kessler* 165–169

Nonpeptidic $\alpha_v\beta_3$ Integrin Antagonist Libraries: On-Bead Screening and Mass Spectrometric Identification without Tagging

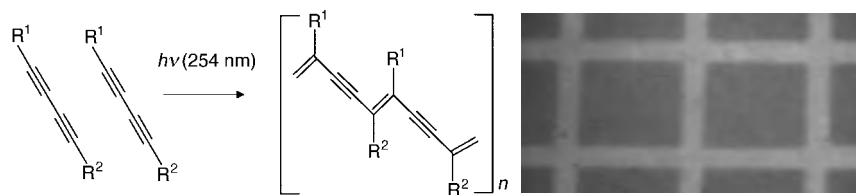
Keywords: combinatorial chemistry • drug research • Integrins • mass spectrometry • peptide mimetics

F. Hollmann, A. Schmid,* E. Steckhan† 169–171

The First Synthetic Application of a Monooxygenase Employing Indirect Electrochemical NADH Regeneration

Keywords: coenzymes • electrochemistry • enzyme catalysis • hydroxylation • oxygenations

Micropatterned lipid bilayers have been created on solid supports by using lithographic polymerization of a diacetylene lipid (see picture). The domains of polymerized (light) serve, after removal of the monomers, as a two-dimensional master structure for the incorporation of biologically relevant lipid bilayer membranes.



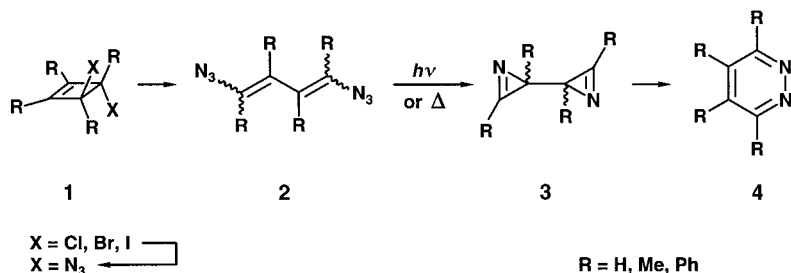
Angew. Chem. **2001**, *113*, 184–186

K. Morigaki,* T. Baumgart,
A. Offenhäusser, W. Knoll 172–174

Patterning Solid-Supported Lipid Bilayer
Membranes by Lithographic
Polymerization of a Diacetylene Lipid

Keywords: imprinting • lipids •
membranes • microstructuring •
polymerization

Highly strained and highly explosive: The highly strained heterocycles **3** are generated by thermolysis or photolysis of the azides **2** which resulted from ring cleavage of cyclobutenes **1**. Even at -25°C , the aromatization **3**→**4** occurs. On photochemical or silver-salt induced reactions, **3** can also be transformed into pyrimidines.



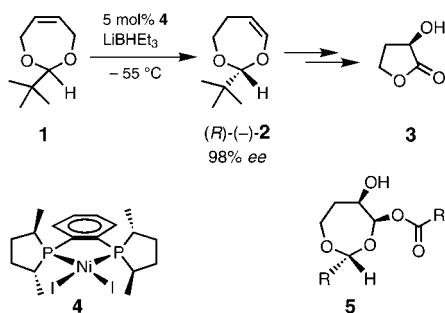
Angew. Chem. **2001**, *113*, 173–176

K. Banert,* F. Köhler 174–177

Synthesis of 1,4-Diazidobuta-1,3-dienes
by Electrocyclic Ring Opening:
Precursors for Bi-2*H*-azirin-2-yls and
Their Valence Isomerization to
Diazabenzenes

Keywords: azides • electrocyclic
reactions • nitrogen heterocycles •
photochemistry • valence isomerization

A breakthrough in the asymmetric isomerization of 4,7-dihydro-1,3-dioxepins **1** was achieved by using DuPHOS-modified dihalogenonickel complexes such as **4** as catalyst precursors. The absolute configurations of the isomerization products were determined by transforming **2** into 2-hydroxy- γ -butyrolactone **3** and 1,2,4-butanetriol through a new oxidation-ring contraction sequence. The relative configuration of the oxidation product **5** was established by crystal structure analysis.



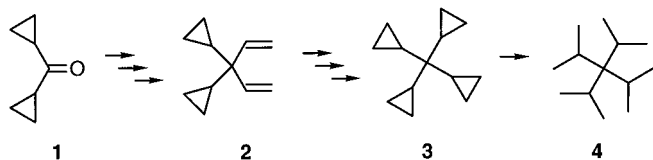
Angew. Chem. **2001**, *113*, 176–178

H. Frauenrath,* D. Brethauer, S. Reim,
M. Maurer, G. Raabe 177–179

Highly Enantioselective Isomerization of
4,7-Dihydro-1,3-dioxepins Catalyzed by
Me-DuPHOS-Modified
Dihalogenonickel Complexes and
Determination of the Absolute
Configuration of the Isomerization
Products

Keywords: asymmetric catalysis •
heterocycles • isomerization • nickel •
ring contraction

Surprising symmetry, surprising synthesis: Dicyclopropyldiethenylmethane (**2**), prepared from dicyclopropylketone (**1**) in several steps, was successfully cyclopropanated with a large excess of diazomethane in the presence of palladium(II) acetate yielding the structurally interesting tetracyclopropylmethane (**3**; 92% yield). Upon catalytic hydrogenation, **3** was quantitatively converted into tetraisopropylmethane (**4**). X-ray structure analysis established S_4 symmetry for **3** and D_{2d} symmetry for **4**, in excellent agreement with the B3LYP/6-31 + G** computed structures.



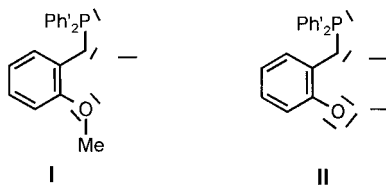
Angew. Chem. **2001**, *113*, 179–182

S. I. Kozhushkov, R. R. Kostikov,
A. P. Molchanov, R. Boese,
J. Benet-Buchholz, P. R. Schreiner,
C. Rinderspacher, I. Ghiviriga,
A. de Meijere* 180–183

Tetracyclopropylmethane: A Unique
Hydrocarbon with S_4 Symmetry

Keywords: ab initio calculations •
alkenes • cyclopropanation •
hydrogenations • small ring systems

Hard and soft centers: the donors O (hard), P and C (soft) are together in the multidentate, oxygen-substituted, anionic phosphanes **I** and **II**, which are particularly suitable for the synthesis of novel calcium organyls. With these mono- and dianionic ligands calcium organyl compounds, without cyclopentadiene ligands, could be prepared and structurally characterized: a sodium trialkyl calcate(II) and the first calcium organyl compound with a heterocubane structure. Ph' = *p*-tolyl.



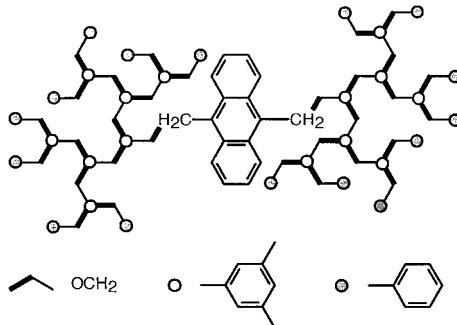
Angew. Chem. **2001**, *113*, 187–190

V. Knapp, G. Müller* 183–186

Cyclopentadienyl-Free Calcium Alkyls
with Heteroelement-Substituted Anionic
Phosphane Ligands: Synthesis and
Structure of a Trialkyl Calcate(II) and of
an Organocalcium Heterocubane

Keywords: alkaline earth metals •
ate complexes • calcium • cubane

A remarkable antenna effect observed in dendrimers with an anthracene core and dendrons of the Fréchet type (see picture) results in strongly increased fluorescence quantum yields relative to that of anthracene. The UV-induced $[4\pi+4\pi]$ cycloaddition, in which the anthracene core reacts with a benzene ring of the dendrons, leads to novel photodimers.



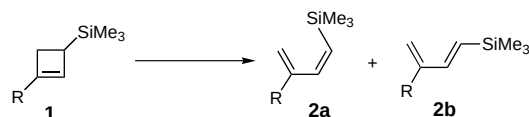
Angew. Chem. **2001**, *113*, 193–195

D. Cao, H. Meier* 186–188

The Unusual Photochemistry of
Dendrimers with an Anthracene Core

Keywords: cycloadditions • dendrimers •
energy transfer • photodimerization

A preference for inward over outward rotation is found for the thermal conrotatory ring-opening reaction of 1-cyclobutene **1**, to produce 1,3-butadiene **2**, when a silyl substituent is located at the 3-position. This preference exists in spite of the bulkiness of the substituent.



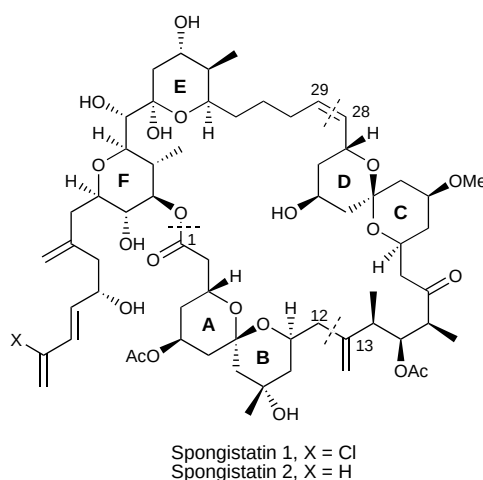
Angew. Chem. **2001**, *113*, 182–184

M. Murakami,* Y. Miyamoto,
Y. Ito* 189–190

A Silyl Substituent Can Dictate a
Concerted Electrocyclic Pathway: Inward
Torquoselectivity in the Ring Opening of
3-Silyl-1-cyclobutene

Keywords: density functional calculations
• electrocyclic reactions • hyper-
conjugation • silicon • substituent
effects

An advanced ABCD fragment (see picture) constructed on the way to the total synthesis of the potent antitumor agent (+)-spongistatin 2 has also been used in a formal total synthesis of (+)-spongistatin 1. In both cases the critical step was an acid-mediated epimerization in the presence of Ca^{2+} ions to stabilize the axial–equatorial CD spiroketal.



A. B. Smith III,* V. A. Doughty, Q. Lin, L. Zhuang, M. D. McBriar, A. M. Boldi, W. H. Moser, N. Murase, K. Nakayama, M. Sobukawa 191–195

The Spongistatins: Architecturally Complex Natural Products—Part One: A Formal Synthesis of (+)-Spongistatin 1 by Construction of an Advanced ABCD Fragment

A. B. Smith III,* Q. Lin, V. A. Doughty, L. Zhuang, M. D. McBriar, J. K. Kerns, C. S. Brook, N. Murase, K. Nakayama 196–199

The Spongistatins: Architecturally Complex Natural Products—Part Two: Synthesis of the C(29–51) Subunit, Fragment Assembly, and Final Elaboration to (+)-Spongistatin 2

Keywords: antitumor agents • macrocycles • natural products • total synthesis

Angew. Chem. **2001**, *113*, 197–201

Angew. Chem. **2001**, *113*, 202–205

A closed spherical structure which can self-maintain or grow/reproduce depending upon the chemical parameter setting would be a simple chemical model of the homeostatic cell. One such model is presented here. It is based on oleic acid/oleate vesicles which host two competitive reactions which take place within the boundary of the bilayer, that is, one reaction which produces more vesicles and one which destroys them.

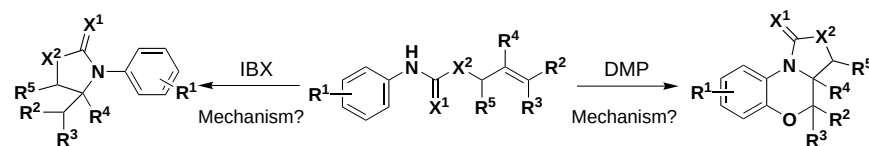
H. H. Zepik, E. Blöchliger, P. L. Luisi* 199–202

A Chemical Model of Homeostasis

Keywords: biomimetic synthesis • homeostasis • liposomes • nanostructures • supramolecular chemistry

Angew. Chem. **2001**, *113*, 205–208

The intriguing mechanisms by which *o*-iodoxybenzoic acid (IBX) and Dess–Martin periodinane (DMP) transform anilides to heterocyclic systems (see scheme) have been extensively studied and elucidated, which has led to the design of further synthetic technologies.



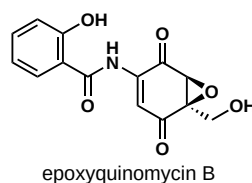
K. C. Nicolaou,* P. S. Baran, R. Kranich, Y.-L. Zhong, K. Sugita, N. Zou 202–206

Mechanistic Studies of Periodinane-Mediated Reactions of Anilides and Related Systems

Keywords: anilides • heterocycles • iodine reagents • oxidations • reaction mechanisms

Angew. Chem. **2001**, *113*, 208–212

A mechanistically inspired tandem Dess–Martin periodinane (DMP) induced oxidation sequence converts anilides into *N*-substituted *p*-quinones or *o*-azaquinones depending on the aromatic nucleus substitution. The application of this technology resulted in an expedient total synthesis of the potent anti-arthritic agent epoxyquinomycin B (see picture).



K. C. Nicolaou,* K. Sugita, P. S. Baran, Y.-L. Zhong 207–210

New Synthetic Technology for the Construction of N-Containing Quinones and Derivatives Thereof: Total Synthesis of Epoxyquinomycin B

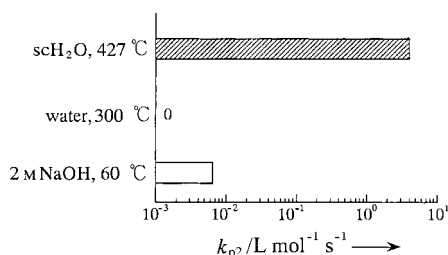
Keywords: iodine reagents • natural products • oxidations • quinones • total synthesis

Angew. Chem. **2001**, *113*, 213–216

Catalyst and reaction medium in

one: that is the dual role of supercritical water (scH₂O) in the disproportionation of benzaldehyde. In the near-critical region the reaction rates (k_{p2}) are significantly greater than those found in water and aqueous NaOH (see picture, values for scH₂O and water are at 25 MPa), also unequivocal chemical evidence for the participation of the OH⁻ ion, not the OH[•] radical, is obtained.

Angew. Chem. **2001**, *113*, 216–219

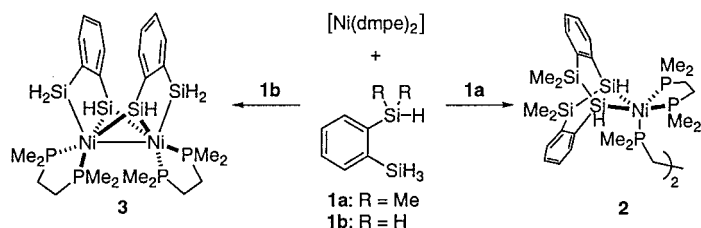


Y. Ikushima,* K. Hatakeda, O. Sato, T. Yokoyama, M. Arai 210–213

Structure and Base Catalysis of Supercritical Water in the Noncatalytic Benzaldehyde Disproportionation Using Water at High Temperatures and Pressures

Keywords: aldehydes • disproportionation reactions • IR spectroscopy • reaction mechanisms • supercritical fluids

An eight-membered cyclic dimer of the hydrosilane **1a** is produced through dehydrogenative Si–Si bond formation during the reaction of **1a** with a nickel complex to give **2**. A possible intermediate in this dehydrocoupling reaction is the dinuclear silyl(μ -silylene)nickel(III) complex **3**, which could be isolated from the reaction of the analogous hydrosilane **1b** with [Ni(dmpe)₂]. dmpe = 1,2-bis(dimethylphosphanyl)ethane.



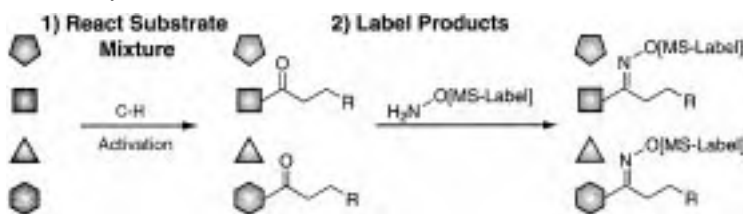
Angew. Chem. **2001**, *113*, 219–222

S. Shimada, M. L. N. Rao, T. Hayashi, M. Tanaka * 213–216

Isolation of Dinuclear (μ -Silylene)-(silyl)nickel Complexes and Si–Si Bond Formation on a Dinuclear Nickel Framework

Keywords: dimerizations • nickel • silicon

The functional groups and heterocyclic classes known to be compatible with a directed C–H activation with [Ru₃(CO)₁₂] has been expanded through development of a new substrate screening strategy. Following C–H activation, a library of products is MS-labeled and rapidly evaluated by positive ion electrospray ionization mass spectrometry (see scheme) to directly identify successful products and their yields.



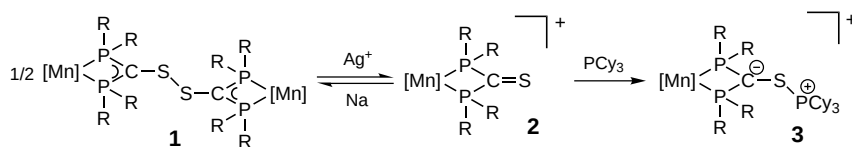
Angew. Chem. **2001**, *113*, 222–225

J. W. Szewczyk, R. L. Zuckerman, R. G. Bergman,* J. A. Ellman * 216–219

A Mass Spectrometric Labeling Strategy for High-Throughput Reaction Evaluation and Optimization: Exploring C–H Activation

Keywords: C–H activation • combinatorial chemistry • high-throughput screening • mass spectrometry

An isolated reaction intermediate in the desulfurization of thiones promoted by phosphanes is provided by the ylide derivative **3**, which is obtained by thiophilic addition of PCy₃ to **2**. Complex **2** is formed from the disulfide-containing dimetallic complex **1** by scission of the S–S bond. [Mn] = Mn(CO)₄⁺, R = Ph.



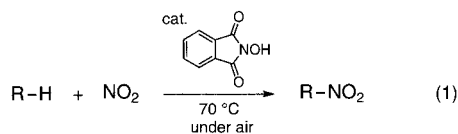
Angew. Chem. **2001**, *113*, 226–228

J. Ruiz,* M. Ceroni, O. V. Quinzani, V. Riera, O. E. Piro 220–222

Reversible S–S Bond Breaking and Bond Formation in Disulfide-Containing Dinuclear Complexes of Mn^I

Keywords: manganese • phosphanes • sulfur • ylides

Higher alkanes such as cyclohexane, cyclooctane, and adamantane undergo nitration with NO_2 in the presence of a catalytic amount of *N*-hydroxyphthalimide to form the corresponding nitroalkanes [Eq. (1)]. Furthermore, the nitration is conducted under air, and NO generated in the course of the reaction can be reoxidized by O_2 to NO_2 , and thus reused in the nitration.



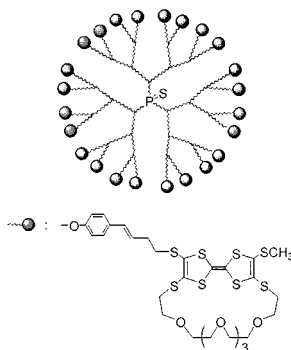
Angew. Chem. **2001**, *113*, 228–230

S. Sakaguchi, Y. Nishiwaki, T. Kitamura, Y. Ishii* 222–224

Efficient Catalytic Alkane Nitration with NO_2 under Air Assisted by *N*-Hydroxyphthalimide

Keywords: catalysts • hydrocarbons • nitrations • nitrogen oxides • radicals

Electrodeposition of dendrimers containing redox-active tetrathiafulvalene units and coordinating crown ether moieties provides a novel strategy for producing modified electrodes that respond to the presence of a particular metal cation. Application of the third-generation dendrimer (see schematic diagram) to platinum gave an electrode whose first oxidation potential is a function of Ba^{2+} concentration in the range $(1-8) \times 10^{-4}\text{M}$.



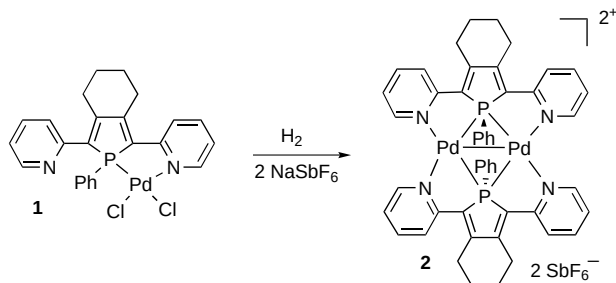
Angew. Chem. **2001**, *113*, 230–233

F. Le Derf, E. Levillain, G. Trippé, A. Gorgues, M. Sallé,* R.-M. Sebastián, A.-M. Caminade, J.-P. Majoral* 224–227

Immobilization of Redox-Active Ligands on an Electrode: The Dendrimer Route

Keywords: dendrimers • electrochemistry • immobilizations • O ligands • sensors

A simple reduction of the Pd^{II} complex **1** affords the Pd^{I} dimer **2**, featuring a μ_2 symmetrically bridging phosphole unit, and thus a novel coordination mode for a tertiary phosphane. Complex **2** appears to be very stable towards additional ligands such as CO and PPh_3 , and the structural data are in accordance with calculations, which reveal that the Pd–Pd and Pd–P bonding is highly delocalized.



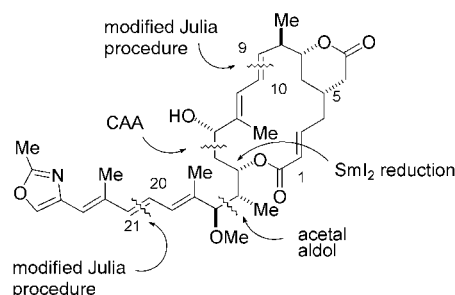
Angew. Chem. **2001**, *113*, 234–237

M. Sauthier, B. Le Guennic, V. Deborde, L. Toupet, J.-F. Halet,* R. Réau* 228–231

A Rare Phosphane Coordination Mode: A Symmetrically μ_2 -Bridging Phosphole in a Dinuclear Palladium(I) Complex

Keywords: coordination modes • density functional calculations • palladium • phosphorus heterocycles • tridentate ligands

Catalytic asymmetric allylation (CAA) using tributyl-(2-ethylallyl)-stannane as a methyl ethyl ketone equivalent plays a key role in this synthesis of rhizoxin D. A subsequent substrate-directed acetal aldol reaction, fragment assembly by a modified Julia procedure, and directed electron transfer reduction are used to complete the synthesis (see scheme).



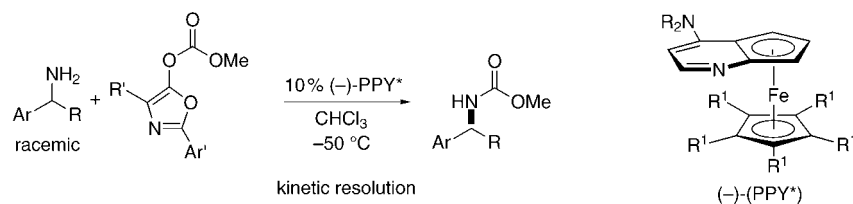
Angew. Chem. **2001**, *113*, 237–240

G. E. Keck,* C. A. Wager, T. T. Wager, K. A. Savin, J. A. Covell, M. D. McLaws, D. Krishnamurthy, V. J. Cee ... 231–234

Asymmetric Total Synthesis of Rhizoxin D

Keywords: allylation • antitumor agents • asymmetric catalysis • samarium • total synthesis

A planar-chiral DMAP derivative, in conjunction with a readily available, novel acylating agent, effects the kinetic resolution of α -arylamines, a biologically important class of compounds, with a selectivity factor of up to 27 (see scheme). The catalyst used, PPY*, is the first effective nonenzymatic catalyst for the enantioselective acylation of amines. DMAP = 4-dimethylaminopyridine.



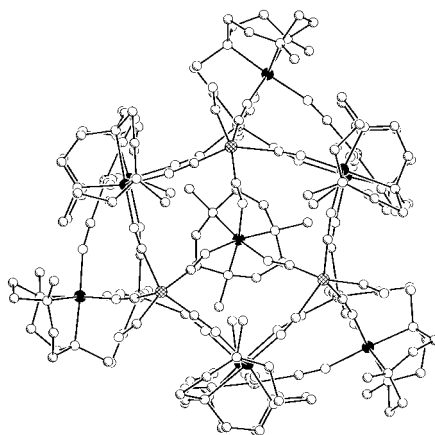
Angew. Chem. **2001**, *113*, 240–242

S. Arai, S. Bellemin-Laponnaz,
G. C. Fu* 234–236

Kinetic Resolution of Amines by a
Nonenzymatic Acylation Catalyst

Keywords: acylations • amines •
catalysts • chirality • kinetic resolution

Unprecedented geometries are displayed by two chromium–nickel–cyanide clusters that have recently been synthesized. $[(\text{Me}_3\text{tacn})_8\text{Cr}_8\text{Ni}_5(\text{CN})_{24}]^{10+}$ exhibits a face-centered cubic structure with a Ni^{2+} ion missing from one face. This species reacts with $[\text{Ni}(\text{CN})_4]^{2-}$ to yield $[(\text{Me}_3\text{tacn})_{10}\text{Cr}_{10}\text{Ni}_9(\text{CN})_{42}]^{6+}$ (shown in the picture), incorporating square-pyramidal and trigonal-bipyramidal $[\text{Ni}(\text{CN})_5]^{3-}$ and square-planar $[\text{Ni}(\text{CN})_4]^{2-}$ units in the largest metal–cyanide cluster reported to date. $\text{Me}_3\text{tacn} = N,N',N''$ -trimethyl-1,4,7-triazacyclononane.



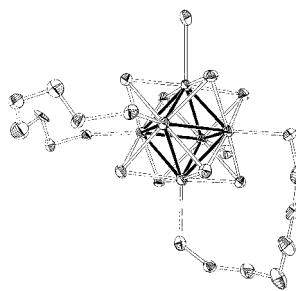
Angew. Chem. **2001**, *113*, 242–245

J. J. Sokol, M. P. Shores,
J. R. Long* 236–239

High-Nuclearity Chromium–Nickel–
Cyanide Clusters: An Open
 $\text{Cr}_8\text{Ni}_5(\text{CN})_{24}$ Cage and a C_3 -Symmetric
 $\text{Cr}_{10}\text{Ni}_9(\text{CN})_{42}$ Cluster Incorporating
Three Forms of Cyanonickelate

Keywords: cage compounds • cluster
compounds • coordination chemistry •
cyanides • magnetic properties

Substitution of the iodide ions in the octahedral hexarhenium cluster $[\text{Re}_6\text{Se}_8\text{I}_6]^{3-}$ by the diphosphane $\text{Ph}_2\text{P}(\text{CH}_2)_n\text{PPh}_2$ generates “bridge–chelate” complexes when $n=6$ (dpph) with general formula $[\text{Re}_6\text{Se}_8\text{I}_{6-2m}(\mu\text{-dpph})_m]^{2m-4}$ ($m=1-3$; the picture shows the *trans* isomer for $m=2$), whereas for $n=5$ only a monodentate binding mode of the diphosphane is found. Stepwise substitution by dpph strongly affects the redox processes, while the photophysical properties associated with the $[\text{Re}_6\text{Se}_8]^{2+}$ core change only moderately.



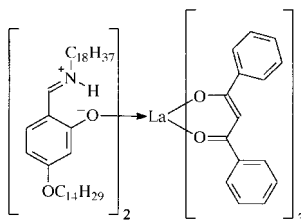
Angew. Chem. **2001**, *113*, 245–248

Z.-N. Chen, T. Yoshimura, M. Abe,
Y. Sasaki,* S. Ishizaka, H.-B. Kim,
N. Kitamura 239–242

Chelate Formation around a
Hexarhenium Cluster Core by the
Diphosphane Ligand $\text{Ph}_2\text{P}(\text{CH}_2)_6\text{PPh}_2$

Keywords: cluster compounds •
coordination modes • luminescence •
P ligands • rhenium

A monotropic smectic A phase is exhibited by adducts of tris(β -diketonato)lanthanide(III) complexes with a non-mesomorphic salicylalimine Schiff base as Lewis base. Only four terminal alkyl chains were necessary in the Schiff base to induce mesomorphism in $[\text{La}(\text{dbm})_3]$ (see formula). $\text{Hdbm} = 1,3$ -diphenyl-1,3-propanedione (dibenzoylmethane).



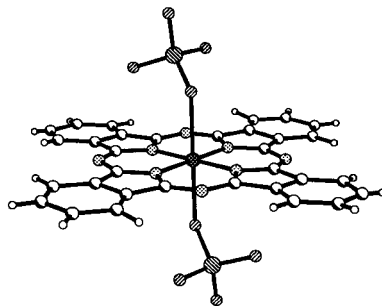
Angew. Chem. **2001**, *113*, 248–250

K. Binnemans,*
K. Lodewyckx 242–244

Coordinatively Unsaturated Metal
Centers as Building Blocks for High
Coordination Number Metallomesogens

Keywords: lanthanides • liquid crystals •
metallomesogens • rare-earth
compounds • supramolecular chemistry

One ring, two oxidations: The first doubly ring-oxidized metal phthalocyanine complex has been synthesized by galvanostatic electrocrystallization. Copper phthalocyanine was oxidized in the presence of perrhenate anions to form the new molecular compounds $[\text{Cu}(\text{pc})(\text{ReO}_4)]$ and $[\text{Cu}(\text{pc})(\text{ReO}_4)_2]$ (structure shown). Single-crystal EPR results show that the oxidation of $[\text{Cu}(\text{pc})(\text{ReO}_4)_2]$ is entirely ring-based.



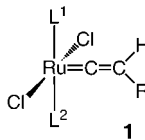
A. S. Gardberg, P. E. Doan,
B. M. Hoffman,* J. A. Ibers* . . . 244–246

Singly and Doubly Oxidized
Phthalocyanine (pc) Rings:
 $[\text{Cu}(\text{pc})(\text{ReO}_4)]$ and $[\text{Cu}(\text{pc})(\text{ReO}_4)_2]$

Keywords: copper • electrocrystallization
• EPR spectroscopy • oxidations •
phthalocyanines

Angew. Chem. **2001**, *113*, 250–252

Ruthenium vinylidenes: metathesis catalysis on the bench? Ruthenium vinylidene compounds **1**, generated in situ from readily available, air-stable precursors, are used to catalyze ring-closing metathesis, ene–yne metathesis, cross-metathesis, and ring-opening metathesis polymerization. Bulky imidazolydene ligands and terminal alkynes were found to be necessary components for achieving high catalytic activity.



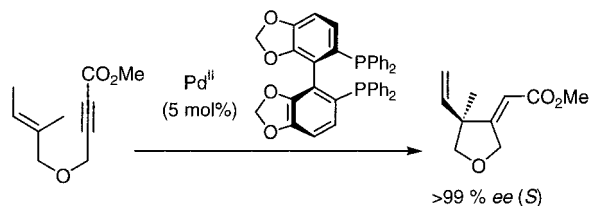
J. Louie, R. H. Grubbs* 247–249

Highly Active Metathesis Catalysts
Generated In Situ from Inexpensive and
Air-Stable Precursors

Keywords: carbenes • homogeneous
catalysis • metathesis • ruthenium •
vinylidene complexes

Angew. Chem. **2001**, *113*, 253–255

 **Enantioenriched five-membered rings** with a quaternary chiral center are prepared with remarkable efficiency by the ene-type carbocyclization of 1,6-enynes catalyzed by chiral palladium complexes (see scheme). Possible mechanisms including neutral (five-coordinate) and cationic (four-coordinate) intermediates have also been proposed.



Angew. Chem. **2001**, *113*, 255–259

M. Hatano, M. Terada,
K. Mikami* 249–253

Highly Enantioselective Palladium-
Catalyzed Ene-Type Cyclization of a
1,6-Enyne

Keywords: asymmetric catalysis •
cyclizations • enynes • palladium

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

* Author to whom correspondence should be addressed



BOOKS

Combinatorial Chemistry	Preface	S. Dahmen, M. Lormann, S. Bräse . . . 255
Organic Synthesis on Solid Phase— Supports, Linkers, Reactions	Florencio Zaragoza Dörwald	M. Lormann, S. Bräse 256
Solid-Phase Synthesis and Combina- torial Technologies	Pierfausto Seneci	S. Dahmen, S. Bräse 256
Combinatorial Chemistry— A Practical Approach	Willi Bannwarth, Eduard Felder	S. Bräse 257
Colour and Optical Properties of Materials	Richard J. D. Tilley	J. J. Wolff 257
Cisplatin	Bernhard Lippert	N. Metzler-Nolte 258
Chemistry of Fireworks	Michael S. Russell	K. Menke 259



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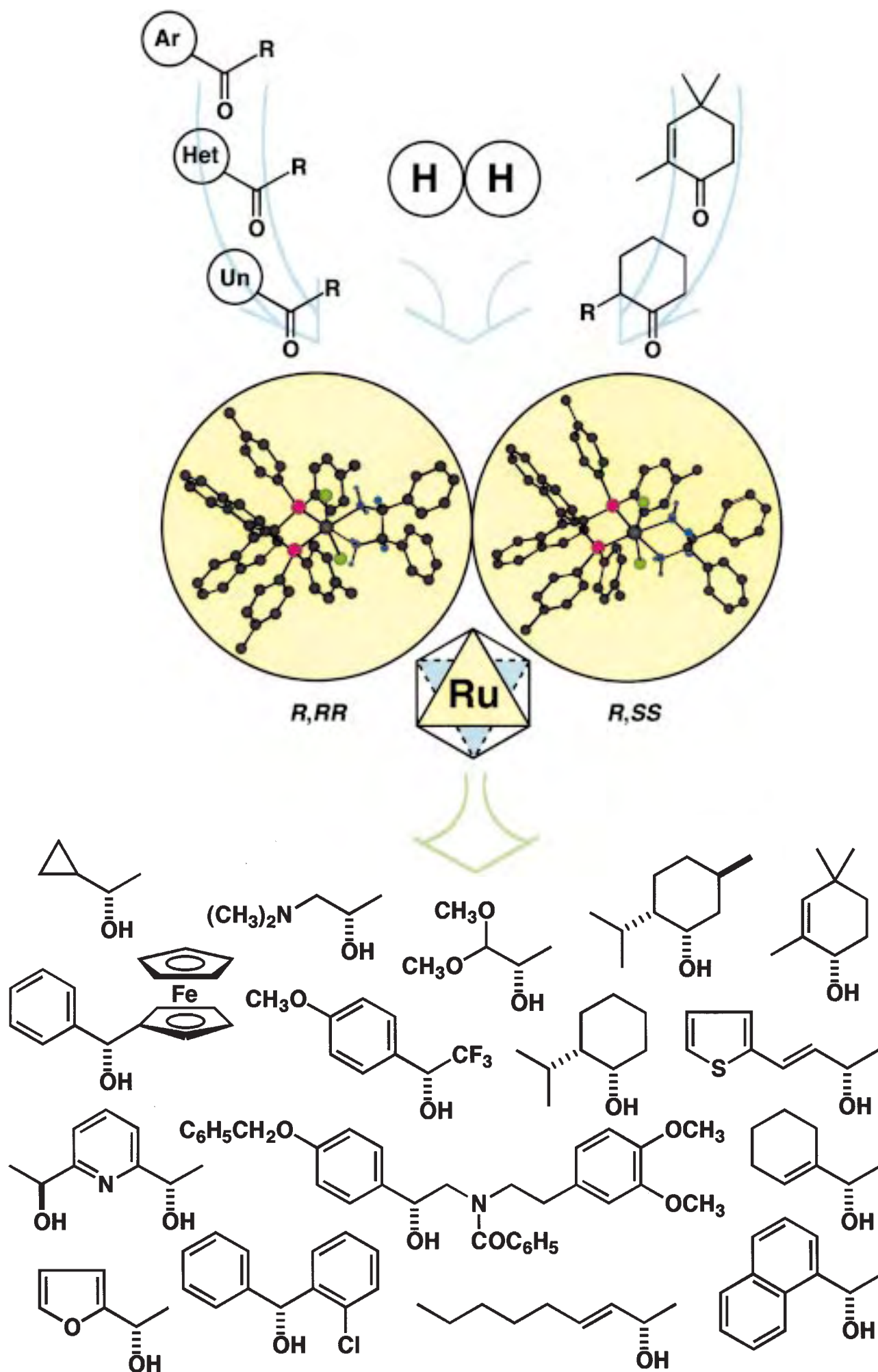
M. Müller 261

SERVICE

• VIPs	9	• Events	A4
• Notice to Authors	21	• Classifieds	A5
• Checklist	31	• Keywords	262
• Contents of <i>Chemistry— A European Journal</i>	35	• Autors	263
• Sources	A1	• Preview	264

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Don't forget all the Tables of Contents
from 1995 onwards may be still found
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Asymmetric Catalysis by Architectural and Functional Molecular Engineering: Practical Chemo- and Stereoselective Hydrogenation of Ketones

Ryoji Noyori* and Takeshi Ohkuma

Hydrogenation is a core technology in chemical synthesis. High rates and selectivities are attainable only by the coordination of structurally well-designed catalysts and suitable reaction conditions. The newly devised $[\text{RuCl}_2\text{-(phosphane)}_2(1,2\text{-diamine})]$ complexes are excellent precatalysts for homogeneous hydrogenation of simple ketones which lack any functionality capable of interacting with the metal center. This catalyst system allows for the preferential reduction of a C=O function over a coexisting C=C linkage in a 2-propanol solution containing an alkaline base. The hydrogenation tolerates many substituents including F, Cl, Br, I, CF_3 , OCH_3 , $\text{OCH}_2\text{C}_6\text{H}_5$, $\text{COOCH}(\text{CH}_3)_2$, NO_2 , NH_2 , and NRCOR as well as various electron-rich and -deficient heterocycles. Fur-

thermore, stereoselectivity is easily controlled by the electronic and steric properties (bulkiness and chirality) of the ligands as well as the reaction conditions. Diastereoselectivities observed in the catalytic hydrogenation of cyclic and acyclic ketones with the standard triphenylphosphane/ethylene-diamine combination compare well with the best conventional hydride reductions. The use of appropriate chiral diphosphanes, particularly BINAP compounds, and chiral diamines results in rapid and productive asymmetric hydrogenation of a range of aromatic and heteroaromatic ketones and gives a consistently high enantioselectivity. Certain amino and alkoxy ketones can be used as substrates. Cyclic and acyclic α,β -unsaturated ketones can be converted into

chiral allyl alcohols of high enantiomeric purity. Hydrogenation of configurationally labile ketones allows for the dynamic kinetic discrimination of diastereomers, epimers, and enantiomers. This new method shows promise in the practical synthesis of a wide variety of chiral alcohols from achiral and chiral ketone substrates. Its versatility is manifested by the asymmetric synthesis of some biologically significant chiral compounds. The high rate and carbonyl selectivity are based on non-classical metal–ligand bifunctional catalysis involving an 18-electron amino ruthenium hydride complex and a 16-electron amido ruthenium species.

Keywords: asymmetric hydrogenation • carbonyl hydrogenation • P ligands • ruthenium • synthetic methods

1. Introduction

Catalysis plays a vital role in chemical synthesis. In particular, efficient molecular organometallic catalysis^[1] provides a logical basis for molecular science and related technologies. Although selectivity, particularly in the control of absolute stereochemistry,^[2, 3] is a major concern in modern organic synthesis, reactivity and productivity are also important in making reactions efficient and practical.^[4, 5]

A useful catalysis must show a high turnover number (TON), defined as mols of product per mol of catalyst, and a high turnover frequency (TOF), defined as TON per h or s. In addition, reactions should be operationally simple, safe, and

environmentally friendly. These important attributes can be obtained only by designing suitable molecular catalysts and reaction conditions through a deep understanding of, or a unique insight into, the catalytic cycle. In fact, to a large extent the discovery of efficient catalytic reactions still relies on serendipity but originates from sound, comprehensive chemical knowledge.

Combinatorial approaches coupled with high-throughput screening techniques obviously facilitate the discovery process^[6] but their powers are still that not evident in the field of molecular catalysis. Most excellent new catalysts are optimized forms of existing catalysts rather than being truly novel. Neither current sophisticated quantum theory nor elaborate force field methods or combinations thereof can yet predict the best catalyst.

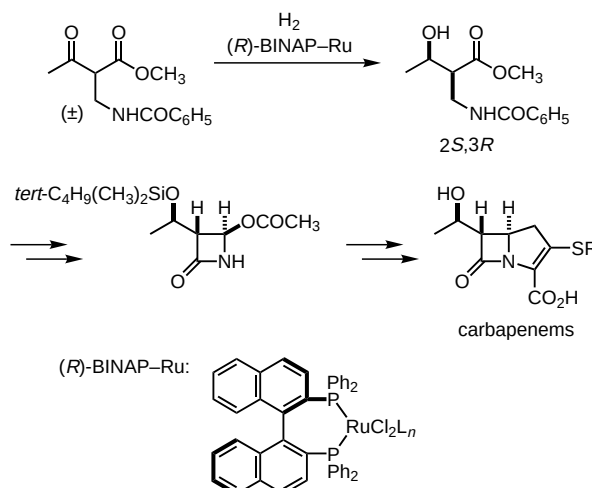
Hydrogen (H_2) is the simplest molecule and its properties are fully understood. Because this clean resource is available in abundance at a very low cost, catalytic hydrogenation is a core technology in both research and industry.^[4, 5, 7, 8] Never-

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theless, the ways to manipulate H_2 chemically have remained limited. During our studies on homogeneous hydrogenation over two decades,^[2, 9–11] our approaches and our choices, particularly chiral multiplication,^[2] have been solely intuitive. Herein we describe the discovery and development of an uncommonly practical homogeneous hydrogenation process. The relative and absolute stereochemistry can be controlled efficiently and flexibly by molecular engineering. Prior to this, no general catalysts that effect selective ketone hydrogenation have existed.^[10–13]

1.1. Research Background

Asymmetric catalysis is having a revolutionary impact on the chemical synthesis of chiral compounds.^[2, 3, 5, 14, 15] Scheme 1 illustrates the situation of our research project on asymmetric hydrogenation in the early 1990s.^[9–11] The BINAP–Ru^{II} complexes^[16] effect highly enantioselective hydrogenation of various β -keto esters to chiral β -hydroxy esters.^[17] By combining this asymmetric reaction with dynamic kinetic resolution,^[18, 19] an important industrial process was realized. Thus, asymmetric hydrogenation of methyl α -(benzamidomethyl)acetoacetate utilizing in situ stereochemical inversion of the configurationally labile substrate leads selectively to the 2*S*,3*R*-configured *erythro* isomer of the four possible stereoisomers.^[20–23] Takasago International Co. commercialized this enantio- and diastereoselective hydrogenation method for the production of a chiral intermediate for the synthesis of carbapenem antibiotics (Scheme 1).^[4d, 5a, 9–11] However, this significant reaction is merely one of the applications of the BINAP–Ru-catalyzed asymmetric hydrogenation of functionalized ketones which are generalized in Scheme 2.^[9–11] The



Scheme 1. Industrial application of BINAP–Ru catalyzed hydrogenation to the asymmetric synthesis of carbapenem antibiotics.

reaction is optimized in alcoholic solvents. In a similar manner, a large range of functionalized olefins can be hydrogenated with a high level of enantioselectivity.^[9, 10, 11c] A wide variety of in situ prepared and preformed BINAP–Ru^{II} complexes can be used for these reactions.^[11, 12i, 22, 24]

Scheme 3 presents our proposed mechanism for the asymmetric reaction of β -keto esters.^[10c] The hydrogenation probably proceeds via a Ru^{II} monohydride **2** formed by the heterolysis of a hydrogen molecule by the ruthenium dichloride **1**. The Ru hydride **2** interacts reversibly with the keto ester to form the chelating complex **3**. Protonation of the keto oxygen changes the geometry of **3** from the σ to the π complex and, at the same time, increases the electrophilicity of the

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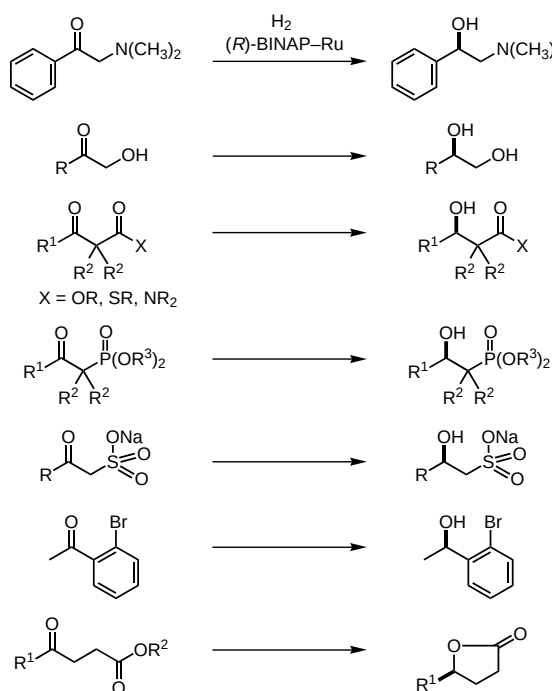


R. Noyori

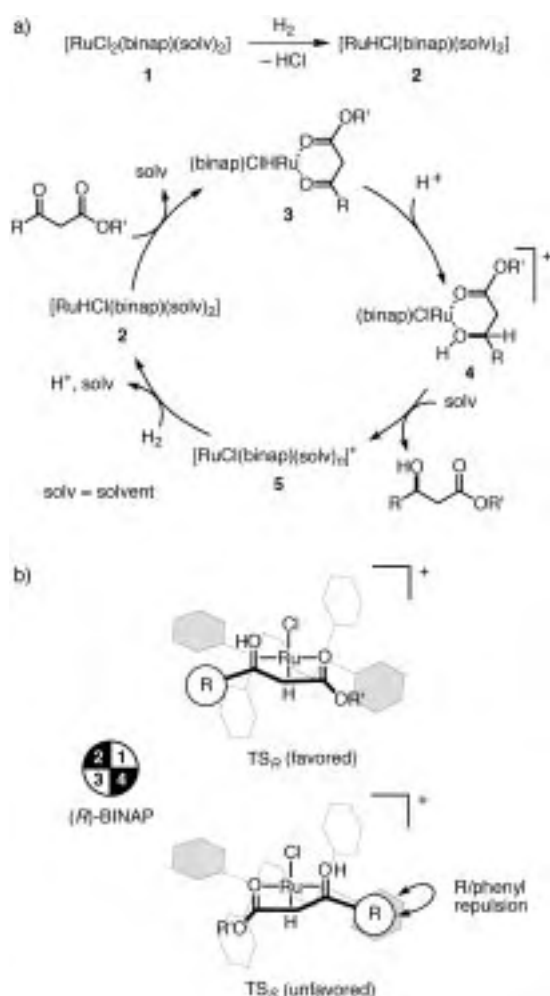


T. Ohkuma

Takeshi Ohkuma, born in Gunma, Japan, in 1962, studied chemistry at Keio University, and completed his M.Sc. under the supervision of the late Professor Gen-ichi Tsuchihashi. He moved to Nagoya University to join the Professor Noyori's research group and worked in the field of molecular catalysis. After obtaining his Ph.D. in 1991, he worked with Professor Paul A. Wender at Stanford University until 1992. In the same year he joined the ERATO Noyori Molecular Catalysis Project. In 1996 he became an Associate Professor at the Department of Chemistry, Nagoya University. His research interests encompass the development of new catalytic reactions with high reactivity and selectivity. He received The Progress Award in Synthetic Organic Chemistry, Japan, in 1997.



Scheme 2. General BINAP–Ru catalyzed asymmetric hydrogenation of functionalized ketones.



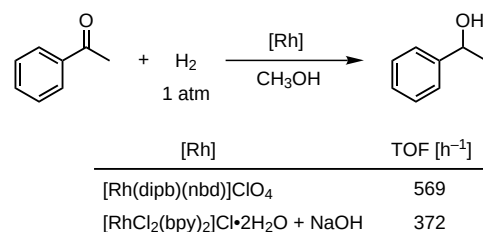
Scheme 3. Mechanism of (*R*)-BINAP–Ru catalyzed hydrogenation of β -keto esters; a) catalytic cycle and b) enantio-determining transition states.

carbonyl carbon, facilitating intramolecular hydride transfer.^[25, 26] The resulting Ru–hydroxy ester complex **4** readily releases the chiral product by the action of solvent molecules. The cationic ruthenium species **5** reacts with hydrogen to revert back to **2**, completing the catalytic cycle. When an (*R*)-BINAP–Ru complex is used, the *R* product is obtained in >99% *ee*. Structures TS_R and TS_S illustrated in Scheme 3b show the diastereomeric transition states that provide a distinct bias for the stereo-determining hydride-transfer step.^[9g, 10c, 18, 26] The C_2 symmetry of (*R*)-BINAP binding to the Ru^{II} center provides a chiral backbone with a fixed λ -oriented seven-membered chelate ring.^[27] In TS_R leading to the *R* product, the chiral template accommodates the keto ester in such a way as to minimize the nonbonded interaction with the equatorial phenyl rings, while diastereomeric TS_S undergoes a significant nonbonded repulsion between the *R* group and the phenyl ring.^[9g, 10c, 18, 26] The presence of an additional substituent at C-2 induces further *erythro/threo* diastereoselection,^[23] enabling the asymmetric synthesis shown in Scheme 1. The coordination of the ester carbonyl oxygen to the ruthenium center not only accelerates the reaction but also makes a highly organized, stereo-differentiating transition state.

Noteworthy is that methyl 3-oxobutyrate is hydrogenated even in aqueous acetone containing $[RuCl_2\{(R)\text{-binap}\}(dmf)_n]$ to give (*R*)-methyl-3-hydroxybutyrate in 97% *ee*.^[28] Acetone, the simplest, unfunctionalized ketone, is almost inert under such reaction conditions. This is a pivotal feature of our earlier BINAP–Ru chemistry.

1.2. Historical Aspects of Ketone Hydrogenation

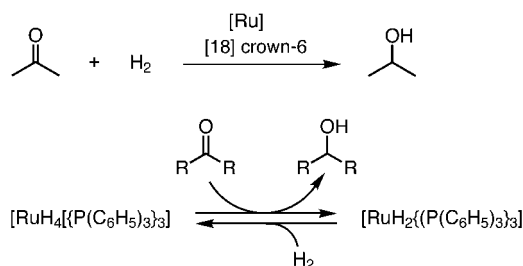
Ketones are the most common unsaturated substrates. In spite of extensive studies, only a limited number of transition metal catalysts were known to exhibit satisfactory activity in hydrogenation of simple ketones that have no functionality close to the carbonyl group.^[7, 8, 11] Schrock and Osborn found that $[RhH_2\{P(C_6H_5)(CH_3)_2\}_2L_2]X$ (L = solvent, X = PF_6 or ClO_4) effectively reduces acetone under 1 atm of H_2 in the presence of a small amount of water.^[29] Tani and Otsuka achieved hydrogenation of ketonic substrates using a cationic rhodium complex with a fully alkylated bidentate diphosphane (Scheme 4).^[30] In these cases, the high basicity of the ligands^[31] increases the electron density of the rhodium center so that the oxidative addition of H_2 might be accelerated.^[30, 32] A bipyridine-based rhodium complex showed high catalytic



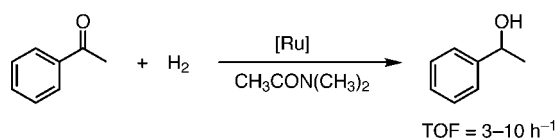
Scheme 4. Hydrogenation of acetophenone catalyzed by rhodium complexes. NBD = norbornadiene, DIPB = 1,4-bis(diisopropylphosphino)butane, bpy = bipyridine.

activity in the presence of methanolic NaOH (Scheme 4),^[33] where the $[\text{Rh}(\text{bpy})_2]^+$ species (bpy = bipyridine) was proposed as a catalyst.^[34] $[\text{Rh}_2\text{Cl}_2(\text{OCOH})_2(\text{bpy})_2]$ ^[35] and a $[\text{RhCl}(\text{C}_6\text{H}_5)_3(\text{cod})]/\text{NaBH}_4$ combined system^[36] (cod = cycloocta-1,5-diene) also effected hydrogenation under basic conditions. Some phosphane–ruthenium complexes were known to hydrogenate simple ketones,^[37, 38] but their activities were normally lower than those of the rhodium complexes. Grey, Pez, and Wallo claimed that $\text{K}_2[\text{Ru}_2\text{H}_4\{\text{P}(\text{C}_6\text{H}_5)_3\}_2\cdot 2\text{O}(\text{CH}_2\text{CH}_2\text{OCH}_3)_2]$, an anionic ruthenium complex, coupled with [18]crown-6 acts as a catalyst in the hydrogenation of acetone in toluene at 7 atm and 85 °C (Scheme 5).^[39] Later Halpern and Linn concluded that the actual active species is neutral $[\text{RuH}_4\{\text{P}(\text{C}_6\text{H}_5)_3\}_3]$ complex.^[40] A trinuclear ruthenium complex, $[\{\text{RuHCl}(\text{dppb})\}_3]$ (dppb = 1,1'-bis(diphenylphosphanyl)butane) as reported by James et al., slowly catalyzes hydrogenation of acetophenone under 1 atm of H_2 at 50 °C in *N,N*-dimethylacetamide (Scheme 5b).^[41] Thus, synthetically versatile catalyst systems remained unknown.

a) $\text{K}_2[\text{Ru}_2\text{H}_4\{\text{P}(\text{C}_6\text{H}_5)_2\}\{\text{P}(\text{C}_6\text{H}_5)_3\}_2\cdot 2\text{O}(\text{CH}_2\text{CH}_2\text{OCH}_3)_2]$

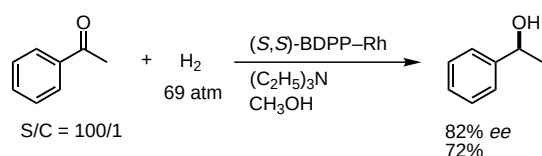


b) $[\{\text{RuHCl}(\text{C}_6\text{H}_5)_2\text{P}(\text{CH}_2)_4\text{P}(\text{C}_6\text{H}_5)_2\}_3]$



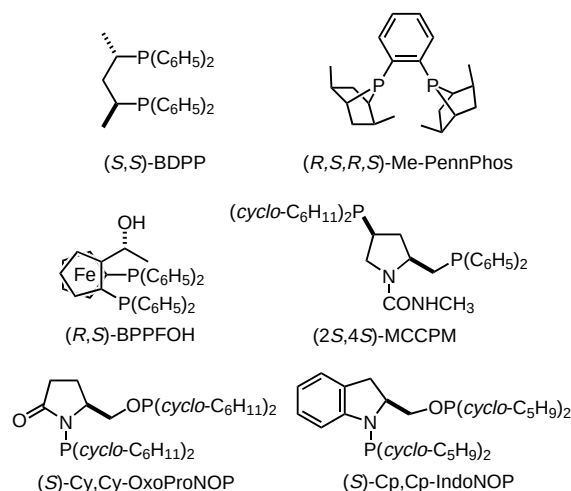
Scheme 5. Ruthenium complexes for the hydrogenation of simple ketones.

Asymmetric hydrogenation of simple achiral ketones was even more difficult.^[11] Although it appears to be simple, in fact, it is a serious challenge for synthetic chemists. In 1985, Markó et al. reported that a BDPP–Rh complex in methanol and triethylamine at a substrate to catalyst ratio (S/C) of 100/1 catalyzes hydrogenation of acetophenone under 69 atm H_2 and 50 °C to afford 1-phenylethanol in 82 % *ee* (Scheme 6).^[42] Based on this observation, various chiral phosphane–rhodium,^[43, 44] –iridium,^[45] and –ruthenium complexes^[46, 47] were



Scheme 6. Asymmetric hydrogenation of acetophenone with a BDPP–Rh catalyst. Conditions: (S,S)-BDPP–Rh = 1/2 $[\text{RhCl}(\text{nbd})]_2 + (\text{S,S})\text{-BDPP}$ (Scheme 7), ketone:Rh:amine = 100:1:5, 50 °C, 24 h.

devised for asymmetric hydrogenation (Scheme 7), however, the number of substrates giving reasonable enantioselectivity was limited and the reactivity and selectivity remained unsatisfactory. Therefore, asymmetric hydroboration^[48–53] and



Scheme 7. Structures of some chiral P ligands that can be employed in hydrogenation catalysts.

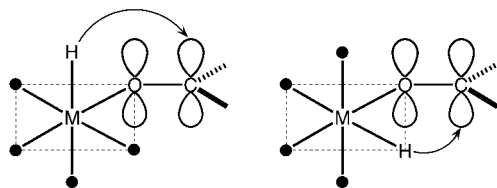
hydrosilylation^[54, 55] as well as transfer hydrogenation^[11b,c, 56–58] using organic hydrogen donors have been utilized as the major tools for catalytic conversion of ketones into chiral secondary alcohols.^[59, 60] Obviously a direct and practical hydrogenation method was needed.

1.3. Early Attempts

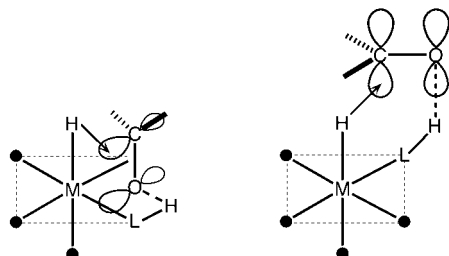
Conventional diphosphane–ruthenium(II) complexes were mostly useless for the hydrogenation of simple ketones. Since the hydrogen molecule is readily activated by ruthenium complexes regardless of the substrate structures (Scheme 2 and 3), the lack of reactivity of simple ketones is merely because of the absence of coordinating heteroatoms near the carbonyl group. A new way to *catalytically* activate the carbonyl group was needed. Despite insufficient mechanistic information about ketone hydrogenation, our initial attempts were directed toward designing new ruthenium catalysts.

Since electrophilic metals tend to form σ complexes rather than π complexes with carbonyl compounds,^[61, 62] the relative locations of the nucleophile and carbonyl carbon are inappropriate for reaction. This may also be the case in catalytic hydrogenation which involves metal hydride species MH. As illustrated in Scheme 8a, the delivery of hydride from the metal center to the carbonyl carbon is difficult for geometric reasons. The requisite interaction between the M–H bond and π face of the C=O group is achieved only through drastic geometric changes of the ground-state σ structures. The ground-state π complexation is achieved only with electropositive transition metals and carbonyl compounds with a low-lying LUMO, which facilitate the metal to substrate backbonding.^[63] Furthermore, the resulting metal alkoxide

a) Difficult pathways



b) Pathways assisted by hydrogen bond



inner-sphere reaction

outer-sphere reaction

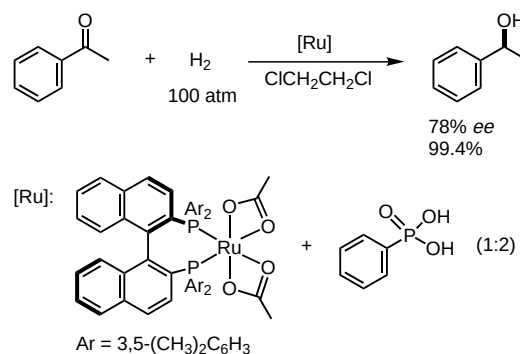
Scheme 8. Hydride transfer from the metal center M to the carbonyl carbon. LH = protic neutral ligand.

intermediate may undergo reverse β -elimination,^[64] unless some subsequent process rapidly cleaves the O–M bond.

Although most textbooks state that reactions between carbonyl compounds and metal alkyls or hydrides occur with a 1:1 C=O:metal stoichiometry, the simple $[\pi 2 + \sigma 2]$ process may be kinetically unfavorable.^[65] Instead, many organometallic reactions are now considered to involve *two* metal centers in the transition states, in which one metal carries a nucleophile and the other interacts with the carbonyl oxygen atom enhancing the nucleophilicity of the carbon atom.^[48, 65–67] Protonation or hydrogen bonding to the carbonyl oxygen atom would also facilitate the π -face attack of a nucleophile on the metal center. In fact, unlike in the reaction of a functionalized ketone (Scheme 2),^[25, 26] addition of strong acids does not assist hydrogenation of acetophenone in the presence of $[\text{RuCl}_2\{(\text{R})\text{-binap}\}(\text{dmf})_n]$, because the bimolecular reaction between a RuH intermediate and the protonated ketone, both present in low concentrations in a catalytic reaction system, is unfavorable. However, if the anionic ligand on the metal center, for example, X in $[\text{RuHX}(\text{binap})(\text{solv})_2]$, is protic, then it might facilitate the hydride delivery with the aid of ligand/substrate hydrogen bonding (Scheme 8b). Furthermore, unlike the pathway involving metal alkoxide intermediates, such a process would produce alcohol products directly without a subsequent reaction.

In this context, we anticipated that the requisite BINAP–Ru complexes could form by ligand-exchange reactions between the BINAP–Ru diacetate complex and hydroxy carboxylic acid, amino acids, phosphoric acid, hydroxy phosphonic acids, etc. Reaction of the BINAP–Ru dichloride and sodium or potassium salts of weak acids would also lead to the corresponding ligand-exchange products under thermodynamic control. Thus, various (pre)catalysts were prepared in situ and tested in the asymmetric hydrogenation of acetophenone. Of more than 200 such experiments the best

results were with a catalyst prepared in situ from $[\text{Ru}(\text{OCOCH}_3)_2\{(\text{R})\text{-xylbinap}\}]$ ^[16] and phenylphosphonic acid in a 1:2 ratio (Scheme 9).^[68] This catalyst system effected hydrogenation of acetophenone with an S/C ratio of 700/1 in 1,2-dichloroethane under 100 atm H_2 at 100 °C for 18 h to afford



Scheme 9. Asymmetric hydrogenation of acetophenone catalyzed by a XylBINAP–Ru diacetate complex aided by phenylphosphonic acid. Conditions: 100 °C, 18 h.

(*S*)-1-phenylethanol in 78% *ee* and in 99.4% yield. The phosphonic acid appeared to activate the chiral diphosphane–ruthenium complex probably by the formation of a RuH–phosphonate complex in which the anionic ligand has an additional OH group which interacts with the carbonyl oxygen. Although this was a positive result, the enantioselectivity was moderate and the reaction was rather slow. Despite the sustained efforts of our able young collaborators for many years, the efficiency did not meet the standards required by modern organic synthesis.^[2, 14, 15]

2. Hydrogenation of Simple Ketones

2.1. Conceptual Turning Point: Metal–Ligand Cooperation in Molecular Functions

Although the early efforts to achieve efficient asymmetric hydrogenation of acetophenone were not fruitful, the failure provided us with the opportunity for a new discovery. We set a more ambitious goal for ourselves, namely replacing a range of metal hydride reductions by catalytic hydrogenation. For over half a century the selective reduction of carbonyl compounds to alcohols has relied heavily on the use of the hydrides of boron, aluminum, and silicon,^[48–55, 59, 60] however, for scientific, technical, and economic reasons, particularly for large-scale reactions, homogeneous hydrogenation is obviously more desirable than stoichiometric hydride reduction. Heterogeneous hydrogenation^[8, 13, 69] is technically advantageous but often nonselective and/or the reaction course is less predictable.

The mechanism of homogeneous hydrogenation is known. Our first task was to generate high reactivity by designing molecular catalysts, we concentrated on the use of protic, neutral ligands. Most hydrogenation catalysts that have been developed utilize aprotic neutral ligands (L) such as tertiary phosphanes, phosphites, tertiary amines, ethers and dienes, or

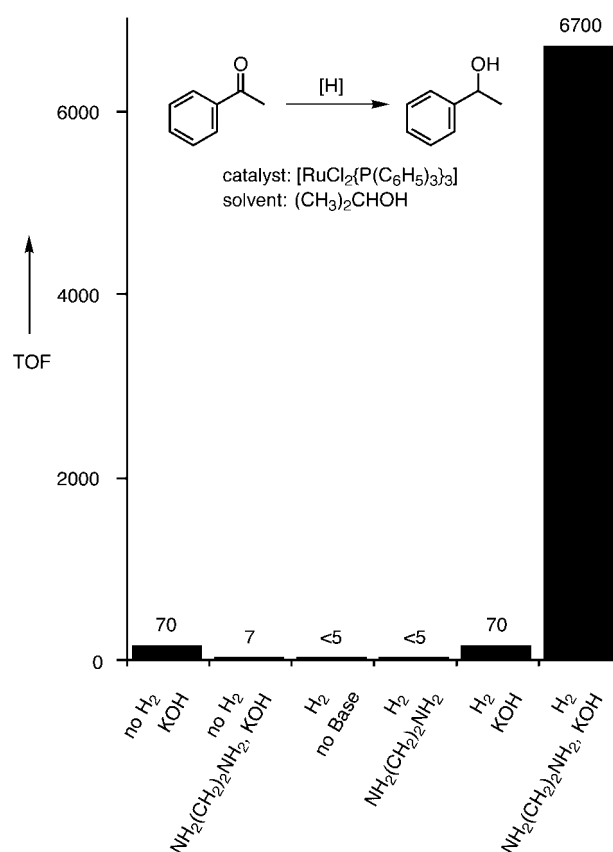
anionic ligands (X) including halides, alkoxides, and carboxylates.^[3d, 15i, 70] On the other hand, the use of protic neutral ligands (LH) such as alcohols had been largely unexplored. The LH ligands were considered as mere spectators or weak donors, often indicated as solvent molecules (solv), whose liberation from metals forms catalytically active, coordinatively unsaturated complexes. We were intrigued to see if the characteristics of LH could be utilized in a more positive fashion.

Hydrogen bonding is an ubiquitous electrostatic interaction that is very important in chemistry. If strength of hydrogen bonding is greater in the transition state than in the ground-state molecules, then hydrogen bonding must contribute to the acceleration of chemical reactions. Scheme 8b illustrates a possible hydrogen-bond-assisted hydride transfer from M to a carbonyl carbon atom. The alcohol product may form in either the inner or outer coordination sphere of the MH species. The presence of the LH...OC hydrogen bond facilitates the interaction between the M–H linkage and the π face of the C=O unit.^[71] This is an extension of the idea given in Section 1.3 but is more concrete.^[72] In this context, we were impressed by the origin of the anticancer activity of cisplatin, *cis*-[PtCl₂(NH₃)₂], and its analogues which utilize ammonia or primary or secondary amines as ligands, but not tertiary amines.^[73] A free NH proton is not a strong hydrogen-bond donor, however, when the nitrogen atom interacts with the Pt center, the NH group has increased acidity allowing for interaction with a phosphate moiety in DNA. As a consequence, the DNA double-stranded structure is perturbed and the Pt center forms a complex with a guanine moiety. Thus, the Pt metal and protic neutral ligand cooperate in developing antitumor activity. We anticipated that this chemical principle based on an NH function could be utilized for homogeneous hydrogenation by metal–ligand difunctional catalysis.

2.2. Discovery of a Highly Reactive Catalyst System

Based on the above concept, we pursued the catalytic saturation of C=O bonds by using both hydrogen gas (hydrogenation) and stable organic compounds, including 2-propanol (transfer hydrogenation),^[11b,c, 58a] with the aid of Ru^{II} complexes. In our search for a reactive catalyst system, we used a standard system of 1.4 M acetophenone solution in 2-propanol containing [RuCl₂{P(C₆H₅)₃}₃] and KOH (ketone:Ru:base = 5000:1:20).^[74]

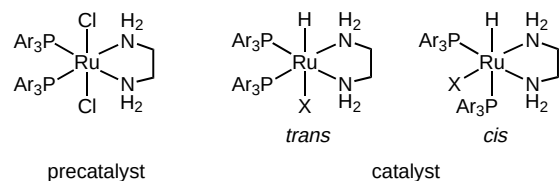
A combined system of a transition metal complex and an alkaline base in 2-propanol has frequently been used for the transfer hydrogenation of ketones.^[11b,c, 56–58] In fact, under such conditions even in the absence of hydrogen gas, the reduction of acetophenone proceeded with a TOF of 70 h^{−1} at 28 °C (Scheme 10). However, the addition of one equivalent of ethylenediamine retarded the transfer hydrogenation, the TOF being only 7 h^{−1} under otherwise identical conditions. This was surprising because other experiments showed that structurally similar compounds, ethanolamine and *N*-tosylethylenediamine, significantly accelerate the transfer hydrogenation of simple ketones catalyzed by [[RuCl₂(η^6 -arene)]₂] and KOH or other strong bases.^[58, 75] More significantly,



Scheme 10. Reduction of acetophenone catalyzed by a ruthenium complex. TOF = moles of product/mole of Ru $\times$ h. Conditions: Ketone:[RuCl₂{P(C₆H₅)₃}₃] = 5000:1, [ketone] = 1.4 M, 28 °C, common (but not always utilized) reagents: 20 equivalents of KOH, 1 equivalent of NH₂(CH₂)₂NH₂, 3 atm H₂.

however, ethylenediamine enormously accelerated *hydrogenation with molecular hydrogen* giving a TOF number of 6700 h^{−1} at 3 atm (Scheme 10).^[76] This is a net hydrogenation; the absence of transfer hydrogenation was confirmed by a deuterium-labeling experiment using [2-D]2-propanol which yielded no deuterated 1-phenylethanol or acetone.^[74] However, formation of a reactive ruthenium hydride species from the ruthenium chloride precatalyst in the induction step might be facilitated by the 2-propanol solvent.^[58, 77, 78] It should be noted that [RuCl₂{P(C₆H₅)₃}₃] is a poor catalyst for ketone hydrogenation; without ethylenediamine or KOH, the TOF remained less than 5 h^{−1}. The TOF of 70 h^{−1} obtained with KOH but without the diamine is probably a result of background transfer hydrogenation with 2-propanol.^[78] Thus, both the organic and inorganic bases are necessary for the catalytic hydrogenation. A minimum of 2 equivalents of a strong base is required to generate sufficient activity. As to the chelating diamine auxiliary, at least one primary or secondary amine end is necessary; *N,N,N',N'*-tetramethylethylenediamine (TMEDA), for example, is totally ineffective. 2-Propanol is the solvent of choice, although various alcohols and DMF can also be used. The rate is highly sensitive to the pressure of hydrogen, and hydrogenation with an S/C of 500/1 at 1 atm gave a TOF of only 880 h^{−1} but a TOF of 23000 h^{−1} was obtained with an S/C of 10000/1 at 50 atm.

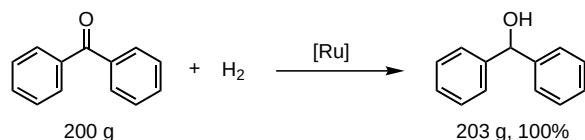
Subsequently we found that the preformed *trans*-[RuCl₂ (phosphane)₂(1,2-diamine)] complexes (Scheme 11) serve as stable precatalysts and effect the even more rapid and productive hydrogenation of ketones.^[79–81] For example, when



Scheme 11. Structures of a catalyst precursor and possible catalytic (reducing) species. Ar = 4-CH₃C₆H₄, X = H, OR.

a 2.1M solution of cyclohexanone in 2-propanol containing *trans*-[RuCl₂{P(C₆H₄-4-CH₃)₃]₂[NH₂(CH₂)₂NH₂]] and (CH₃)₃COK (ketone:Ru:base = 100 000:1:450) was stirred under 10 atm of hydrogen at 60 °C for 2 h, cyclohexanol was produced in 96 % yield. The reaction rate and productivity are some two orders of magnitude higher than those obtained with the ruthenium complexes generated in situ; the reaction took place with an initial TOF of 563 000 h⁻¹ or 156 s⁻¹.^[79, 82] Thus, the phosphane/diamine ruthenium complexes are among the most reactive (pre)catalysts for the homogeneous hydrogenation of ketones (compare the TOF with the values in Scheme 10).

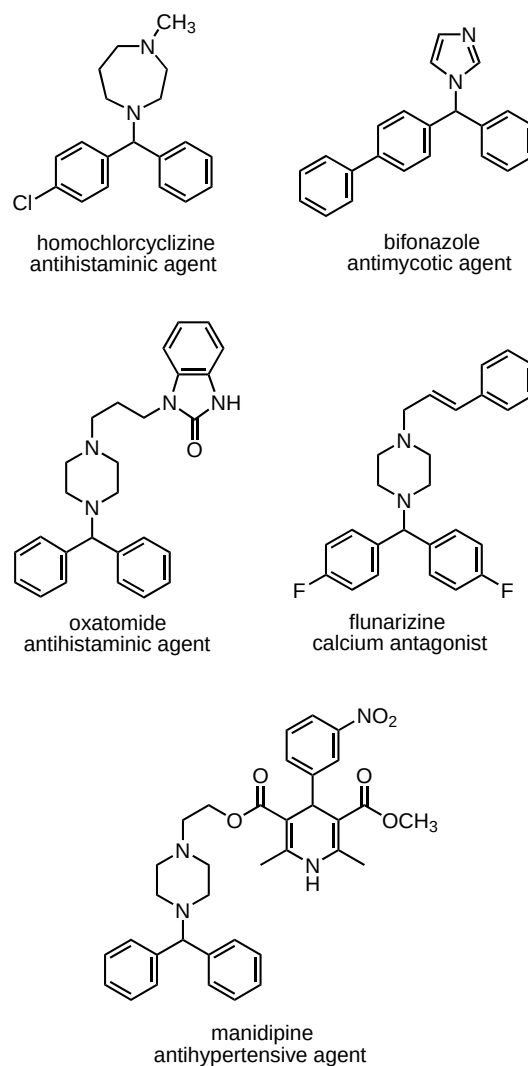
This hydrogenation of ketones does not proceed via their enol forms. In the presence of *trans*-[RuCl₂{P(C₆H₄-4-CH₃)₃]₂][NH₂(CH₂)₂NH₂]] and (CH₃)₃COK with an S/C ratio as high as 20000/1 various benzophenone derivatives are cleanly converted into benzhydrols under 8 atm H₂ and 23–35 °C.^[83] Scheme 12 illustrates the corresponding reaction of



Scheme 12. Hydrogenation of benzophenone with a phosphane/diamine–ruthenium catalyst. Conditions: [Ru] = *trans*-[RuCl₂P(C₆H₄-4-CH₃)₃]₂[NH₂(CH₂)₂NH₂] (46 mg), (CH₃)₃COK (0.49 g), ketone:Ru:base = 20000:1:80, [ketone] = 2.7 M, (CH₃)₂CHOH (200 mL), 8 atm H₂, 35 °C, 48 h.

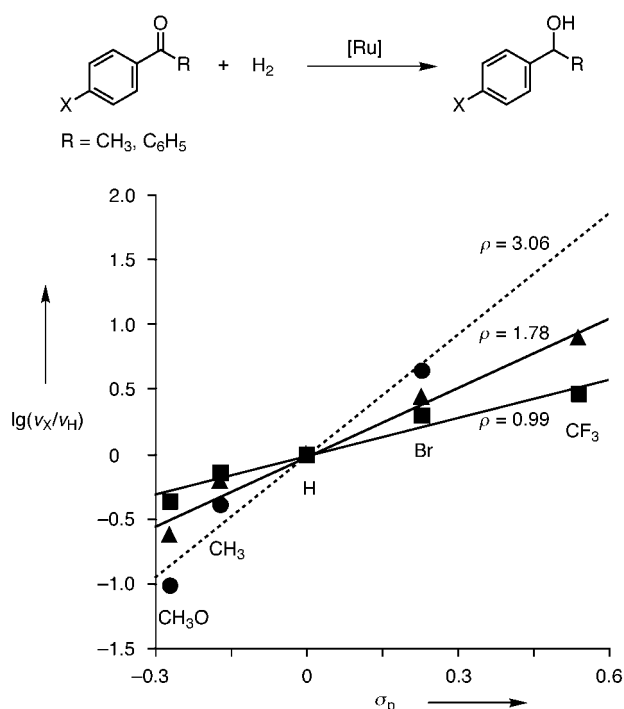
parent benzophenone; also sterically hindered *ortho*-substituted benzophenones can be employed as substrates. Unlike many other hydrogenation methods, this reaction did not produce any diphenylmethane products. The reaction does not require a homogeneous 2-propanol solution of ketonic substrates, sparingly soluble solid benzophenones can be subjected to the reaction as a slurry whereby a high reaction rate is maintained. Benzhydrols are used widely as intermediates for the commercial synthesis of pharmaceuticals as illustrated in Scheme 13.^[84] This method is particularly useful for the large-scale synthesis of benzhydrols.

Substrates possessing an electron-withdrawing group are more reactive than those with an electron-donating substituent.



Scheme 13. Pharmaceutically important benzhydryl compounds.

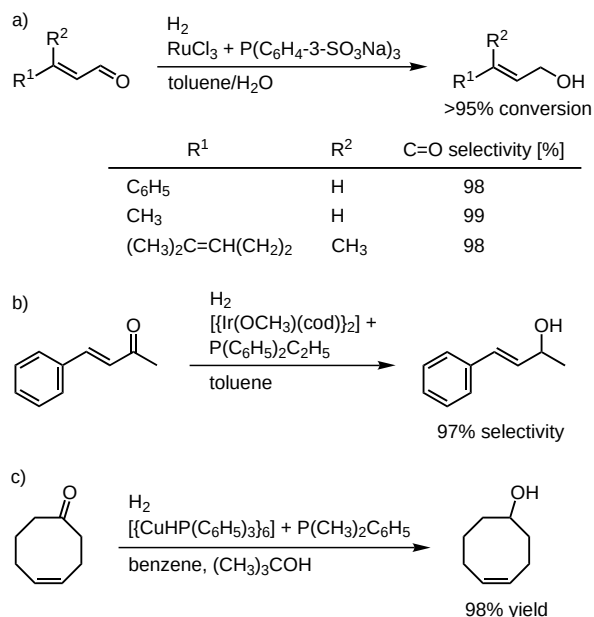
ent; *p*-trifluoromethylbenzophenone was hydrogenated 11 times faster than the *p*-methoxy ketone at 5 atm and 28 °C, but this is unimportant from a synthetic point of view. Competition experiments using an equimolar mixture of benzophenone and a series of *para*-substituted derivatives and *trans*-[RuCl₂{P(C₆H₄-4-CH₃)₃]₂{NH₂(CH₂)₂NH₂}] showed a linear relationship between the relative rate and σ_p constant with a ρ value of +1.78 (Scheme 14).^[83] Similarly, hydrogenation of acetophenone derivatives gave a ρ value of +0.99. The electron influence is smaller than that observed with the NaBH₄ reduction of acetophenones, ρ = +3.1.^[85] Although the actual catalyst formed under the hydrogenation conditions remains to be elucidated, we consider that the reducing species is a ruthenium hydride or dihydride formulated as *trans*- or *cis*-[RuHX(phosphane)₂(diamine)] (X = H or OR) (Scheme 11). Since the isolated phosphane/diamine ruthenium complexes and in situ formed complexes exhibit very similar selectivity (see Section 3.5), the same reactive species would be generated during the hydrogenation reaction. *trans*-[RuHCl{P(C₆H₅)₃]₂{NH₂(CH₂)₂NH₂}] showed no catalytic activity for the hydrogenation of acetophenone in the absence of a strong base.^[28]



Scheme 14. Hammett plots for hydrogenation of *para*-substituted acetophenones (■) and benzophenones (▲) with *trans*-[RuCl₂[P(C₆H₄-4-CH₃)₃]₂[NH₂(CH₂)₂NH₂]] and (CH₃)₃COK in (CH₃)₂CHOH (5 atm H₂, 28 °C). Reduction of *para*-substituted acetophenones with NaBH₄^[85] is shown by ●.

3. Chemoselective Hydrogenation

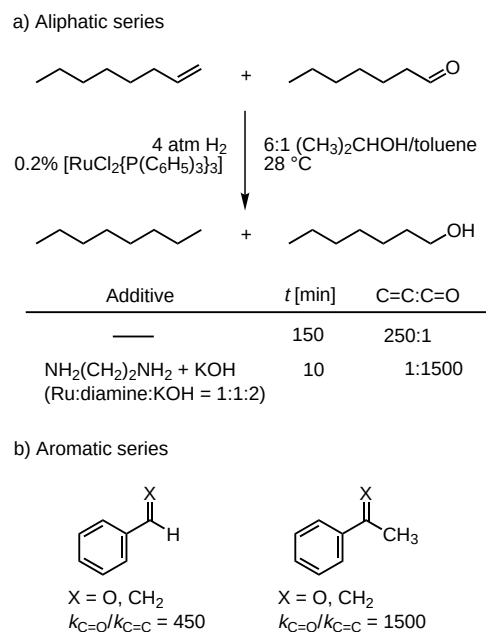
Many kinds of ketonic substrates exist. We first raised the very simple question of how to reduce the carbonyl group in olefinic ketones such as C₆H₅COCH₂CH₂CH=CH₂. Various metal hydride reagents, including NaBH₄ and LiAlH₄, saturate the C=O linkage selectively.^[86] On the other hand, despite a century of extensive efforts in hydrogenation chemistry, there are no general catalysts effecting selective hydrogenation of a carbonyl function in the presence of an olefinic linkage.^[11a, 58] Currently available catalyst systems, either homogeneous or heterogeneous, are mostly selective for C=C bonds.^[7, 8, 87] A notable exception is the two-phase hydrogenation of α,β -unsaturated aldehydes to allyl alcohols catalyzed by a water-soluble P(C₆H₄-3-SO₃Na)₃-Ru catalyst which is used in industrial processes.^[88–91] Scheme 15 gives some examples of aldehyde-selective hydrogenations. However, keto groups in α,β -enones are much less reactive. An iridium catalyst with a sterically demanding phosphane ligand effects a carbonyl-selective hydrogenation of benzalacetone (Scheme 15b).^[92, 93] Some unconjugated enals and enones are converted preferentially into the unsaturated alcohols with Cu,^[94] Ir,^[95] and Rh^[33b] catalysts.^[96] However, the scope of these reactions is unclear. Thus, this selectivity problem has received only fragmentary attention in spite of its significance. Development of general and reliable hydrogenation catalysts with excellent carbonyl selectivity is highly desirable particularly for practical reasons. A system comprising *trans*-[RuCl₂(phosphane)₂(1,2-diamine)] and an alkaline base or a



Scheme 15. Selected examples of carbonyl-selective hydrogenation of olefinic aldehydes and ketones.

ternary system consisting of [RuCl₂(phosphane)₃], 1,2-diamine, and a strong base was a major breakthrough.

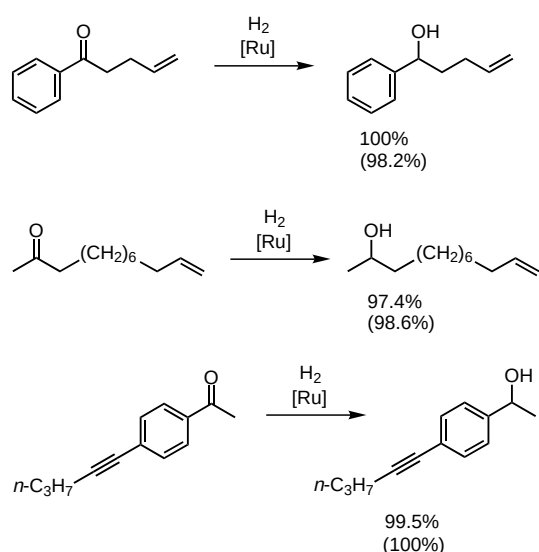
First, we compared the reactivity of 1-octene and heptanal.^[97] [RuCl₂[P(C₆H₅)₃]₃] is an excellent catalyst for hydrogenation of terminal olefins^[7, 37, 98] but very inactive for reaction of carbonyl compounds. An intermolecular competition experiment using an equimolar mixture of 1-octene and heptanal with [RuCl₂[P(C₆H₅)₃]₃] in a 2-propanol/toluene mixture under 4 atm of H₂ and 28 °C showed that 1-octene is 250 times more reactive than heptanal (Scheme 16a). However, when one equivalent of ethylenediamine and two equivalents of KOH with respect to ruthenium (not sub-



Scheme 16. The diamine effect on the relative reactivities of olefins and carbonyl compounds in ruthenium catalyzed hydrogenation.

strates) were added, the selectivity was reversed dramatically, hydrogenating the aldehyde 1500 times faster than the olefin. Thus, the combined effects of the diamine and KOH has been proven to decelerate olefin hydrogenation catalyzed by $[\text{RuCl}_2\{\text{P}(\text{C}_6\text{H}_5)_3\}_3]$ and in turn accelerate aldehyde hydrogenation. Very small quantities of the diamine and inorganic base change the $\text{C}=\text{O}/\text{C}=\text{C}$ selectivity profile by a factor of 375 000. This marked effect reflects differences in the mechanism in the presence or absence of the basic agents. In a similar manner, the hydrogenation of a mixture of styrene and benzaldehyde proceeded with a $\text{C}=\text{O}/\text{C}=\text{C}$ selectivity of 450/1 to give mostly benzyl alcohol (Scheme 16b). Acetophenone was hydrogenated 1500 times faster than α -methylstyrene.^[28]

This selective hydrogenation is applicable to a variety of carbonyl compounds having an unsaturated carbon–carbon bond.^[97] Scheme 17 illustrates examples of intramolecular



Scheme 17. Carbonyl-selective hydrogenation of unsaturated ketones. Conditions: $[\text{Ru}] = [\text{RuCl}_2\{\text{P}(\text{C}_6\text{H}_5)_3\}_3]$, $\text{NH}_2(\text{CH}_2)_2\text{NH}_2$, KOH, ketone:Ru:diamine:KOH = 500:1:1:2, $(\text{CH}_3)_2\text{CHOH}$ or a 6:1 $(\text{CH}_3)_2\text{CHOH}$ /toluene mixture, 4 atm H_2 , 28 °C. The selectivity is given in parentheses.

$\text{C}=\text{O}/\text{C}=\text{C}$ competition effecting selective conversion of unsaturated ketones into unsaturated alcohols. The hydrogenation with S/C ratios of 500/1 to 10 000/1 took place smoothly at 1–8 atm, and very rapidly at 50 atm, giving a near quantitative yield. Aliphatic and aromatic ketones with an unconjugated terminal olefinic bond were hydrogenated preferentially at the carbonyl site and the products were 98–100% pure. Although $[\text{RuCl}_2\{\text{P}(\text{C}_6\text{H}_5)_3\}_3]$ is known to isomerize terminal olefins to internal olefins during hydrogenation,^[37] no migration of $\text{C}=\text{C}$ bonds took place under the conditions employed. Internal acetylenic bonds are also tolerated, while terminal acetylenes and α,β -acetylenic ketones diminish the catalytic activity of the ruthenium complexes.^[99] The excellent $\text{C}=\text{O}$ selectivity is reminiscent of that attained by the stoichiometric NaBH_4 reduction. The chemoselectivity arises mainly from the electrophilic reactivity of carbonyl carbon versus the nucleophilic reactivity of an olefinic bond.

In contrast in α,β -unsaturated aldehydes and ketones the carbonyl carbon reacts only with nucleophiles, while the olefinic part reacts with both nucleophiles and electrophiles. As shown in Table 1, conjugated enals including 2-undecenal,

Table 1. Carbonyl-selective hydrogenation of α,β -unsaturated carbonyl compounds.^[a]

Substrate	Conversion [%]	$\text{C}=\text{O}$ selectivity [%] ^[b]
$n\text{-C}_8\text{H}_{17}\text{CH=CHCHO}$	100	100
	99.7	99.8
	100	100
	100	> 99.9
	> 99	100
	98.2	99.6
	100	70
	9.8	> 99.9

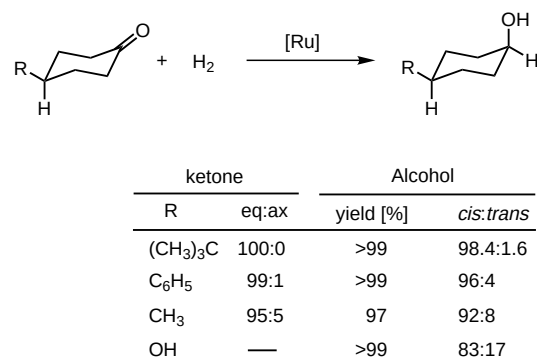
[a] Reactions were conducted at 4 or 8 atm of H_2 and at 28 °C in 2-propanol or a 6:1 2-propanol/toluene mixture containing $[\text{RuCl}_2\{\text{P}(\text{C}_6\text{H}_5)_3\}_3]$, $\text{NH}_2(\text{CH}_2)_2\text{NH}_2$, and KOH. Ketone:Ru:diamine:KOH = 500:1:1:2. [b] A percent distribution of the unsaturated alcohol relative to all the hydrogenated products. [c] Ketone:Ru:diamine:KOH = 10 000:1:1:2.

cinnamaldehyde, and citral were hydrogenated to the corresponding allyl alcohols with excellent chemoselectivity.^[97] Benzalacetone (30.0 g), an open-chain α,β -enone, was hydrogenated under 4 atm H_2 (28 °C, 18 h) in 2-propanol (100 mL) containing $[\text{RuCl}_2\{\text{P}(\text{C}_6\text{H}_5)_3\}_3]$ (19.7 mg), ethylenediamine (1.2 mg), and KOH (2.3 mg) with an S/C ratio of 10 000/1 to the corresponding allyl alcohol (29.4 g) with a 97% isolated yield. Hydrogenation of 1-acetylcyclohexene, another type of α,β -enone, also showed a very high $\text{C}=\text{O}$ selectivity (Table 1 entry 6). β -Ionone, a dienone, exhibited perfect selectivity, forming only β -ionol (Table 1 entry 5). There are some problems with this hydrogenation of 2-cyclohexenones; as with NaBH_4 , simple 2-cyclohexenone (entry 7) underwent 1,2- and 1,4-reduction competitively to give a 7:3 mixture of unsaturated and saturated alcohols. However, a perfect keto selectivity was obtained by introducing a methyl group at the β position, the hydrogenation of 3-methyl-2-cyclohexenone gave solely the allyl alcohol (entry 8).

4. Diastereoselective Hydrogenation

Diastereoselective conversion of ketones into secondary alcohols is a major subject in organic synthesis. This desired stereoselectivity was accomplished by stoichiometric reactions with boron-based hydride reagents.^[86, 100–103] Although various hydride reagents are available, each one has a limited scope of reaction linked to its inherent chemical properties and the difficulties in modifying its structure.

The new hydrogenation reaction using a phosphane/diamine–ruthenium catalyst system is a beneficial tool for the diastereoselective reduction of simple ketones. First, when 4-*tert*-butylcyclohexanone (30 g) was hydrogenated with the standard $[\text{RuCl}_2[\text{P}(\text{C}_6\text{H}_5)_3]_3]/\text{NH}_2(\text{CH}_2)_2\text{NH}_2/\text{KOH}$ system ($\text{S}/\text{C} = 10000/1$) under 4 atm H_2 and 28 °C, a 98.4:1.6 mixture of *cis*-4-*tert*-butylcyclohexanol and its *trans* isomer was obtained (Scheme 18).^[104, 105] Thus, in the conformationally

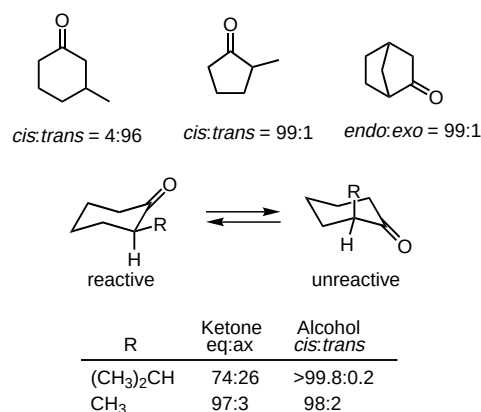


Scheme 18. Diastereoselective hydrogenation of 4-substituted cyclohexanones. Conditions: $[\text{Ru}] = [\text{RuCl}_2[\text{P}(\text{C}_6\text{H}_5)_3]_3]$, $\text{NH}_2(\text{CH}_2)_2\text{NH}_2$, KOH, ketone:Ru:diamine:KOH = 10 000:1:1:2, (CH₃)₂CHOH, 4 atm H_2 , 28 °C.

anchored substrate the ruthenium hydride species appeared to approach the carbonyl carbon atom preferentially from the less-crowded equatorial side.^[106] Use of preformed *trans*- $[\text{RuCl}_2[\text{P}(\text{C}_6\text{H}_4\text{-4-CH}_3)_3]_2[\text{NH}_2(\text{CH}_2)_2\text{NH}_2]]$ effected rapid hydrogenation in 2-propanol containing (CH₃)₃COK (ketone:Ru:base = 50000:1:250, 10 atm H_2 , 60 °C) with a *cis:trans* selectivity of 97:3. The TOF was 178000 h^{−1} or 49 s^{−1}.^[79] Similar *cis* selectivity was attained earlier by heterogeneous Rh^[107] and PtO₂^[108] catalysts.^[8, 69a] Homogeneous hydrogenation with certain Rh^[29, 30a, 32a] or Cu catalysts^[94, 109] tends to result in *trans* selectivity.

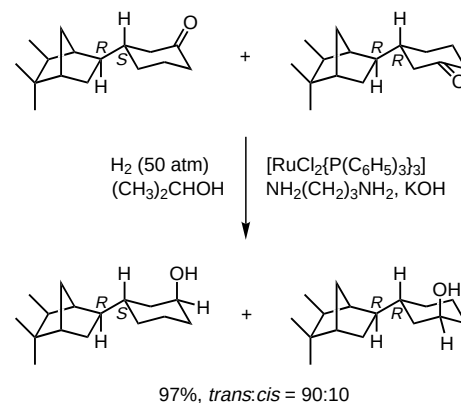
Scheme 18 shows the diastereoselectivity of reactions of various 4-substituted cyclohexanones.^[104] With conformationally flexible substrates, the extent of stereoselection is essentially controlled by the relative populations of the equatorial and axial conformers,^[110] resulting in a predominance of the *cis* alcohols. Reaction of 4-phenylcyclohexanone with either the in situ catalyst or the preformed catalyst gave a 96:4 mixture of the *cis* and *trans* alcohols.

In a similar manner, some other cyclic ketones are hydrogenated with a high diastereoselectivity (Scheme 19).^[104] Reaction of 3-methylcyclohexanone gave *trans*-3-methylcyclohexanol and the *cis* isomer with a 96:4 selectivity and a 100% yield. There is a conformational reason for this *trans*



Scheme 19. Diastereoselective hydrogenation of cyclic ketones. Conditions: $[\text{RuCl}_2[\text{P}(\text{C}_6\text{H}_5)_3]_3]$, $\text{NH}_2(\text{CH}_2)_2\text{NH}_2$, KOH, (CH₃)₂CHOH, 4 atm, 28 °C.

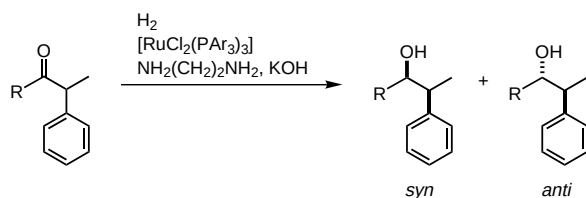
preference. Cyclohexanones alkylated in the 2-position were hydrogenated to give predominantly the *cis* alcohol. Notably, hydrogenation of 2-isopropylcyclohexanone gave the *cis* and *trans* alcohols in a >99.8:0.2 ratio. The selectivity is much higher than the equatorial:axial equilibrium ratio of 74:26,^[111, 112] and this is probably a result of the repulsive interaction between the axial 2-isopropyl substituent and incoming ruthenium hydride species which prevents the *trans* alcohol formation. 2-Methylcyclopentanone afforded the *cis* alcohol with a diastereoselectivity of 99:1 and bicyclo[2.2.1]-heptan-2-one showed a 99:1 *endo:exo* selectivity. Scheme 20 illustrates the stereoselective synthesis of a substitute for



Scheme 20. Fragrance synthesis by ruthenium-catalyzed diastereoselective hydrogenation. The products shown are substitutes for α and β -santalol.

α - and β -santalol, an expensive fragrance from sandalwood oil, by hydrogenation of a 3-substituted cyclohexanone.^[113] The substrate is a diastereomeric mixture, because the isocamphyl group is derived from a natural source, while the product alcohols have a 1,3-*trans* relationship regardless of the chirality of the C-3 substituent.

A high degree of Cram selectivity^[23, 114–117] was seen in the hydrogenation of open-chain chiral ketones.^[28, 104] As shown in Scheme 21, in the reactions of conformationally flexible 1-phenylethyl ketones, the *syn* alcohols predominate. This

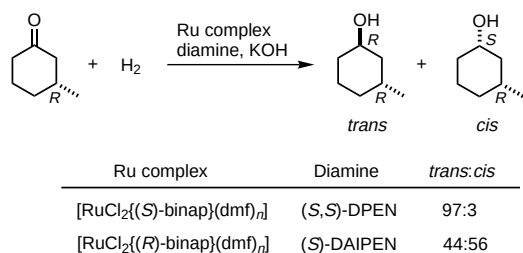


R	PAr ₃		Alcohol syn:anti
	Ar	ν [cm ⁻¹] ^[a]	
C ₆ H ₅	C ₆ H ₅		98:2
(E)-C ₆ H ₅ CH=CH	C ₆ H ₅		75:25
cyclo-C ₆ H ₁₁	C ₆ H ₅		96:4
n-C ₄ H ₉	C ₆ H ₅		93:7
CH ₃	C ₆ H ₄ -4-OCH ₃	2066.1	96:4
CH ₃	C ₆ H ₄ -4-CH ₃	2066.7	95:5
CH ₃	C ₆ H ₅	2068.9	86:14
CH ₃	C ₆ H ₄ -4-F	2071.3	78:22

Scheme 21. Diastereoselective hydrogenation of acyclic ketones of type 1-phenylethylketone. Conditions: S/C = 500/1, (CH₃)₂CHOH, 4 atm H₂, 28 °C. [a] $\nu_{\text{CO}}(\text{A}_1)$ for [Ni(CO)₃(PAr₃)] in CH₂Cl₂ (Tolman, 1977^[31]).

and the foregoing stereoselective reactions indicate that the reactive species generated in this hydrogenation behave as “bulky hydrides”. The levels of the diastereoface selectivity attained with the standard triphenylphosphane/ethylenediamine–ruthenium catalyst compare well with those of stoichiometric reduction using L-Selectride reagents.^[101] A major beneficial characteristic of this catalyst system is the high tunability of its stereochemical and electronic properties through structural modifications of the phosphane and diamine ligands. The stereoselectivity was subtly influenced by the electronic properties of the phosphane ligands.^[31] Thus, although the Cram selectivity in the reaction of 3-phenyl-2-butanone (R = CH₃, Scheme 21) with the standard catalyst remained 86:14, it was improved simply by using electron-donating triarylphosphane ligands in tandem with ethylenediamine and reached 96:4 (see Scheme 21).^[104]

Diastereoselectivity in the hydrogenation of a chiral ketonic substrate is affected profoundly by the chirality of the phosphane and diamine ligands.^[118] A typical example is given in Scheme 22. Thus hydrogenation of (*R*)-3-methylcyclohexanone with a ruthenium complex modified by (*S*)-BINAP and (*S,S*)-DPEN^[16, 119] formed a 97:3 mixture of the *trans* (1*R*,3*R*) and *cis* (1*S*,3*R*) alcohols, respectively.^[104] When the diphosphane and diamine were replaced by (*R*)-BINAP and (*S*)-DAIPEN,^[16, 120] a slightly *cis*-enriched (44:56) product mixture was obtained.

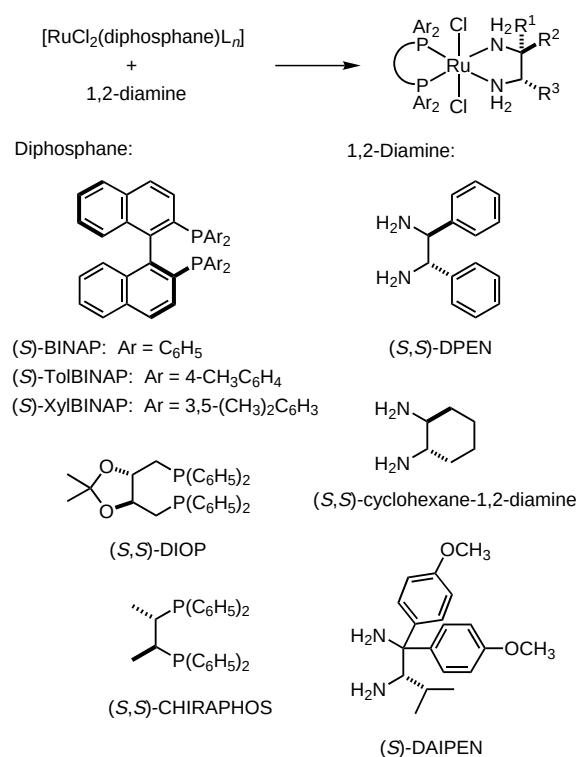


Ru complex	Diamine	trans:cis
[RuCl ₂ ((<i>S</i>)-binap)(dmf) ₃]	(<i>S,S</i>)-DPEN	97:3
[RuCl ₂ ((<i>R</i>)-binap)(dmf) ₃]	(<i>S</i>)-DAIPEN	44:56

Scheme 22. Multiple stereodifferentiation in hydrogenation of a chiral ketone. Conditions: S/C = 500/1, (CH₃)₂CHOH, 4 atm H₂, 28 °C.

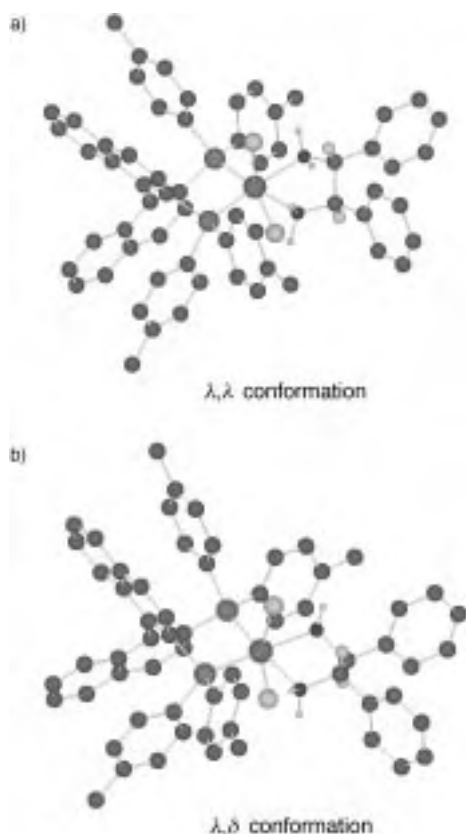
5. Enantioselective Hydrogenation

A major goal of our endeavor is the development of an asymmetric hydrogenation with a wide scope of application.^[121] Over the last 15 years a variety of chiral catalysts have been developed,^[2, 3, 9–14] in particular BINAP-based catalysts have displayed excellent stereoinductive properties. No single catalyst, however, can be universal because of the structurally diverse array of unsaturated substrates. To obtain a highly enantioselective reaction, the correct catalyst as well as appropriate reaction conditions must be selected, depending on the structures and properties of the ketonic substrates. This new hydrogenation system has the flexibility to cope with such diverse situations through modification of catalyst structures and reaction parameters. A wide range of chiral ruthenium catalysts can be prepared by different combinations of chiral phosphane and diamine ligands (Scheme 23). Both in situ generated complexes^[74] and preformed complexes^[79, 80, 122] are



Scheme 23. Synthesis of shelf-stable *trans*-[RuCl₂(diphosphane)(1,2-diamine)] complexes. For the abbreviation of the ligands, see ref [16].

usable, although the latter exhibit a higher TON. An X-ray analysis of the isolated (*R*)-TolBINAP/(*R,R*)-DPEN–ruthenium complex shows a distorted octahedral coordination geometry of the ruthenium center, to which both the diphosphane and diamine ligands are coordinated in a λ fashion (Scheme 24a).^[79, 123] In the *R/S,S* diastereomer (Scheme 24b), the TolBINAP ligand forms a λ seven-membered structure, while the DPEN ligand assumes a δ five-membered ring. ¹H and ³¹P NMR spectral analyses of these compounds showed that they exist as a single conformer in [D₆]benzene. Although all the isolated complexes possess a *trans*-dichloro *OC-6-13* geometry, this does not secure the

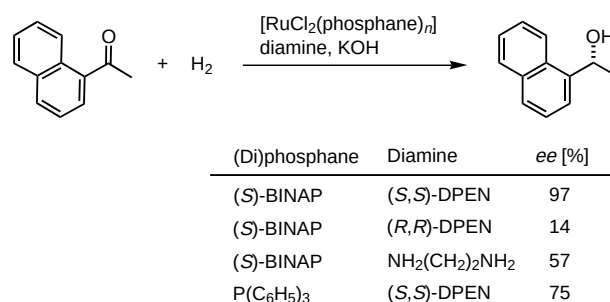


Scheme 24. Molecular structures of a) $\text{trans-[RuCl}_2\{(\text{R})\text{-tolbinap}\}\{(\text{R,R})\text{-dpn}\}}$ and b) $\text{trans-[RuCl}_2\{(\text{R})\text{-tolbinap}\}\{(\text{S,S})\text{-dpn}\}}$. All the hydrogen atoms except for the amino and methine groups of DPEN are omitted for clarity.

stereochemistry of the reactive hydride species (see Scheme 11). Depending on the structures of the phosphane and diamine ligands as well as the properties of the anionic ligands, several diastereomers are possible.

5.1. Aromatic Ketones

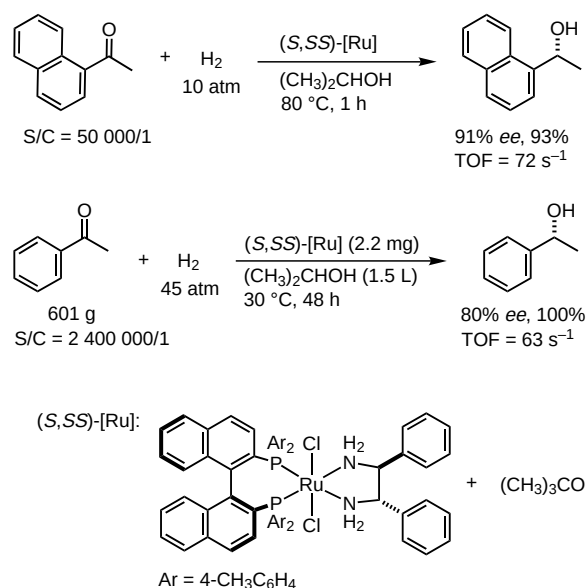
The pioneering work of Markó et al.^[42, 124] spurred research on the asymmetric hydrogenation of simple aromatic ketones but without significant success (Schemes 6 and 9). The enantioselectivity and/or reactivity was insufficient in most cases. We found that hydrogenation of 1'-acetonaphthone with a catalyst system consisting of $[\text{RuCl}_2\{(\text{S})\text{-binap}\}(\text{dmf})_n]$, (S,S)-DPEN, and KOH (1:1:2 mol ratio) in 2-propanol under 4 atm H_2 and 28 °C afforded the *R* alcohol in 97% *ee* in quantitative yield.^[74] The high degree of enantioselectivity is a result of the synergistic effects of the chiral diphosphane and diamine,^[118] as illustrated in Scheme 25. Replacement of the *S,S* diamine by the *R,R* enantiomer led to the *R* alcohol in only 14% *ee*. A combination of the (S)-BINAP–Ru complex and achiral ethylenediamine or achiral $[\text{RuCl}_2\{\text{P}(\text{C}_6\text{H}_5)_3\}_3]$ and (S,S)-DPEN formed the *R* alcohol with a moderate *ee* value. The (R)-1-(1-naphthyl)ethanol product has been utilized for desymmetrization of prochiral 3-substituted glutaric anhydrides giving chiral building blocks for the synthesis of



Scheme 25. Double stereodifferentiation in the asymmetric hydrogenation of 1'-acetonaphthone catalyzed by chiral phosphane/diamine–ruthenium complexes. Conditions: ketone:Ru:KOH = 500:1:1:2, $(\text{CH}_3)_2\text{CHOH}$, 4 atm H_2 , 28 °C.

(+)-compactin, an HMG-CoA-reductase inhibitor, and 1233A, a hypocholesterolemic agent.^[125]

Rapid, highly productive asymmetric hydrogenation is achievable with a preformed diphosphane/diamine–ruthenium complex (Scheme 26).^[79] Thus, reaction using a 2.1M 2-propanol solution of the same ketone with $\text{trans-[RuCl}_2\{(\text{S})\text{-tolbinap}\}\{(\text{S,S})\text{-dpn}\}]$ and $(\text{CH}_3)_3\text{COK}$ (*S/C* = 50000/1) under 10 atm H_2 and 80 °C proceeded with an initial



Scheme 26. Rapid, productive, and enantioselective hydrogenation of aromatic ketones.

TOF of 259000 h⁻¹ or 72 s⁻¹, and after 1 h afforded the *R* alcohol in 91% *ee* and a 93% yield.^[126] In a similar manner, when a mixture of acetophenone (601 g), the (S)-TolBINAP/(S,S)-DPEN–ruthenium complex (2.2 mg), and $(\text{CH}_3)_3\text{COK}$ (5.6 g) in 2-propanol (1.5 L) was stirred under 45 atm H_2 at 30 °C for 48 h, the *R* alcohol is obtained with 80% *ee* and a 100% yield.^[127] The substrate concentration was as high as 30% (w/v). Under such conditions, the TON is at least 240000, while the TOF at 30% conversion is 228000 h⁻¹ or 63 s⁻¹.^[79] In contrast, β -keto esters, the best substrates for the standard BINAP–Ru catalyzed hydrogenation (see

Schemes 1 and 3), are not hydrogenated under these new catalytic conditions.

Although the extent of enantioselectivity obtained with the TolBINAP/DPEN system was unsatisfactory, it was improved greatly by combining (*S*)-XylBINAP and (*S*)-DAIPEN (or *R* and *R*).^[16] The latter *C*₁ symmetric diamine is obtained readily from leucine.^[120] The utility of the XylBINAP/DAIPEN complex in reactions of type illustrated in Eq. (1) is shown in Table 2 and

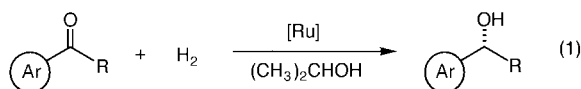


Table 3.^[28, 74, 79, 126] This combination very often gave the best result;^[128] for example, by this simple method reactions with an S/C ratio of 100 000/1 gave various ring-substituted 1-phenylethanols with high *ee* values. Thus, hydrogenation of acetophenone with *trans*-[RuCl₂{(*S*)-xylbinap}{(*S*)-daipen}] and (CH₃)₃COK with an S/C of 100 000/1 under 8 atm H₂ afforded the *R* alcohol in 99% *ee*.^[128] Although the catalyst possesses bulky diphosphane and diamine ligands, the reaction of acetophenone is only 1.3 times slower than that with the sterically less demanding TolBINAP/DPEN–ruthenium complex under otherwise identical reaction conditions.

With the use of the XylBINAP/DAIPEN–ruthenium complex, various *ortho*-, *meta*-, and *para*-substituted acetophenones have been hydrogenated with consistently high enantioselectivity (Table 2).^[128] This hydrogenation tolerates many ring substituents including F, Cl, Br, I, CF₃, OCH₃, COOCH(CH₃)₂, NO₂, NH₂, N(CH₃)₂, and NHCOCH₃. Esters can also be used, although they undergo transesterification with the 2-propanol solvent. The acid-sensitive compound 1-(3,4,5-trimethoxyphenyl)ethanol was obtained in 99% *ee* (Table 3). The electronic effects of *para* and *meta* substituents on the *ee* values are relatively small and steric hindrance resulting from bulky *ortho*-substituents is not significant either. Higher analogues of acetophenone are also hydrogenated with high enantioselectivity, the one exception being pivalophenone which was almost inert under the standard reaction conditions. Hydrogenation of 3-butenyl phenyl ketone, an unsaturated aromatic ketone, gives a chiral alcohol selectively leaving the olefinic bond intact (Table 3).^[97] The reaction is also applicable to 2,2,2-trifluoroacetophenone and its derivatives (Scheme 27)^[128] and unlike the reaction with many boron-based reducing agents,^[48, 129, 130] the asymmetric sense is identical to that observed with nonfluorinated acetophenones.

The Horeau effect is sometimes applicable to increase enantioselectivity (Scheme 28).^[131, 132] Hydrogenation of acetophenone and its *para*-substituted derivatives with an (*S*)-TolBINAP/(*S*)-DAIPEN (not XylBINAP/DAIPEN) combined system gave the *R* alcohols normally with less than 90% *ee*. However, reaction of 1,4-diacetylbenzene afforded enantiomerically pure *R,R* diol in 85% yield at the expense of

Table 2. *ee* Values for the asymmetric hydrogenation of aromatic ketones catalyzed by diphosphane/diamine–ruthenium complexes as in Eq. (1). The abbreviations for the ligands are given in ref [16].

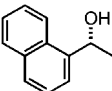
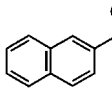
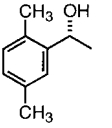
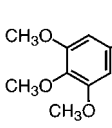
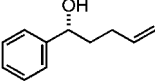
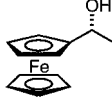
Alcohol	R or X	(<i>S</i>)-XylBINAP/ (<i>S</i>)-DAIPEN	(<i>S</i>)-TolBINAP/ (<i>S</i>)-DAIPEN	(<i>S</i>)-BINAP/ (<i>S,S</i>)-DPEN
	CH ₃	99	91	87 ^[a]
	C ₂ H ₅	99	92	
	<i>n</i> -C ₃ H ₇		94	
	<i>n</i> -C ₄ H ₉			90 ^[b]
	C ₆ H ₅ CH ₂		98	
	(CH ₃) ₂ CH	99		
	Cyclopropyl	96	92	
	(CH ₃) ₃ C			61 ^[c]
	CH ₃	99	99	95
	F	97	82	
	Cl	98	94	
	Br	96	98	
	CF ₃	99	99	
	CH ₃ O	92	82	
	CH ₃ CONH	98	86	
	CH ₃	100	87	
	F	98	88	
	Br	99.5	77	
	CF ₃	99	83	
	CH ₃ O	99	88	88 ^[a]
	CH ₃	98	84	94 ^[a]
	C ₂ H ₅		97	89 ^[a]
	<i>n</i> -C ₄ H ₉	98	93	
	(CH ₃) ₂ CHCH ₂		96 ^[d]	
	<i>cyclo</i> -C ₆ H ₁₁		95	
	(CH ₃) ₃ C		96	
	C ₆ H ₅	97	87	
	F	97		73
	Br	99.6		84 ^[a]
	I	99	83	71 ^[a]
	CF ₃	99.6	78	
	CH ₃ O	100	86	92 ^[a]
	(CH ₃) ₂ CHOCO	99		
	(CH ₃) ₂ NCO		88	
	NO ₂	99.8		83 ^[a]
	NH ₂	99		
	CH ₃ CONH		95	
	(CH ₃) ₂ N			94 ^[a]
	CH ₃		95	
	F	99 ^[e]	92	
	Cl	99 ^[e]	86 ^[d]	87 ^[a]
	CH ₃ O		95	
	CH ₃	99 ^[e]	99	
	F	97	77	
	Cl	96 ^[e]	94	
	CF ₃	99.5		

[a] With (*S*)-BINAP/(*S*)-DAIPEN. [b] With (*S*)-BINAP/(*S*)-DAMEN. [c] Under 50 atm H₂, 6% yield. Absolute configuration undetermined. [d] With (*S*)-TolBINAP/(*S,S*)-DPEN. [e] With (*S*)-XylBINAP/(*S,S*)-DPEN.

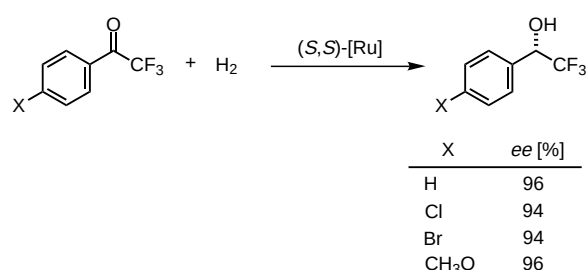
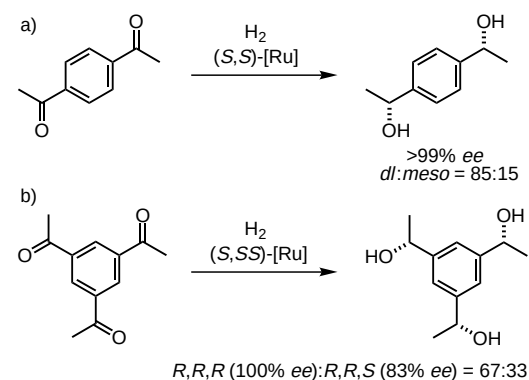
the minor *S* alcohol formed initially in the second hydrogenation (Scheme 28).^[74] In a similar manner, triple hydrogenation of 1,3,5-triacetylbenzene with (*S*)-BINAP/(*S,S*)-DPEN gave the enantiomerically pure *R,R,R* triol in 67% yield.^[133]

This asymmetric reaction is normally achieved by the tandem use of a chiral diphosphane and chiral 1,2-diamine but some chiral P,N ligands may also be used. Thus, a ruthenium complex generated in situ from a [{RuCl₂(*η*⁶-arene)}₂] and

Table 3. *ee* Values for the asymmetric hydrogenation of aromatic ketones catalyzed by diphosphane/diamine–ruthenium complexes as in Eq (1). The abbreviations for the ligands are given in ref [16].

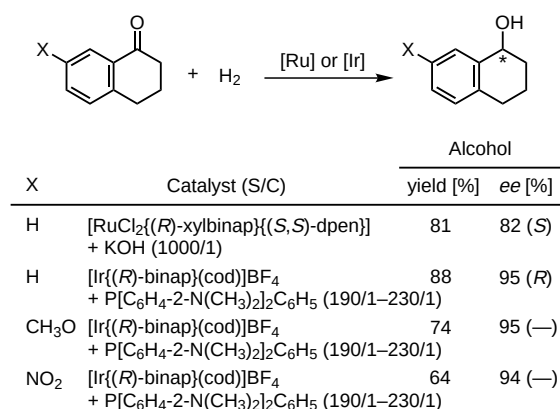
Product alcohol	Ligand combination	<i>ee</i> [%]	Product alcohol	Ligand combination	<i>ee</i> [%]
	(<i>S</i>)-TolBINAP/(<i>S,S</i>)-DPEN	98		(<i>S</i>)-TolBINAP/(<i>S</i>)-DAIPEN	98
	(<i>S</i>)-BINAP/(<i>S,S</i>)-DPEN	97		(<i>S</i>)-XylBINAP/(<i>S</i>)-DAIPEN	98
	(<i>S</i>)-XylBINAP/(<i>S,S</i>)-DPEN	99			
	(<i>S</i>)-TolBINAP/(<i>S</i>)-DAIPEN	99		(<i>S</i>)-XylBINAP/(<i>S</i>)-DAIPEN	99
	(<i>S</i>)-BINAP/(<i>S</i>)-DAIPEN	90 ^[a]		(<i>S</i>)-TolBINAP/(<i>S</i>)-DAIPEN	87

[a] The C=O selectivity was 98.9%.

Scheme 27. Asymmetric hydrogenation of 2,2,2-trifluoroacetophenones. Conditions: (*S,S*)-[Ru] = *trans*-[RuCl₂[(*S*)-xylbinap][(S)-daipen]], (CH₃)₃COK, (CH₃)₂CHOH, 8–10 atm H₂, 28 °C.Scheme 28. The Horeau effect in asymmetric hydrogenation of a) 1,4-diacetylbenzene and b) 1,3,5-triacetylbenzene. Conditions: a) (*S,S*)-[Ru] = [RuCl₂[(*S*)-tolbinap](dmf)_n], (*S*)-DAIPEN, KOH, (CH₃)₂CHOH, 4 atm H₂, 28 °C; b) (*S,S,S*)-[Ru] = [RuCl₂[(*S*)-binap](dmf)_n], (*S,S*)-DPEN, KOH, (CH₃)₂CHOH, 8 atm H₂, 28 °C.

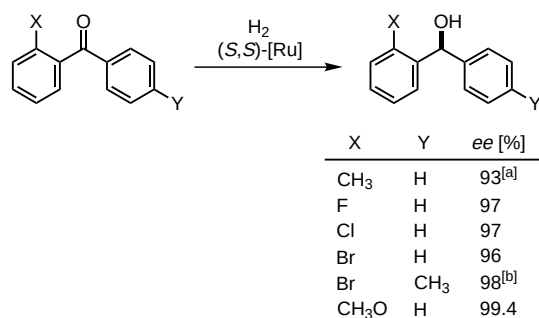
(*S*)-1-(2-(diphenylphosphano)phenyl)ethylamine (Ru:P,N ligand in a 1:2 mol ratio) had activity similar to the BINAP/DPEN–ruthenium complex in the hydrogenation of acetophenone, although the *ee* value of the *S* product was only 35%.^[28] Further structural elaboration is necessary for developing an efficient asymmetric reaction. It is relevant that a PennPhos/rhodium catalyst developed by Zhang et al. promotes hydrogenation of several aromatic ketones with up to 96% *ee* (S/C = 100/1, 30 atm H₂).^[43]

α -Tetralone is a difficult substrate, its hydrogenation using an (*R*)-XylBINAP/(*S,S*)-DPEN/KOH combined catalyst (S/C = 1000/1, 15 atm H₂, 30 °C, 6 h) gave the *S* alcohol in only 82% *ee* (Scheme 29).^[28] For the asymmetric hydrogenation of 1,2-benzocycloalken-3-ones, better enantioselectivity

Scheme 29. Asymmetric hydrogenation of α -tetralones.

was obtained by the [Ir]((*R*)-binap)(cod)]BF₄/P[C₆H₄-2-N(CH₃)₂]₂C₆H₅ mixed system of Takaya et al. (S/C ~ 200/1), although the reaction requires a hydrogen pressure of > 50 atm and a temperature as high as 90 °C.^[45] This catalyst system, however, is not appropriate for the asymmetric hydrogenation of simple aryl alkyl ketones, for example acetophenone and valerophenone gave the alcohols in only 54 and 3% *ee*, respectively.^[134] Benzo-fused cyclic ketones are converted enantioselectively into the chiral alcohols by various methods: our Ru-catalyzed transfer hydrogenation with 2-propanol or formic acid (S/C = 200/1),^[58a, 135] Corey hydroboration (S/C = 4/1–100/1),^[48, 136, 137] Mukaiyama cobalt-aided NaBH₄ reduction (S/C = 20/1),^[49] and Rh-catalyzed hydrosilylation (S/C = 100/1)^[55b,e,g] as well as stoichiometric aluminum hydride or organoboron reduction.^[138, 139]

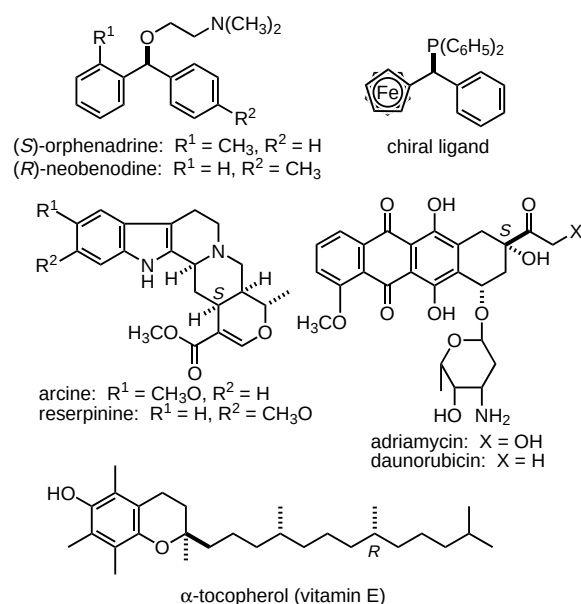
Use of *trans*-[RuCl₂[(*S*)-xylbinap]][(S)-daipen] allows for asymmetric hydrogenation of *ortho*-substituted benzophenones with an S/C ratio of up to 20000/1.^[83, 140, 141] Some examples are given in Scheme 30.^[126] The (*S*)-2-methyl-



Scheme 30. Asymmetric hydrogenation of *ortho*-substituted benzophenones. Conditions: (S,S)-[Ru] = *trans*-[RuCl₂[(S)-xylbinap]][(S)-daipen]], (CH₃)₃COK, (CH₃)₂CHOH, 8 atm H₂, 28–35 °C. [a] A precursor of (S)-orphenadrine, see Scheme 31. [b] A precursor of (R)-neobenodine, see Scheme 31.

benzhydrol thus obtained is a precursor of (S)-orphenadrine which has potent antihistaminic and anticholinergic activity (see Scheme 31).^[142] The methyl, fluoro, chloro, and bromo derivatives exhibit the same sense of asymmetric induction, which indicates that the possible ruthenium/heteroatom interaction is not the origin of the enantioselection.

As might be expected, simple *meta*- and *para*-substituted benzophenones were hydrogenated with low or only moderate enantioselectivity. The highest *ee* value was 47 %, obtained with *p*-trifluoromethylbenzophenone. However, the antihistaminic (R)-neobenodine (Scheme 31)^[142] has been synthesized using asymmetric hydrogenation of *o*-bromo-*p*'-methylbenzophenone as a key step.^[83]

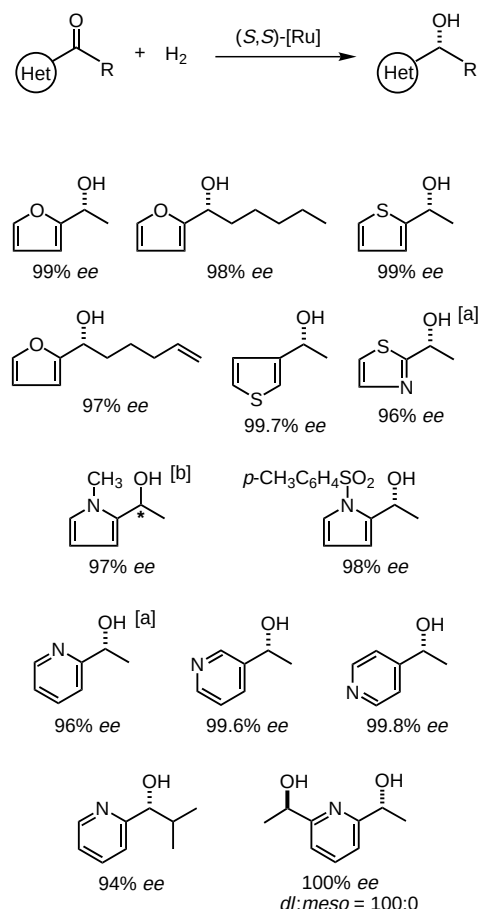


Scheme 31. Products obtained by routes involving asymmetric hydrogenation catalyzed by chiral diphosphane/diamine–ruthenium complexes.

In the presence of the (S)-TolBINAP/(S)-DAIPEN catalyst, ferrocenyl phenyl ketone was hydrogenated to give the *S* alcohol in 95 % *ee*.^[83] This alcohol can be converted into a chiral ferrocenylphosphane with retention of configuration (Scheme 31).^[143, 83]

5.2. Heteroaromatic Ketones

Various ketones possessing an electron-rich or -deficient heterocycle substituent can be used as substrates (Scheme 32).^[144] When a 5 M solution of 2-acetylfuran



Scheme 32. Asymmetric hydrogenation of heteroaromatic ketones. Usually yields of >96 % are obtained. Conditions: (S,S)-[Ru] = *trans*-[RuCl₂[(S)-xylbinap]][(S)-daipen]], (CH₃)₃COK, (CH₃)₂CHOH, 8 atm H₂, 25–30 °C. [a] B[OCH(CH₃)₂]₃ was added (ketone:Ru:borate = 2000:1:20). [b] 61 % yield. Absolute configuration undetermined. Het = heteroaryl.

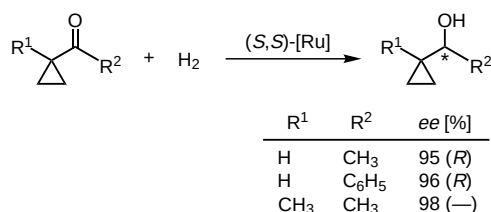
(110 g) in 2-propanol was hydrogenated with an (S)-XylBINAP/(S)-DAIPEN–ruthenium catalyst at an S/C of 40 000/1, (R)-1-(2-furyl)ethanol was obtained in 99 % *ee* without reduction of the furan ring.^[126, 145] Hydrogenation of 2- and 3-acetylthiophenes gave the chiral alcohols in >99 % *ee*, the sulfur-containing heterocycles did not disturb the catalytic activity. Although hydrogenation of 2-acetylthiazole and 2-acetylpyridine was sluggish under the standard conditions, in the presence of B[OCH(CH₃)₂]₃ (ketone:Ru:borate = 2000:1:20)^[53, 139] the reaction gave the corresponding chiral alcohols quantitatively. The reactions of 3- and 4-acetylpyridines gave the chiral alcohols in high yield and *ee* values without B[OCH(CH₃)₂]₃. Double hydrogenation of 2,6-diacetylpyridine gave the enantiomerically pure *R,R* diol.^[144, 146] In all cases, the sense of asymmetric induction was identical to that observed with aromatic ketones. This method, like asymmetric hydroboration, is very general.^[48, 51c, 139, 141i, 147] A

combination of BICP (a chiral 1,4-diphosphane) and DPEN also gives enantioselective hydrogenation of acetylthiophenes.^[47] 2-Acetylfuran is reduced enantioselectively by asymmetric hydrogenation using a PennPhos/rhodium complex^[43] or by transfer hydrogenation with formic acid, catalyzed by a chiral ruthenium complex.^[135b]

Chiral 1-(3-pyridyl)- and 1-(4-pyridyl)ethanols have been used for stereoselective condensation with racemic α -arylcarboxylic anhydrides to give the diastereomerically enriched esters.^[148] (*R*)-1-(3-Pyridyl)ethanol is an intermediate in the synthesis of heteroyohimbine alkaloids such as arcin and reserpinin (Scheme 31),^[149] the (*S,S*)- or (*R,R*)-2,6-di(1-hydroxyethyl)pyridines serve as a key precursor of C_2 symmetric P,N,P-tridentate ligands,^[150] and the alkyl(2-thiazolyl)methanol products can be converted into synthetically useful chiral α -hydroxy aldehydes.^[151]

5.3. Cyclopropyl Ketones

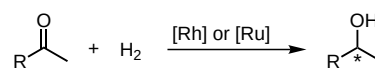
Hydrogenation of cyclopropyl methyl ketone in the presence of the (*S*)-XylBINAP/(*S*)-DAIPEN catalyst and $(CH_3)_3COK$ proceeded without cleavage of the cyclopropane ring, forming the *R* alcohol in 95% *ee* (Scheme 33).^[128] The cyclopropyl group exerts an electronic effect in the transition state thus generating the stereochemical bias.^[141f] Cyclopropyl phenyl ketone gave the alcohol in 96% *ee* with an opposite sense of asymmetric induction.^[128] Hydrogenation of 1-acetyl-1-methylcyclopropane gave the alcohol (with an unknown absolute configuration) in 98% *ee*.^[28] The structurally similar pinacolone was inert under these conditions.



Scheme 33. Asymmetric hydrogenation of cyclopropyl ketones. Conditions: (*S,S*)-[Ru] = *trans*-[RuCl₂][(S)-xylbinap][(S)-daipen]], $(CH_3)_3COK$, $(CH_3)_2CHOH$, 8 or 10 atm H₂, 28 °C.

5.4. Dialkyl Ketones

Asymmetric hydrogenation of simple dialkyl ketones is still difficult. Hydrogenation of cyclohexyl methyl ketone catalyzed by the (*R*)-XylBINAP/(*R*)-DAIPEN complex and $(CH_3)_3COK$ (*S/C* = 10000/1) gave an *S* alcohol in 85% *ee* (Scheme 34), while 2-nonanone gave nearly racemic 2-nonanol.^[128] Hydrogenation of 4-phenyl-2-butanone with (*R*)-XylBINAP/(*S,S*)-DPEN catalyst gave 4-phenyl-2-butanol in 51% *ee*.^[28] Currently, the best catalyst for this purpose is a PennPhos–rhodium complex, although an improvement in catalytic activity (*S/C* = 100/1) is desirable.^[43] A DEGU-PHOS–rhodium complex hydrogenates pinacolone to give the alcohol in 84% *ee*.^[44] Heterogeneous hydrogenation of 2-alkanones in the presence of a tartaric acid modified Raney



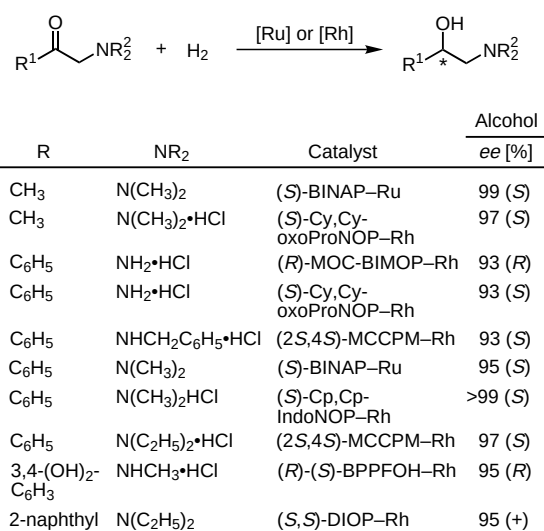
R	Catalyst (S/C)	Alcohol	
		yield [%]	ee [%]
<i>n</i> -C ₄ H ₉	(<i>R,S,R,S</i>)-Me-PennPhos–Rh (100/1)	96	75 (<i>S</i>)
<i>n</i> -C ₇ H ₁₅	(<i>R</i>)-XylBINAP/(<i>R</i>)-DAIPEN Ru (2000/1)	100	1
C ₆ H ₅ (CH ₂) ₂	(<i>R,S,R,S</i>)-Me-PennPhos–Rh (100/1)	99	73 (<i>S</i>)
C ₆ H ₅ (CH ₂) ₂	(<i>R</i>)-XylBINAP/(<i>S,S</i>)-DPEN Ru (1000/1)	100	51
(CH ₃) ₂ CH	(<i>R,S,R,S</i>)-Me-PennPhos–Rh (100/1)	99	84 (<i>S</i>)
<i>cyclo</i> -C ₆ H ₁₁	(<i>R,S,R,S</i>)-Me-PennPhos–Rh (100/1)	90	92 (<i>S</i>)
<i>cyclo</i> -C ₆ H ₁₁	(<i>R</i>)-XylBINAP/(<i>R</i>)-DAIPEN Ru (10 000/1)	99	85 (<i>S</i>)
(CH ₃) ₃ C	(<i>R,S,R,S</i>)-Me-PennPhos–Rh (100/1)	51	94 (<i>S</i>)

Scheme 34. Asymmetric hydrogenation of dialkyl ketones. For the structures of the chiral ligands, see Schemes 7 and 23.

Ni and an excess amount of pivalic acid gives 2-alkanols in up to 85% *ee*.^[152] 2,5-Dimethylborolane is known to reduce a variety of alkanones to afford the chiral alkanols with a high optical purity.^[53]

5.5. Amino Ketones

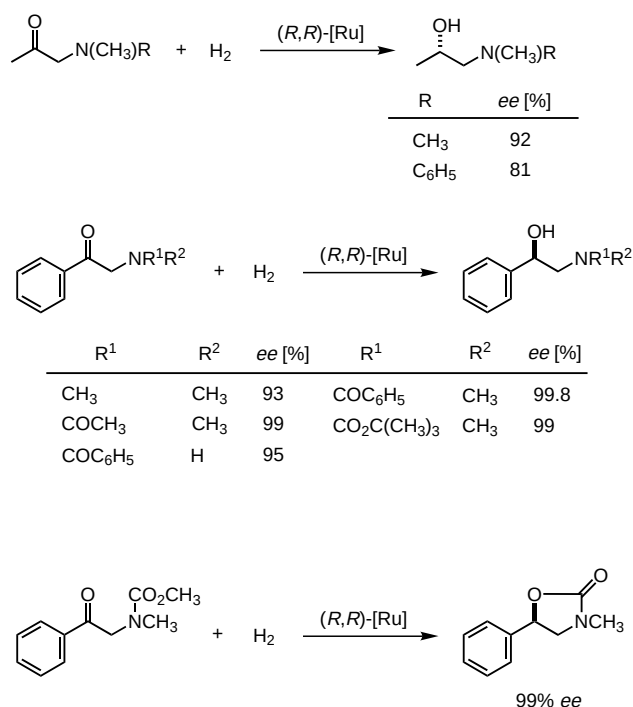
Kumada and co-workers pioneered the development of asymmetric hydrogenation of 2-(alkylamino)acetophenone derivatives catalyzed by chiral ferrocenylphosphane-based rhodium complexes.^[153] In this regard, Achiwa's MCCPM–rhodium complex catalyzed hydrogenation of 2-(diethylamino)acetophenone hydrochloride in methanol (*S/C* of 100 000/1 20 atm of H₂, 50 °C, 20 h) in a 96% optical yield.^[154] Some related examples are given in Scheme 35.^[153–155] BINAP–Ru



Scheme 35. Asymmetric hydrogenation of α -amino ketones with chiral ruthenium and rhodium catalysts. For the structures of the chiral ligands, see Schemes 7 and 23.

catalysts also gave highly enantioselective hydrogenation of α -dialkylamino ketones (*S/C* = 1000/1) (see Scheme 2),^[22, 156] but the catalytic activity was modest requiring a hydrogen pressure as high as 100 atm. The XylBINAP/DAIPEN–ruthenium complex appears to be an efficient catalyst for this

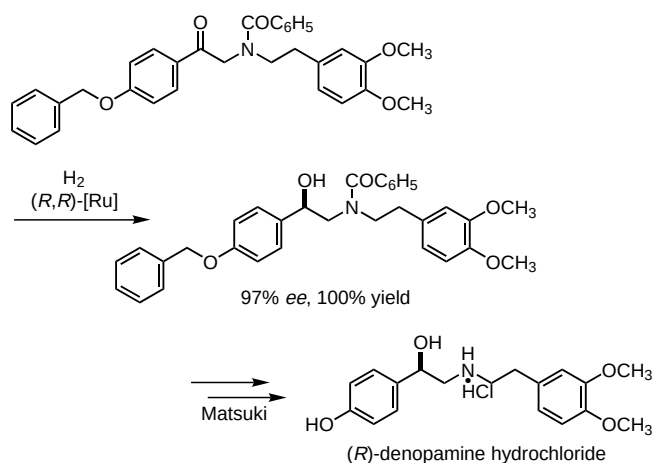
purpose. For example, hydrogenation of α -(dimethylamino)-acetone with the *R,R* catalyst and with an S/C of 2000/1 under 8 atm of H₂ gave the *S* alcohol in 92 % *ee* (Scheme 36).^[157] The reaction does not involve the coordination of the amino group to the ruthenium center; thus, the sense of enantioselection is opposite to that of the reaction with the diamine-free BINAP–Ru catalysts which is triggered by nitrogen/ruthenium interaction as seen with β -keto ester substrates (see Scheme 3).^[9–11] 2-(Dimethylamino)acetophenone was hydrogenated under 8 atm of H₂ with the *R,R* catalyst to give the *R* alcohol in 93 % *ee* (Scheme 36). The hydrogenation using an



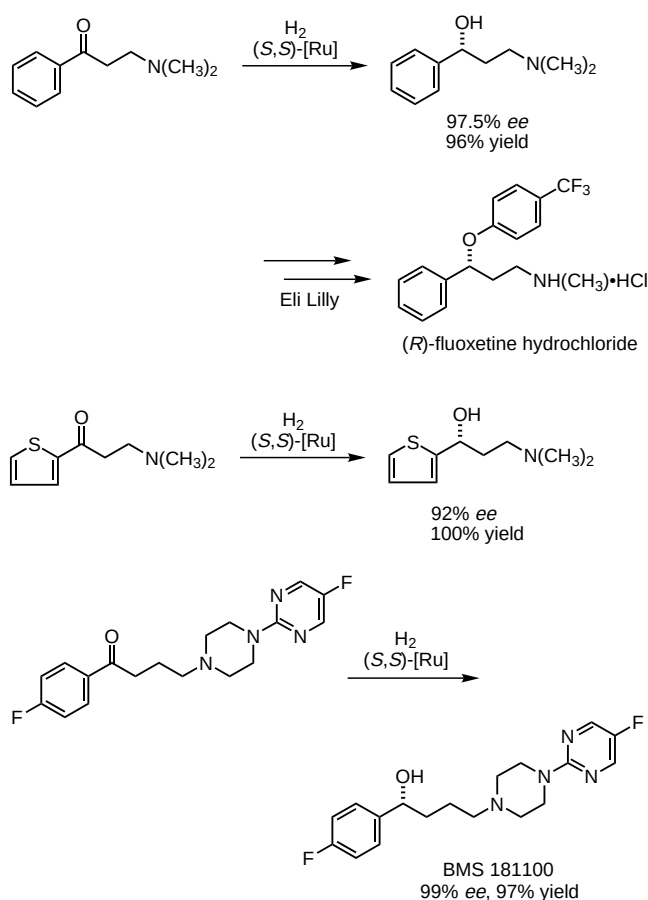
Scheme 36. Asymmetric hydrogenation of α -amino ketones. Conditions: (*R,R*)-[Ru] = *trans*-[RuCl₂](*R*)-xylbinap][(*R*)-daipen], (CH₃)₃COK, (CH₃)₂CHOH, S/C = 2000/1, 8 atm H₂, 25 °C.

α -amido ketone was applied to the enantioselective synthesis of (*R*)-denopamine, a β_1 -receptor agonist used for treating congestive heart failure (Scheme 37).^[157–159] Again, in this hydrogenation the protected 2-aminoacetophenone behaves as a simple aromatic ketone and the amide group does not exert any directive influence.

The XylBINAP/DAIPEN–ruthenium complex was utilized successfully for the asymmetric hydrogenation of certain β - or γ -amino ketones. Hydrogenation of 3-(dimethylamino)-propiophenone with an (*S*)-XylBINAP/(*S*)-DAIPEN ruthenium complex with an S/C ratio of 10000/1 gave the corresponding *R* amino alcohol in 97.5 % *ee* (Scheme 38),^[157] which is a synthetic intermediate of (*R*)-fluoxetine, a selective serotonin-uptake inhibitor.^[160] Eli Lilly sells racemic fluoxetine hydrochloride as the antidepressant Prozac with a market value of \$2.6 billion (1997).^[161] However, the *R* enantiomer is more potent. Furthermore, as illustrated in Scheme 38, asymmetric hydrogenation of a γ -amino ketone (S/C = 10000/1) allows for the direct asymmetric synthesis of the potent antipsychotic BMS 181100.^[157, 162] This approach



Scheme 37. Asymmetric synthesis of (*R*)-denopamine. Conditions of hydrogenation: (*R,R*)-[Ru] = *trans*-[RuCl₂](*R*)-xylbinap][(*R*)-daipen], (CH₃)₃COK, (CH₃)₂CHOH, S/C = 2000/1, 8 atm H₂, 25 °C.



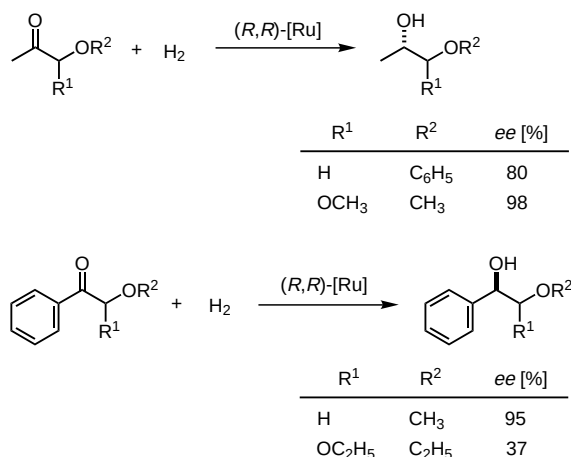
Scheme 38. Asymmetric hydrogenation of β - and γ -amino ketones including application to the synthesis of fluoxetine and BMS 181100. Conditions of hydrogenation: (*S,S*)-[Ru] = *trans*-[RuCl₂](*S*)-xylbinap][(*S*)-daipen], (CH₃)₃COK, (CH₃)₂CHOH, S/C = 2000/1 or 10000/1, 8 atm H₂, 25 °C.

is superior to the reaction using chiral rhodium complexes that requires a high catalyst loading (S/C = 200/1 – 1000/1) and relatively high H₂ pressure (30–50 atm).^[155d, 163]

Thus, this asymmetric hydrogenation is applicable to the synthesis of a wide variety of important pharmaceutical chiral amino alcohols and their derivatives.

5.6. α -Alkoxy Ketones

α -Phenoxyacetone and 2-methoxyacetophenone were hydrogenated under 8 atm of H_2 in the presence of the (*R*)-XylBINAP/(*R*)-DAIPEN complex to give the corresponding *S* and *R* alcohols in 80 and 95 % *ee*, respectively (Scheme 39).^[28] Hydrogenation of pyruvic aldehyde dimethylacetal gave the *S* alcohol in 98 % *ee*,^[28] while the reduction of



Scheme 39. Asymmetric hydrogenation of α -alkoxy ketones. Conditions: (*R,R*)-[Ru] = *trans*-[RuCl₂](*R*)-xylbinap][(*R*)-daipen], (CH₃)₃COK, (CH₃)₂CHOH, S/C = 2000/1, 8 atm H_2 , 25–28 °C.

2,2-diethoxyacetophenone gave the *R* alcohol in only 37 % *ee*.^[28] Thus, the alkoxy or phenoxy group possesses a significant stereo-directing ability but its function is not coordinative in nature. The effect of a phenyl group is overwhelming. It is relevant that certain chiral rhodium complexes are known to hydrogenate pyruvic aldehyde dimethylacetal in up to 75 % *ee*.^[164] Cinchona modified Pt/Al₂O₃ catalysts provide the chiral alcohol in up to 97 % *ee*.^[165]

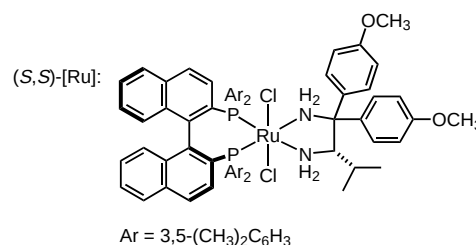
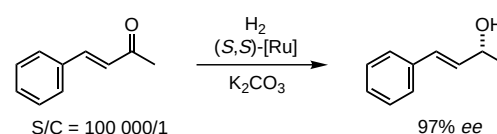
5.7. Olefinic Ketones

Efficient asymmetric hydrogenation of α,β -unsaturated ketones is an enduring problem in organic chemistry and has been our cardinal focus. Chiral allyl alcohol products are important not only for their own sake but also in connection with Claisen technology and various S_N2' substitution reactions.^[166–168] This transformation has been achieved only by stoichiometric use of metal hydride reagents.^[51a, 55d,e,h, 130a, 136, 138, 141f, 169–171] Alternatively, chiral allyl alcohols are obtained by the Sharpless kinetic resolution (acyclic compounds)^[172] or our ruthenium-catalyzed hydrogenation^[173] or our transfer hydrogenation (cyclic substrates).^[174] The ideal stereoselective hydrogenation of alkenyl ketones, however, was difficult because of the conformational flexibility and the presence of two kinds of unsaturated groups, C=C and C=O, the former having higher reactivity in conventional hydrogenation. A BINAP–Ir complex is known to hydrogenate benzalacetone in 65 % optical yield and 97 % keto selectivity.^[93] Earlier we found that hydrogenation of the same ketone with an in situ generated BINAP/DPEN–ruthenium catalyst in 2-propanol

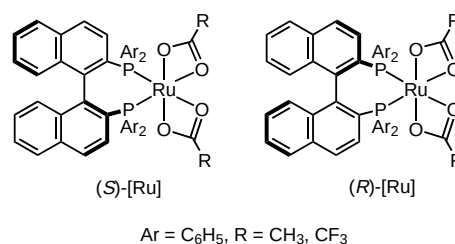
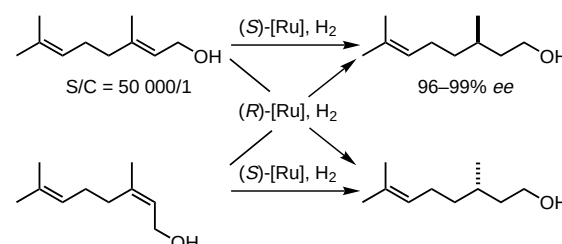
containing KOH showed perfect keto selectivity but with only 70 % optical yield.^[97] In addition, some simple enones are highly sensitive to basic conditions, hampering the utility of our original procedure.

Fortunately, this long-standing problem has now been solved by the development of the XylBINAP/DAIPEN–ruthenium catalyst and by the use of K₂CO₃, a weak base cocatalyst, in place of conventional KOH or (CH₃)₃COK.^[128] Thus, reaction of benzalacetone (100 g) in 2-propanol (150 mL) containing the (*S*)-XylBINAP/(*S*)-DAIPEN–ruthenium catalyst (8.3 mg) and K₂CO₃ (9.4 g) under 80 atm of H_2 (S/C = 100 000/1, 2.7 M solution) gave the *R* alcohol in 97 % *ee* (Scheme 40 a). With an S/C of 10 000/1 hydrogenation

a) Selective formation of allyl alcohol



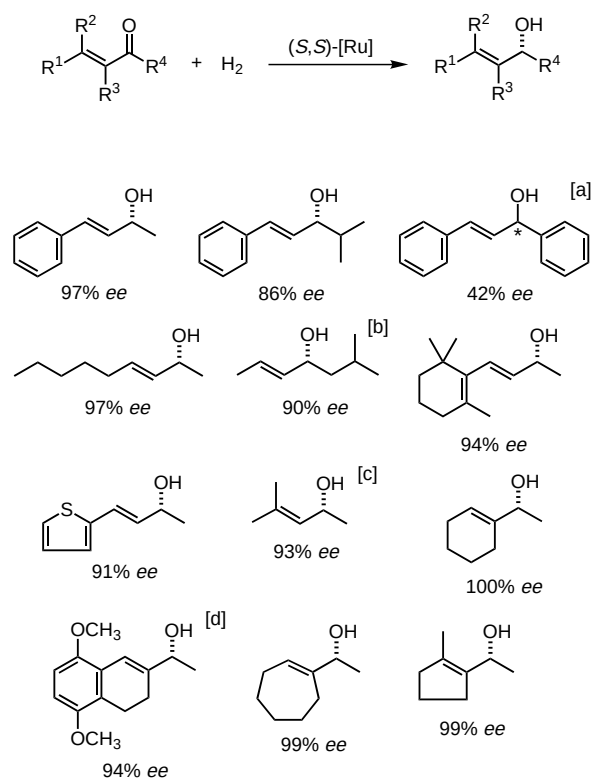
b) Selective reaction of allyl alcohols



Scheme 40. ruthenium-catalyzed asymmetric hydrogenation of a) benzalacetone ((CH₃)₂CHOH, 80 atm H_2 , 30 °C, 100 % yield) and b) geraniol and nerol (CH₃OH, 30 atm H_2 , 18–20 °C, 97–100 % yield).

was accomplished smoothly under 10 atm of H_2 . The absence of any trace of C=C reduction products is noteworthy, because the related diamine-free BINAP–Ru complexes, developed in our laboratories, exhibit eminent catalytic activity for the hydrogenation of the C=C unit of allyl alcohols such as geraniol and nerol (Scheme 40 b).^[175] The chemistries of both systems are thus entirely different.

Scheme 41 illustrates asymmetric hydrogenation of structurally flexible enones with various substitution patterns to the corresponding chiral allyl alcohols.^[126, 128] Highly base-sensitive 3-nonen-2-one is convertible to the allyl alcohol in 97% *ee* by using a dilute (0.1M) 2-propanol solution to minimize undesired polymerization. Hydrogenation of (*E*)-6-methyl-2-hepten-4-one catalyzed with an (*R*)-XylBINAP/(*R*)-DAIPEN – ruthenium catalyst afforded the *S* allyl alcohol with 90% *ee*, which serves as a key building block for the preparation of the side chain of α -tocopherol (vitamin E; see Scheme 31).^[128, 176] More substituted, less base-sensitive

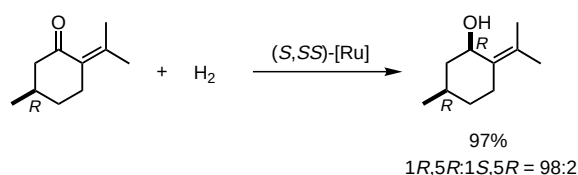


Scheme 41. Asymmetric hydrogenation of α,β -olefinic ketones. The yields are >96%. Conditions: (*S,S*)-[Ru] = *trans*-[RuCl₂][(S)-xylbinap][(S)-daipen]], K₂CO₃ or (CH₃)₃COK, (CH₃)₂CHOH, 8–10 atm H₂ (S/C = 2000/1–13000/1) or 80 atm H₂ (S/C = 100000/1), 25–30 °C. [a] Absolute configuration undetermined. [b] A precursor of α -tocopherol side chain, see Scheme 31. [c] Reduction with an (*S*)-XylBINAP/(*S,S*)-DPEN – ruthenium catalyst. [d] The *S* enantiomer obtained with an (*R*)-BINAP/(*R*)-DAIPEN – ruthenium catalyst is a precursor of anthracycline antibiotics, see Scheme 31.

enones can be hydrogenated more rapidly and conveniently by using a strong-base cocatalyst. 1-Acetylcycloalkenes were hydrogenated to 1-hydroxyethylcycloalkenes with high *ee* values. This method allows asymmetric synthesis of a key intermediate for anthracycline antibiotics (adriamycin and daunorubicin in Scheme 31).^[97, 177] β -Ionone, a dienone, is converted into β -ionol in 94% *ee* and the hydrogenation of (*E*)-4-(2-thienyl)-3-buten-2-one gave the chiral allyl alcohol without saturation of the olefinic bond or the thiophene ring.^[28] Here the combination of the *S* diphosphane and *S* diamine (or *R* and *R*) is crucial for obtaining a high level of enantioselection, as has been observed in the reactions of

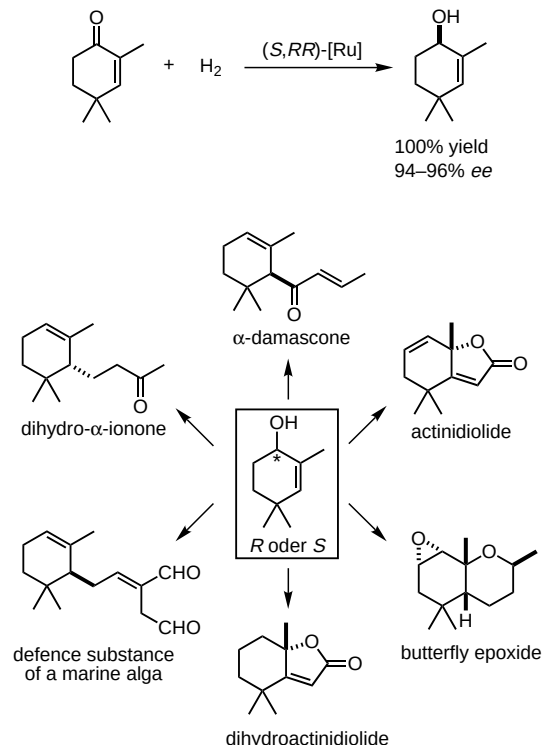
aromatic ketones. Differentiation between aromatic and vinyl groups is difficult. Chalcone was hydrogenated to the allyl alcohol in only 42% *ee*.^[28] Simple vinyl ketones undergo both 1,2- and 1,4-hydrogenation competitively. For example, the reaction of 2-methyl-1-decen-3-one under 8 atm H₂ with an (*S*)-XylBINAP/(*S*)-DAIPEN catalyst gave a mixture of the expected *R* allyl alcohol (99% *ee*), saturated ketone, and saturated alcohol in a 59:40.5:0.5 ratio.^[28]

(*R*)-Pulegone, a chiral *s-cis* enone, was hydrogenated smoothly under 8 atm H₂ by using a simple (*S*)-BINAP/(*S,S*)-DPEN catalyst system to give a 98:2 mixture of the 1*R*,5*R* and 1*S*,5*R* alcohols in 97% yield together with 1.8% of other minor products (Scheme 42).^[178] Use of an (*R*)-BINAP/(*R,R*)-DPEN system led to somewhat lower diastereoselectivity (1*R*,5*R*:1*S*,5*R* = 95:5) with concomitant formation of (1*S*,2*S*,5*R*)-2-isopropenyl-5-methylcyclohexanol (9.7%).



Scheme 42. Diastereoselective hydrogenation of pulegone. Conditions: (*S,SS*)-[Ru] = [RuCl₂][(S)-binap](dmf)_n], (*S,S*)-DPEN, KOH, (CH₃)₂CHOH, S/C = 250/1, 8 atm H₂, 28 °C.

Certain cyclic enones can also be hydrogenated with high enantioselection. Scheme 43 shows the useful application of this method to Mori chemistry.^[179] When 2,4,4-trimethyl-2-

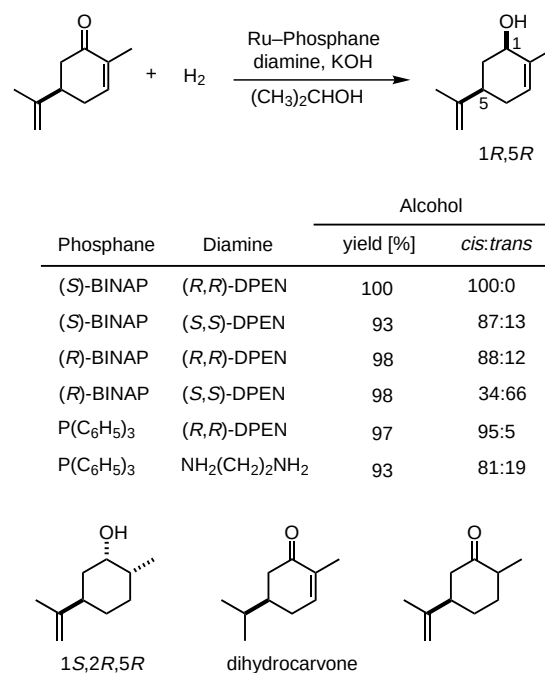


Scheme 43. Combination of the ruthenium-catalyzed asymmetric hydrogenation and Mori chemistry. Conditions of hydrogenation: (*S,RR*)-[Ru] = *trans*-[RuCl₂][(S)-tolbinap][(R,R)-dpn]], (CH₃)₃COK, (CH₃)₂CHOH, S/C = 10000/1 at 10 atm H₂ and 28 °C or S/C = 500/1 at 8 atm H₂ and 0 °C.

cyclohexenone was hydrogenated by using the (*S*)-TolBINAP/(*R,R*)-DPEN–ruthenium catalyst in 2-propanol containing (CH₃)₃COK with an S/C of 10000/1 under 10 atm H₂ at room temperature, the C=O group was selectively saturated to give (*R*)-2,4,4-trimethyl-2-cyclohexenol with 94 % *ee* and in 100 % yield.^[79, 178] No conjugate reduction product was detected. The *ee* value was increased to 96 % by lowering the temperature to 0 °C.^[180] The *R* and *S* alcohols, coupled with the Claisen reaction, can be converted into a series of carotenoid-derived odorants and other bioactive terpenes.^[179, 181] The selectivity of this catalytic reaction appears to depend on the synergistic effects of the chiral diphosphane and diamine ligands as well as the structures of ketones. In this case, unlike the asymmetric reactions described above, the combined use of the (*S*)-BINAP and (*R,R*)-DPEN (or *R* and *S,S*) is necessary for the high stereoselection. A reaction using the *R* diphosphane and the *R,R* diamine gave the *S* alcohol in only 26 % *ee*.^[79, 178] In addition, the *ee* value obtained with the BINAP/DPEN catalyst was superior to the 80 % *ee* obtained with the (*S*)-XylBINAP/(*R,R*)-DPEN system.^[28]

The presence of the methyl substituent at the C-2 position is crucial for efficient generation of the C-1 stereogenic center. Hydrogenation of simple 2-cyclohexenone under 4 atm H₂ with an (*R*)-BINAP/(*R,R*)-DPEN system gave a mixture of (*R*)-2-cyclohexenol in 58 % *ee* (65 % yield), cyclohexanol (2 %), and polymeric material (30 %).^[178, 182] In the presence of the same catalyst, 3-methyl-2-cyclohexenol gave (*R*)-3-methyl-2-cyclohexenol with 45 % *ee* in 99 % yield. Reaction of 4,4-dimethyl-2-cyclohexenone with an (*S*)-BINAP/(*R,R*)-DPEN system produced (*S*)-4,4-dimethyl-2-cyclohexenol in only 47 % *ee* in 100 % yield. Thus, more suitable catalysts and conditions need to be developed for these enone substrates. Currently, efficient catalytic access to 2-unsubstituted 2-cyclohexenols with high enantiomeric purity is limited to kinetic resolution by asymmetric hydrogenation^[173] or transfer hydrogenation catalyzed by chiral ruthenium catalysts.^[174]

(*R*)-Carvone a compound which possesses three unsaturated bonds and a C-5 stereogenic center poses many selectivity problems: 1) 1,2 versus 1,4 selectivity in the α,β -enone moiety, 2) chemoselectivity between the conjugated and isolated C=C linkage, and 3) *cis* versus *trans* diastereoselectivity with respect to the C-5 substituent in the C=O saturation. With no control over selectivity, 17 different hydrogenation products are possible! In fact, hydrogenation of the dienone under 4 atm H₂ with an (*S*)-BINAP/(*R,R*)-DPEN combined system resulted in perfect chemo- and diastereoselectivity, giving solely (1*R*,5*R*)-carveol in 100 % yield (Scheme 44).^[178] The 5*R* configuration of the chiral ketone significantly affects the rate and stereoselectivity. Thus, in the presence of the (*R*)-BINAP/(*S,S*)-DPEN combined system, the *R* dienone was hydrogenated rather slowly, giving a 34:66 mixture of the 1*R*,5*R* (*cis*) and 1*S*,5*R* (*trans*) alcohols. Use of the achiral P(C₆H₅)₃/NH₂(CH₂)₂NH₂ system gives the allyl alcohol in 93 % yield (*cis:trans* = 81:19) in addition to 7 % of the 2,3-saturated 1*S*,2*R*,5*R* product arising from 1,4-addition followed by diastereoselective C=O hydrogenation. Notably, hydrogenation of carvone with [RhCl(P(C₆H₅)₃)₃] in toluene takes place selectively at the nonconjugated C=C bond to give (*R*)-5-isopropyl-2-methyl-2-



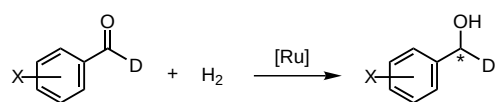
Scheme 44. Stereoselective hydrogenation of (*R*)-carvone.

cyclohexenone((*R*)-dihydrocarvone).^[183] Stoichiometric reduction of carvone with L-Selectride in THF at –78 °C is known to give the 1,4-reduction product, (*R*)-isopropenyl-2-methylcyclohexanone (*trans:cis* = 81:19) exclusively,^[178, 184] whereas the use of an equimolar mixture of NaBH₄ and CeCl₃ in methanol gives a 97:3 mixture of (1*R*,5*R*)-carveol and the 1*S*,5*R* isomer quantitatively.^[178, 185]

Asymmetric methods for hydrogenating α,β -acetylenic ketones to chiral propargyl alcohols are still unavailable.^[99] Enantioselective reduction requires ruthenium-catalyzed transfer hydrogenation employing 2-propanol^[186] or the use of metal hydride reagents.^[169c, 187–190]

5.8. 1-Deuteriobenzaldehydes

Chiral 1-deuterio alcohols are useful for mechanistic studies of various chemical and biochemical reactions.^[191] Hydrogenation of 1-deuterio-*o*-methylbenzaldehyde with an (*S*)-TolBINAP/(*S*)-DAIPEN ruthenium complex in the presence of base at 28 °C and 8 atm H₂ gave the (*S*)-alcohol in 89 % *ee* (Scheme 45).^[28] The asymmetric sense was opposite to that in the hydrogenation of *o*-methylacetophenone with the same catalyst system (*R* alcohol in 99 % *ee*, see Table 2).^[79] The XylBINAP/DAIPEN system showed lower selectivity. Simple 1-deuteriobenzaldehyde was hydrogenated in only 46 % *ee*.^[28] In comparison, hydrogenation of 1-deuteriobenzaldehydes with [Ru(OCOCH₃)₂](*R*)-binap] in the presence of a strong acid gave (*S*)-1-deuterio alcohols in up to 89 % *ee* (Scheme 45).^[192] At present, transfer hydrogenation using a chiral arene–ruthenium complex and 2-propanol or formic acid is better than hydrogenation.^[193] The Corey, Bakshi, Shibata (CBS) reduction of aldehydes^[48] using a deuterated catecholborane gives the chiral deuterated primary alcohols in up to 95 % *ee*.^[136c]



X	Catalyst	Alcohol ee [%]
H	<i>trans</i> -[RuCl ₂]{(S)-tolbinap}[(S)-daipen] + (CH ₃) ₃ COK	46 (S)
H	[Ru(OCOCH ₃) ₂]{(R)-binap}] + HCl	65 (S)
2-CH ₃	<i>trans</i> -[RuCl ₂]{(S)-tolbinap}[(S)-daipen] + (CH ₃) ₃ COK	89 (S)
2-Br	[Ru(OCOCH ₃) ₂]{(R)-binap}] + HCl	89 (S)
3-Cl	[Ru(OCOCH ₃) ₂]{(R)-binap}] + HCl	73 (—)
4-Cl	[Ru(OCOCH ₃) ₂]{(R)-binap}] + HCl	70 (—)

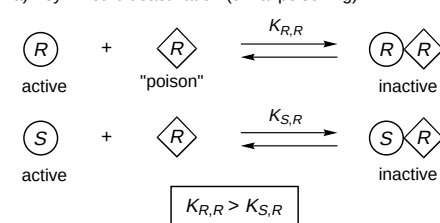
Scheme 45. Asymmetric hydrogenation of 1-deuteriobenzaldehydes with chiral ruthenium complexes.

6. Asymmetric Activation

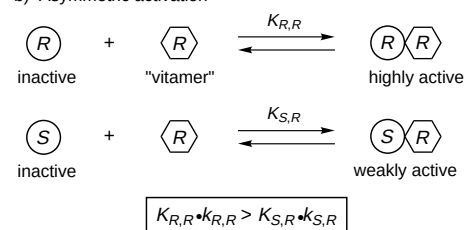
Racemic catalysts normally give racemic products. However, sometimes the chemical attributes of enantiomeric molecules can be affected strongly by a surrounding non-racemic compound.^[132] Diastereomeric interactions lead to unequal stabilities (K_{R^*,R^*} vs K_{S^*,R^*}) and reactivities (k_{R^*,R^*} vs k_{S^*,R^*}) of the associates, resulting in unique chemical consequences. As schematically illustrated in Scheme 46, when one of the enantiomeric catalysts can be selectively deactivated by a nonracemic compound acting as a “poison”, asymmetric catalysis can be achieved by the remaining enantiomer.^[194] Another useful strategy employing racemic compounds is the asymmetric activation of an inactive racemic metal complex by a nonracemic compound,^[76, 195] which we call a “vitamer” (Scheme 46b). Thus, a diastereomeric catalyst, formed by enantioselective activation of racemic metal complexes, if its architecture is suitable, can promote a highly selective asymmetric reaction. This has been realized by the activation of racemic diphosphane–ruthenium complexes with an enantiomerically pure 1,2-diamine as a vitamer.

The target was the challenging allyl alcohol, (*R*)- or (*S*)-2,4,4-trimethyl-2-cyclohexenol. As described in Section 1.1, racemic [RuCl₂(tolbinap)(dmf)_n]^[24a,b] is a feeble catalyst for hydrogenation of unfunctionalized ketones. However, when 2,4,4-trimethyl-2-cyclohexenone was hydrogenated in the presence of (*S,S*)-DPEN (diamine/ruthenium = 1/1), and KOH under 8 atm H₂ and 0 °C, the *S* allyl alcohol was obtained in 95% ee in 100% yield (Scheme 47).^[180] The ee value is close to the 96% attained with the enantiomerically pure (*R*)-TolBINAP/(*S,S*)-DPEN system. The reaction using the diastereomeric *R,R,R* phosphane–diamine combination occurred rather slowly to give the *S* alcohol in only 26% ee. As illustrated in Scheme 47, increasing the amount of added (*S,S*)-DPEN enhanced the rate of hydrogenation, reaching a near maximum value with a molar ratio of diamine:ruthenium of 1:1.^[180] The ee value of the *S* alcohol, on the other hand, was consistently high from the beginning (diamine/ruthenium > 0.25). Thus, under this hydrogenation

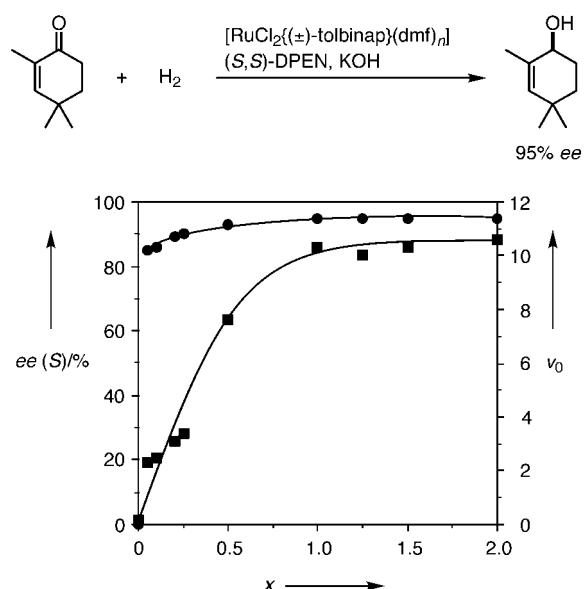
a) Asymmetric deactivation (chiral poisoning)



b) Asymmetric activation



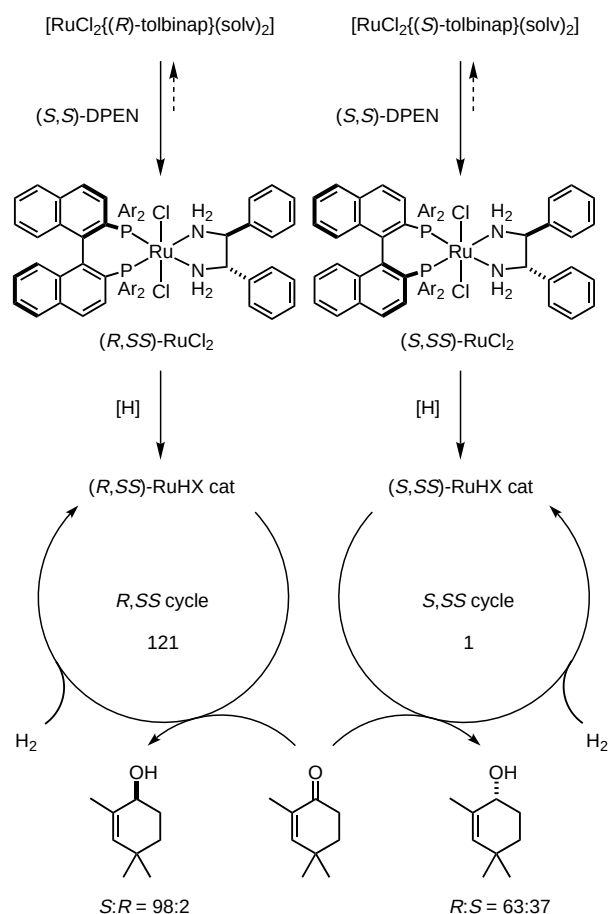
Scheme 46. Strategies for asymmetric catalysis using racemic metal complexes. a) Asymmetric deactivation and b) asymmetric activation by nonracemic compounds.



Scheme 47. Asymmetric hydrogenation of a cyclohexenone using a racemic TolBINAP–Ru complex and an enantiomerically pure diamine. v_0 (■) = Initial rate in moles of product/mol of Ru $\times$ min. x = Mol diamine per mol Ru. ● = ee Value. Conditions: 7/1 (CH₃)₂CHOH/toluene, S/C = 500/1, 8 atm H₂, 0 °C.

condition the (*S,S*)-DPEN vitamer effectively activated the (*R*)-TolBINAP–ruthenium enantiomer of the racemate. A mixed-ligand complex prepared from equimolar amounts of the racemic TolBINAP–ruthenium complex and (*S,S*)-DPEN resulted in enantioselective hydrogenation even in the presence of an equimolar amount of (*R,R*)-DPEN. This result indicates that the initial interaction of the [RuCl₂(diphosphane)] complex with DPEN is virtually irreversible, as was also demonstrated by a ³¹P NMR study.

Scheme 48 provides the simplest explanation of the mechanism of asymmetric activation of the racemic TolBINAP–ruthenium complex, although molecular association of the catalysts or its precursors may lead to further complicated



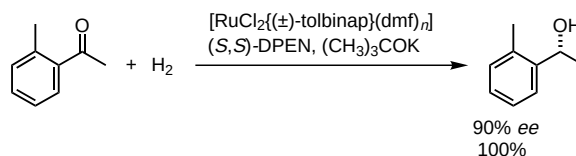
Ar = 4-CH₃C₆H₄; solv = DMF or other ligands
X = H, OR, etc.

Scheme 48. Mechanism of asymmetric activation.

nonlinear effects.^[132, 196] The observed enantioselectivity of hydrogenation reflects the relative TOFs of the competing *R,SS* and *S,SS* catalytic cycles, and the ratio is determined by the relative concentrations and reactivities of the coexisting diastereomeric diphosphane/diamine–ruthenium catalysts. The TolBINAP–Ru dichloride complex which exists as aggregates is almost inactive for the hydrogenation of ketones. Under the reaction conditions, the labile solvent ligands (solv) are displaced by (*S,S*)-DPEN to generate a monomeric TolBINAP/DPEN complex. The equilibrium lies far toward the mixed-ligand complex, regardless of the chirality of the ligands forming the diastereomeric (*R,SS*)- and (*S,SS*)-RuCl₂ complexes^[197] with ³¹P NMR chemical shifts (1/7 (CD₃)₂CDOD/C₆D₅CD₃) of δ = 45.8 and 46.2, respectively. The real catalysts, ruthenium hydride or dihydride species (see Scheme 11) are formed from the dichloride under the basic reductive conditions. The *R,SS* cycle with an *S*:*R* enantioselectivity of 98:2 turns-over 121 times faster than the *S,SS* cycle having an *S*:*R* selectivity of 37:63.^[180]

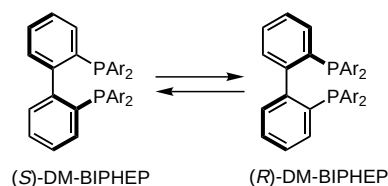
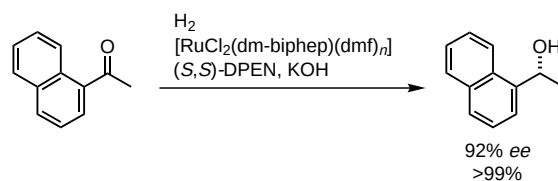
Noteworthy is that the relative significance of the diastereomeric cycles, *R,SS* and *S,SS*, as well as the direction and degree of asymmetric induction is highly dependent on the structures of the ketonic substrates. When *o*-methylacetophenone was used as the hydrogenation substrate, (*S,S*)-DPEN enhanced the activity of the (*S*)-TolBINAP–Ru complex

more than the (*R*)-TolBINAP–Ru enantiomer. The hydrogenation catalyzed by racemic TolBINAP–Ru complex and (*S,S*)-DPEN gave the *R* alcohol in 90 % *ee* and in 100 % yield (Scheme 49).^[180] In this case, unlike the above reaction, the *S,SS* cycle with an *S*:*R* enantioselectivity of 1.3:98.7 occurred 13 times faster than the *R,SS* cycle with an *S*:*R* selectivity of 54:46.



Scheme 49. Asymmetric hydrogenation of an aromatic ketone using a racemic TolBINAP–Ru complex and an enantiomerically pure diamine. Conditions: 7/1 (CH₃)₂CHOH/toluene, S/C = 500/1, 4 atm H₂, 0 °C.

2,2'-Bis(3,5-dimethylphenyl)phosphino-1,1'-biphenyl (DM-BIPHEP) is a conformationally flexible diphosphane (Scheme 50).^[198] When it was combined with (*S,S*)-DPEN in the formation of the ruthenium complex, the diastereomeric DM-BIPHEP/(*S,S*)-DPEN–RuCl₂ complexes^[197] were produced in a 3:1 ratio, in which the major *S,S,S* complex was more reactive in the hydrogenation of aromatic ketones.^[199] Hydrogenation of 1'-acetonaphthone using a mixture of DM-BIPHEP–RuCl₂ complex, (*S,S*)-DPEN, and KOH gave the *R* alcohol in 92 % *ee* and >99 % yield.



Scheme 50. Asymmetric hydrogenation of an aromatic ketone using a racemic phosphane–ruthenium complex and a nonracemic diamine. Conditions: (CH₃)₂CHOH, Ru:DPEN:KOH = 1:1:2, S/C = 250/1, 40 atm H₂, –35 °C. Ar = 3,5-(CH₃)₂C₆H₃.

Thus, enantiomer-selective activation of racemic metal complexes by a chiral vitamer is becoming a viable approach for practical asymmetric catalysis when enantiomerically pure ligands are not readily available.

7. Dynamic Kinetic Discrimination of Stereoisomers

The greatest advantage of this hydrogenation method is the flexible molecular design of the mixed-ligand ruthenium catalysts. The stabilities of product-determining transition states are determined variably by stereo- and electro-complementary assemblies of the (di)phosphanes, diamines, and other ligands on the ruthenium center and the ketonic substrate. In addition, the reaction conditions can be highly optimized. These attributes allow for systematic variation of

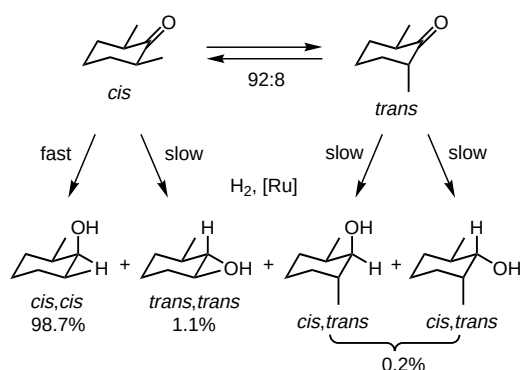
reactivity and selectivity. The described diastereo- and enantioselectivity, when coupled with appropriate kinetic parameters, leads to a new type of stereoselective hydrogenation of ketones. In general, stereoisomeric ketones react at different rates. Thus, when a configurationally labile α -substituted ketone is used, dynamic kinetic discrimination of the stereoisomers is achievable by hydrogenation. The key is the facile configurational inversion of the ketonic substrate, which is facilitated by an alkaline base in a protic solvent.

7.1. Diastereomers

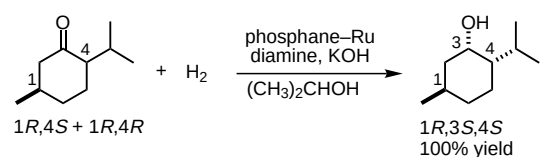
2,6-Dimethylcyclohexanone undergoes highly diastereoselective hydrogenation by kinetic discrimination of the diastereomers.^[104] In 2-propanol containing KOH this ketone is in rapid equilibrium between the *cis* and *trans* isomers. The diequatorial:equatorial,axial:diaxial ratios are 92:8:0 (experiment) or 97:3:0 (ab initio MO calculation).^[104, 111, 112] However, the *trans* isomer is rather unreactive because the equatorial approach of the ruthenium hydride species to the carbonyl carbon is blocked by the axially oriented methyl substituent at the α position, as shown in Scheme 19, while there is no such problem in the *cis* isomer with two equatorial methyl groups. Therefore, hydrogenation in the presence of a $[\text{RuCl}_2\{\text{P}(\text{C}_6\text{H}_5)_3\}_3]/\text{NH}_2(\text{CH}_2)_2\text{NH}_2/\text{KOH}$ catalyst system (Ru:base 1:20 instead of the standard 1:2 ratio) in 2-propanol under 4 atm H_2 gave the *cis,cis* (98.7%), *trans,trans* (1.1%), and *cis,trans* alcohols (0.2%; Scheme 51). The distribution of the *cis,trans* isomer (0.2%) was much less than the equilibrium population of the *trans*-dimethyl ketone (8%).

7.2. Epimers

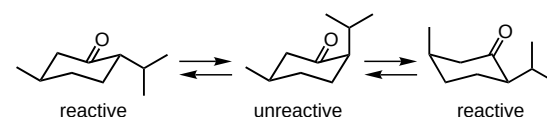
(-)-Menthone has a stable 1*R* stereogenic center and an unstable 4*S* center, in equilibrium with isomenthone, the 4*R* epimer. As illustrated in Scheme 52, when this ketone was subjected to hydrogenation with an achiral $[\text{RuCl}_2\{\text{P}(\text{C}_6\text{H}_5)_3\}_3]/\text{NH}_2(\text{CH}_2)_2\text{NH}_2$ catalyst, a 93.7:6.1:0.2 mixture of (+)-neomenthol with the 1*R*,3*S*,4*S* configuration, menthol (the 1*R*,3*R*,4*R* isomer), and neoisomenthol (the 1*R*,3*R*,4*S*



Scheme 51. Dynamic kinetic discrimination of diastereomeric ketones by ruthenium-catalyzed hydrogenation. Conditions: $[\text{Ru}] = [\text{RuCl}_2\{\text{P}(\text{C}_6\text{H}_5)_3\}_3]$, $\text{NH}_2(\text{CH}_2)_2\text{NH}_2$, KOH (1:1:20), $(\text{CH}_3)_2\text{CHOH}$, S/C = 500/1, 4 atm H_2 , 28 °C.



Phosphane	Diamine	1 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> :1 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> :1 <i>R</i> ,3 <i>R</i> ,4 <i>S</i>
$\text{P}(\text{C}_6\text{H}_5)_3$	$\text{NH}_2(\text{CH}_2)_2\text{NH}_2$	93.7:6.1:0.2
(<i>R</i>)-BINAP	(<i>S,S</i>)-DPEN	100:0:0



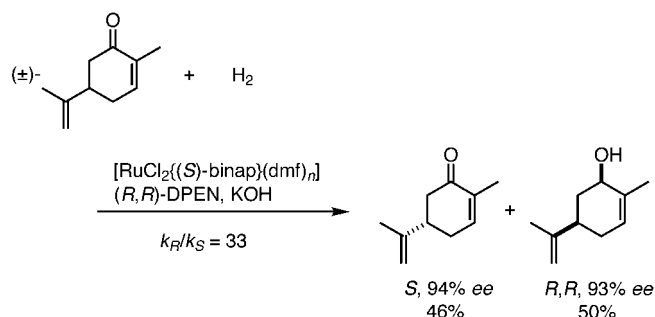
Scheme 52. Dynamic kinetic discrimination of epimeric ketones by ruthenium-catalyzed hydrogenation.

isomer) was produced.^[104] The high 1,2-*cis* stereoselectivity induced by the C-4 isopropyl group is not surprising (Scheme 19). Although the achiral catalyst showed a high stereodistinction, it became more evident when a chiral system was employed for the reaction of the chiral, non-racemic ketone. In fact, hydrogenation with a chiral (*R*)-BINAP/(*S,S*)-DPEN system led exclusively to (+)-neomenthol (Scheme 52). The overall stereochemical outcome is determined by the structural characteristics of the substrate and catalyst as well as the kinetic parameters affecting the epimerization and hydrogenation of the ketone.

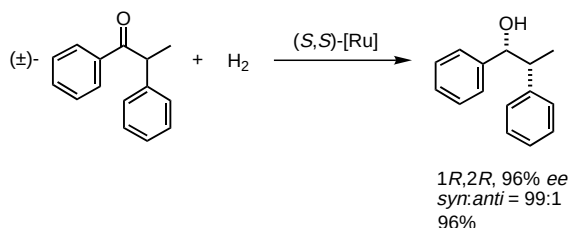
7.3. Enantiomers

As expected, certain racemic ketones can be resolved kinetically. For example, when racemic carvone was hydrogenated with an (*S*)-BINAP/(*R,R*)-DPEN–ruthenium catalyst in 2-propanol containing KOH, it gave, at 54% conversion, the starting (*S*)-carvone in 94% *ee* (46%) together with (1*R*,5*R*)-carveol in 93% *ee* (50%) and some other minor alcohols (3.7%) (Scheme 53).^[178] The extent of the enantiomer differentiation, $k_{\text{fast}}/k_{\text{slow}}$, was calculated to be 33.^[200]

Dynamic kinetic resolution provides a stereoselective method to convert racemic ketones with an α -stereogenic center into a single stereoisomer of the four possible isomers.^[18–22] Thus, as shown in Scheme 54, racemic 2-phenylpropiophenone hydrogenated with an (*S*)-XylBINAP/(*S*)-DAIPEN–ruthenium catalyst under basic, protic conditions



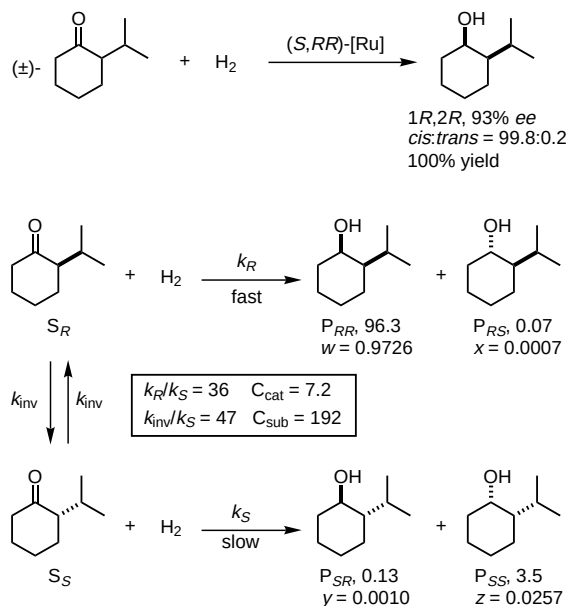
Scheme 53. Kinetic resolution of carvone by ruthenium-catalyzed hydrogenation. Conditions: $(\text{CH}_3)_2\text{CHOH}$, S/C = 1000/1, 4 atm H_2 , 28 °C.



Scheme 54. Dynamic kinetic resolution of a racemic acyclic ketone. Conditions: (S,S)-[Ru] = *trans*-[RuCl₂[(S)-xylbinap]][(S)-daipen]], (CH₃)₃COK (1:10), [ketone] = 0.2 M in (CH₃)₂CHOH, S/C = 1000/1, 4 atm H₂, 28 °C.

gave a 99:1 mixture of (1*R*,2*R*)-1,2-diphenyl-1-propanol (*syn*) in 96% *ee* and the 1*R*,2*S* isomer (*anti*) in 39% *ee*.^[28] A very high Cram selectivity was seen, as with an achiral catalyst (Scheme 21). The degree and sense of enantioselectivity are consistent with those in reactions of simple aromatic ketones (Table 2).

Hydrogenation of racemic 2-isopropylcyclohexanone in the presence of an (S)-BINAP/(*R,R*)-DPEN – ruthenium catalyst under 4 atm of H₂ gave quantitatively a 99.8:0.2 mixture of the *cis* 1*R*,2*R* alcohol in 93% *ee*, and the *trans* 1*R*,2*S* isomer in 28% *ee* (Scheme 55).^[104] The predominance of the *cis* product is in accord with the diastereoselectivity observed in the achiral hydrogenation of 2-substituted cyclohexanones (see Scheme 19). Scheme 55 explains why this hydrogenation



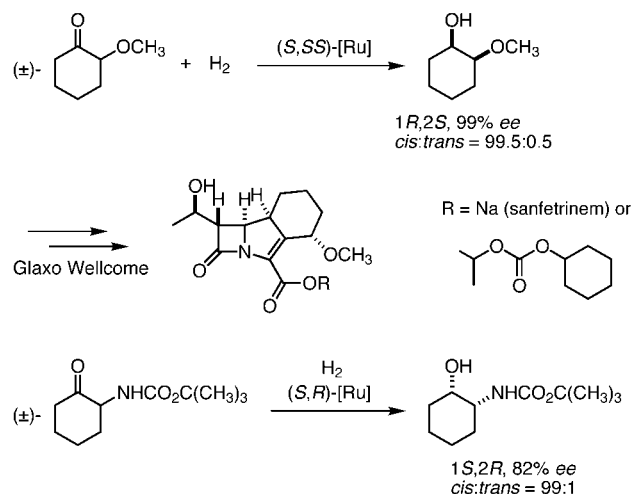
Scheme 55. Dynamic kinetic resolution of a racemic cyclic ketone. Conditions: (S,RR)-[Ru] = [RuCl₂[(S)-binap](dmf)_n], (*R,R*)-DPEN, KOH (1:1:20), [ketone] = 0.8 M in (CH₃)₂CHOH, S/C = 500/1, 4 atm H₂, 28 °C.

proceeds with such a high stereoselectivity giving 96.3% of the 1*R*,2*R* alcohol of the four possible stereoisomers. Computer-aided analysis^[18, 21] of the reaction revealed that 1) the inherent, highest 1*R*,2*R*:1*S*,2*S*:1*R*,2*S*:1*S*,2*R* selectivity at time *t* = 0 (*w*:*x*:*y*:*z* partition parameter, where the *R* and *S* enantiomers are assumed to exist in equal amounts) is 97.26:2.57:0.10:0.07; 2) under this reaction condition, the *R*

ketone is hydrogenated 36 times faster than the *S* isomer; 3) the slow-reacting *S* substrate undergoes in situ stereochemical inversion 47 times faster than it is hydrogenated; 4) the extent of the substrate-based asymmetric induction (*cis*/*trans*) is 192 in favor of the *cis* isomer; and 5) the catalyst-controlled asymmetric induction (*R*/*S*) is 7.2/1. Thus, the kinetic and stereochemical factors are well coordinated to accomplish this diastereo- and enantioselective hydrogenation.^[104]

This methodology was successfully applied to the asymmetric synthesis of sanfetrinem and its metabolically labile ester which has potent antibacterial activity (Scheme 56).^[201, 202] The key step is the hydrogenation of racemic 2-methoxycyclohexanone with an (S)-XylBINAP/(S,S)-DPEN catalyst leading to (1*R*,2*S*)-2-methoxycyclohexanol with near-perfect stereoselectivity.

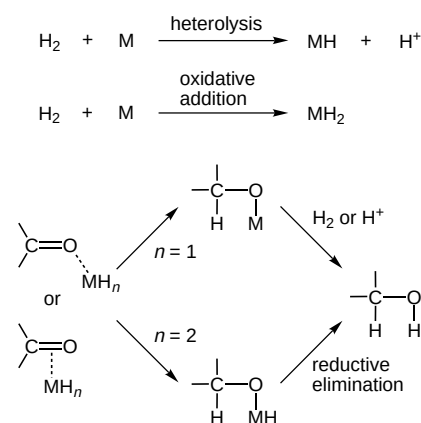
Thus, the synthetic utility of this hydrogenation is greatly enhanced by the application of dynamic kinetic resolution of configurationally labile diastereomeric, epimeric, and enantiomeric ketones.



Scheme 56. Dynamic kinetic resolution of racemic cyclic ketones and the application to the asymmetric synthesis of a carbapenem antibiotic. Conditions for reduction of 2-methoxycyclohexanone: (S,SS)-[Ru] = [NH₂(C₂H₅)₂][[RuCl₂[(S)-xylbinap]]₂(μ-Cl)₃], (S,S)-DPEN, KOH, (CH₃)₂CHOH, 50 atm H₂, 5 °C. Conditions for reaction of the amino ketone: (S,R)-[Ru] = *trans*-[RuCl₂[(S)-xylbinap]][(*R*)-daipen]], KOH (1:200), [ketone] = 0.2 M in (CH₃)₂CHOH, S/C = 300/1, 8 atm H₂, 25 °C.

8. Metal-Ligand Difunctional Catalysis: Origin of the High Rate and Chemoselectivity

Homogeneous hydrogenation of simple ketones is generally conceived to occur by a [π2+σ2] pathway as depicted in Scheme 57,^[29, 30, 39, 203] although there are some mechanistic constraints, as noted earlier in Scheme 8a. Certain transition metal complexes cleave molecular hydrogen to generate metal hydrides.^[64, 77] The metal monohydride, MH, generated by heterolysis of H₂ first forms a σ or π complex with a ketonic substrate.^[61–63] The conversion into a metal alkoxide intermediate^[204] is followed by hydrogenolysis or protonolysis of the M–O bond to give an alcohol product. Alternatively, oxidative addition of H₂ to a metal catalyst generates a metal



Scheme 57. Putative pathways of homogeneous hydrogenation of ketones by transition metal monohydride and dihydride species.

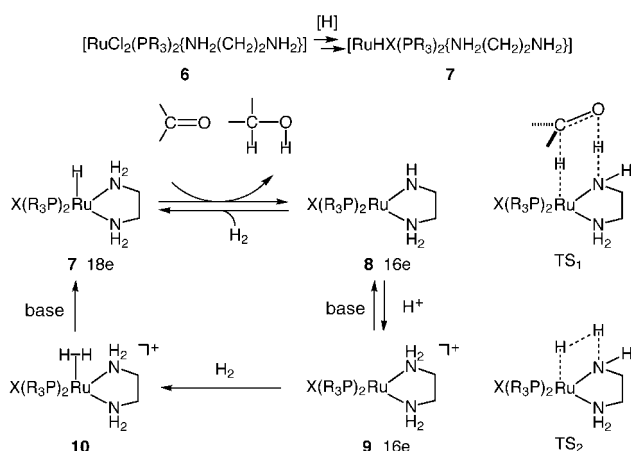
dihydride, MH₂.^[7a, 64] Subsequent reaction with a ketone, giving an alkoxy metal hydride, followed by reductive elimination, forms an alcohol product. In both cases, the ability of transition metals to form π complexes,^[63] in the ground state and/or the transition state, their Lewis acidity, as well as their oxophilicity contributes to the carbonyl reduction.

We believe, however, that the rapid hydrogenation occurs by an entirely different mechanism, that is catalysis with a metal-ligand difunctionality. Scheme 58 presents our current view of the mechanism. First, [RuCl₂(PR₃)₂{NH₂(CH₂)₂NH₂}] (6) is converted into [RuHX(PR₃)₂{NH₂(CH₂)₂NH₂}] (7; X = H or OR) in the presence of an alkaline base and a hydride source (H₂ and a trace of 2-propanol).^[58, 77, 78] The major role of the strong base (2 equivalents relative to Ru) is to neutralize HCl formed in this process. The catalytic cycle involves two ground-state components, 7 and 8, which are linked by transition states TS₁ and TS₂. The NH proton in 7 plays a key role in hydrogen delivery to ketones, while the amide nitrogen in 8 cleaves H₂. The high turnover efficiency relies on the universal functions of the complexes 7 and 8, in which the metal centers and the ligands directly cooperate in the bond-breaking and -forming reactions. The operation of the metal-ligand difunctional mechanism has been substantiated experimentally (structures and kinetics^[205]) and theoret-

ically (ab initio MO and DFT^[206]) in the closely related Ru^{II}-catalyzed transfer hydrogenation of ketones with 2-propanol. Although several diastereomers are possible for the reducing species 7 (see Scheme 11), the hydride and two nitrogen atoms must have a *fac* relationship in the octahedral geometry. The 18-electron ruthenium hydride 7 reacts with a ketonic substrate via a six-membered, pericyclic transition state TS₁, giving a product alcohol and the 16-electron complex 8.^[58, 205, 206] The hydrogenative reactivity of coordinatively saturated 7 originates from the charge-alternating H^{δ-}-Ru^{δ+}-N^{δ-}-H^{δ+} arrangement. Thus, the hydride ligand at the ruthenium center possesses sufficient nucleophilicity, while the NH moiety exhibits a unique hydrogen-bonding ability^[71, 73, 207] to activate the carbonyl substrate. The structure of the 1,4-dipole fits well with the carbonyl dipole, stabilizing the pericyclic transition state TS₁. The NH...O hydrogen bonding not only perturbs the electronic properties of the C=O bond but also creates a three-dimensional assembly appropriate for hydride transfer to the π face. The 16-electron complex 8 can form an 18-electron complex with a Ru=N bond (resonance), since the amide nitrogen can donate its free electron pair (the nonbonding electrons) to the electron-deficient ruthenium center.^[205, 208, 209] Because of this unique Ru^{δ+}-N^{δ-} dipolar bond, 8 splits H₂ molecules in a heterolytic manner^[210] via transition state TS₂ thus restoring the ruthenium hydride 7. In view of the marked dependency of the rate on hydrogen pressure this H₂ cleavage would be the turnover-limiting step. Alternatively, 7 may be regenerated from 8 and H₂ by way of 9 and 10 by the action of a protic medium and base. Most notably, unlike in conventional metal hydride reactions (see Scheme 57), the carbonyl oxygen does not interact with the metal center. Neither a ketone/ruthenium complex nor a ruthenium alkoxide are involved in this reaction mechanism. The alcohol forms directly from the ketone. Alcohols may add across the polar Ru-N bond of 8 but in a reversible manner, where the resulting ruthenium alkoxides act merely as reservoirs for 8. Therefore, the ketone reduction does not require any coordinative unsaturation at the ruthenium center but rather occurs in an outer coordination sphere of the 18-electron complex 7 (see Scheme 8b). This is the main origin of the high rate of this catalytic hydrogenation. Furthermore, this nonclassical mechanistic model also explains the uncommon functional selectivity in favor of the C=O group.

9. Conclusion

Homogeneous hydrogenation has remained underutilized in chemical synthesis largely a result of insufficient selectivity as well as low TON and TOF. However, we are now close to achieving the ambitious goal which was set some years ago. First, unlike classical hydrogenation catalysts, the phosphane/1,2-diamine-ruthenium complexes catalyze efficient hydrogenation of a large variety of simple ketones. In view of the existence of so many ketonic compounds, the full scope of the usefulness of the new homogeneous hydrogenation has not been defined. This catalysis can replace most of the current stoichiometric hydride reductions, particularly for large-scale



Scheme 58. Metal-ligand difunctional mechanism for hydrogenation of ketones. X = H, OR etc.

reactions.^[4, 5] This method is general but also remarkably selective. The selectivities rival those of the best metal hydride reductions. The high C=O/C=C selectivity is similar to that of NaBH₄ reduction.^[86] In addition, this hydrogenation tolerates various substituents including F, Cl, Br, I, CF₃, OCH₃, OCH₂C₆H₅, COOCH(CH₃)₂, NO₂, NH₂, NR₂, and NR¹COR² (R¹=H, alkyl; R²=alkyl, aryl), and various heterocyclic groups. The hydrogenation is also diastereoselective, to an extent which compares well with that of the reagent L-Selectride.^[101] Furthermore, asymmetric hydrogenation is performed by using appropriate chiral diphosphanes and 1,2-diamines, where structural permutations are virtually unlimited. Also, the scope of the ketonic substrates showing high enantioselectivity is very wide. This catalytic reaction is rapid and productive and, therefore, is truly efficient. The reaction can normally be performed with < 8 atm of H₂ and at room temperature with a high S/C ratio (up to 2400000/1 under 45 atm of H₂) and a substrate concentration as high as 30 % (w/v), leading to very high volumetric productivity.

Asymmetric catalysis is "four-dimensional chemistry".^[2] The high efficiency can only be achieved through the coordination of both an ideal three-dimensional structure (*x*, *y*, *z*) and suitable kinetics (*t*). To achieve maximum chiral multiplication, efficient catalyst systems must be created that permit precise discrimination among the enantiotopic atoms, groups, or faces in achiral molecules with a very high turnover efficiency. Special molecular design to stabilize stereochemistry-determining transition states is of prime importance. Metal-ligand difunctional catalysis provides a new basis for developing efficient catalytic reactions. Furthermore, suitable kinetic parameters must be selected to facilitate the catalytic cycle. The BINAP–RuCl₂ complexes are effective for asymmetric hydrogenation of both functionalized ketones and simple ketones. Notably, however, the former reaction (see Scheme 2) is markedly accelerated by the addition of a strong acid,^[25, 26] while the latter reaction requires the presence of a strong base.

New technologies must meet technical, economic, and environmental requirements. Because chemical products tend to be more dependent on catalytic synthesis, better catalytic efficiency leads directly to a number of scientific and economic benefits. In particular, enantioselective catalysis is rapidly becoming more important in the areas of pharmaceuticals, agrochemicals, flavors, and fragrances which require high degrees of chemical precision.^[4, 5] In this regard, molecular catalysis is complementary to biotechnology.^[211] Furthermore, creation of some chiral polymers, advanced materials with nonlinear optical properties, ferroelectric liquid crystals, etc. also relies on the availability of chiral building blocks. Therefore de novo development of efficient catalysts must have a significant impact on chemical research and industry. Although the art and science of asymmetric catalysis has reached a very sophisticated level, relatively few homogeneous enantioselective catalysts have been used on an industrial scale.^[4, 5, 7] This practical asymmetric hydrogenation has a very wide scope and provides entry to a diverse array of significant chiral substances. Finally, hydrogenation is "green" chemistry that eliminates the use and generation of hazardous substances. In comparison to conventional stoichiometric

hydride reductions, waste is greatly reduced by using this catalytic method.

We are especially indebted to our able collaborators for their sustained intellectual and experimental efforts. Their names are acknowledged in the publications cited from our laboratories at Nagoya University and in the ERATO Molecular Catalysis Project (Japan Science and Technology Corporation, 1991–1996). This work was also aided by grants from the Ministry of Education, Science, Sports, and Culture of Japan (Nos. 07CE2004 and 11440188).

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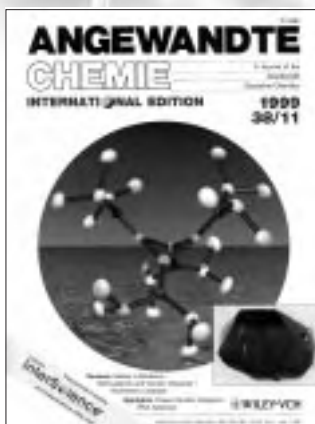
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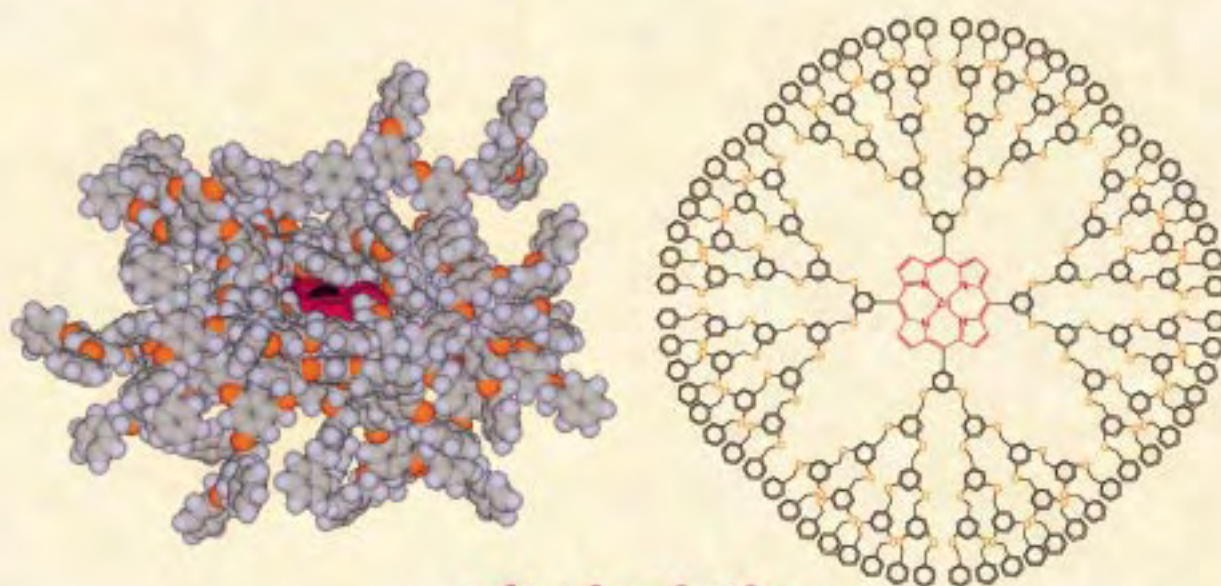
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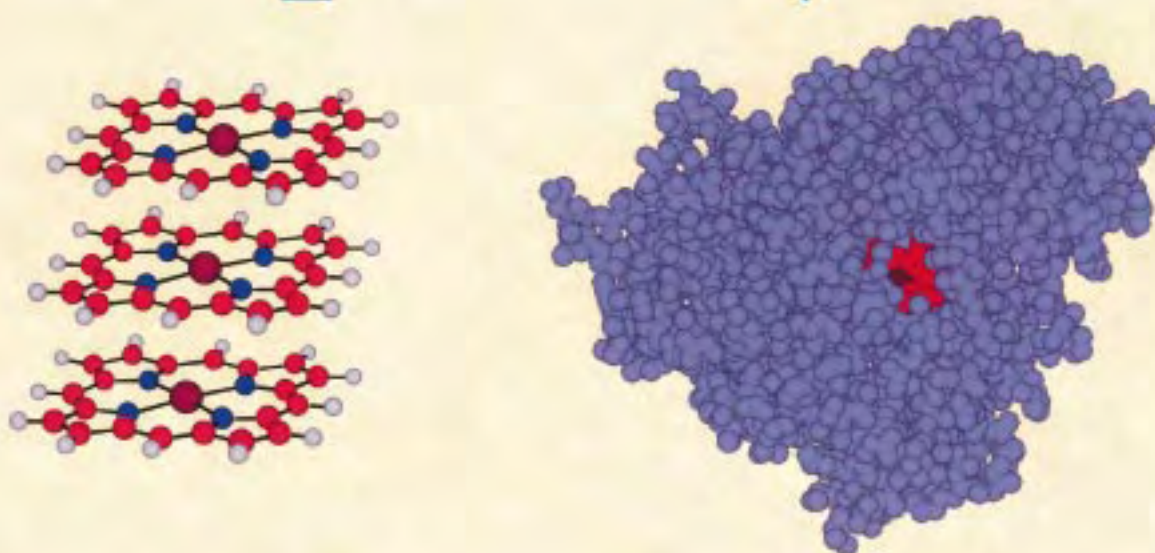
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Dendritic Encapsulation of Function



site isolation



porphyrin π stack

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Dendritic Encapsulation of Function: Applying Nature's Site Isolation Principle from Biomimetics to Materials Science

Stefan Hecht and Jean M. J. Fréchet*

The convergence of our understanding of structure–property relationships for selected biological macromolecules and our increased ability to prepare large synthetic macromolecules with a structural precision that approaches that of proteins have spawned a new area of research where chemistry and materials science join with biology. While evolution has enabled nature to perfect processes involving energy transfer or catalysis by incorporating functions such as self-replication and repair, synthetic macromolecules still depend on our synthetic skills and abilities to mesh structure and function in our designs. Clearly, we can take advantage of our understanding of natural systems to mimic the structural features that lead to optimized function. For example, numerous biological

systems make use of the concept of site isolation whereby an active center or catalytic site is encapsulated, frequently within a protein, to afford properties that would not be encountered in the bulk state. The ability of the dendritic shell to encapsulate functional core moieties and to create specific site-isolated nanoenvironments, and thereby affect molecular properties, has been explored. By utilizing the distinct properties of the dendrimer architecture active sites that have either photochemical, photochemical, electrochemical, or catalytic functions have been placed at the core. Applying the general concept of site isolation to problems in materials research is likely to prove extremely fruitful in the long term, with short-term applications in areas such as the construction of im-

proved optoelectronic devices. This review focuses on the evolution of a natural design principle that contributes to bridging the gap between biology and materials science. The recent progress in the synthesis of dendrimer-encapsulated molecules and their study by a variety of techniques is discussed. These investigations have implications that range from the preliminary design of artificial enzymes, catalysts, or light-harvesting systems to the construction of insulated molecular wires, light-emitting diodes, and fiber optics.

Keywords: dendrimers • materials science • molecular devices • structure–property relationships

1. Introduction

The field of dendrimer chemistry^[1] has undergone a very rapid development and has evolved from the discovery and the establishment of synthetic approaches to the characterization of dendrimer properties and the design of functional dendrimers.^[2] The dendritic scaffold may therefore be used for the spatial arrangement of functionalities and the tailoring of properties through the interplay of the structural subunits. Dendrimers truly represent unique artificial building blocks as a result of the fine control that can be exerted over both their size and their molecular architecture, and therefore their three-dimensional nanoscale structure.^[3]

Significant progress has been made in the use of dendritic frameworks to surround active core molecules. This process involves exploiting the inherent topological features of a dendrimer in which a core is surrounded by a branched shell that carries external “surface” groups. Dendritic shielding actually amounts to an encapsulation that can create a distinct microenvironment around the core moiety and hence affect its properties. This effect may result from the synergistic combination of the intrinsic chemistry of the building blocks of the dendrimer and the reduced accessibility of its core.

The encapsulation motif draws its inspiration from our increasing understanding of molecular biology. Enzymes provide an impressive demonstration of the profound effect a protein shell has on the active site of the enzyme. For example, the remarkable C–H bond activation performed by the heme protein cytochrome P450^[4] and the long-range electron-transfer processes mediated by other cytochromes^[5] would not be possible with unprotected hemes.^[6] In many cases nature appears to create functional diversity by chang-

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ing the architecture around the active entity rather than by direct chemical modification of that entity. For instance, in a light-harvesting antenna complex of photosynthetic bacteria the bacteriochlorophyll molecules exist as two distinct chromophore subunits that have different absorption characteristics as a consequence of their spatial arrangement.^[7] Working mostly with small molecules, chemists traditionally synthesize new molecules^[8] to tailor the properties.^[9] However, the challenge of mimicking nature by applying the design principle of property variation by architectural modification continues to fascinate.

In this attempt to summarize recent investigations dealing with dendritically encapsulated functionalities, we mainly focus on dendrimers with covalently attached cores that are either photochemically, electrochemically, or catalytically active. Clearly, today's accomplishments with dendrimer encapsulation pale in comparison to those achievable by natural systems, yet tantalizing leads have been uncovered.

2. Design Concepts, Synthetic Approaches, and Experimental Methods

The astonishing structural diversity of natural systems such as enzymes is achieved by a combination of different amino acid building blocks and a variety of interactions that lead to macroscopic organization. Seemingly complex folding processes give rise to the secondary and tertiary structure. Further interactions between the individual subunits can lead to even higher order quaternary structures, which are impressively demonstrated in "molecular machines" such as ATP synthetase. The globular structure of proteins is primarily based on the hydrophobic effect that exposes hydrophilic residues to the surrounding medium while sequestering hydrophobic fragments in the interior. The occurrence of specific interactions such as hydrogen bonding at the active site contributes to the stabilization of the transition states, and thereby favors

certain reaction pathways. Without the benefit of evolution, dendrimers already provide unadorned steric protection and a unique—though still unsophisticated—"inner" environment that reflects the nature of its building blocks.

The geometric encapsulation of a core moiety by dendritic wedges ideally gives rise to a sphere or ovoid with a radius determined by the size of the core, as well as by the size and number of dendrons surrounding it. An alternative, if less common topology, wraps an inner elongated core or rigid rod with dendrons to afford cylindrically shaped dendrimers^[10] (Figure 1). It is important to note that in all cases the steric

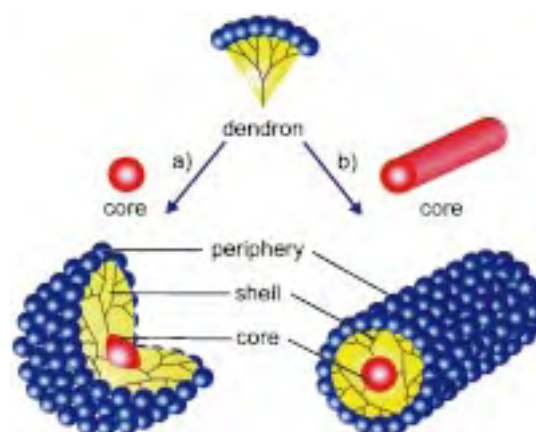


Figure 1. Attachment of multiple dendrons to polyfunctional cores gives rise to either spherically (a) or cylindrically shaped dendrimers (b). Idealized fully extended conformations are shown, in which the terminal groups (blue) are not mixed with the inner building blocks (yellow) or the core (red).

crowding between the dendritic segments induces the shape of the molecule. The steric crowding itself is strongly dependent on the flexibility of the dendritic building block, the branching pattern, the size (or generation number) of the dendrons, as well as the interactions of the dendrons and the chain ends,

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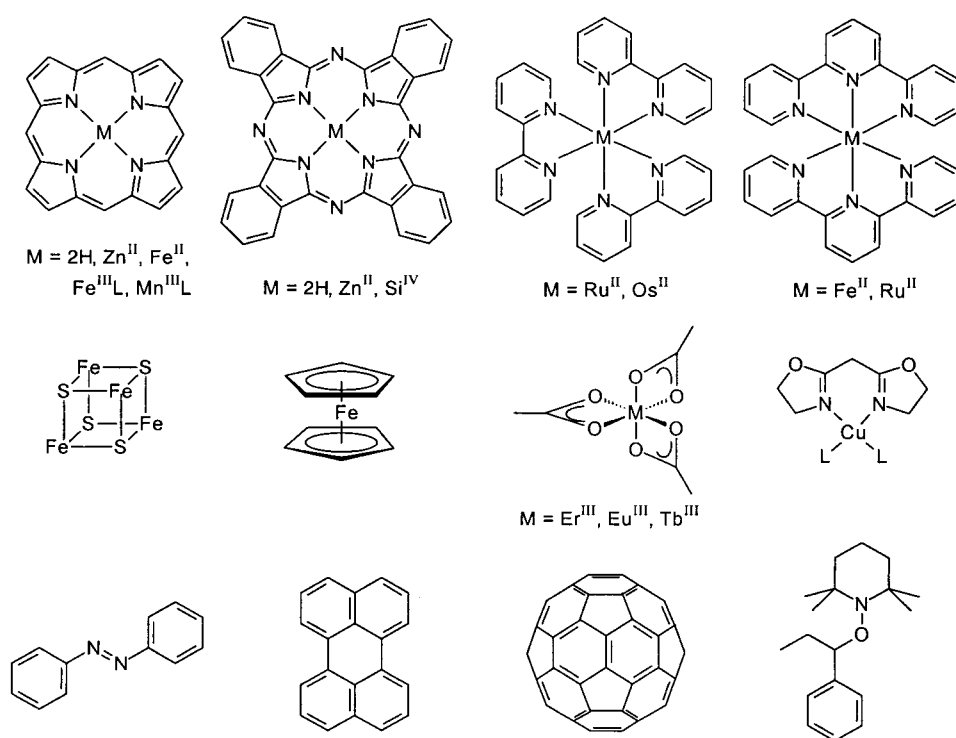
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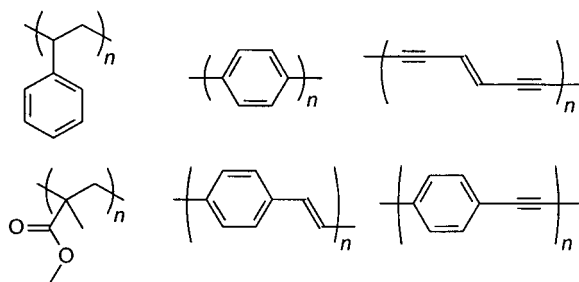
Jean M. J. Fréchet obtained his first degree at the Institut de Chimie et Physique Industrielles (now CPE) in Lyon, France, and Ph.D. degrees from the College of Environmental Sciences and Forestry (SUNY-CESF) and Syracuse University. Following academic appointments at the University of Ottawa (1973–86) and Cornell University (1987–96), he joined the department of chemistry at the University of California, Berkeley. He has received both the American Chemical Society award in Polymer Chemistry and in Applied Polymer Science; he was elected a Fellow of the American Academy of Arts and Sciences, a member of the National Academy of Science, and a member of the National Academy of Engineering.

not only with each other but also with the surrounding medium. In addition, the degree of encapsulation of the core is a function of its size and the specific directional orientation of the dendrons.

Some of the most common core functionalities are shown in Schemes 1 and 2. For spherical dendrimers, these vary greatly in size—from compact metal ion complexes to large buckyballs or even porphyrins. In the case of cylindrical dendrimers, the most successful core motif to date involves rigid conjugated polymeric backbones, although even flexible backbones can give rise to cylindrical structures in the solid state.



Scheme 1. Examples of core functionalities exploited in spherical encapsulation.



Scheme 2. Examples of core functionalities used in cylindrical encapsulation.

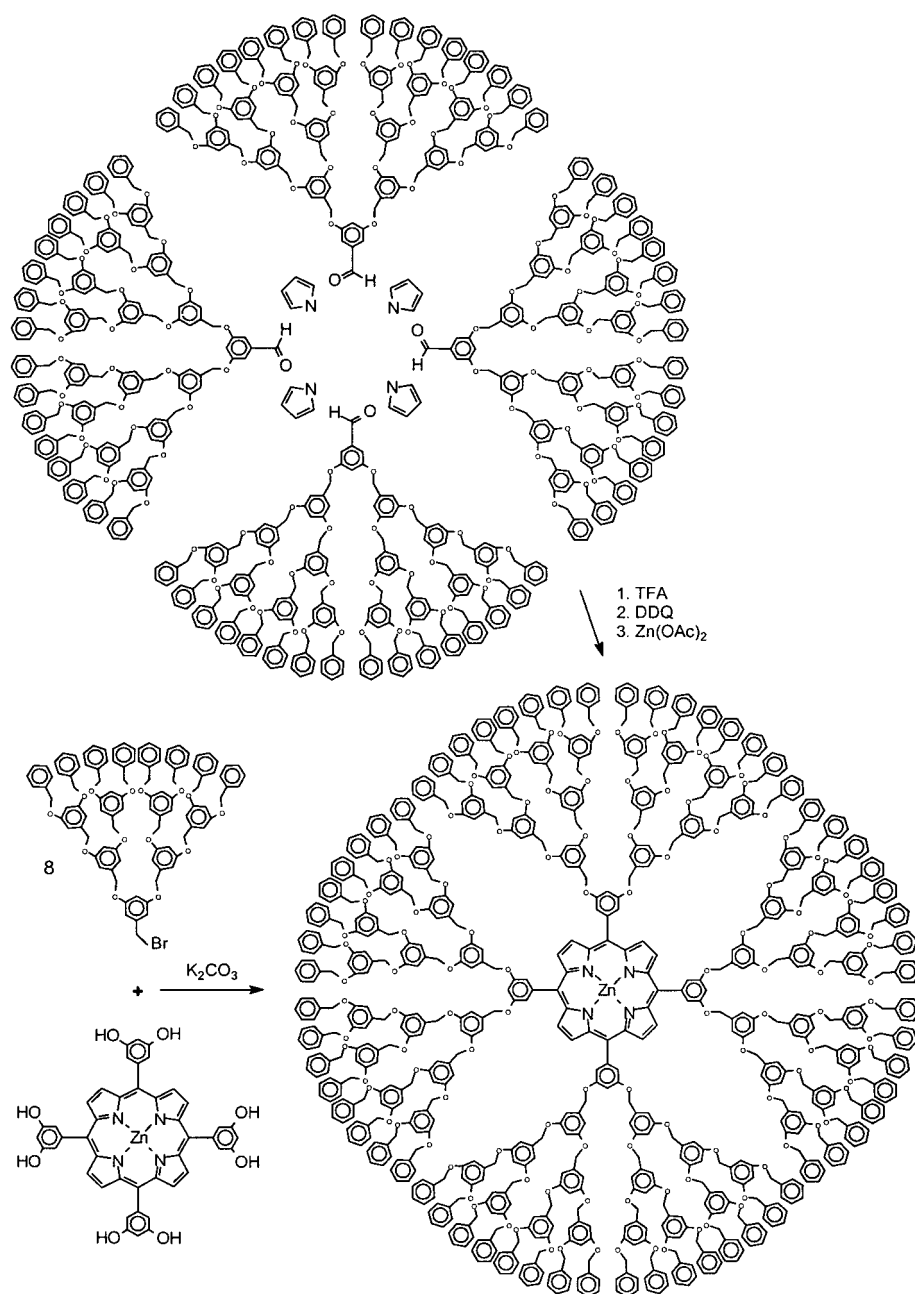
While both convergent and divergent strategies^[1] may be used to achieve encapsulation, the convergent strategy appears to be more versatile as it avoids multiple synthetic operations on the often-exotic core and leads to more precise and uniform material.^[2b] Within the last few years elegant synthetic protocols have been developed that form the core moiety directly from dendritic precursors in the final step of the sequence.^[11] This direct method usually facilitates chro-

matographic purification, as a result of the more pronounced difference in the elution behavior of substrates versus products, whereas the more conventional process of grafting dendrons onto a polyfunctional core benefits from higher yields and added synthetic flexibility. For example, dendrimers with porphyrin cores have been prepared by Fréchet and co-workers and the chemical modification of a preformed core compared with a direct core-forming condensation (Scheme 3).^[12] The reaction of zinc tetrakis(3,5-dihydroxyphenyl)porphyrin with poly(benzyl ether) dendrons under standard Williamson ether conditions gave the desired

dendrimers. However, as the size of the dendrons increased, a larger excess was needed to drive the reaction to completion since the separation of partially reacted side products from the desired product was not possible. Despite this drawback, this modular approach is clearly advantageous since both the dendrons and functionalized porphyrin core are readily available. Alternatively, a Lindsey-type condensation^[13] of dendritic aldehydes with an equivalent amount of pyrrole followed by metalation yielded the same products. The ease of the chromatographic purification associated with this approach is somewhat offset by the relatively low chemical yield of the Lindsey synthesis and is further affected by the high steric demand of this particular reaction.

An analogous study by Schlüter and co-workers explored the preparation of “cylindrical” moieties by the direct synthesis and core modification approaches (Scheme 4).^[14] Poly(*p*-phenylene) was functionalized with a three- to fivefold excess of Fréchet-type dendrons using standard Williamson ether chemistry. Not unexpectedly, the use of higher generation dendrimers resulted in less than quantitative coupling reactions. In contrast, the use of dendrons with a focal point capable of acting as a monomer in a Suzuki-type polymerization led to the desired products even at higher generations. As a consequence of the inherent perfect dendritic coverage this direct approach is superior to the dendron-grafting route and it has since been further improved.^[15] Numerous reviews with information regarding dendrimer synthesis and purification issues are available.^[1]

In addition to the often complicated and time-consuming preparation and isolation of the compounds, the choice of experimental technique used to ascertain the effect of the dendritic shell is crucial and depends mainly on the core functionality. A variety of experimental tools have been employed to study the shape of the molecule in solution and to quantify the shielding of the core moiety (Table 1).



Scheme 3. Synthesis of a fourth generation dendrimer with a zinc porphyrin core using either chemical modification or direct condensation.^[12] TFA = trifluoroacetic acid; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

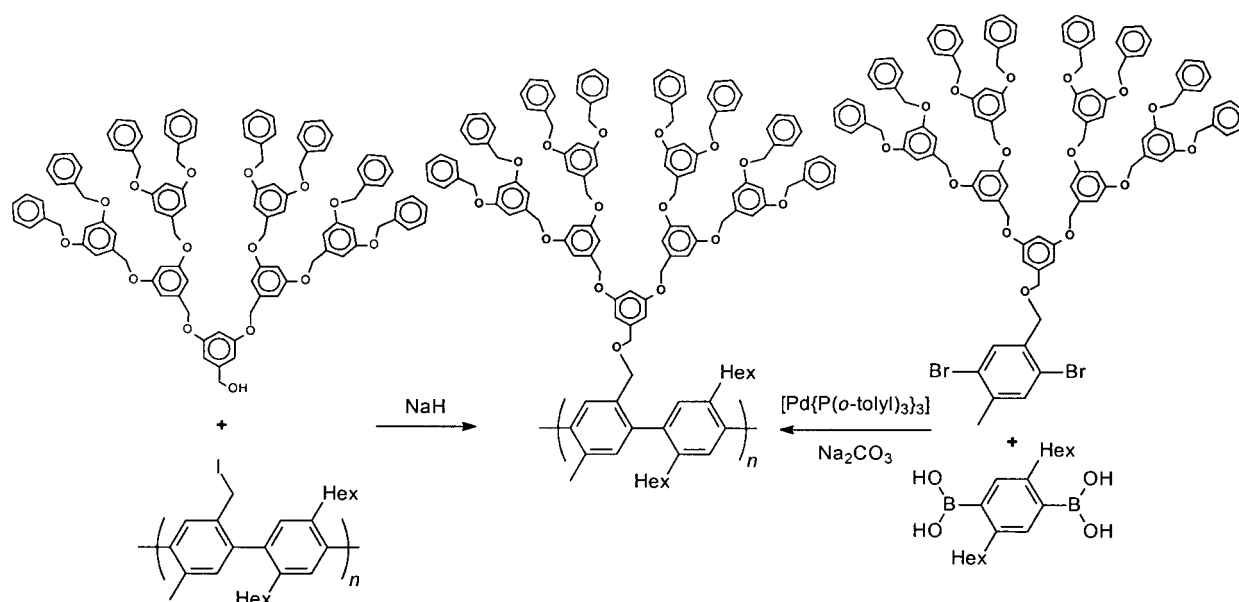
Changes in the microenvironment of core dyes are conveniently analyzed by absorption and emission techniques that rely on the stabilizing or destabilizing effect of the local medium on the electronic states of the chromophore. Parameters such as medium polarity (from spectral shifts)^[16] or viscosity (from fluorescence anisotropy decays)^[17] can be deduced from such measurements. Classic Stern–Volmer experiments have also been used extensively. Herein, the bimolecular deactivation of the excited state caused by penetration of an external quencher molecule through the dendritic shell allows for an evaluation of the accessibility of the core.^[18] Other kinetic methods that do not involve a fluorescence signal include cyclic voltammetry (CV)^[19] as well

as chemical reactions performed within the dendrimer itself. The occurrence of reversible or irreversible electron transfer and the change in redox potential in CV measurements provide information about the isolation of the core moiety; whereas, rates, chemical yields, and selectivity in kinetic studies give insight into substrate diffusion and the binding to the reactive or catalytic site. A vast number of physical methods are available to complement the above mentioned techniques, for instance, NMR relaxation experiments can be used in connection with paramagnetic cores,^[20] with conventional proton relaxation,^[21] or even to probe the entire dendritic framework.^[11] Other methods dealing with dendrimer conformation and dynamics, such as gel-permeation chromatography (GPC), differential viscometry, and computational methods have been reviewed recently by Bosman, Janssen, and Meijer.^[1b]

3. Photoresponsive Systems

The environment of a chromophore is able to affect its photo-physical properties, such as absorption and emission characteristics, as well as its photochemical behavior. We have already mentioned nature's perfection in creating such environments and even to spatially arrange multiple chromophores with respect to each other to further enhance performance in a synergistic fashion. In a first simple approach to study the effect of the microenvironment on the properties of an encapsulated dye, Hawker, Wooley, and Fréchet

attached solvatochromic probes to the core or focal point of dendrimers.^[16a] Analysis of the UV/Vis absorption spectra of a series of Fréchet-type dendrons with a *p*-nitroaniline solvatochromic probe attached to their focal point (Figure 2) showed a pronounced bathochromic shift of the absorption maxima in nonpolar solvents such as CCl₄ or toluene with increasing generation. The most dramatic change occurred between the third and fourth generations, presumably as a consequence of the transition from an extended to a more globular structure that better encapsulates the core. Correlation with Taft's solvent polarizability parameter π^* ^[22] indicated that at high generation the local environment near the chromophore resembles that of highly polar solvents such as DMF.



Scheme 4. Synthesis of a third generation dendrimer with a poly(*p*-phenylene) core using either chemical modification or a dendritic monomer route.^[14]

Table 1. Experimental techniques available for the evaluation of the microenvironment and accessibility of the core moiety.

Technique	Information used for the evaluation of the dendritic shielding effect	Ref.
UV/Vis and emission spectroscopy	spectral shift and intensity	[16, 21, 25, 29, 30b, 31, 58–60]
time-resolved emission spectroscopy/ fluorescence anisotropy	excited-state lifetime from signal decay/anisotropy decay	[17, 21c, 25, 34b]
emission quenching	bimolecular quenching rate constant from Stern–Volmer analysis	[18, 23–26, 27b, 30a, 30c, 85]
cyclic voltammetry	occurrence and ease of electron transfer to an electrode surface/shift in redox potential	[24, 39, 40, 42, 43, 45–47, 58]
kinetics	rate constants and selectivities of a given chemical reaction	[21a, 21b, 30d, 32, 65–68, 71–79, 86]
NMR	spin lattice relaxation times	[11, 20, 21]

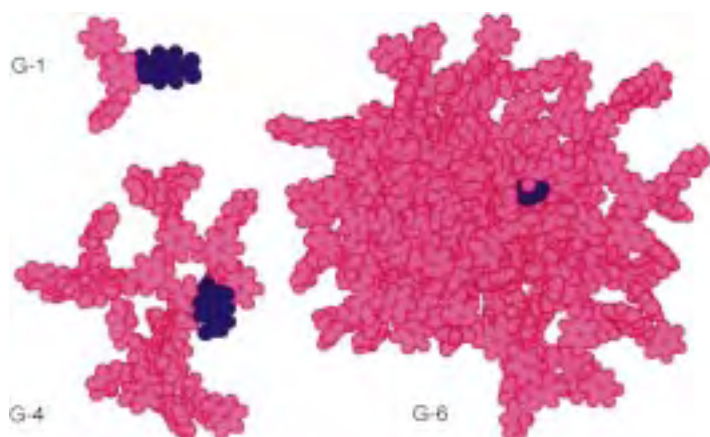


Figure 2. Dendritic *p*-nitroanilines as solvatochromic probes. The space-filling model illustrates increasing encapsulation of the focal chromophore (blue) by the dendrimer backbone (pink).^[16a]

In subsequent work, Moore and co-workers utilized the emission of phenylacetylene dendrimers modified with an electron donor at the focal point to probe the local environment.^[16b] An anomalous spectral shift in the fluorescence maximum of the charge transfer state was observed with higher generations. An abrupt change was observed between

the fourth and fifth generations, which suggests the occurrence of dendritic encapsulation and corroborates the earlier findings of Hawker et al.^[16a] Even more recently, Smith and Müller studied Newkome-type dendrimers having a tryptophan core, and correlated the observed spectral shifts to the ability of the solvent to form hydrogen bonds and therefore stabilize the emitting state.^[16c]

Dendrimers with a porphyrin core have been of considerable interest for their potential in catalysis as well as artificial photosynthesis, and have been studied extensively in the Aida, Diederich, and Fréchet laboratories. In their initial publication,^[23] Aida and co-workers observed that the fluorescence of a fourth generation dendrimer was quenched more efficiently than that of a smaller first generation dendrimer by a small molecule quencher such as Vitamin K₃. However, the opposite effect was observed when a larger molecule such as a first generation dendritic porphyrin in the form of a free base was used as the quencher. These results led to the conclusion that, in higher generation dendrimers, the dendrons act as a trap for small molecules for which they have an affinity, but cooperatively serve as a barrier for larger ones. Later, investigations performed by Fréchet and co-workers^[24] using a similar series of dendrimers and benzyl viologen as the quencher showed a comparable increase in quenching efficiency at higher generation. Sadamoto et al. introduced

peripheral anionic groups that led to pre-complexation of the cationic methyl viologen quencher and were able to observe an electron-transfer reaction through the dendrimer backbone.^[25] Consequently, efficient fluorescence quenching in self-assembled ensembles of free base porphyrins and zinc porphyrins having oppositely charged peripheral groups was reported.^[26] In an alternative and very elegant approach to demonstrate the accessibility of the core as well as the influence of the size of the penetrating molecule, Aida and co-workers examined the interaction of dendritic imidazoles with dendrimers containing a zinc porphyrin core (Figure 3).^[21a] Evaluation of the measured binding constants showed that dendritic interpenetration is greatly diminished at higher generations of both the zinc porphyrin and the ligand.

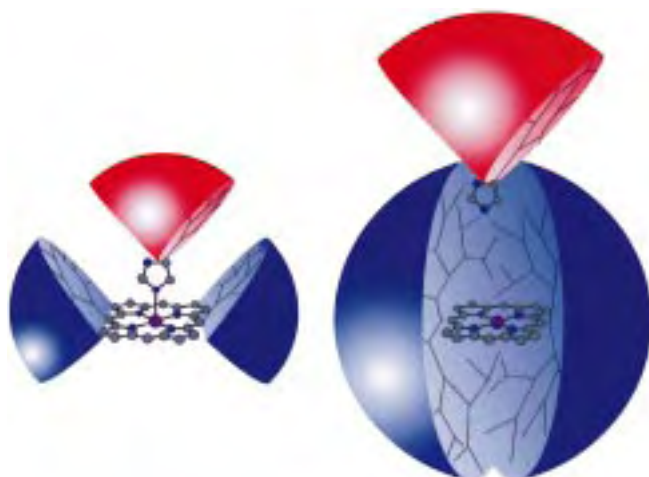
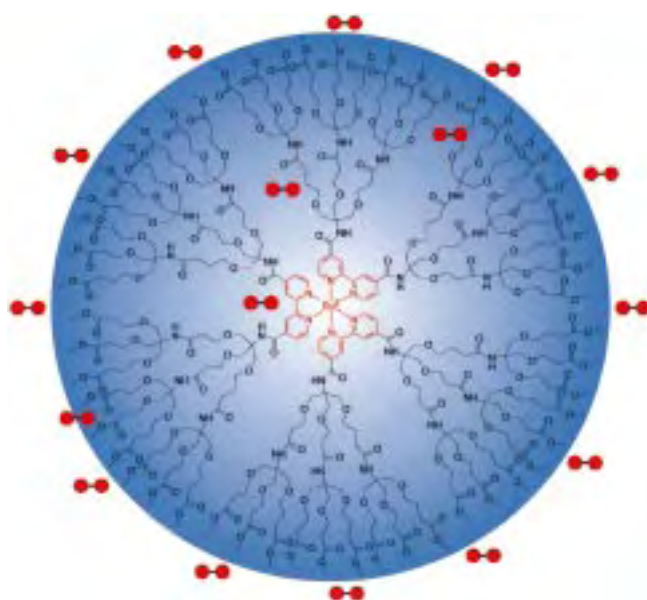


Figure 3. Ligand of dendrimers with zinc porphyrin cores (blue) by dendritic imidazoles (red). The interaction of a low generation complex and ligand gives rise to a high binding constant (left), whereas the interaction of a high generation complex and ligand leads to a small binding constant (right).^[21a]

Further insight into the role of the dendritic shell as a barrier for external quenching agents, leading to an increasing lifetime of the excited state, was provided by the groups of Balzani and Vögtle, who investigated dendrimers with a tris(bipyridine)ruthenium core.^[27, 28] In aerated solution, the higher generation Newkome-type poly(ether amide) dendrimers (Scheme 5) exhibited increased emission quantum yields as well as enhanced excited-state lifetimes as a result of the shielding effect of the dendritic shell limiting the quenching by molecular oxygen.^[27a] The reduced quenching efficiency of molecular oxygen can be attributed to its lower solubility in the dendritic interior, a possibly decreased diffusion rate, and/or better core solvation. More recently, the authors found a similar trend with related poly(benzyl ether) dendrimers.^[27b] These studies enable a comparison of the effect of the different dendrimer backbones, namely the Newkome- and Fréchet-types. A solution of the second generation Newkome-type compound in aerated acetonitrile at room temperature has an excited state with twice the lifetime and an emission that is red-shifted by 30 nm relative to the third generation Fréchet-type compound. Clearly, the more polar poly(ether amide) dendrons stabilize the metal $\rightarrow$ ligand charge transfer

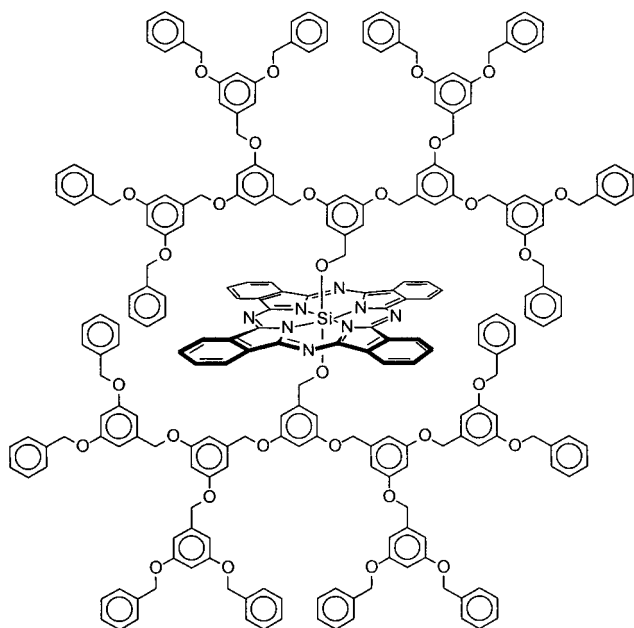


Scheme 5. An increase in the emission quantum yield and excited state lifetime in dendrimers with a tris(bipyridine)ruthenium core is attributed to diminished quenching by molecular oxygen (red).^[27a]

(MLCT) excited state more efficiently than the less polar poly(benzyl ether) dendrons.

One of the major aims of the introduction of bulky dendrons around a central moiety has been to prevent self-aggregation of dye molecules in the solid state. This self-aggregation is mainly caused by π - π stacking interactions. The isolation of the individual chromophores greatly enhances their optical properties as a result of reduced self-quenching. Unfortunately, as the size of the core dye increases, larger or higher generation dendrons have to be used to achieve efficient shielding.^[17b] To overcome this problem, McKeown and co-workers took advantage of the coordination sphere of a silicon phthalocyanine to attach Fréchet-type dendrons in the axial positions.^[29a, 30] The third generation compounds having an axial dendritic substitution (Scheme 6) showed a significant decrease in exciton coupling in the solid state as a consequence of an efficient separation of the chromophores, while the equatorial analogues exhibited strong aggregation.

Kawa and Fréchet demonstrated recently the use of self-assembled dendritic carboxylate ligands to encapsulate lanthanide ions, thereby greatly improving their luminescence properties.^[31] Assembly of three anionic dendrons around erbium(III), europium(III), or terbium(III) ions (Figure 4) led to an enhancement of luminescence efficiency with increasing generation as a result of site isolation of the lumophores, which drastically reduced their rate of self-quenching. In the context of fiber optics applications, the match of the 980 nm excitation with the typically used pumping wavelength makes the dendrimers with the erbium(III) cores, as well as their conceptual analogues, interesting candidates for glass-fiber amplifiers. In addition, the authors observed an antenna effect which resulted in the efficient sensitization of the core luminescence by the dendritic ligands. Interestingly, the energy transfer was dramatically reduced in an isomeric complex having a 1,2,5-branching pattern instead of the more



Scheme 6. Dendritic substituents in the axial position of silicon phthalocyanine moieties prevent self-aggregation by π - π stacking interactions in the solid state.^[29]

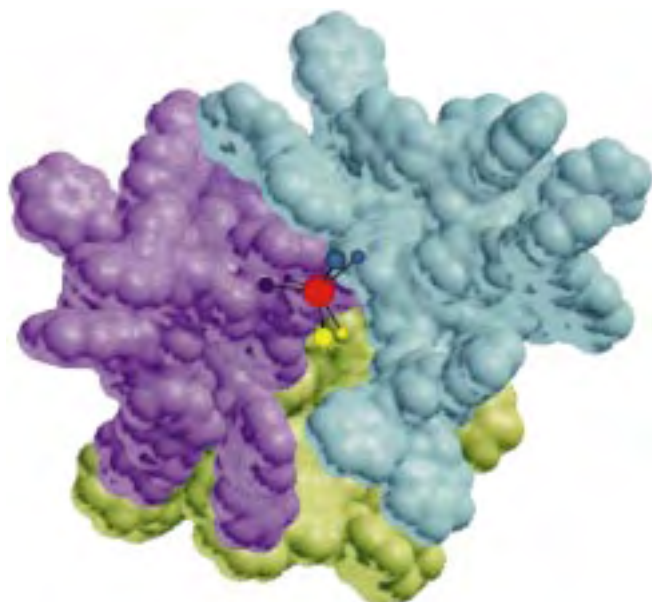


Figure 4. The assembly of three dendritic wedges (light blue, violet, and yellow) having a focal carboxylate functionality around a lanthanide ion (red) leads to site isolation and greatly enhanced luminescence properties.^[31] The core has been moved to the front for better visibility.

common 1,3,5-substitution at the focal point. Clearly, the focal aromatic structure plays a crucial role in the observed antenna effect.

Recently, Jiang and Aida thoroughly studied similar morphology effects on the antenna effect in a series of free base porphyrins substituted with various numbers of high-generation dendrons (Figure 5).^[21c] Migration of excitation energy was found to be extremely efficient in the fully labeled porphyrins, which indicated complete encapsulation and cooperativity of the dendritic subunits in the spherical morphology.

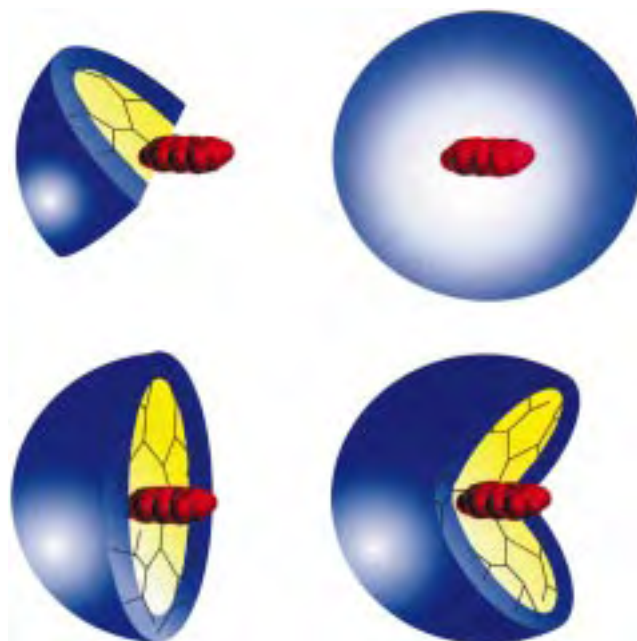
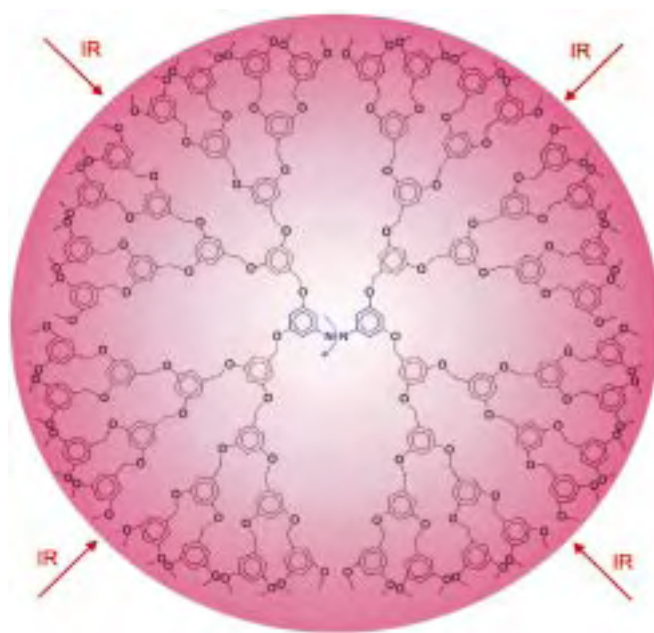


Figure 5. Increasing the number of dendritic substituents leads to more efficient encapsulation of the porphyrin core (red). Energy transfer from the dendrimer backbone to the core is greatly enhanced in the spherical morphology.^[21c]

An impressive demonstration of the effect of morphology on energy transfer was provided by the same authors investigating the IR-accelerated *cis*–*trans* isomerization of an azobenzene core moiety (Scheme 7).^[21b] They noted that after achieving full encapsulation by using either fourth or fifth generation dendrimers the rate of isomerization was two orders of magnitude faster under controlled IR irradiation than was the case for a purely thermal reaction. This phenomenon was reported to occur only when a particular



Scheme 7. The harvesting of multiple IR photons by a fifth generation dendrimer with an azobenzene core leads to an acceleration of the *cis*–*trans* isomerization.^[21b]

IR stretching frequency of the aromatic branching units (1597 cm^{-1}) was employed for irradiation. The authors concluded from the activation barrier for the *cis*–*trans* isomerization ($21.4\text{ kcal mol}^{-1}$) that this process involved approximately five low-energy IR photons (1597 cm^{-1} corresponds to 4.6 kcal mol^{-1}). Junge and McGrath investigated the effect of large dendrons on the rate of thermal *cis*–*trans* reversion of photo-isomerizable units using somewhat similar molecules.^[32, 33] Not unexpectedly, given the large degree of conformational freedom that prevailed in the investigated poly(benzyl ether)-type dendrimers, the small disturbance created by isomerization at the core is quickly dissipated through the bulky but flexible shell.

In addition to steric protection, a dendrimer molecule is uniquely suited to arrange multiple peripheral functional groups around a single core unit. By introducing an energy-transfer interaction or similar electronic “communication” between the periphery and the core, the design of dendritic light-harvesting antennae becomes feasible. In such systems an array of terminal donor chromophores may collect many photons and transfer their energy to the core acceptor unit, which can also be excited independently of the periphery. Since emission is observed from the core only, the system serves as a spatial and spectral energy concentrator or “molecular lens” (Figure 6). Essentially, this mimics the primary events in photosynthesis, where the light-harvesting complex funnels its excitation energy to the special pair leading to subsequent charge separation. Two types of systems which either use the dendritic architecture solely as a scaffold^[34] or involve the dendrimer backbone in the energy-transfer event^[21b,c, 30c, 31, 35] have been explored. Our group has recently shown that an amplification of the core acceptor emission can be achieved in high-generation dendrons labeled with multiple donor chromophores at the periphery.^[34a–c] The amplification effect has its origin in the enhanced donor absorption cross-section and the extremely fast rate of through-space energy transfer to the core, which gives rise to efficient light harvesting.^[34b] Another key finding was reported by Moore and co-workers, who demonstrated a significant acceleration of energy transfer within dendrimers having an internal energy gradient, which arose from a stepwise decrease in the HOMO–LUMO gaps of the branching units when progressing toward the acceptor.^[35b] Balzani and co-workers constructed bipyridine-based polynuclear metal complexes and were able to control the direction of energy transfer through alteration of the excited-state energies by introducing appropriate metal ions.^[35f] This strategy

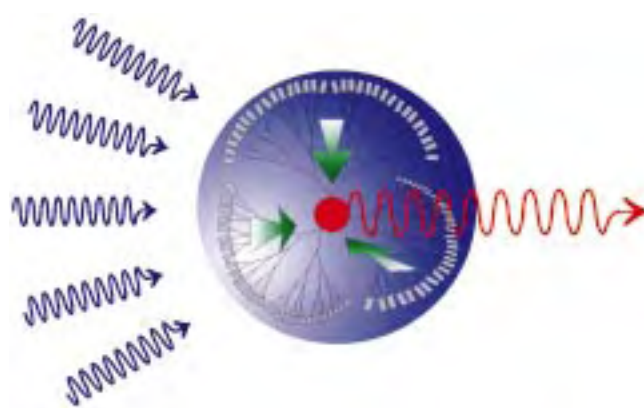
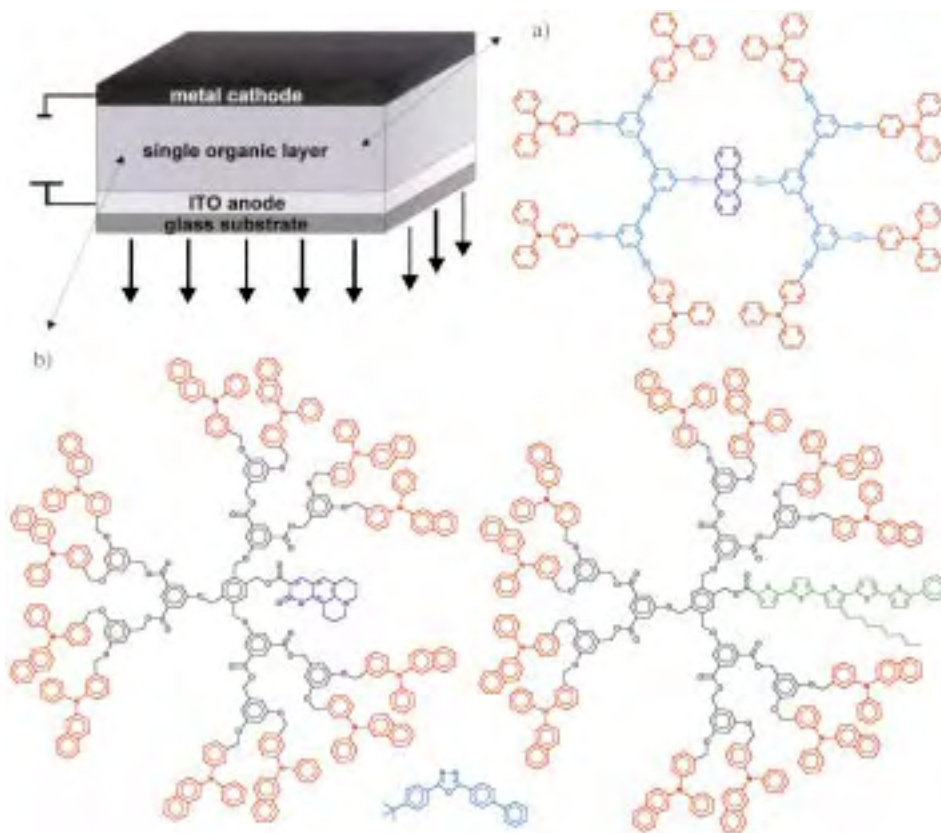


Figure 6. Illustration of a dendritic light-harvesting antenna. The absorption of light of a broad spectral range by peripheral chromophores leads to an enhanced emission from the core (red) as a result of efficient energy transfer (green arrows).

impressively demonstrates how supramolecular chemistry can be used to assemble multiple chromophores and furthermore control their relative orientation.

From a more applied perspective, dendritic scaffolds have been used to spatially arrange the different components necessary for the construction of organic light-emitting diodes. The good film properties obtained from spin casting combined with the formation of a single layer only (having either one or multiple components) offer the potential advantage for the very economic fabrication of devices (Scheme 8). Moore and co-workers have described devices



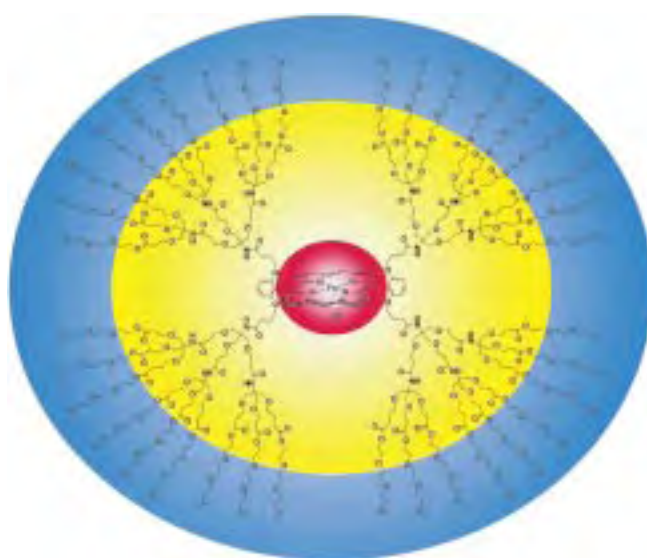
Scheme 8. Single layer organic light-emitting diodes consisting of one component (a)^[36] or multiple components (b) for color tunability.^[38] Hole-transporting units are shown in red, electron-transporting units in cyan, and the lumophores in their respective emission color.

based on phenylacetylene dendrimers having a luminescent anthracene core and peripheral tertiary aromatic amines.^[36] The triaryl amines in their dendrimers served as the hole-transporting element, while the phenylacetylene dendrons acted as electron transporters. The dendrimer backbone was shown to be capable of efficient energy transfer,^[35a,b] and charge recombination within the dendrimer led to a directed transduction of excitation energy to the emitting core. Although a good correlation was found between the photoluminescence and the electroluminescence spectra, the devices had a very low efficiency as a result of self-quenching caused by solid-state aggregation.

The device efficiency of a related system based on stilbene dendrimers^[37] was found to increase by nearly an order of magnitude from the first to the second generation, again demonstrating the value of the site-isolation concept. More recently, Freeman et al. prepared naphthyldiphenylamine-terminated poly(benzyl ether) dendrimers having coumarin or pentathiophene cores (Scheme 8b).^[38] Two-component single-layer devices consisting of the dendrimer, which served as both hole transporter and emitter, as well as an oxadiazole derivative, which acted as the external electron transporter, were fabricated and good matching of the photoluminescence and electroluminescence was observed. The modular design of this approach and the partial site isolation of the central dye by the dendritic framework allows for a combination of dendrimers having differently emitting cores and thus affords a color-tunable system.

4. Electroactive Systems

For decades biologists and chemists have been fascinated by electron transfer proteins and their superior design that allows for efficient charge transfer over long distances. Cytochrome c and ferredoxin, for instance, participate in the respiratory chain by delivering the necessary electrons to the reaction center that reduces oxygen to water. Dendritically encapsulated metalloporphyrins and their electrochemistry have been studied extensively as simple synthetic models for heme-containing electron-transfer proteins such as cytochrome c. Diederich and co-workers systematically changed the microenvironment of the core by varying the generation number to gain further insight into the role of the protein shell in achieving remarkably high oxidation potentials in such enzymes.^[39] Initially, the authors reported that the increasingly electron-rich environment around the core in higher generation Newkome-type dendrimers with zinc porphyrin cores led to facilitated oxidation and inhibited reduction processes.^[39a,c] Subsequently, the first water-soluble dendritic iron porphyrins were synthesized.^[39b,c] Remarkably, the second generation dendrimer dissolved in water (Scheme 9) exhibited a $\text{Fe}^{\text{III}}/\text{Fe}^{\text{II}}$ reduction potential 420 mV more positive than that of the first generation compound. This finding was attributed to the enhanced shielding of the iron porphyrin core which led to reduced contact with the external solvent and therefore destabilization of the higher charge oxidation state. In more recent work, Diederich and co-workers reported the preparation of related dendrimers with



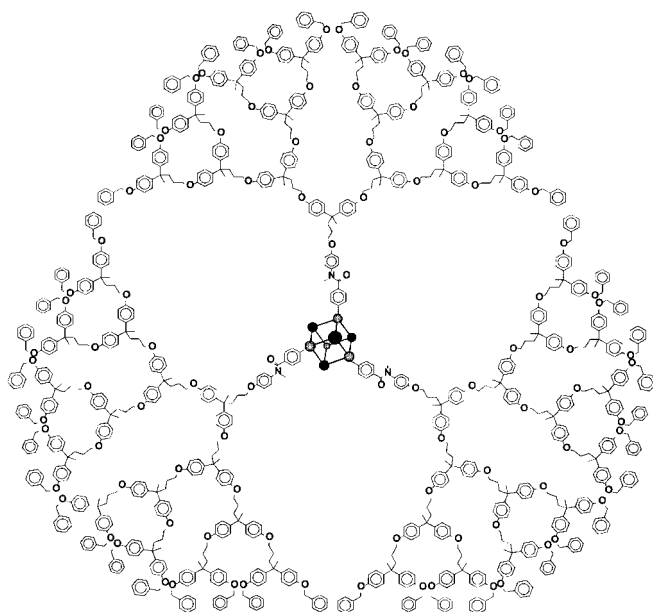
Scheme 9. A unimolecular dendrimer with an iron porphyrin core as a dendritic cytochrome c mimic.^[39] The hydrophobic interior (yellow) encircling the redox center (red) is itself surrounded by a hydrophilic periphery (blue).

iron porphyrin cores that had two tethered imidazole ligands to provide intramolecular axial ligation.^[39d] Again, the reduction took place at a much more positive potential when sufficient dendritic shielding was achieved.

A related study by our own research group involving poly(benzyl ether) dendrimers with zinc porphyrin cores (Scheme 3)^[24] demonstrates most clearly the effect of the dendritic environment on the electrochemical characteristics of the core. Increasingly slow electron transfer kinetics were observed, as judged by a decrease in the peak current and an increase in the peak potential differences, as the size of the dendritic shell increased. In fact, shielding was so effective for the fourth generation compound that no electron transfer at all could take place. This result illustrates clearly the dendritic shell effect that leads to a more hindered approach of the core to the electrode. Both studies^[24, 39] independently illustrate that changes in redox potential with increasing core isolation can mainly be correlated to dendritic solvation, namely, the difference between the chemical nature of the dendritic interior and the exterior solvent.

In an attempt to mimic a non-heme iron-based electron-transfer protein, such as ferredoxin Gorman and co-workers studied cubic iron–sulfur clusters (Scheme 10)^[40] prepared through a ligand-exchange reaction using poly(aryl ether) dendrons having an aromatic thiol functionality at their focal point.^[41] The increasing steric bulk of the higher generation ligands led to a more difficult reduction of the core, both kinetically and thermodynamically—as indicated by shifts of reduction potentials to more negative values and increasing peak potential differences. As illustrated above, electron transfer between the core and the electrode slows down in higher generations as a consequence of dendritic insulation.

Newkome et al. also took advantage of electrochemical methods (CV) to probe the interaction of “lock” and “key” dendritic segments mediated by a bis(terpyridine)ruthenium(II) complex.^[42] Whereas a combination of second genera-

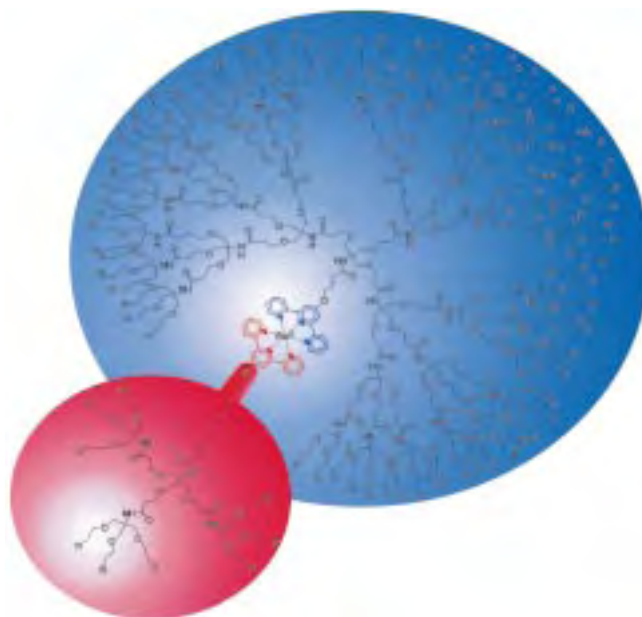


Scheme 10. Dendrimers with iron–sulfur cluster cores as dendritic ferredoxin mimics.^[40]

tion “key” and second generation “lock” displayed a reversible redox cycle, the use of the fourth generation “lock” (Scheme 11) led to a completely irreversible behavior, which indicated highly efficient shielding of the ruthenium(II) core. Chow and co-workers subsequently reported a systematic study^[43] of related bis(terpyridine)iron(II) complexes encapsulated within poly(ether) dendrimers.^[44] X-ray photoelectron spectroscopy showed no significant changes in the bonding environment of the central iron atom in different generations. Once again, CV revealed an increasingly difficult metal redox process in higher generation dendrimers as a result of the thicker dendritic coating leading to an increased remoteness of the metal center from the electrode surface.

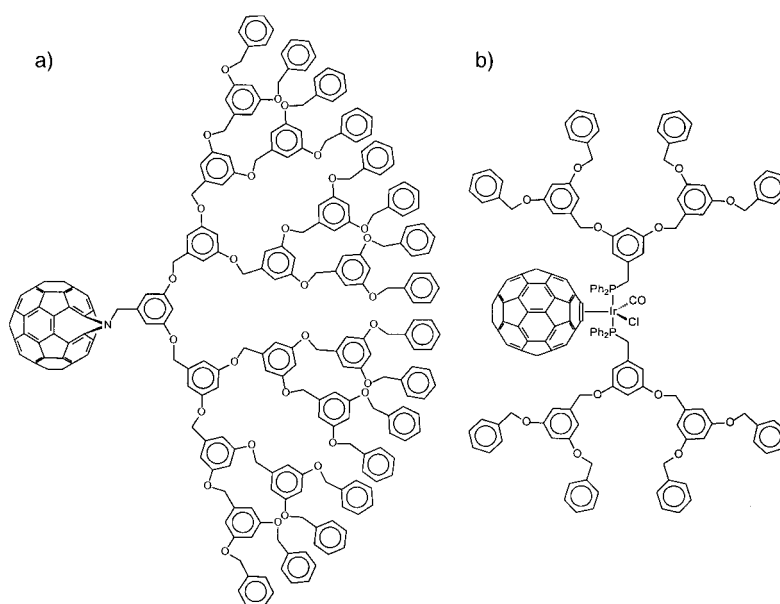
A detailed analysis of the observed electrochemical irreversibility was provided by Kaifer and co-workers, who thoroughly studied ferrocene modified with dendritic ligands.^[45] The authors showed that the heterogeneous electron-transfer rate constant as well as the diffusion coefficients decreased as the generation number increased.^[45a, 46] Strong orientational effects on the heterogeneous electron transfer were also observed when ionizable surface groups capable of interacting with a modified electrode surface were introduced on the dendrimer.^[45b]

The chemistry of fullerenes has seen many creative forays in the past two decades and it continues to stimulate a broad spectrum of research activity. While C_{60} itself is significantly smaller than most dendrimers, combinations involving the two globular species with their extremely versatile chemistries and tunable properties appeared attractive. Hence, the first C_{60} -dendrimer hybrids were reported by the groups of Wudl and Fréchet, who used a conventional Williamson ether synthesis of fullerenes carrying two phenolic sites with Fréchet-type dendrons having benzylic bromides at the focal point.^[47a] This



Scheme 11. The interaction of a second generation “key” (red) with a fourth generation “lock” segment (blue) leads to an efficient shielding of the core.^[42]

initial approach was complicated by side reactions related to the functionalized fullerene and required preparative gel-permeation chromatography (GPC) for purification. An alternative synthesis involving the coupling of dendritic azides to C_{60} proved better, and the hybrid (Scheme 12 a) displayed a dramatically enhanced solubility relative to fullerene itself.^[47b] CV measurements indicated that the attached dendron had an insulating effect on the fullerene. In a very elegant study Catalano and Parodi demonstrated the reversible binding of a Vaska-type iridium complex containing dendritic phosphane ligands coordinated to C_{60} (Scheme 12 b).^[48] More recently, Hirsch and co-workers attached twelve Fréchet-type den-



Scheme 12. Dendritic fullerenes having either a covalent (a)^[47] or a coordinative linkage (b).^[48]

drons to a fullerene by a cyclopropanation route.^[49] Subsequently, they also introduced a tetraphenylporphyrin unit and observed photoinduced electron transfer in their dendritic donor–acceptor dyad.^[50]

In addition to the numerous examples of organic dendrimer shells used to encapsulate various electroactive cores presented above, metallodendrimers based on coordinative linkages involving multifunctional ligands and connecting metals have recently received much attention.^[3c,d, 51]

5. Cylindrical Encapsulation and Electroactive Systems

The dimensionality of a cylinder (Figure 1) introduces the directionality required for charge-transfer processes. Therefore, dendritically substituted conjugated rigid rods^[52, 53] should ideally give rise to an insulated “molecular wire”, an attractive goal for molecular-scale electronics.^[54] Schlüter and Percec have independently proposed cylindrical dendrimers based on steric repulsions between dendritic segments attached to a central linear polymeric core to enforce an overall extended, rodlike shape (Figure 7).^[10] Following up on early work on polymers with dendritic pendant groups by

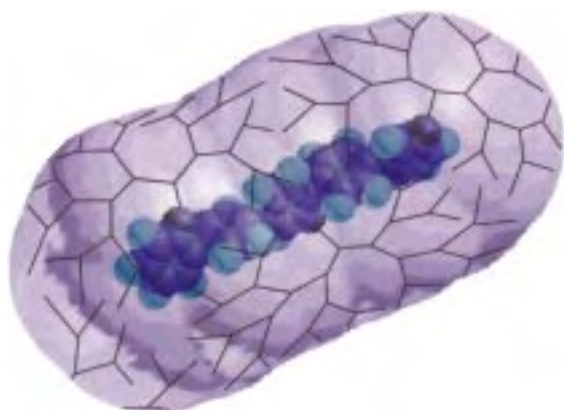


Figure 7. Illustration of a cylindrically shaped dendrimer formed as a consequence of the steric repulsion between dendritic substituents attached to a rigid rodlike core, for example, poly(*p*-phenylene).

Hawker and Fréchet,^[55] Schlüter and co-workers carried out a definitive study of “dendronized” polymers.^[14, 15, 56] Their efficient and elegant synthetic approaches afforded well-defined macromolecules consisting of poly(styrene) or poly(*p*-phenylene) cores substituted by Fréchet-type polyether dendrons. Small-angle neutron scattering experiments showed that both the dendron generation and the presence of charged peripheral groups had a strong influence on the diameter of the cylinderlike molecule.^[56d] In another study, scanning force microscopy revealed that the poly(*p*-phenylene) core nanorods (Figure 7) were approximately 90 nm long and 4.8 nm in diameter.^[15]

In an exquisite and completely different approach Percec et al. reported on styrenic and methacrylic polymers with tapered dendritic side chains that form cylindrical structures in the solid state through a supramolecular self-assembly

process reminiscent of that of the tobacco mosaic virus (Figure 8).^[57] It was shown that polymerization of dendritic monomers within the dendritic coat was accelerated^[57b] and that the degree of polymerization of the resulting polymer determined the overall shape of the macromolecule, namely, cylindrical or spherical, as a consequence of maximized self-encapsulation.^[57c]

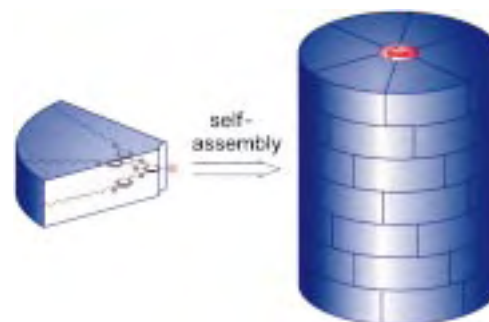


Figure 8. Self-assembly of linear polystyrene (red) having tapered dendritic side chains (blue) into cylindrical superstructures.^[57]

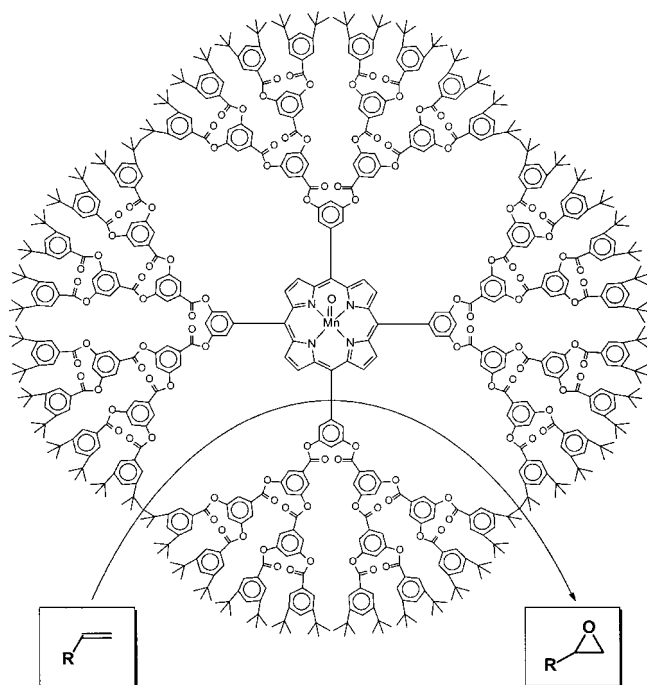
Building on these concepts, many promising systems using conjugated rodlike cores have been reported recently. For instance, Diederich and co-workers described the synthesis and study of dendritic poly(triacetylene) oligomers of precise lengths.^[58] CV experiments suggested that the dendritic layer protected the central backbone without altering its electronic properties, as shown by UV/Vis spectroscopy. An important advantage of the monodisperse oligomers over the related polymerized species is the precise control over the length of the molecular wire. Bao et al. investigated emissive dendrimers with poly(phenylenevinylene) cores and showed that the bulky dendritic wedges enhanced main-chain separation in the solid state as verified by X-ray diffraction measurements.^[59] Therefore, self-quenching is reduced in the solid state—a necessary prerequisite for high photoluminescence and electroluminescence quantum yields. In a related study Sato et al. reported on dendrimers with poly(phenyleneethynylene) cores as blue light emitting dendritic rods.^[60] The authors found that the quantum yields for luminescence approached unity for the fourth generation compound, even when used at high concentration in solution. The efficiency was further enhanced by a facile energy transfer from the dendrons to the core leading to efficient light harvesting. An amphiphilic cylinder has also been described very recently by Bo et al.^[61] This type of structure opens the possibility of building higher order architectures similar to the natural ion channels based on an array of amphiphilic peptide helices. The surface differentiation was accomplished by the attachment of hydrophobic and hydrophilic dendritic segments to the monomer followed by polymerization.

6. Catalytically Active Systems

The size of a dendrimer is roughly comparable to that of many enzymes and, just like enzymes, dendrimers are able to create a microenvironment around a reactive site. While

nature has had an ample opportunity to optimize enzymes through evolutionary processes, one of our best tools for the optimization of dendrimers is mimicry, even if based on grossly simplified models. Significant advances have been made in the last few years and more sophisticated dendritic molecules that perform more and more catalytic operations will continue to appear. Numerous reports have already outlined approaches to the use of dendrimers as molecular-scale chemical reactors. Ideally, the dendritic superstructure would provide a tool to tune and enhance the activity and selectivity of a single encapsulated active site.^[62, 63]

Among the most attractive targets is the mimicry of natural oxidation catalysts, in particular, heme-based oxygenases.^[64] Manganese porphyrins carrying oxidatively robust poly(phenyl ester) dendrons were reported by Moore and co-workers^[65] and were found to catalyze the shape-selective^[66] epoxidation of alkenes when iodosobenzene was used as the oxidizing agent (Scheme 13). In both intra- and intermolecular competition



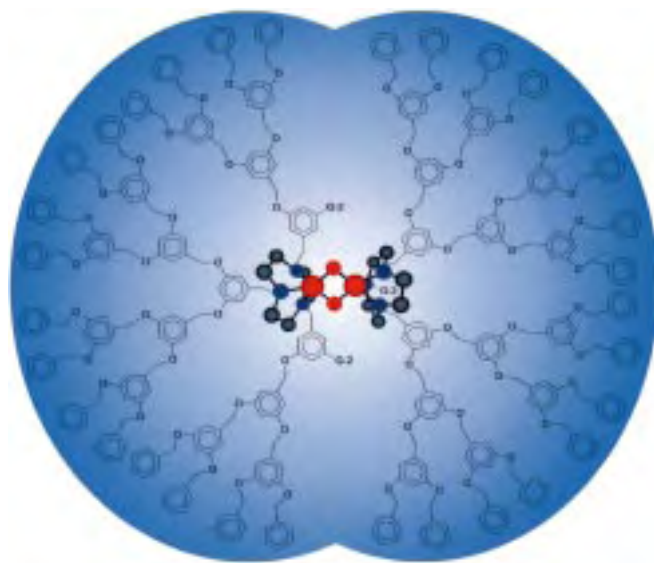
Scheme 13. Shape-selective olefin epoxidation using dendrimers with a manganese(III) porphyrin core as catalysts.^[65]

studies, the second generation dendrimer-based catalyst was up to four times more selective towards less-hindered terminal double bonds than a simple manganese tetraphenylporphyrin used for comparison purposes. The dendritic catalysts showed excellent oxidative stability as a consequence of their efficient shielding. More recently, Kimura et al. published their first results of employing dendrimers with cobalt phthalocyanine cores to catalyze the oxidative transformation of thiols to disulfides using molecular oxygen as the oxidant.^[30d] The authors found that the catalytic activity of the second generation catalyst dropped by 20 % relative to that of the first generation, which suggested there was no significant restriction in the penetration of the substrate into the dendrimer. Not surprisingly, the larger, higher generation

catalyst displayed enhanced stability as a result of its better protection by the dendritic shell.

Heme proteins are known to bind dioxygen either prior to activation, to yield the catalytically active oxo species, or simply for transport reasons, such as in monomeric myoglobin or tetrameric hemoglobin. Dendritic iron(II) porphyrins have been investigated in an attempt to mimic oxygen binding. Jiang and Aida reported that the lifetime of the oxygen adduct dramatically increased with increasing dendritic shielding and leading to 95 % survival after two months in the case of the somewhat stiffer fifth generation dendrimer.^[67] The authors suggested that the more crowded dendritic poly(benzyl ether) barrier lowered the effective gas permeability and acted to reduce the entry of water molecules, therefore, providing both steric and hydrophobic protection to the oxygen complex. Collman, Diederich, and co-workers measured the oxygen and carbon monoxide equilibrium binding constants of their Newkome-type poly(ether amide) dendrimers using 1,2-dimethylimidazole as the axial ligand to form a five-coordinate, high-spin iron(II) precursor complex.^[68] They found a remarkably high oxygen affinity, 1500 times greater than that of the T state of hemoglobin. This result was attributed to possible hydrogen-bonding interactions of the amide protons with the terminal oxygen atom. Interestingly, the measured carbon monoxide affinity was very low.

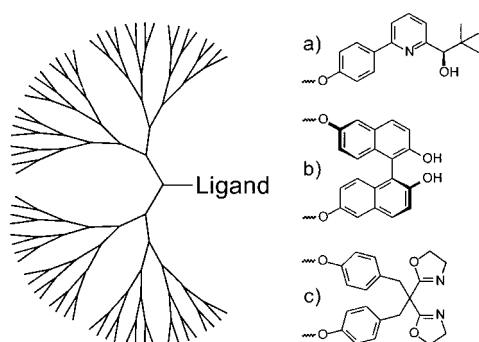
Multicopper motifs^[69] have also been investigated as non-heme models for oxygen carriers.^[70] Enomoto and Aida described the oxygen driven self-assembly of a copper-ligating dendrimer to yield a bis(μ -oxo)copper dimer (Scheme 14).^[71] The decay of the oxygen complexes was very dependent on dendrimer size, with high generation dimers displaying longer lifetimes. Kinetic analysis revealed that a more negative entropy of activation was the cause for the slower unimolecular decay. However, the oxygen adduct cannot be formed at all at a higher generation because of the steric bulk of the dendritic subunits.



Scheme 14. Dendritic non-heme dioxygen carrier. A bis(μ -oxo)copper dimer based on a triazacyclononane (TACN)-copper(II) complex is shown.^[71]

The application of dendrimers in the design of sensors for sulfur dioxide gas was demonstrated with poly(phenyl ester) dendrimers bearing multiple platinum pincer complexes.^[72] These metalated dendritic sensors showed a direct optical response, were highly selective towards sulfur dioxide, and fully reversible, thus providing the opportunity to tune the detection sensitivity through variations in the number of platinum sites.

Brunner introduced dendritic ligands carrying optically active groups for enantioselective catalysis.^[73] The molecules, termed “dendrzymes”, were designed to transfer the chiral information inherent in the dendrimer backbone over a long range to the asymmetric metal center. However, enantioselectivities were usually found to be rather low. Interestingly, in one case a 1,3,5-branched ligand led to a rate acceleration whereas the 1,2,5-isomer showed a rate retardation. This finding is in agreement with other studies mentioned earlier,^[21c, 31] which illustrate the important effect of the dendritic branching pattern on the ultimate properties of the material. Dendritically expanded chiral ligands have been explored in the asymmetric addition of carbonyl groups. Whereas Bolm and co-workers used dendritic pyridyl alcohols (Scheme 15a) for the asymmetric addition of diethylzinc to benzaldehyde,^[74] Yoshida et al. reported on dendrimers with binaphthol core as

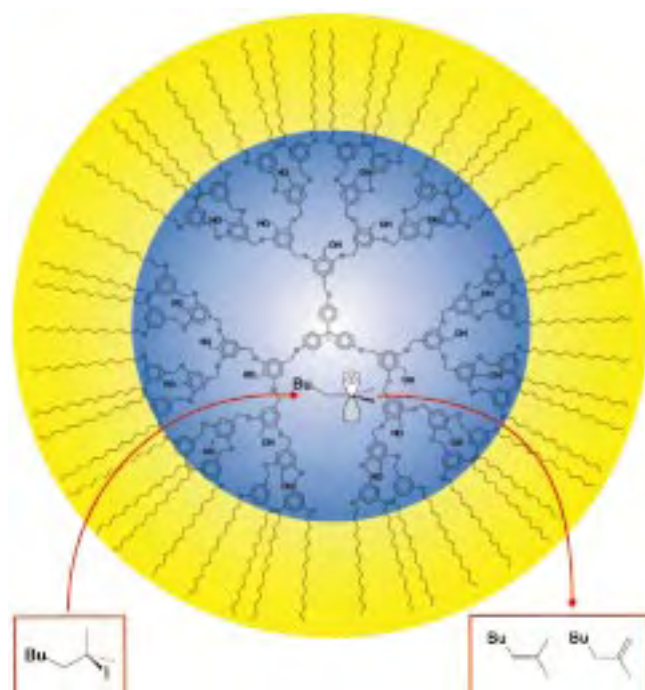


Scheme 15. Dendritically modified chiral ligands for asymmetric catalysis.^[74–76]

chiral ligands in the titanium-mediated allylation of the same substrate (Scheme 15b).^[75] The key result in both studies is that the enantioselectivities remained constant with increasing generation. A detailed mechanistic analysis has been performed by Chow and co-workers, who investigated dendritic bis(oxazoline)copper(II) catalysts in Diels–Alder reactions (Scheme 15c).^[76] Precomplexation of the dienophile to the catalyst became increasingly difficult as the generation number increases. The rate of the subsequent reaction of the catalyst–substrate complex with the diene remained initially constant, then dropped when changing from the second to the third generation. For the higher generation catalyst, a slightly enhanced selectivity was observed for sterically less demanding dienophiles. A similar finding was reported by van Leeuwen and co-workers, who investigated palladium-catalyzed allylation reactions using a bisphosphane ligand incorporated in a carbosilane dendrimer.^[77] Increasing the generation number of the catalysts led to a rate decrease as well as a change in the regioselectivity of the catalyst.

It is clear that simply building chirality into the dendritic analogue of a small molecule catalyst is not sufficient to produce enzyme-like catalytic enhancements. In addition, increasing the generation number and therefore the thickness of the dendritic shell may—depending on the flexibility and exact nature of the building block—lead to increasingly difficult mass transport and therefore diminished catalytic activity. Clearly, the application of more thorough design concepts including tailored microenvironments and even structural features that assist in transport and in lowering the energy of key transition states and intermediates will be required before dendritic catalysts can reach their full potential.

In collaboration with Hawker, our research group has recently designed a very simple dendrimer catalyst (Scheme 16) that incorporates design features that favor a low-energy transition state while also providing for the



Scheme 16. A unimolecular reverse micelle that efficiently catalyzes the elimination of tertiary halides.^[78] The nonpolar corona (yellow) shields the polar interior (blue) of hydroxyl functionalities, which are able to stabilize the carbocation intermediate.

preferential entry of the reagents and thermodynamically driven exclusion of the product to avoid product inhibition of the catalytic site.^[78] The dendrimer behaves as an (inverse) unimolecular micelle-like container with a hydrophilic interior environment that stabilizes polar transition states and intermediates, and a hydrophobic exterior that helps to solubilize the catalyst and drive products away from the catalytic site. The catalyst was tested in simple E1-type eliminations from tertiary alkyl halides. As a result of their polarity, the alkyl halide moieties are drawn to the highly polar core, where formation of the carbocationic intermediate and subsequent elimination occurs to yield the nonpolar alkene that is then rapidly driven from the core to the

nonpolar corona and surrounding solvent to minimize the free energy of the system. Consideration of Le Chatelier's principle explains the high turnover number (17 400) obtained as the substrate is driven in and the product driven out of the catalytic site. Hence the dendrimer functions as a catalytic "pump" and almost quantitative conversions can be achieved with very low catalyst loading (less than 0.01 mol %). In a related approach, acid–base catalysis has been explored by Morao and Cossío, who used a single tertiary amine at the core of poly(benzyl ether) dendrimers to catalyze nitroaldol reactions.^[79]

Finally, catalytically active sites, initially located at the focal point of dendrons, have been thoroughly investigated by Fréchet and co-workers with regard to their use as macromolecular initiators.^[80] This approach provides access to a new class of hybrid materials of dendritic–linear block copolymers. By choosing an appropriate initiator, a variety of monomers could be polymerized successfully. For instance, dendritic alkoxides have been employed in the ring-opening polymerization of ϵ -caprolactone,^[80a] dendritic chlorides initiated the atom-transfer radical polymerization of styrene,^[80b] while dendritic nitroxides led to the living free-radical polymerization of styrene (Figure 9).^[80b] Dumbbell-like triblock materials could be obtained when a combination of a dendritic initiator and a dendritic capping group was used.^[80c]

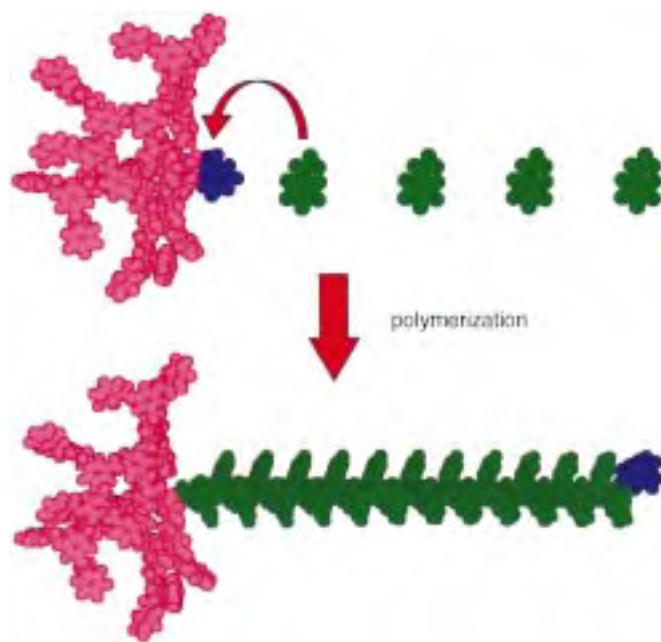


Figure 9. A fourth generation poly(benzyl ether) dendron (pink) having a nitroxide focal point functionality (blue) serves as an initiator for the living free-radical polymerization of styrene (green).^[80b]

7. Outlook

Throughout this review we have focussed on the encapsulation motif utilizing dendritic building blocks. Clearly, the preparation of such materials requires great synthetic efforts, typically involving multistep procedures and chromatographic separations. In a practical sense, the whole field of dendrimer

chemistry suffers from this disadvantage and alternative synthetic methods are still needed.^[81, 82] Different approaches to encapsulate single active core functionalities have recently been explored and include branched star polymers^[83] as well as dendritically cross-linked polystyrene based resins.^[84] Furthermore, polymer-imprinting techniques have been applied to yield "cored" dendrimers having the potential to encapsulate small molecule guests resembling their template.^[85] Accompanying alternative encapsulation strategies, the incorporation of new core functionalities, especially nanosized inorganic clusters, has received increasing attention. Such materials combine the unique properties of inorganic clusters with the superior processability of organic polymers. Recent efforts include, for instance, silicon dioxide core materials^[86] and encapsulated quantum dots.^[87] Alternatively, noncovalent methods utilizing dendrimers as hosts for nanoparticles have been explored in the laboratories of Crooks and Tomalia.^[88]

The future will surely witness extensive research at the interface of inorganic chemistry and polymer science, with particular focus on such new hybrid materials. Furthermore, the synthesis of increasingly large and complex target structures through supramolecular interactions will be an important future milestone. Control over the spatial arrangement of isolated moieties will be the key to achieving new collective properties. Finally, future studies will enable us to gain more insight into the crucial role of dendrimer morphology in energy-transfer phenomena, which will ultimately lead to a better understanding of photosynthesis and the construction of new, improved systems for solar-energy conversion as well as superior light-emitting devices.

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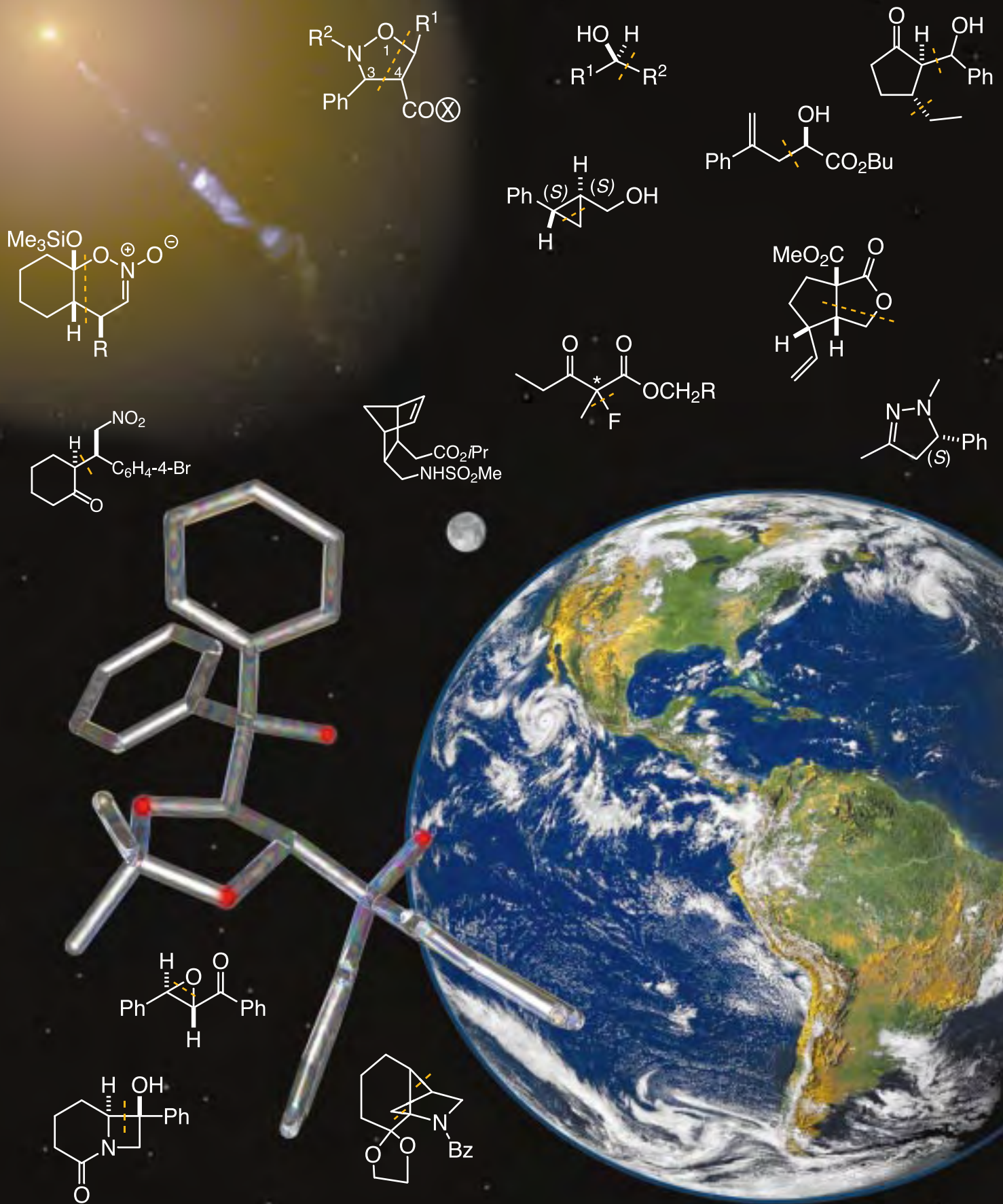
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TADDOLs, Their Derivatives, and TADDOL Analogues: Versatile Chiral Auxiliaries

Dieter Seebach,* Albert K. Beck, and Alexander Heckel

TADDOLs, which contain two adjacent diarylhydroxymethyl groups in a *trans* relationship on a 1,3-dioxolane ring, can be prepared from acetals or ketals of tartrate esters by reaction of the latter with aromatic Grignard reagents. They are extraordinarily versatile chiral auxiliaries. Here, a historical review of the subject is followed by discussion of the preparation of TADDOLs and analogous systems, including TADDOLs with N-, P-, O-, and S-heteroatom ligands appropriate for metals. Crystal structure analysis reveals that the heteroatoms on the diarylmethyl groups are almost always in close proximity to each other, joined together by H-bonds, and predisposed to form chelate complexes in which the metallic centers reside in propeller-like chiral environments. Applications of TADDOL derivatives in enantioselective synthesis extend from utilization as stoichiometric chiral reagents or in Lewis acid mediated reactions, to roles

in catalytic hydrogenation and stereoregular metathesis polymerization. Derivatives and complexes based on the following metals have so far been investigated: Li, B, Mg, Al, Si, Cu, Zn, Ce, Ti, Zr, Mo, Rh, Ir, Pd, Pt. The number of stereoselective reactions already accomplished with TADDOLs is correspondingly large. It is also easy to prepare TADDOL derivatives that are readily polymerizable and graftable, and to transform them into immobilized solid-phase catalysts. The result is catalysts, simply or dendritically immobilized in polystyrene or on silica gel and characterized by unexpected stability even after multiple use in titanium TADDOLate mediated reactions. TADDOLs show further unusual characteristics that make them useful for applications in material science and supramolecular chemistry: they are the most effective doping agents known for phase transformations of achiral (nematic) into chiral (cholesteric) liq-

uid crystals. The TADDOL OH group that is not involved in intramolecular H-bonding shows a strong tendency to associate intermolecularly with H-bond acceptors. In the process of crystallization this leads, enantioselectively, to the formation of inclusion compounds that lend themselves to the separation of racemic mixtures not otherwise suited to the classical method of crystallization through diastereomeric salts. The high melting points of TADDOLs even make possible the resolution of racemates by distillation! Host-guest compounds formed between TADDOLs and achiral partners can serve as platforms for enantioselective photoreactions. It seems safe to predict that many more applications will be discovered for the TADDOLs and their derivatives.

Keywords: asymmetric catalysis • asymmetric synthesis • enantiomer separation • TADDOL

1. Introduction and Historical Background

Degradation of carboxylic acids to their next lower homologues was employed for purposes of structure determination based on chemical correlation early in the twentieth century. One strategy took advantage of the Barbier-Wie-

land reaction sequence: transformation of an ester into a tertiary alcohol (a “benzhydrol” or “diphenylcarbinol”), which was dehydrated and then subjected to oxidative C–C bond cleavage to produce a new carboxylic acid containing one less carbon atom in the chain (Figure 1 a).^[1] In the 1930s, attention was directed toward the study of reaction mechanisms, and Georg Wittig took advantage of the reaction of cyclohexanedicarboxylic acid esters (*cis*, *rac-trans*, and (+)-*trans*!) with phenylmagnesium bromide as a route to ethers of tertiary alcohols for investigation of the cleavage—today we would describe it as fragmenting—of ethers with potassium (Figure 1 b).^[2] Decades later, derivatives of the same type appeared yet again (indeed, twice!): On one hand in the context of a novel route to their synthesis^[4] (Figure 1 d), and on the other with respect to the question of whether the

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presence of a four-membered ring in the 2,3-position might lead to an isolable “optically active” (helical chiral) 1,1,4,4-tetraphenylbutadiene (Figure 1c).^[3, 5]

Toward the end of the twentieth century, the preparation of enantiomerically pure^[6] compounds (EPCs^[7–12]) was recognized to be one of the most important goals in the methodology of organic synthesis, and—in fulfillment of a prediction offered in 1990^[11]—chemists now are already well on the way toward having at their disposal (catalytic) enantioselective variants of all the standard synthetic methods, permitting the preparation of chiral products from achiral precursors or intermediates.^[13–20] With respect to this goal as well, the reaction of aryl Grignard reagents with (enantiomerically pure!) esters, mainly ones derived from natural products, has played a key role. The first systematic application involved the compound TADDOL,^[21–24] derived from tartaric acid (Scheme 1).

Relative to classical Li and Mg derivatives, organotitanium derivatives react with similar functionalities (for example, aldehydes/ketones/esters), but with much more selectivity with respect to diastereotopic groups and faces present in the substrate molecules.^[25–31] It was thus obvious that enantioselective titanium derivatives would be worth seeking. One of the first chiral ligands we utilized successfully in this context was the TADDOLate shown in Scheme 1.

TADDOLs and analogous compounds, as well as various derivatives in which one or both of the OH groups is derivatized or replaced by another functional group, have since 1982^[23] been found to be so useful that one can now speak in a formal sense of a “TADDOL auxiliary system”. We wish to emphasize that the term “chiral auxiliary” should here be understood in the broadest possible sense, that is, as a way of describing a compound or a class or family^[33] of compounds with the aid of which it becomes possible to “introduce

Dieter Seebach was born in Karlsruhe (Germany) in 1937. He studied chemistry at the University of Karlsruhe, where he completed doctoral work on small rings and peroxides under the supervision of R. Criegee (1964). After a nearly two-year sojourn at Harvard University as postdoctoral fellow (working with E. J. Corey) and lecturer, he returned to Karlsruhe and qualified for habilitation in 1969 with a paper based on sulfur- and selenium-stabilized carbanion and carbene derivatives. He was appointed to professorial positions first at the Justus Liebig University in Giessen in 1971 and subsequently (in 1977) at the Eidgenössische Technische Hochschule (ETH) in Zürich. His current research activity relates primarily to the development of new synthetic methods, preparation and secondary structural investigations of β -peptides, synthesis and applications of oligomers of (R)-3-hydroxybutyric acid (HB) and of the biopolymer PHB, the synthesis of chiral dendrimers, and applications of chiral titanates to organic synthesis. Dieter Seebach has been a visiting professor at numerous prestigious universities, and is a member of the Deutschen Akademie der Naturforscher Leopoldina and the Swiss Academy of Technical Sciences (SATW) as well as a corresponding member of the Akademie der Wissenschaften und Literatur in Mainz. He has been awarded an honorary doctorate by the University of Montpellier.



A. K. Beck

D. Seebach

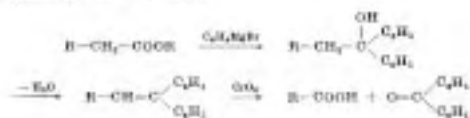
A. Heckel

Albert Karl Beck was born in 1947 in Karlsruhe (Germany), and after completing secondary school he undertook a chemistry technician's apprenticeship at the Institute for Organic Chemistry of the University of Karlsruhe from 1963 to 1966. Following 18 months of military service he joined the Seebach research group in 1968. Between 1969 and 1972 he continued his education, obtaining official certification as a chemical technician at the Fachschule für Chemotechnik in Karlsruhe. In 1971 he followed D. Seebach to the Institute for Organic Chemistry at the University of Giessen, and in 1974 he engaged in a six-month research visit to the California Institute of Technology in Pasadena. Albert K. Beck has been an active part of the Laboratory for Organic Chemistry at the ETH in Zürich since the time of Seebach's arrival there. During his long association with the Seebach research group he has participated in essentially all of the group's research themes, as evidenced by his coauthorship of more than 70 publications. In recent years he has been occupied primarily with the chemistry of TADDOLs and TADDOL derivatives.

Alexander Heckel was born in 1972 in Lindau on Lake Constance (Germany). He studied chemistry from 1992 to 1997 at the University of Constance with the aid of a Hundhammer Fellowship, and he graduated with honors. His diploma thesis dealt with oligosaccharide solid-phase synthesis, work carried out under the direction of R. R. Schmidt. He subsequently moved to the ETH in Zürich, where he is currently completing doctoral work in the area of heterogeneous enantioselective catalysis under D. Seebach. In his free time he does volunteer work as a paramedic with the Red Cross.

a) Carbonsäure-Abbau BARBIER-WIELAND

zum nächst niedrigeren Homologen. Der Methyl ester wird mit Phenylmagnesiumbromid in einen tertiären Alkohol übergeführt, aus dem mit Essigsäureanhydrid Wasser abgespalten und so eine Doppelbindung eingeführt wird. Diese ungesättigte Verbindung wird mit Chromtrioxid zur Säure oxidiert, die nun ein C-Atom weniger enthält. Auf diese Weise können auch Seitenketten in komplizierten organischen Verbindungen (z.B. Steroiden) stufenweise abgebaut werden.



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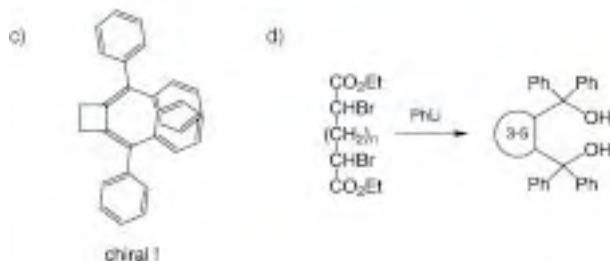
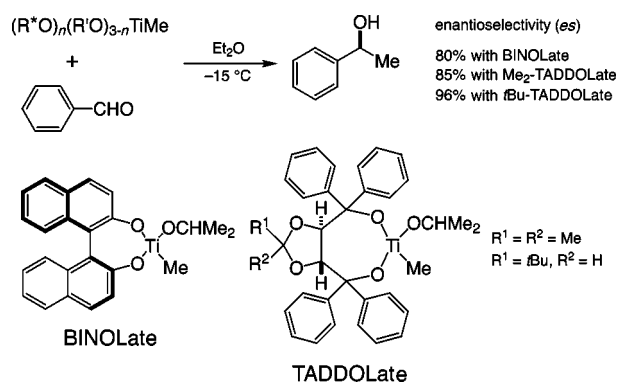


Figure 1. The reaction of carboxylic acid esters with phenyl Grignard reagents at various junctures in the history of organic chemistry. a) The Barbier-Wieland method for degrading carboxylic acids.^[1] b) Wittig's investigation of ether cleavage with the breaking of C–C bonds.^[2] c) The search for a helical π system.^[3] d) An original synthetic pathway for preparing a diarylmethanol derivative.^[4]

chirality". Such a material should be capable of creating a "chiral environment" not only around a specific reaction center, but also—through supramolecular interactions—in solution, within a liquid crystalline system, or in the solid state.

2. Preparation of TADDOLs and Their Analogues

If one chooses not to start from the commercially available acetonide of a tartrate,^[34] a 2,2-dimethyl-1,3-dioxolane deriv-



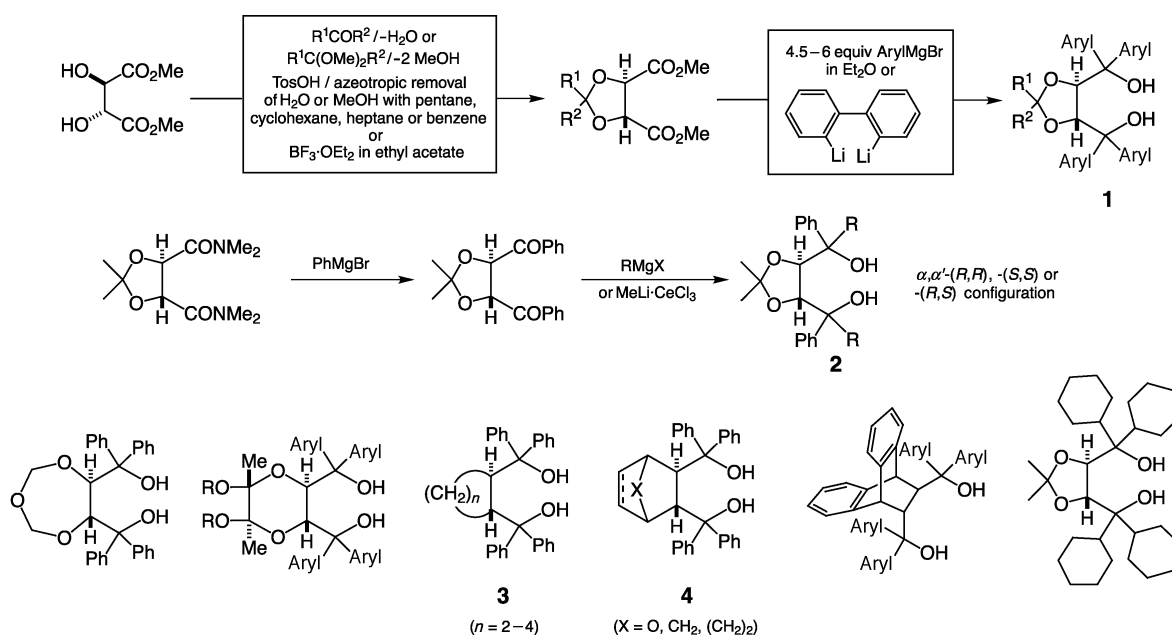
Scheme 1. The first use of TADDOLs (derived from tartrate esters and phenyl Grignard reagents) for enantioselective nucleophilic addition to aldehydes. Apart from BINOL and TADDOL, numerous other chiral alcohols and diols have also been tested, but with only modest success.^[25–27, 32]

ative, then alternative precursors to TADDOLs **1** are most readily obtained by treatment of dimethyl or diethyl tartrate with the appropriate aldehyde or ketone under acid catalysis and with azeotropic removal of water. The products are then reacted with aryl Grignard reagents. A related and often more effective method is acid-catalyzed transacetalization, in which dimethyl tartrate is treated with the dimethyl acetal or ketal of some aldehyde or ketone with concurrent removal of the resulting methanol. Rather than resorting to distillation, one can also remove the byproduct methanol or water by treatment with an equimolar amount of $\text{BF}_3 \cdot \text{OEt}_2$; for literature references, see Scheme 2.

The most frequently utilized TADDOLs, **1a–p**, are presented in Table 1. Given the number of aldehydes, ketones, and aromatic halides available for incorporation, it should come as no surprise that several hundred different TADDOLs and TADDOL analogues have already been described.^[61] (See the Supporting Information for a list which is, to the best of our knowledge, complete and represents the state of the literature at the beginning of 2000). All the substances described are nonvolatile solids, with most showing a strong tendency to crystallize. They are also characterized by high optical rotation values (in most cases compounds prepared from *(R,R)*-tartaric acid are levorotatory in aprotic solvents;^[36, 68] see also Section 5 and Figure 9), and they behave like nonpolar materials in terms of solubility and chromatographic R_f values. Even though TADDOLs with two methyl groups in the 2-position of the dioxolane ring are acetonides, they are extraordinarily stable, and they survive acidic workup with no problems whatsoever. The thermal stability of these "benzhydrol" derivatives is also high; the compounds melt without decomposition at temperatures between approximately 180 and 220 °C.

3. Derivatization and Substitution of the OH Groups in TADDOLs

The OH groups in TADDOLs are subject to the usual chemical reactions: ether formation, esterification, silylation (with ClSiR_3 or Cl_2SiR_2), and treatment with ClPR_2 , Cl_2PR ,



Scheme 2. Preparation of TADDOLs and analogous 1,4-diols from cyclic carboxylic acid esters (only one enantiomer is shown in each case). Detailed standard conditions for acetalization/ketalization,^[35] for the reaction with phenylmagnesium bromide, and for isolation and purification of the TADDOLs **1** have been published.^[35–37] New TADDOLs introduced for the first time in this review were prepared similarly^[38–43] (see also the literature references in Table 1). Derivatives **2** containing various groups on the methanol units (which thereby become stereocenters) are accessible via the diketones shown in the middle.^[44, 45] The trioxacycloheptane derivative shown at the lower left resulted from an “accident” encountered during the preparation of TADDOL **1** with $\text{R}^1 = \text{R}^2 = \text{H}$ and $\text{Aryl} = \text{C}_6\text{H}_5$. The 1,4-dioxandimethanols (TARTROLS) are derived from tartrate esters, butan-2,3-dione, methanol or ethanol, and ArylMgX .^[46–49] Of the carbocyclic analogues **3** ($n = 2$,^[44] **3**,^[44] and **4**,^[2, 44]), the one most commonly prepared is that derived from the *trans*-cyclohexane dicarboxylic acid. Bicyclic derivatives **4** ($X = \text{O}$,^[44] CH_2 ,^[44, 50] $(\text{CH}_2)_2$,^[44, 51]), the dibenzobicyclo[2.2.2]octadiene derivative,^[51–59] and the tetracyclohexyl analogue (prepared by hydrogenation of **1a**^[60]) would so far be classed among the more exotic of the chiral complexing agents. Tos = toluene-4-sulfonyl.

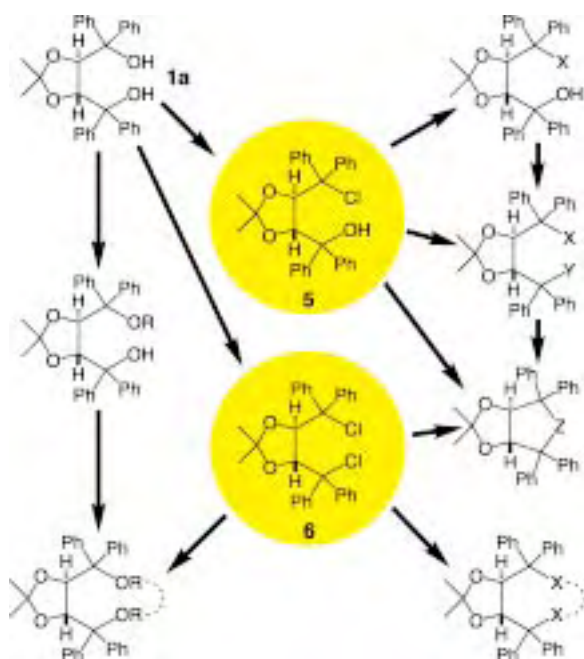
Table 1. The most frequently utilized TADDOLs **1a–p**.^[a]

R^1	R^2	Aryl	1	Ref.
Me	Me	Ph	a	[35, 36]
Me	Ph	Ph	b	[44, 64]
	$(\text{CH}_2)_4$	Ph	c	[65]
	$(\text{CH}_2)_5$	Ph	d	[35, 36]
Me	Me	1-Nph	e	[36]
Me	Me	2-Nph	f	[36]
Ph	Ph	Ph	g	[66–68]
Ph	H	Ph	h	[35]
<i>t</i> Bu	H	Ph	i	[35, 36]
Me	Me	3,5-Me ₂ C ₆ H ₃	j	[37]
Et	Et	Ph	k	[69]
Et	Et	3,5-Me ₂ C ₆ H ₃	l	[37, 69]
Me	Me	4-HOC ₆ H ₄	m	[63]
H	H	4-(Me ₂ N)C ₆ H ₄	n	[70]
4-(HOCH ₂)C ₆ H ₄	H	Ph	o	[71]
4-(CH ₂ =CH)C ₆ H ₄	H	Ph	p	[71]

[a] Literature references in each case contain information about preparation and characterization of the compounds. Commercially available materials include **1a**, **1b**, **1e**, **1f**, and **1i**.^[62] Hexol **1m** is used for preparation of dendritic TADDOLs.^[63] Compound **1n** is stable even to strong aqueous acid, and can therefore be extracted out of organic solutions. The TADDOLs **1o** and **1p** are used for the preparation of copolymers with styrene and for immobilization (See Section 9).

Cl_3P , or Cl_2SO , in the course of which bicyclic compounds may be produced (Scheme 3). In particular, experience with the hexahydroxy derivative **1m** has shown that *one* OH group in the two diarylmethanol units is significantly more acidic than the other,^[63] consistent with the presence of an intramolecular hydrogen bond.

Key intermediates in the substitution process are the monochloride **5** and dichloride **6**. The former is obtained selectively^[72] by treatment with $\text{CCl}_4/\text{PPh}_3$ (Appel reaction^[73]), whereas the latter forms with SOCl_2 .^[74, 75] Both compounds (and especially the analogous bromine and naphthyl derivatives!) are highly reactive, and readily undergo solvolysis (even on silica gel!), for which reason purification, especially on a large scale, should be effected by crystallization. Reactions with nucleophiles such as alcohols, phenols, ammonia and amines, anilines, azide, phosphites, phosphinites, thiols, thiocyanate, and thiourea lead to products of the types indicated in Scheme 3. Simply to demonstrate the versatility of structures accessible in this way we have assembled in Figure 2 what amounts to a collage—complete with literature references—of compounds derived from TADDOL **1a** (see also the Supporting Information). These compounds are available for use as chiral ligands with metallic centers, as auxiliaries, and as reagents for EPC syntheses. We delayed venturing into substitution reactions with TADDOLs for a long time: one would anticipate that such transformations should inevitably take place through $\text{S}_{\text{N}}1$ mechanisms (that is, via carbocations), and we were con-



Scheme 3. Overview of routes leading from the original (*R,R*)-TADDOL to various derivatives and substitution products. The OH groups of TADDOL are ultimately replaced—by way of mono- and dichlorides **5** and **6**—with carbon substituents (using *N*-methylaniline or diphenylamine), NH_2 , NHR , NR_2 , $\text{P}(\text{O})\text{R}_2$, $\text{PO}(\text{OR})_2$, *O*-Alkyl, *O*-Aryl, OOH , SH , or SR (see Figure 2 for examples). The bold arrows represent reaction pathways, which are not always single reaction steps.

cerned that we would therefore also encounter eliminations, fragmentations, and rearrangements. The high yields actually achieved show that our fears were in fact unfounded. On the other hand, if one starts not with TADDOL **1a**, which contains unsubstituted benzene rings, but rather with the tetra(4-methoxy) analogue, problems of this nature can indeed arise^[68] (Scheme 4, top). We have also observed that interesting reductive eliminations and fragmentations accompany attempts to introduce PR_2 groups by substitution with HPR_2 and LiPR_2 ^[89] (Scheme 4, bottom).

In summary, it should be noted that TADDOLs and their analogues are extraordinarily easy to prepare, and that it is possible to carry out “combinatorial” optimization for a particular application. The commercially available building blocks alone—namely, chiral cyclic 1,2-*trans*-dicarboxylic acid esters or tartrate esters, aldehydes or ketones, aryl halides, and heteroaromatic halides in combination with C, N, P, O, and S nucleophiles—provide the potential for innumerable possibilities with respect to structural variation (Figure 3). At the diarylmethanol center (dialkyl analogues do not work well as ligands; see also Schemes 26 and 27), steric hindrance can be increased through the series phenyl, 2-tolyl, 1-naphthyl, and 9-phenanthryl, continuing all the way to fluorenylides. At the ketal/acetal center it is possible to go from two hydrogen atoms, two methyl or ethyl groups, five- and six-membered rings, or two phenyl groups again as far as fluorenylides, or, dispensing with C_2 symmetry, to combinations like Ph/Me,

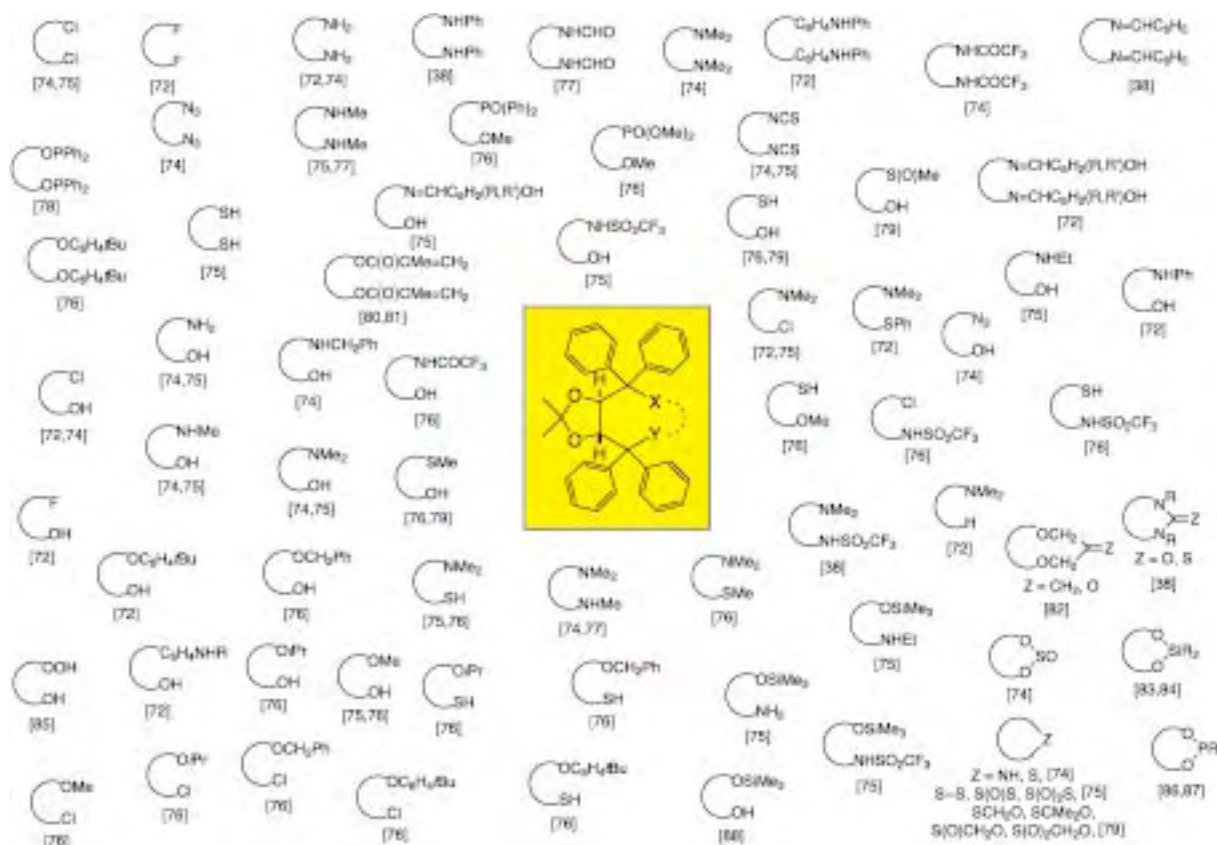
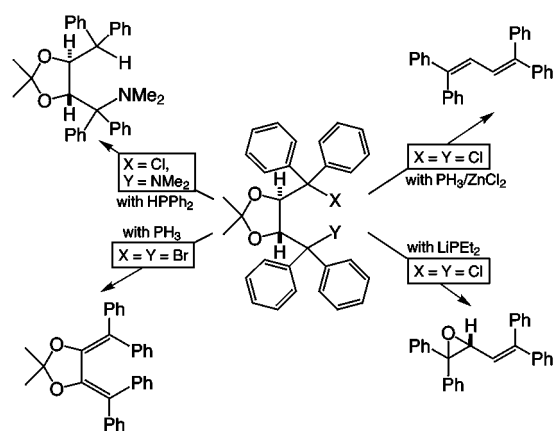
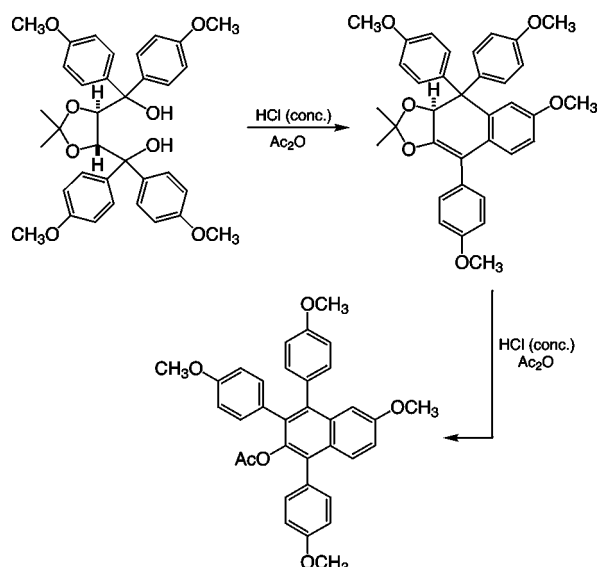


Figure 2. Schematic representation of C_2 -symmetrical dioxolanes and bicyclic, as well as unsymmetrical derivatives, that have to date been prepared from TADDOL **1a**. The literature citations refer to papers containing typical experimental procedures. Applications are discussed in subsequent sections. Substitution of the OH groups is also possible with the hexaphenyl derivative **1g**, which has been transformed into OH/Cl, OH/ NMe_2 , and OH/ SH derivatives, and with the 2-naphthyl derivative **1f**, which so far has been converted into unsymmetrical compounds containing OH/Cl, OH/OMe, OMe/Cl, and OMe/ SH .^[76]



Scheme 4. Dehydration, intramolecular Friedel-Crafts reaction, and reductive elimination in TADDOLs. Top: Bis(4-methoxyphenyl)methyl carbocations are produced upon treatment of the 2,2-dimethyltetraanisyl derivative with $\text{HCl}/\text{Ac}_2\text{O}$.^[68] These cations can deprotonate and can effect electrophilic attack on neighboring methoxyphenyl groups. The final product has an achiral 1,2,4-trianisyl-naphthalene skeleton. Analogous reactions occur also with the TADDOL that is unsubstituted in the 2-position of the dioxolane ring, as well as with the 2-methoxyphenyl isomers. Bottom: Phosphanes and phosphides cause reduction and/or elimination of chlorides and bromides derived from TADDOL; starting from the chloroamine, the monoamine forms in a yield of approximately 50%,^[72] the bis(diphenylmethylene)dioxanone in about 15%, the tetraphenylbutadiene in up to 80%, and the corresponding epoxide in about 85% yield.^[89] Cl/P substitution is successful with TADDOL derivatives only by way of the Michaelis–Arbuzov reaction.^[76] Ac = acetyl.

Ph/H, 1-naphthyl/H, or *t*Bu/H (see also Table 1 and the Supporting Information). In place of a dioxolane ring, carbocyclic or bicyclic systems can also be used to carry the diarylmethanol groups (Scheme 2). The heteroatoms in the diarylmethyl groups can be varied from oxygen (for oxophilic, polar metallic centers) through nitrogen, phosphorus, and sulfur (for centers involving the late transition metals), and from uncharged to anionic groups (with C_2 symmetry or unsymmetrical). Observed pK_a values range from approximately 35 (for NHalkyl), through 28 (for NHaryl), 17 (for OH and NHCOR), and 10 (for SH , NHCOCF_3 , or NHR_2^+), down to as low as 6 (for NHSO_2CF_3).^[90] After many attempts^[91, 92]

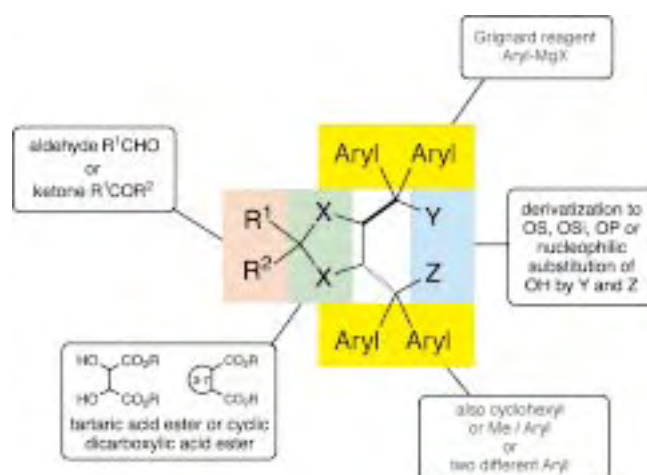


Figure 3. Components for the preparation of TADDOLs and their analogues. For concrete examples, see Schemes 2 and 3, as well as Figure 2, Table 1, and the Supporting Information.

we finally succeeded^[76] in introducing PR_2 groups directly at the diarylmethyl carbon atom (although preparation of a tetraphenyl DIOP derivative^[93] has still not been accomplished).

4. Structures of TADDOLs

The great diversity of readily accessible TADDOLs has generated a wealth of structural information, thanks to the great tendency of these compounds to crystallize. We are aware of roughly 120 crystal structures of compounds of the type shown in Figure 3, 92 of which have been incorporated into the Cambridge Structural Database (CSD; see the Supporting Information). Even though far fewer structural studies have been carried out in solution^[45, 94, 95] (see also Sections 5 and 10), and even though there have been relatively few theoretical computations of TADDOL structures,^[44, 96] the large number of available crystal structures permits one to draw statistically relevant conclusions^[97] about the preferred conformation of TADDOLs and their analogues. Single crystals are best obtained by crystallization from solvents with hydrogen bond accepting characteristics, or at least in the presence of compounds of this type, since this permits the formation of TADDOL inclusion compounds (referred to variously as solvates, clathrates, or “host–guest” compounds^[98]). In the vast majority of cases the TADDOL units are present in conformations with near- C_2 symmetry, which feature perfect staggering about the exocyclic C–C bonds and staggering about the endocyclic C–C bonds that is as near ideal as possible for a dioxolane ring. The TADDOLs also display an antiperiplanar (*ap*) arrangement of endo- and exocyclic C–O bonds, and quasi-axial and quasi-equatorial placement, respectively, of the two members constituting each pair of aryl groups, where in the former case an “edge-on” conformation is preferred and in the latter a “face-on” conformation is preferred when the molecule is observed along the C_2 axis (see the overlay of 35 crystal structures of compounds of type **1** (where $\text{R}^1 = \text{R}^2 = \text{Me}$ or $\text{R}^1 - \text{R}^2 = (\text{CH}_2)_4$, $(\text{CH}_2)_5$; $\text{Aryl} = \text{Ph}$) in Figure 4). An intramolecular

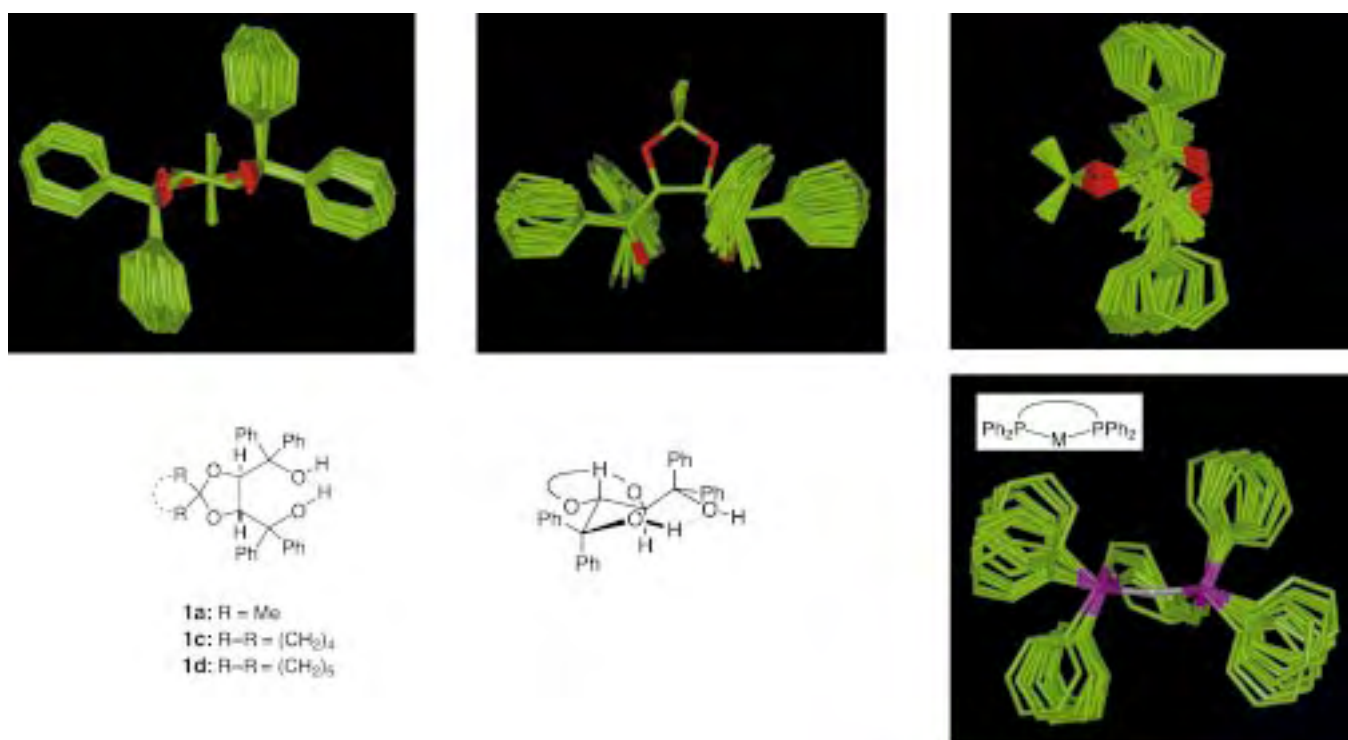


Figure 4. Overlays^[99] of TADDOL structures determined from a total of 35 crystal structure analyses, shown in projection along the C_2 axes of the molecules (left) and in two directions perpendicular to that axis (middle and right). Only structures based on one of the three TADDOLs **1a** (19 examples), **1c** (8 examples), and **1d** have been included (cyclopentane and cyclohexane rings in **1c/1d** have been omitted for clarity). Thirteen additional structures with R = Me, but other aryl groups (see formula bottom left), could have been incorporated without producing any change in the overall picture. For the corresponding CSD Refcodes, see the Supporting Information. Positions of hydrogen atoms in the OH groups are specified in several of these crystal structures (see picture, bottom center). The similarity between the propeller-like structures of the TADDOLs and the bis(diphenylphosphanyl)metal complexes is apparent through a comparison of representations at the top left and the bottom right. CSD Refcodes for the 15 phosphorus complexes shown in the overlay at the bottom right: ALANPD, BAVSAS, BNAPRH, BUTWES, CEJJEG, CUNKUR, CUYAW, FUXSUM, JIPCAM, JUBVUX, JUBWAE, JUBWEI, LEGZOM, SACHIN, VIXZOR.^[100] The principal difference in the two situations is of course the fact that phenyl groups in the diphosphanes are located *on* the complexing heteroatom, whereas in the TADDOLs they are *adjacent* to it.

hydrogen bond forms between the OH groups, so that one OH proton remains available for intermolecular hydrogen bonding. The dioxolane ring and the seven-membered ring that results from hydrogen bonding are disposed in a *trans*-fused bicyclo[5.3.0]decane-like arrangement, whereby the bridging hydrogen atom falls nearly along the C_2 axis—that is, at the very place where a chelate-bonded metal ion would be situated in a seven-membered ring chelate (see below). The similarity between this system and a bis(diphenylphosphanyl) metal complex is quite striking.^[101]

The first set of overlays in Figure 5 shows that substitution products bearing XH/Y rather than OH/OH groups on the diphenylmethyl substituents of the dioxolane rings also assume the same conformation, although in some cases the hydrogen bonds are much weaker. The dimethyl ether of TADDOL **1a** has an identical framework as well,^[102] which shows that the hydrogen bond (where the donor is always the more acidic XH group!) at most contributes to the stability of the propeller-like form of the TADDOLs, with two axial and two equatorial groups. Apparently the preferred arrangement is one with the heteroatoms in close proximity, hence the observed predisposition to ring formation and chelation, driven by the two geminal aryl groups (compare with the influence of geminal methyl groups on rates of ring-closure reactions, the Thorpe–Ingold effect^[103, 104]). It is thus no

wonder that bicyclic TADDOL derivatives in which the heteroatoms at the diphenylmethyl groups participate in six- or seven-membered rings (overlay in the center of Figure 5) show precisely the same orientation of the aryl groups as titanium TADDOLates (Figure 5, right), and that they conform almost exactly with the structures of the TADDOL precursors. Structures of analogues in which other heterocyclic,^[36] carbocyclic (for example, cyclobutane^[44]), or carbobicyclic^[98] ring systems replace the dioxolane ring fall nicely into place as well, as do systems in which all or some of the aryl groups are replaced by cyclohexyl^[37, 60] or methyl^[44] groups.

Of further interest are the structures of TADDOLs whose two substituents are smaller (such as H) or larger (such as Ph in **1g**) than methyl groups, or which have two different substituents at the 2-position of the dioxolane ring (as for example in **1b**, **1h**, **1i**). The overlay for these cases is shown on the left in Figure 6. The corresponding titanium TADDOLates often promote higher enantioselectivities when acting as chiral Lewis acids. The overlay clearly shows that substitution at the acetal/ketal center influences the conformation about the C–aryl bond, where the ligand sphere of a metal ion resting between the oxygen atoms may be subtly transformed! The structure of the palladium bis(diphenylphosphinite) complex^[78] shown in the middle of Figure 6 is

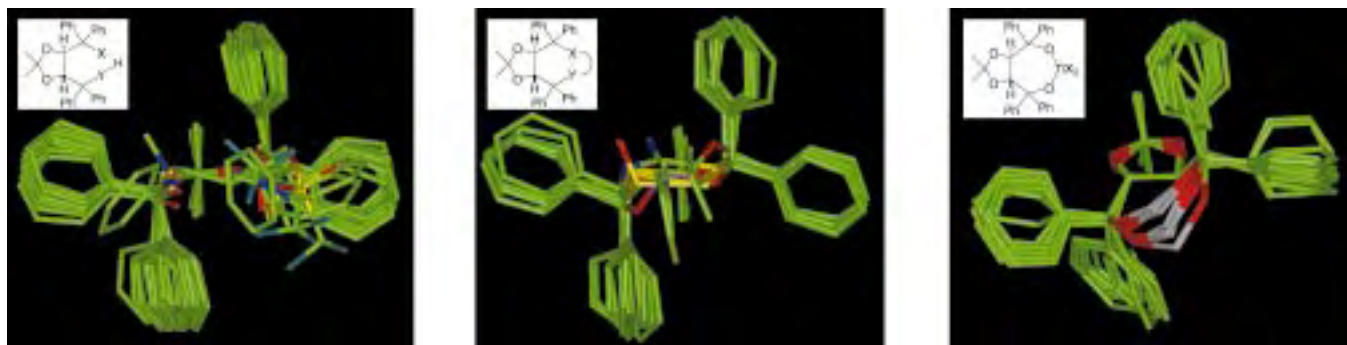


Figure 5. Overlay^[99] of the results of crystal structure determinations for 16 substitution products (left), 7 cyclic derivatives (center), and 11 titanates (right) of TADDOL **1a**. In most cases, structures containing the heterosubstituents NR_2 , OR, and SR have not previously been published, and are taken from an ETH doctoral dissertation;^[76] the groups X/YH are NH_2/NH_2 , NHMe/NHMe , NPh/NPh , $\text{NH}_2/\text{NHSO}_2\text{CF}_3$, NPh/OH , NMe_2/OH , $\text{N}=\text{CHNMe}_2/\text{OH}$, OMe/OH , $\text{O}i\text{Pr}/\text{OH}$, OBn/OH , OCOCF_3/OH , OH/OOH , $\text{SH}/\text{NHSO}_2\text{CF}_3$, SMe/OH , OMe/SH , SH/SH (in the structure of the NMe_2/OH derivative phenyl groups at the 2-position of the dioxolane ring have been omitted for the sake of clarity). The bicyclic systems shown in the center contain in addition to the dioxolane ring a 6- or 7-membered heterocyclic ring: the groups X–Y are $\text{C}(\text{SH})\text{--O}$, $\text{O--P}(\text{NMe}_2)\text{--O}$, O--PPh--O , $\text{O--CMe}_2\text{--S}$, S--S , $\text{S--C}(\text{NH}_2)=\text{N}$, $\text{S}(\text{O})\text{--S}$. On the right is an overlay of titanium TADDOLate structures representing a wide variety of groups X on titanium (CSD Refcodes: JUCHIY, JUPWAS, POPROB, VUDGAC, YUGJAL), wherein TADDOL units present independently in the unit cell have been incorporated separately into the overlay (residual substituents on titanium are not shown); in the case of the spirotitanate (JUPWAS), both titanium TADDOLate units are included. It is worth noting the small deviations in O–Ti–O angles and Ti–O distances in the chelate ring despite the fact that some of the titanium coordination is tetrahedral and some octahedral. Average values for tetrahedral coordination geometry are 103° and $1.78 \text{ \AA}$ for JUPWAS, 99° and $1.81 \text{ \AA}$ for POPROB, and 98° and $1.79 \text{ \AA}$ for VUDGAC; for octahedral coordination geometry the corresponding values are 97° and $1.78 \text{ \AA}$ for YUGJAL and 99° and $1.78 \text{ \AA}$ for JUCHIY. Apparently here, too, the TADDOL dictates the outcome! CSD Refcodes for the published compounds are available from the Supporting Information, where reference is also made to unpublished structures. All the structures shown could also have been included in the overlay of Figure 4 without significantly altering the overall picture! For another representation of the titanium TADDOLate complexes, see Figure 17.

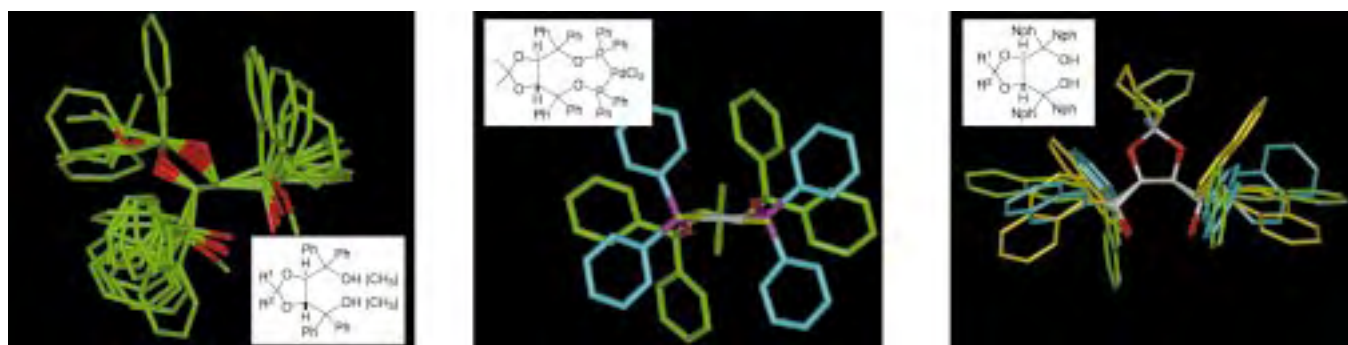


Figure 6. Crystal structures of TADDOLs with substituents other than methyl at the 2-position of the dioxolane ring (left; CSD Refcodes: JUPVIZ, JUPVOF, POPIOT, ROLWIY, YONVIG), of a palladium complex of TADDOL-bis(diphenylphosphinite) (center, ZOCJUW), and of TADDOLs with Aryl = naphthyl (Nph; right).^[99] The structures of the naphthyl derivatives correspond to the compounds with $\text{R}^1=\text{R}^2=\text{CH}_3$, Aryl = β -naphthyl (**1f**, YONVAY, light blue), $\text{R}^1\text{--R}^2=(\text{CH}_2)_5$, Aryl = α -naphthyl (YONVEC, yellow), and $\text{R}^1=\text{Me}$, $\text{R}^2=\text{Ph}$, Aryl = β -naphthyl^[105] (green).

also informative: the eight phenyl groups orient themselves in a consistently staggered way about the nine-membered chelate ring such that a chiral ligand sphere develops around the metal, far removed from the stereogenic centers on the dioxolane ring! Finally, the three known TADDOL structures with naphthyl groups on the diarylmethanol substituents are shown in the form of an overlay on the right in Figure 6. A significant difference is apparent between the 2-naphthyl (phenyl-like) and 1-naphthyl derivatives; in the latter the annellated benzene ring extends forward in the quasi-equatorial position, but back in the quasi-axial position; it is thus not surprising that the stereochemical course of a reaction can reverse itself when carried out successively with the two isomeric naphthyl derivatives,^[37] that 1-naphthyl derivatives show broad NMR signals at room temperature (slow rotation about the C–aryl bond), or that titanium TADDOLates bearing four 1-naphthyl groups often show a

complete absence of catalytic activity^[102] (too much steric hindrance).

Exceptions: are there any?^[106, 107] There of course exist TADDOL derivatives in which the heteroatoms at the diarylmethyl groups do *not* lie in close proximity, and as the “black sheep” in their families they are of special interest. Indeed, they can convey important lessons! We first discovered such a system when we examined the crystal structure of the diazide;^[75] one N_3 group extends forward in the usual way (*ap* conformation O--C--C--N_3), whereas the second hovers over the dioxolane ring in a *gauche* or (+)-synclinal (*sc*) arrangement of N_3 and O, which is favored due to stereoelectronic effects.^[108–110] Similar structures characterize the chloramine and the dichloride (see the overlay in Figure 7a1), whereas in the fluoroalcohol both heteroatoms rest above the dioxolane ring (Figure 7a2). In all four structures, either one heteroatom and a benzene ring or two superimposed benzene rings in

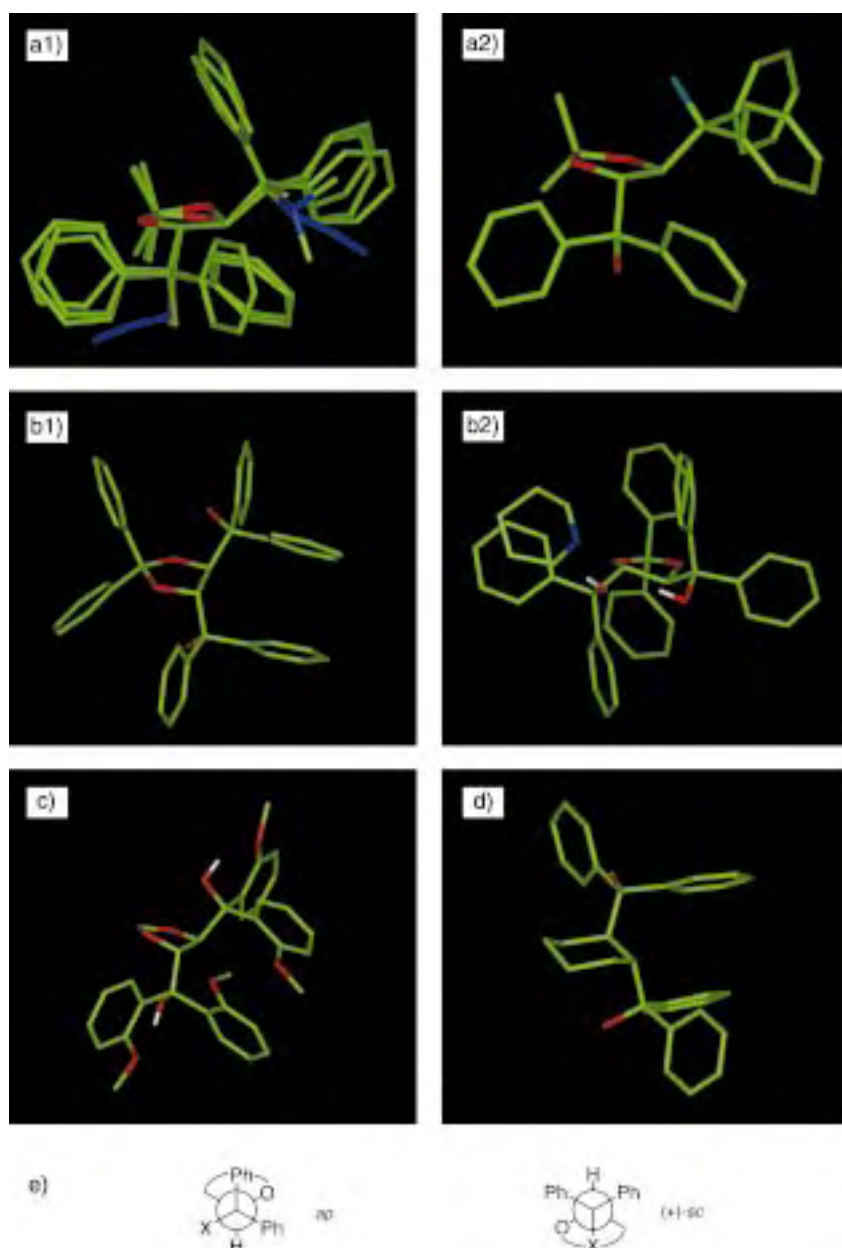


Figure 7. Exceptions to the rule: Crystal structures of TADDOL derivatives and analogues in which heterosubstituents on the diarylmethyl groups are *not* mutually close. a1) The diazide^[75] (CSD Refcode: NIBZIH), the dichloride **6**^[75] (NICBUW), and the chloroamine^[76] all have one heteroatom above the dioxolane ring whereas the second one extends forward. a2) In the structure of the fluoroalcohol^[72] (HOLYAI), both heteroatoms extend to the rear. b1) The hexaphenyl derivative **1g** without inclusion^[67] (anomalous, VUSLEA) and b2) with inclusion^[68] (normal, POPJOT). c) A tetrakis(2-methoxyphenyl) derivative (POPJIN).^[68] d) The cyclohexane analogue of TADDOL, which is present with^[44] (YIHJOO) and without^[44] (YIHJUU) inclusion in the conformation shown here, with large axial substituents on the six-membered chair ring. As in the case of hexaphenyl derivative **1g**, a *single* structure was found for the dibenzobicyclo[2.2.2]octadiene-8,9-bis(diarylmethanols), in which the OH groups together build an intramolecular hydrogen bond (TAXKOS). In most cases, however, (REQXAM, REQXEQ, REQXIU, TAXKUY, TAXLAF) they are rotated away from each other, whereby two aryl groups come to lie parallel and directly above each other (similar to (a2), (b1), (c), and (d), essentially at the van der Waals distance of 3.3–3.5 Å). In (e) the conformation found about the exocyclic C–C bonds in most TADDOL derivatives is illustrated: the antiperiplanar (*ap*) conformation, and, for comparison, the stereoelectronically stabilized synclinal (*sc*) conformation.

van der Waals contact extend forward. It is difficult to say whether the unusual conformation is ultimately a consequence of the absence of a hydrogen bond,^[111] repulsion of the

dipoles, or π interaction between the heteroatom and an aromatic ring. An instructive system is the hexaphenyl derivative **1g**, which in the absence of any guest molecule in the crystal relegates the OH groups “to the back”, with a hydrogen bond to the benzene rings at the ketal center, whereas when it is crystallized in the presence of piperidine an inclusion compound forms instead, with the familiar TADDOL geometry (Figures 7b1 and 7b2). In the TADDOL with no substituents at the 2-position of the dioxolane ring and four 2-methoxyphenyl groups, the OH groups prefer to form a hydrogen bond with an oxygen atom in the *ortho* position rather than with each other, thereby assuming positions above the dioxolane ring (Figure 7c). Finally, special mention should be made here of one other, at first glance unusual, cyclohexane derivative (Figure 7d), the carbocyclic TADDOL analogue in which the large diphenylmethanol groups are *ap* to each other in *axial* positions on a six-membered chair ring (with the OH groups above!).

As both hexaphenyl-TADDOL **1g** and the cyclohexane derivative readily form titanium complexes—which, for example, catalyze nucleophilic addition to aldehydes^[112] as well as Diels-Alder reactions^[113] in the usual way—one must conclude that both diolates function as chelate ligands, and that in this case a rule of thumb that is familiar to inorganic and complex chemists applies: it is not possible to predict the structure of a ligand in a metal complex from that of the ligand alone.

In general, it should be noted again that the TADDOL structures discussed here also serve as valuable models for the corresponding metal complexes, and that the (nearly) universal property of a roughly C_2 -symmetric, propeller-like arrangement for the four phenyl groups provides a solid basis for mechanistic discussions (see Section 10).

As a result of their structures, TADDOLs and related compounds are well suited to a) formation of clathrates (no specific interactions with the guest molecules, which serve mainly as fillers), b) formation of inclusion compounds (hydrogen bonds to the guest molecule),

c) formation of hydrogen-bond donor–acceptor complexes in solution, d) induction of cholesteric phases (the rigid, chiral propellers initiate orientation of the molecules in a liquid-

crystalline medium), e) chelate (bidentate) complexation with metallic centers (the conformation with neighboring heteroatoms is preorganized; no entropic disadvantage exists with respect to the binding of neutral, monoanionic, or dianionic ligands), and f) functioning as chiral reagents.

5. TADDOLs as Chiral Doping Agents in Liquid Crystals

A considerable demand has developed in recent years for cholesteric liquid crystals.^[114, 115] One attractive approach to their preparation is the doping of achiral (nematic) phases with chiral additives.^[116] As in the case of catalysis, it is important that one employ as little doping agent as possible consistent with achieving the desired degree of helicity (step-height of the pitch of the induced helix, reported in μm). The standard measure for this characteristic is called the helical twisting power (HTP, expressed in μm^{-1} , Figure 8).^[117] Before the first TADDOLs were tested as doping agents, HTP values of $100\ \mu\text{m}^{-1}$ were regarded as high,^[119] but experiments based on our stock of TADDOLs quickly resulted in derivatives with HTP values of $300\text{--}400\ \mu\text{m}^{-1}$.^[83] A record of $534\ \mu\text{m}^{-1}$ was achieved with a fluorenylidene derivative containing two tetrakis(2-naphthylmethanol) substituents^[118, 120] (Figure 8). The theory underlying the HTP effect is complicated, and it is still not certain whether TADDOL conformation is the only important factor, or if a change in the orientation of the principal axes of the ordering tensor towards the skeleton of the molecule within the liquid crystal might also play a role (note the substantial HTP decrease from 250 to $150\ \mu\text{m}^{-1}$ at 24°C when the 2-naphthyl-TADDOL **1f** is “protected” as a cyclic OSiMe₂O derivative; Figure 8, bottom right). Commercial utilization of TADDOLs as chiral doping agents appears feasible.^[122, 123]

The inductive effect of TADDOLs in liquid crystals can also be used to learn more about TADDOL conformation(s) in the noncrystalline phase with the aid of NMR and CD spectroscopic methods. It is a striking observation that the sign of the HTP (+ for a helix wound to the right, – for one to the left) can be reversed by changing the substituents in the 2-, 4-, and 5-positions on the dioxolane ring^[83] (as can the optical rotation^[68] and the stereochemical course of metal TADDOL-catalyzed reactions^[37]). Numerous structure- and solvent-dependent UV and CD spectra of TADDOLs have been recorded. Particularly in the region of exciton transitions we have observed not only well-structured curves of the degree of anisotropy (UV spectra) but also major changes in the couplets of the CD spectra (Figure 9), as in the transition from 2,2-dimethyldioxolanes to the corresponding mono- and unsubstituted derivatives (no changes are made in the aryl groups of the diaryl-methanol units).^[120] This argues for a change in conformation about the C–aryl bond. Detailed conclusions should result^[125] from the investigation of a number of deuterated TADDOLs.^[34] TADDOLs may well prove to be the key to understanding the relationship between the structure of a doping agent and the magnitude and sign of an observed HTP effect.

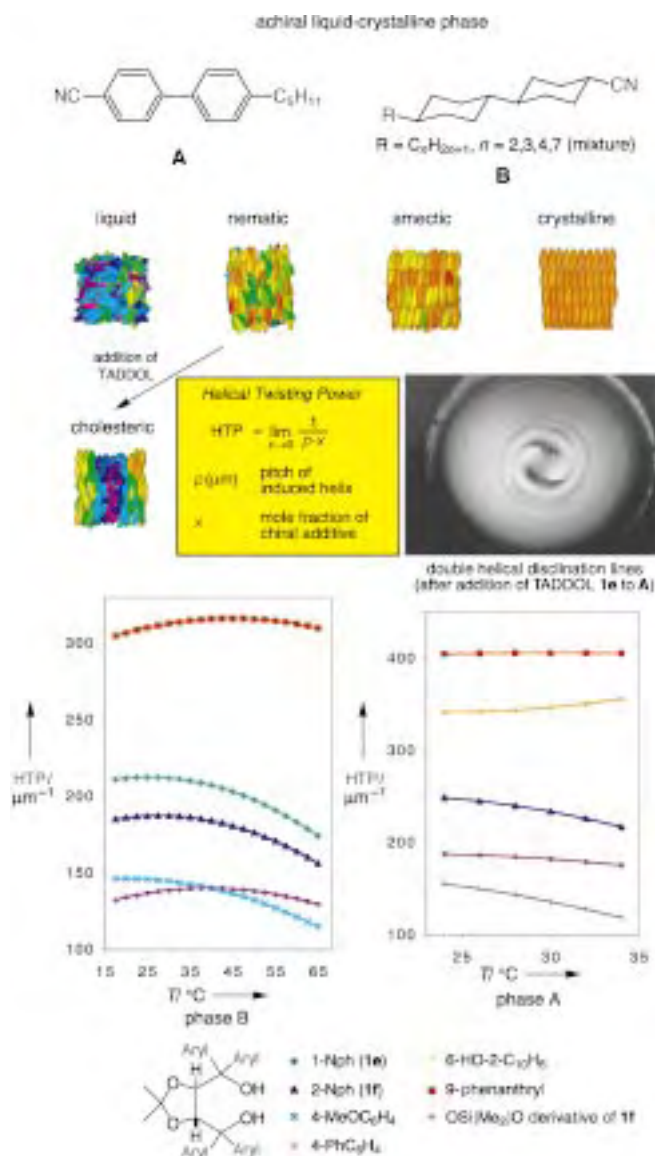


Figure 8. Induction of cholesteric phases by TADDOL addition to achiral, liquid-crystalline compounds in the nematic phase: **A** (K 15, Merck, UK) and **B** (ZLI-1695, Merck, Darmstadt, Germany).^[83, 118] The measure of the effect is the so-called helical twisting power (HTP). The step height is determined microscopically (see disclination lines). The cyanobiphenyl material is characterized by a nearly temperature-independent effect. The highest HTP value so far observed ($534\ \mu\text{m}^{-1}$) was achieved with **A** and a TADDOL which contained a 9-fluorenylidene group in the 2-position of the dioxolane ring and which had four 2-naphthyl groups on the diaryl-methanol substituents.^[118]

6. TADDOLs in the Analysis of Enantiomers^[126]

TADDOLs are chiral hydrogen-bond donors that contain aryl groups in the immediate vicinity of the donor OH groups. As a consequence, hydrogen-bond acceptors that dock on these OH groups enter the shielding or deshielding regions (caused by ring-current effects) of nearby aromatic rings; this raises the possibility that diastereomeric hydrogen-bonding complexes could become distinguishable by NMR spectroscopy. Apart from signals in the aromatic region, C_2 -symmetric TADDOLs show only two singlets in their NMR spectra

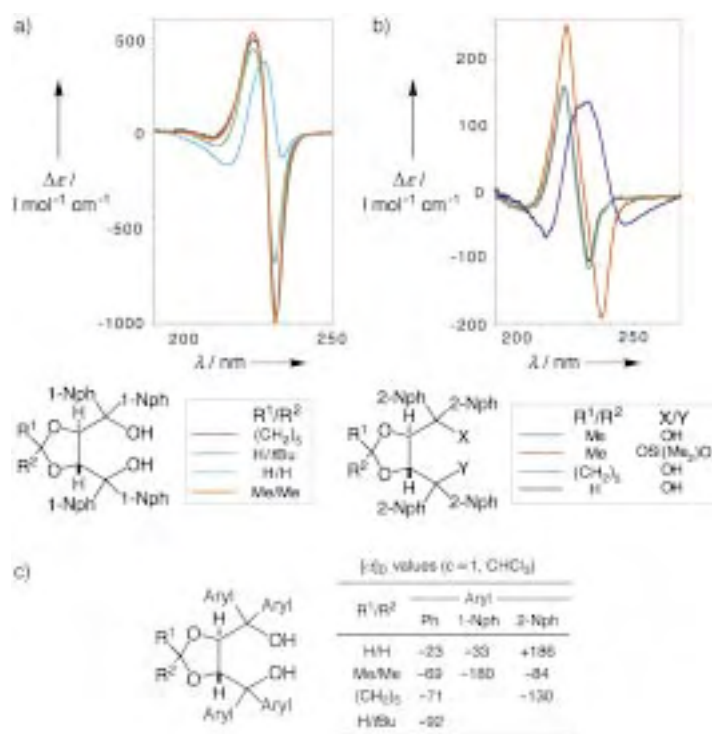


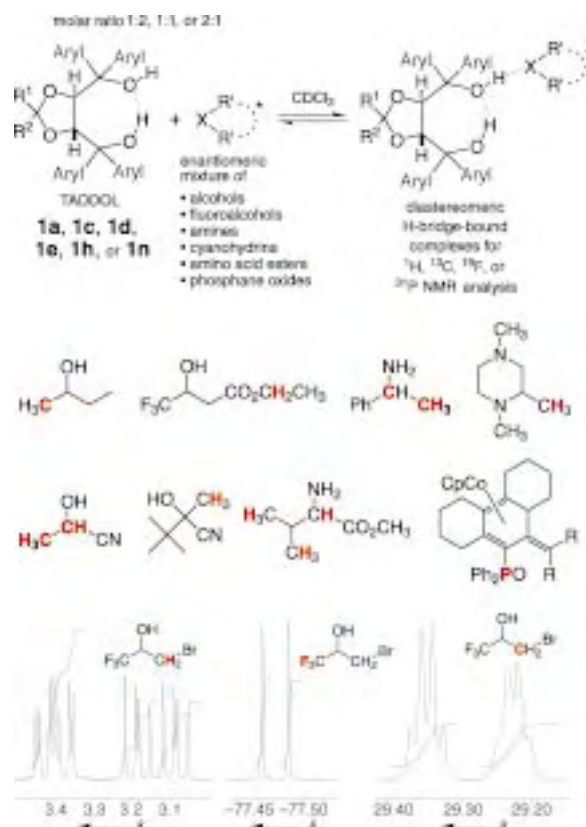
Figure 9. Exciton regions of the circular dichroism spectra (in acetonitrile) of TADDOLs with 1- and 2-naphthyl groups and various substitution patterns at the acetal/ketal center in the 2-position of the dioxolane ring,^[120, 124] as well as $[\alpha]_D$ values for a few TADDOLs in CHCl₃. a) CD Spectra of 1-naphthyl derivatives. b) CD Spectra of 2-naphthyl derivatives. c) Comparisons of rotational values for a selection of TADDOLs. The significant changes observed in the transition from H/H to H/*t*Bu or to Me/Me (intensity and wavelength of the extremes, additional Cotton effects) argue for changes in conformation about the C–aryl bond. Differences are even apparent at the Na_D line. Various substituents in the 2-position of the dioxolane ring also have an influence on stereoselectivities of metal TADDOLate mediated reactions (Section 8) and on X-ray structures of TADDOLs (see Figure 6, left).

(for example, due to CH₃ groups and CH protons at the 4- and 5-positions on the dioxolane ring in **1a**). Broad *windows* are thus open for viewing the ¹H and ¹³C signals of substrate molecules (¹⁹F and ³¹P spectra are of course *completely* free of interference!). In contrast to spectra resulting from the use of lanthanide shift reagents, signals in this case are not subject to line-broadening effects. Examples of this particular application are provided in Scheme 5. By recording a large number of spectra of similar compounds with known absolute configurations (amines, esters of amino acids, cyanohydrins) it is possible on the basis of analogies to assign absolute configurations.^[127]

At a somewhat higher level of sophistication, the absolute configuration of a compound can be established with virtually absolute certainty by X-ray structural analysis of a corresponding inclusion compound with an (*R,R*)- or (*S,S*)-TADDOL (see Section 7.1).

7. Inclusion Compounds Based on TADDOLs

As previously noted, TADDOLs crystallize especially well in the presence of hydrogen-bond acceptors, with which they



Scheme 5. TADDOLs as chiral shift reagents in NMR spectroscopy for determining the enantiomer purity of alcohols, fluorine compounds, amines, cyanohydrins, esters of amino acids,^[70, 127] and phosphine oxides.^[128] Magnetic nuclei whose NMR signals are split in an enantiomer-specific way are printed in red. The lower part of the scheme shows a ¹H NMR spectrum (each enantiomer leads to 2 dd signals for the protons marked in red in the formula), a ¹H-decoupled ¹⁹F NMR spectrum, and an “inverse gated” ¹³C NMR spectrum of a 2:1 mixture of TADDOL **1a** and the racemate of the illustrated fluorinated bromohydrin. Cp = cyclopentadienyl.

also form inclusion compounds. If a TADDOL is crystallized in the absence of such an additive, the “free valence” still associated with one of the OH protons is, in principle, available for additional intra- or intermolecular interactions within the crystal. However, many enantiomerically pure TADDOLs crystallized without additives do not engage in intermolecular H···O interactions in the solid state. In special cases additional intramolecular hydrogen bonds develop (CSD Refcodes: POPJIN, VUSLEA; see Figure 7). In one case, dimer formation becomes possible through crystallographic symmetry (KOGJAR); the special situation in which a hydrogen-bonded TADDOL dimer constitutes the asymmetric unit also arises only once (SEWVUL). This is in sharp contrast to the solid-state structures of *meso*- or *rac*-TADDOLs (SEWWEW, SEWWAS, NIYTIY, NIYTUK), all of which crystallize in centrosymmetric space groups (with, in each case, a single molecule per asymmetric unit) and form dimers through crystallographic symmetry.^[129]

For purposes of purification through recrystallization, and also for preparation of crystals suitable for single-crystal analysis, it is advantageous to introduce specific hydrogen-bond acceptors. Toda, a specialist in the field of solid-state organic chemistry who has also investigated other chiral

compounds as potential *host structures* for specific inclusions,^[130] recognized^[131] at an early stage the value of TADDOLs in this context (roughly 75 Toda papers in which TADDOLs play a role have appeared over the course of time). TADDOL hydrogen-bond donors crystallize readily—and preferentially with hydrogen-bond acceptors—and they can be exploited for the resolution of racemates as well as for promoting enantioselective solid-state reactions.

7.1. Use of TADDOLs in the Separation of Enantiomeric Hydrogen-Bond Acceptors

The separation of enantiomers, that is, resolution of racemates still represents the most frequently followed approach to commercial preparation of enantiomerically pure compounds. The classic technique for separating racemic acids (bases) involves crystallizing the diastereomeric salts that form with chiral bases (acids), where the ultimate source of chirality is always some natural product. More recently, chromatographic procedures have assumed a role in the synthesis of chiral pharmaceuticals, even on the multiton scale (“simulated moving bed” (SMB) chromatography), with amino acids or carbohydrates serving as the chiral components in stationary phases.^[132] Another promising route takes advantage of differential crystallization of TADDOL inclusion compounds, especially in situations where the incorporated partners cannot be classified as bases in the usual sense. Not only enantiomers, but also diastereomers and even compounds differing in constitution, lend themselves to separation by way of TADDOL inclusion compounds.^[66, 133]

The procedure for separating enantiomers in this way is, in principle, quite simple.^[70, 134, 135] For example, one can begin by generating a solution consisting of two equivalents of a racemic compound and one equivalent of a TADDOL dissolved in an “inert” solvent such as toluene or hexane. Crystallization is then allowed to proceed. The resulting crystalline product is heated under vacuum, and the incorporated enantiomer is removed by evaporation. Yields often approach the theoretical limit of 50%, with enantiomer purities greater than 99%. X-ray structures of two inclusion compounds—(*S*)-3,4,4,5-tetramethylcyclohexenone in TADDOL **1a**^[135] and (*S*)-1,3-dimethyl-5-phenyl-4,5-dihydropyrazoline in a TADDOL derivative containing *ortho*-tolyl groups—prepared in this way are presented in Figure 10.^[134]

Instead of allowing the inclusion compound to crystallize from homogeneous solution, one can also—often with greater success—add a stirred suspension of the TADDOL host in hexane or water to a racemic mixture of the material to be resolved. The mixture is later filtered, after which the enantiomerically pure guest is removed under vacuum.

The method of racemate resolution through formation of inclusion compounds is an extraordinarily versatile one, as will be apparent from the limited set of examples collected in Scheme 6. All the compounds shown have been obtained in this way with enantiomer purities (*ep*)^[137] exceeding 98%. The

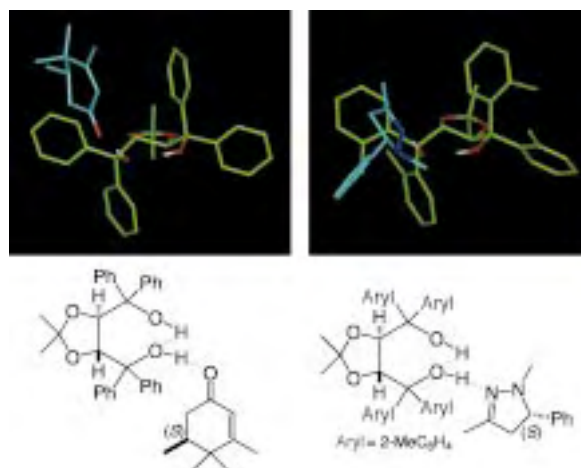


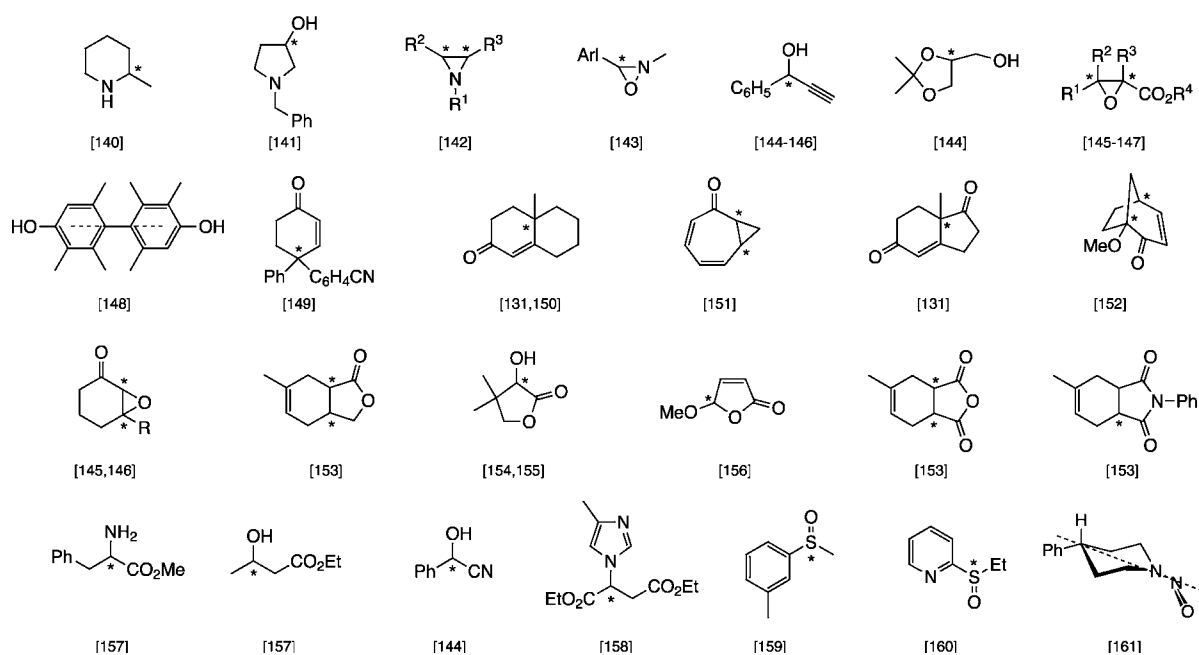
Figure 10. Two inclusion compounds involving TADDOLs prepared with racemate resolution of the guest molecules, and determination of the absolute configurations (by X-ray structure analysis) of the guest molecules (a cyclohexenone (CSD Refcode: RAZSUG), left, and a pyrazoline derivative (ZADMAS), right). The *rac*-cyclohexenone,^[135] as a “neutral” compound, would not have been subject to “classical” resolution through diastereomeric salts; the *rac*-pyrazoline^[134] had previously been separated by chromatography on a triacetylcellulose column.^[136]

cited literature describes many additional examples. Thus, separations have been accomplished with enantiomer mixtures of nitrogen- (amines, nitrosamines, *N*-heterocycles), oxygen- (alcohols, phenols, ethers, ketones, esters, lactones, anhydrides), and sulfur-containing compounds (sulfoxides), as well as such multifunctional materials as esters of hydroxy or amino acids, cyanohydrins, alkoxy lactones, and oxaziridines.

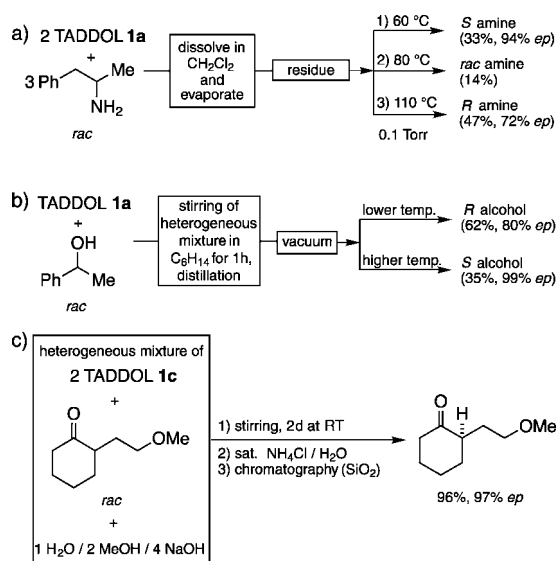
Inclusion compounds with TADDOLs have also made possible the distillatory separation of racemates.^[162, 163] Two examples are shown in Schemes 7a and b. The nonincluded enantiomer is first distilled off at low temperature, followed by the included isomer at higher temperature under vacuum. The TADDOL itself—perhaps after recrystallization—can then be employed in a new process cycle.

Finally, so-called dynamic racemate resolution (previously known also as “asymmetric transformation of the second kind”^[167]) has been accomplished with *rac*-2-allyl-, -2-benzyl-, and -2-methoxyethylcyclohexanones. In this application the two isomers are subjected to equilibration under basic conditions, but only one of them is captured within a TADDOL inclusion compound. Thus, a single 2-substituted cyclohexanone can ultimately be isolated with an enantiomer purity greater than 90% (Scheme 7c).^[165]

This technique using TADDOLs for separation of enantiomers of “neutral” compounds (also feasible in the variant referred to as the “Dutch family” procedure^[33]) is a welcome enhancement to what is still a very attractive approach to preparing enantiomerically pure compounds. Crystallization, both small- and large-scale (today often touted in conjunction with the fashionable label “molecular recognition”^[168]) is perhaps the most esthetically pleasing purification method known to chemistry. Nevertheless, the new distillatory version of racemate resolution, also accomplished with the aid of TADDOLs,^[169] might find broad application as well.



Scheme 6. Compounds whose racemates have been successfully resolved by crystallization in the form of inclusion compounds with TADDOLs. Enantiomer purities > 98% were achieved for all compounds shown (often after only a single crystallization). The TADDOLs utilized were **1a** (the parent molecule), **1c** and **1d** (based on 2,2-tetra- and -pentamethylenedioxaolane), **1b** (the acetophenone derivative), **1h** (a TADDOL with five phenyl groups), and a derivative of **1a** bearing four *ortho*-tolyl groups. The inclusion compounds displayed host:guest ratios of 1:1, 2:1, or (less frequently) 1:2; separation was often accomplished by distillation of the low molecular weight inclusion compound (see also Scheme 7a). During the isolation of products (for example, by kugelrohr distillation) from reaction mixtures into which TADDOL derivatives have been introduced as reagents, mediators, or catalysts it is important that this volatility be borne in mind, because in the process the system might become enriched or depleted with respect to one enantiomer, thereby altering the apparent enantioselectivity of the corresponding reaction (see also Scheme 7). Intentional enrichment in terms of the enantiomer formed in excess is also possible in the workup of such a reaction.^[138, 139]



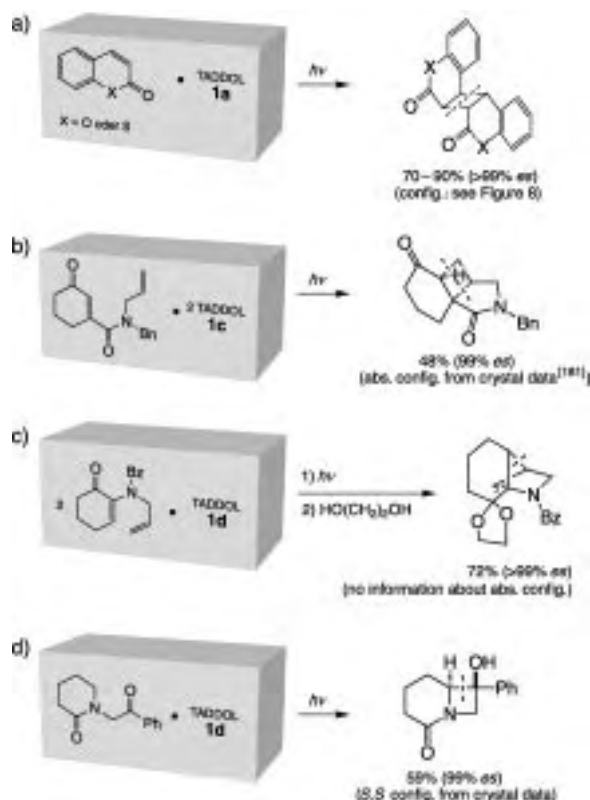
Scheme 7. a), b) Two distillatory resolutions^[162] of racemates with the aid of TADDOL **1a**,^[145, 146, 164] and c) quantitative enantioselective inclusion of (*R*)-2-methoxyethylcyclohexanone in TADDOL **1c** from a heterogeneous reaction mixture consisting of MeOH, H₂O, NaOH, *rac*-ketone, and TADDOL; here the enantiomeric ketones rapidly equilibrate with each other.^[165] Caution: Either type of racemate resolution can, if it happens to occur during workup and isolation of products, alter the apparent results of an enantioselective reaction (in either a positive or a negative sense!); see also the legend to Scheme 6. This is an appropriate place to remind the reader that chromatographic purification of nonracemic mixtures of enantiomers (and of mixtures of *any type* of nonracemic compounds, including TADDOL-containing crude products from enantioselective reactions) can lead to enrichment or depletion of enantiomers in specific fractions!^[166]

7.2. Enantioselective Photoreactions in TADDOL Inclusion Compounds

Once it had been recognized that TADDOLs, upon crystallization, form chiral structures with inclusion cavities capable of distinguishing between enantiomers (which might be regarded as “hotels offering chiral accommodations”), it was a natural step for a solid-state chemist like Toda to attempt to trap achiral molecules in the chiral cavities and thereby carry out (enantioselective) chemical reactions.^[170, 171] Although regioselective^[172] and diastereoselective^[173, 174] transformations have also been observed in TADDOL host–guest compounds, we limit our discussion here to enantioselective transformations, especially photochemical reactions.

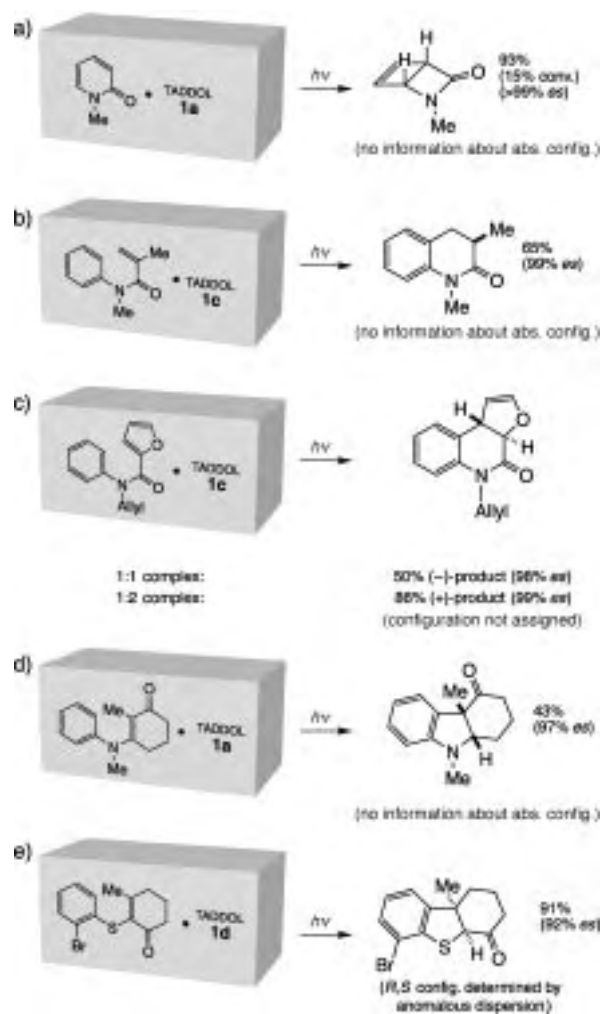
The studies in question were directed toward investigation of inter- and intramolecular [2+2] photocycloadditions,^[175] Norrish type II reactions,^[175] and electrocyclic photoreactions of the Ninomiya type^[176, 177] (Schemes 8 and 9).

Since the pioneering efforts at the Weizmann Institute,^[191] in which it was demonstrated that enantiomorphous crystals of achiral unsaturated compounds produce chiral, nonracemic cyclobutane derivatives upon irradiation, [2+2] photocycloaddition^[107] has assumed a central role in solid-state and crystal chemistry. It is therefore no accident that this reaction has also been intensively investigated in the context of TADDOL inclusion compounds (see the three examples in Scheme 8). All the cyclizations proceed from achiral starting materials that have been incorporated into TADDOL host



Scheme 8. Enantiomerically pure four-membered ring compounds prepared from TADDOL inclusion compounds by photochemical inter- and intramolecular [2+2] cycloadditions and a Norrish type II reaction. a) For the *anti*-head-head dimerization of the coumarins,^[178] see also Figure 11. b) This cyclobutane with annellated rings can be prepared with the aid of TADDOL **1c** by photolysis of a crystalline inclusion compound or by trituration of the oily amide mixture with **1c** in a mortar.^[179–181] c) A bridged and annellated tricyclic system containing a four-membered ring is obtained from a 2:1 inclusion compound.^[182] d) An enantioselective Norrish type II reaction in a TADDOL-host lattice.^[183, 184] Photoreactions were carried out with a high-pressure mercury lamp (Pyrex filter). Bn = benzyl, Bz = benzoyl.

lattices, and they produce essentially enantiomerically pure products. The most spectacular example is certainly the coumarin dimerization, in which a single-crystal to single-crystal reaction has been accomplished. In the inclusion complex consisting of TADDOL **1a** and coumarin there exists a pair of coumarin molecules oriented in an *anti*-head-head orientation to each other, held in place by two TADDOLs through appropriate hydrogen bonds (Figure 11, red structure). Under irradiation the crystal remains intact, but it is nevertheless transformed ultimately into a single crystal of the cyclobutane-TADDOL inclusion compound (light blue structure in the overlay of Figure 11). The classic^[5] photochemical valence isomerization converting pyridone into azabicyclo[2.2.0]hexene leads to an enantiomerically pure product when carried out in an inclusion compound with TADDOL **1a** (see Scheme 9a). The other four reactions presented in this particular scheme are also examples of photoisomerizations taking place within the chiral host lattice. The products obtained are five- (d, e) and six-membered (b, c) heterocyclic ring systems, enantiomerically pure or at least generated through processes that occur with high enantioselectivity.



Scheme 9. Enantioselective photochemical cyclizations in TADDOL inclusion compounds. In addition to an electrocyclic valence isomerization to a cyclobutene derivative (a),^[185] there occurs in this case a photoreaction in which a six-electron π system formally undergoes an electrocyclic reaction followed by a 1,3-sigmatropic hydrogen shift (Ninomiya cyclization).^[176, 177] Anilides of carboxylic acids are introduced in (b) and (c),^[186–188] as is an enamine of 2-methylcyclohexan-1,3-dione (a vinylogous anilide) in (d),^[189] and a 2-arylthiocyclohexenone (a derivative of 3,5-trimethylcyclohexan-1,2-dione) in (e).^[190] In the photoreaction illustrated in (c), a levorotatory product is obtained by irradiation of a 1:1 inclusion compound with TADDOL **1c**, whereas a dextrorotatory product forms from a 1:2 inclusion compound. All reactions were carried out with a high-pressure mercury lamp (Pyrex filter).

Especially noteworthy is formation in the case of the furan derivative of enantiomeric products, depending upon whether a 1:1 or a 2:1 complex is irradiated (Scheme 9c). TADDOLs with four phenyl groups appear especially well-suited to solid-phase photoreactions. (For additional examples see the review article by the Toda group.^[170])

Other solid-state reactions with TADDOLs have so far proven less successful, at least with respect to enantioselectivity. Investigations have been conducted on borane reductions of unsymmetrical ketones,^[65] Baeyer–Villiger oxidations,^[192] ether formations,^[193] Wittig olefinations,^[194] Michael additions of thiols to enones,^[195] and cyclopropanations of α,β -unsaturated carbonyl compounds with sulfoxonium ylides.^[196] In every case, the reagents and TADDOL were mixed,

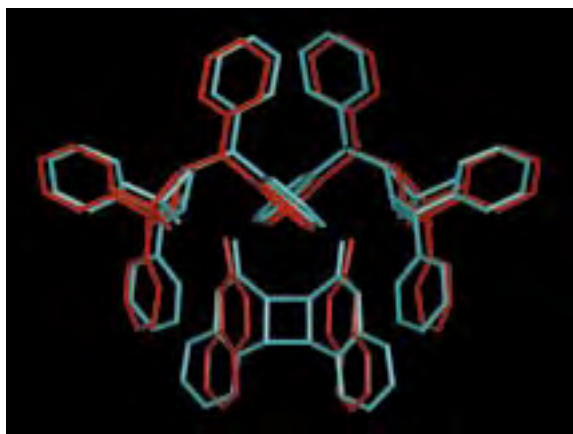


Figure 11. Overlay of structures of starting material and product for the photodimerization of coumarin in an inclusion compound with TADDOL **1a**. This is an unusual case of a single-crystal to single-crystal reaction.^[178] The structure of a 1:1 host–guest crystal of coumarin with **1a** is shown in red. The crystal was irradiated to the point of complete photodimerization. It remained intact, and X-ray analysis showed the resulting structure to be that of a 1:2 *anti*-head-head dimer inclusion complex with **1a** (shown in light blue).

triturerated, and left to stand for a period of time prior to workup. New attempts will undoubtedly be made with the TADDOL substitution products and derivatives described in Section 3, and at least some of the cited reactions will surely evolve to the point of generating product with the crucial level of at least 90 % enantiomer purity.

8. TADDOL Derivatives as Reagents, and also as Ligands in Metal Complexes for Enantioselective Transformations

The strong tendency (documented in Section 7) of TADDOLs to cocrystallize with hydrogen-bond acceptors, which thereby become fixed within a chiral environment, establishes the TADDOLs as novel tools valuable in the separation of enantiomers (“chiral sorting machines”) and the promotion of enantioselective solid-state reactions (“chiral vices”). The interactions responsible for these effects are of course also present in solutions based on suitably selected solvents (see the discussion of NMR shifts in Section 6). More important, however, has been the discovery through structural studies (Sections 4 and 7) that TADDOL derivatives are predisposed structurally to complex with metallic centers, in that heteroatoms in the diarylmethyl units position themselves—with few exceptions—in close proximity to each other, conformationally fixed to act as chelating ligands with well-defined geometry. This opens the way to the most valuable application of TADDOL systems to date from the standpoint of the synthetic organic chemist: enantioselective synthesis. After all, resolution of a racemate can scarcely be regarded as a chemical reaction, and solid-phase photosynthesis represents a very special case, one not necessarily adaptable to the large-scale commercial preparation of enantiomerically pure compounds. Moreover, TADDOL derivatives might also have a future as chiral reagents on a stoichiometric basis. In the

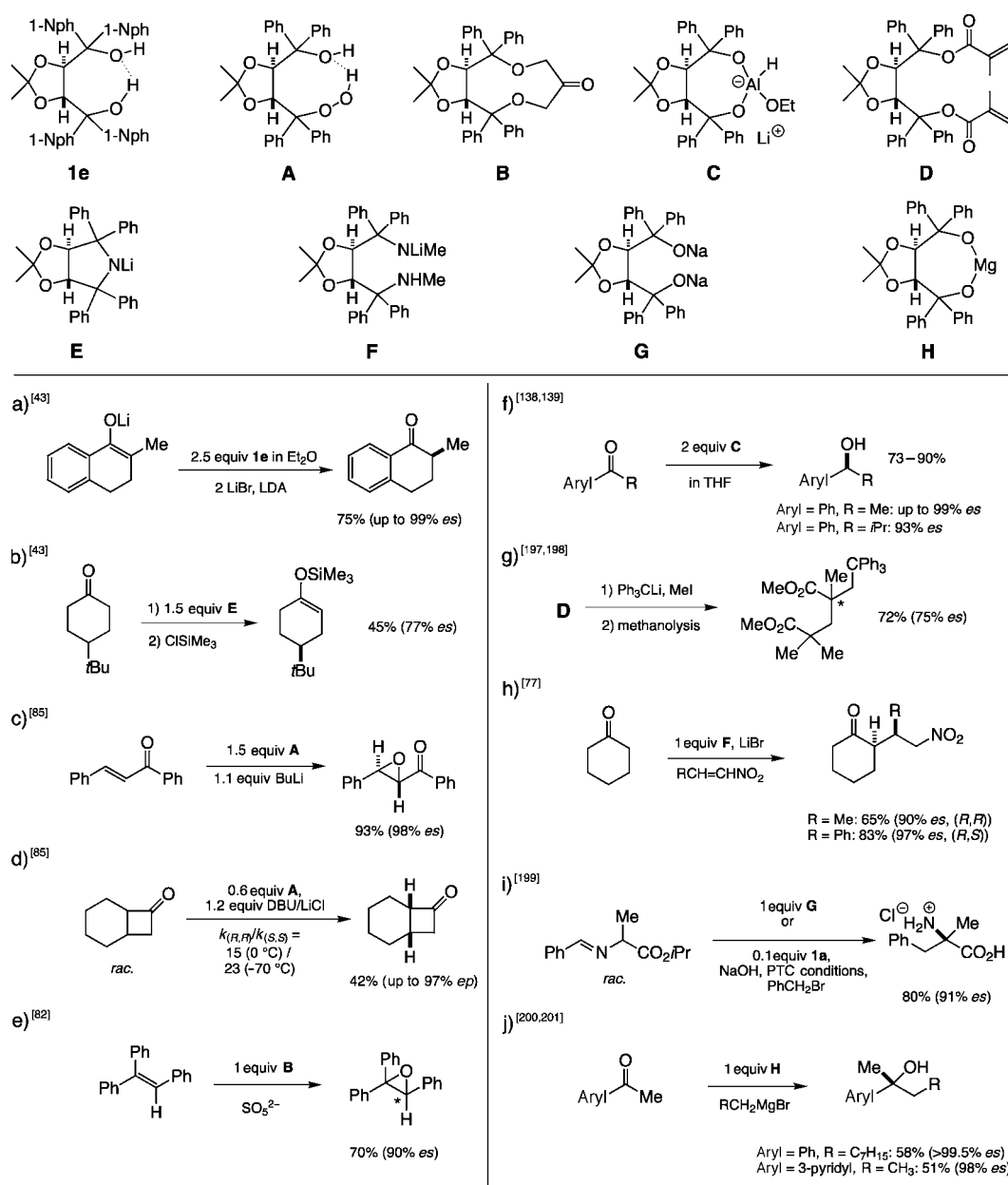
sections that follow we first examine applications involving the chemistry of derivatives of main-group metals (Li, Na, Mg, Al) and stoichiometric transformations (Section 8.1), then the most intensively investigated titanium TADDOLate mediated reactions (Section 8.2), and finally use of TADDOLs as ligands on other transition-metal centers (Section 8.3). In the course of this account it will become clear that TADDOL derivatives can also function as “chiral tools” for assisting in chemical transformations (acting at least figuratively as chiral tweezers, tongs, hammers, chisels, files, and screwdrivers in the accomplishment of molecular processes). In many cases record-breaking results have been achieved, although some of the examples could more accurately be described as promising beginnings.

8.1. Chiral Acids, Bases, Oxidizing/Reducing Agents, and Additives Based on TADDOLs and TADDAMINes

Selected examples of the reactions of interest here are presented in Scheme 10. We begin by showing how the acidity of a TADDOL can be exploited for enantioselective protonation of an achiral enolate, as in the transformation of a *rac*-ketone into its enantiomerically pure form (Scheme 10a).^[202, 203] Initial experiments have shown that the lithium amides **E** and **F** of TADDAMINes (prepared from TADDOLs by OH/NR₂ substitution; see Section 3) are capable of preferentially deprotonating one of the enantiotopic CH₂ groups of 4-*tert*-butylcyclohexanone (Scheme 10b; see the work of Koga,^[204] and Cox and Simpkins^[205]), or causing the achiral lithium enolate of cyclohexanone to add with high enantioselectivity to a nitroolefin (Scheme 10h; see results reported by Koga and co-workers^[204, 206] and reviews of the structure and reactivity of lithium enolates^[207, 208]).

The remarkably stable hydroperoxide TADDOOH (**A** in Scheme 10) can be deprotonated with BuLi (stoichiometrically) or DBU/LiCl (catalytically) and utilized for the epoxidation of unsaturated phenylketones. TADDOOH reacts with cyclobutanones under Baeyer–Villiger oxidation conditions in such a way as to effect enantiomer differentiation, especially at low temperature (Scheme 10c, d^[209, 210]). A ketone derived from dihydroxyacetone and TADDOL **B** has been used as a catalyst (which forms a dioxirane) for enantioselective epoxidations with Caro’s acid (H₂SO₅, Oxone;^[211] Scheme 10e).

Reduction of arylketones can be accomplished with high enantioselectivity using **C**, a lithium aluminum hydride derivative of TADDOL (Scheme 10f). Superb catalytic variants on this reaction are now available as well, for example, the Corey–Itsuno reduction.^[212] A useful feature of the method illustrated here is the fact that in many cases the enantiomer purity of the product can be raised to >99 % during workup by taking advantage of the “enantioselective affinity” of the TADDOL for hydrogen-bond donors. Thus, a crude-product residue is digested with hexane, causing the underrepresented enantiomer to pass preferentially into solution, with the principal enantiomer being retained by the TADDOL.



Scheme 10. Use of TADDOL **1e** and the derivatives **A–H** as reagents (a–d, f–h), as stoichiometric additives (e, h–j), and/or as catalysts (i) in enantioselective protonations (a)/deprotonations (b), oxidations (c–e), reductions (f), and C–C bond formations (g–j). Most of the cited references provide additional examples. The configurations of the chiral centers which are marked with a star in the products have not been defined. 1-Nph = 1-naphthyl, LDA = lithium diisopropylamide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, PTC = phase-transfer catalysis.

In the enantioselective C–C bond-forming reactions shown in Scheme 10 a TADDOL serves (in the formation of glutaric acid esters) as the covalently bonded *RO fragment of a starting diester (**D**, Scheme 10g); in the synthesis of α -branched amino acids, sodium TADDOLate **G** appears to function as a phase-transfer catalyst (Scheme 10i); and in Grignard additions to aromatic, heteroaromatic, and α,β -unsaturated ketones a magnesium TADDOLate **H** (Scheme 10j), introduced in stoichiometric amounts, behaves as a chiral Lewis acid and is responsible for record-breaking selectivity, only one enantiomer of the product being detectable by gas chromatography.

The new nitrogen- and sulfur-containing TADDOL derivatives (Figure 2 and Scheme 5 left and center) should prove

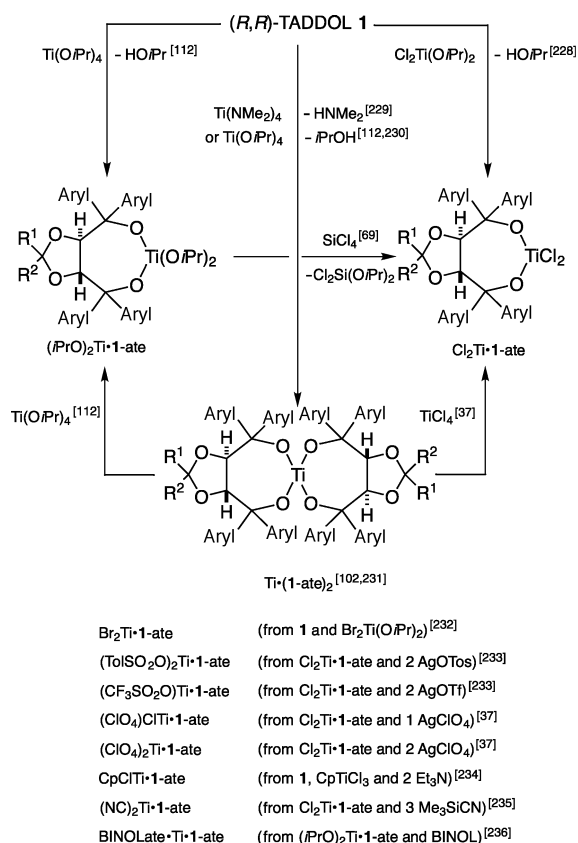
especially well suited to a host of other stoichiometric applications. It should not be forgotten, however, that this involves manipulation of large amounts of the auxiliary (molecular mass of **1a**: 466 Da), and in this context attention should be directed toward Section 9, which deals with polymeric and solid state bound TADDOLs.

8.2. Titanium TADDOLates in Enantioselective Synthesis

Apart from resolution of racemates and solid-state reactions, the principal field of application to date for TADDOLs has been enantioselective syntheses mediated by titanium

TADDOLates. Two types of reaction must here be distinguished: a) nucleophilic additions to aldehydes, ketones, α,β -unsaturated carbonyl compounds, esters, anhydrides, and nitroolefins, along with reactions of nucleophiles with halogenating or oxidizing agents, in which the actual nucleophile may be an $\text{Nu-TiX} \cdot \text{TADDOLate}$;^[213] and b) Lewis acid catalyzed transformations in which the electrophile is activated by an $\text{X}_2\text{Ti-TADDOLate}$ (for example, sulfoxidations, epoxidations, Baeyer–Villiger oxidations, cyclopropanations, and [2+2], [3+2], or [4+2] cycloadditions). With $\text{X}_2\text{Ti-TADDOLates}$, the donor strength or anion stability of the X groups, and thus the Lewis acidity of the titanate,^[214, 215] can be varied from amide (NR_2) through cyclopentadienide, alkoxide, phenoxide, sulfonate, bromide, and chloride all the way to fluoride.^[216] As in the case of classic Lewis acid dependent reactions (such as Friedel–Crafts acylation), a stoichiometric amount of the Lewis acid is often required^[217–226] because this may bind more firmly with the product than with the starting electrophile one wishes to activate.

A few observations regarding the preparation of titanium TADDOLates are in order (Scheme 11) before we discuss these two types of reaction in detail in the sections that follow.



Scheme 11. Preparation and in situ generation of titanium TADDOLates by ligand exchange. The spirotitanate of **1a** is a stable material that can be stored, is useful for the preparation of pure TADDOLates of the type $\text{X}_2\text{Ti} \cdot \mathbf{1a}\text{-ate}$ by “symproportionation”, and often functions itself as a catalyst. In particular, $\text{Cl}_2\text{Ti-TADDOLates}$ are frequently used in the presence of $i\text{PrOH}$, so Brønsted catalysis (HCl!) may play a role in the transformations.^[203, 227] The cited references include typical procedures, or at least data for synthesis or preparation of the corresponding titanates. Tf = trifluoromethanesulfonyl, BINOL = 2,2'-dihydroxy-1,1'-binaphthyl.

Numerous recipes have been proposed by various authors according to which the complexes of interest can be obtained and introduced into reactions. In most cases, a TADDOL is treated with $\text{Ti}(\text{O}i\text{Pr})_4$ or $\text{Cl}_2\text{Ti}(\text{O}i\text{Pr})_2$ in toluene, CH_2Cl_2 , or some other aprotic solvent. With the former titanium reagent, 2-propanol is then removed under vacuum, along with the solvent. In the latter case only one equivalent of alcohol can be removed in this way;^[228] that means, what remains behind is a complex of the type $\text{Cl}_2\text{Ti} \cdot \mathbf{1a}\text{-ate} \cdot i\text{PrOH}$. Often there is simply introduced a solution containing both TADDOL and $\text{Cl}_2\text{Ti}(\text{O}i\text{Pr})_2$, so that various titanium TADDOLates, together with $i\text{PrOH}$ and HCl , may all be present and in equilibrium. The addition of molecular sieves has also been recommended, which might bind traces of water but certainly not $i\text{PrOH}$. If one employs a C_1 -symmetric TADDOL with two different R groups in the 2-position of the dioxolane ring, the catalytically active mixture may contain *cis/trans*-isomeric complexes as well (for example, the $\text{XYTi} \cdot \mathbf{1b}\text{-ates}$). On the other hand, uniform $\text{X}_2\text{Ti-TADDOLates}$ can be obtained by 1:1 reaction of a spirotitanate $\text{Ti} \cdot (\mathbf{1a}\text{-ate})_2$ with TiX_4 . The spiro compound is best prepared by reacting $\text{Ti}(\text{NMe}_2)_4$ with TADDOL in a ratio of 1:2 and removing the resulting dimethylamine under vacuum. The parent compound $\text{Ti} \cdot (\mathbf{1a}\text{-ate})_2$ is a crystalline solid sufficiently stable in air to be suitable for storage. The required quantity can therefore be introduced into a reaction simply by weighing the reagent in the open air. Another trick for preparing a pure $\text{Cl}_2\text{Ti-TADDOLate}$ is treatment of the corresponding $(i\text{PrO})_2$ derivative with SiCl_4 , with removal of $\text{Cl}_2\text{Si}(\text{O}i\text{Pr})_2$ under vacuum. The reader is referred to the literature for experimental details, which can often prove decisive with respect to reproducibility of the reactions presented in the schemes below and, thus, to achieving the reported results. Attention is also directed to review articles dealing with chiral titanates.^[27, 218, 226, 237–240]

8.2.1. Nucleophilic Additions in the Presence of Titanium TADDOLates, and Reactions of Nucleophilic TADDOLato-Titanium Derivatives

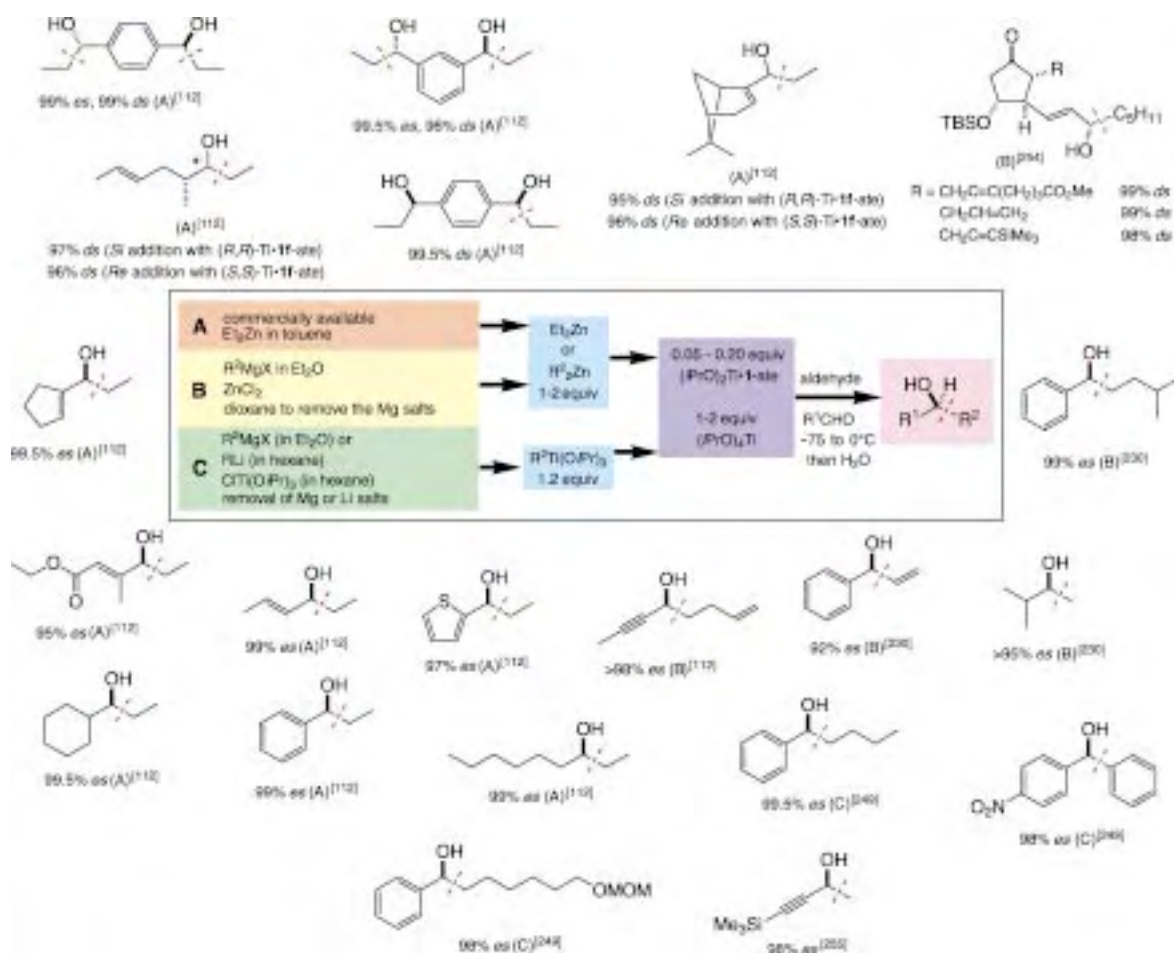
Once early TADDOL experiments had revealed that “Grignard additions” to aldehydes can be rendered enantioselective by exchanging XMg (or Li) in the organometallic compound for $(\text{R}^*\text{O})_3\text{Ti}$, it was of course tempting to seek a catalytic variant of the process. Since the usual polar metal derivatives are much too reactive to profit at ordinary reaction temperatures from the availability of a catalyst, there appeared to be merit in following the trail backward from Grignard to Frankland. Over 150 years ago the latter stumbled across the gateway to organometallic chemistry with the preparation of alkylzinc compounds,^[241] and these react only poorly with aldehydes, even at room temperature. Noyori et al. has in recent years demonstrated that chiral amino alcohols can function as (basic!) catalysts for a highly enantioselective addition of diethylzinc to aldehydes,^[242] and Ohno and co-workers discovered further that a mixture of achiral $\text{Ti}(\text{O}i\text{Pr})_4$ with the bistriflamide of (*R,R*)-1,2-cyclohexanediamine (in a ratio up to 5000:1) is capable of effecting superb (Lewis acidic!) enantioselective catalysis of this reaction.^[243–245] Unfortunately, however, very few organozinc

derivatives are commercially available,^[246] and the prospect of preparing a pure organozinc compound as needed has never been a pleasant one.^[243, 247]

In our research group we discovered^[231] that 0.05–0.20 equivalents of $(i\text{PrO})_2\text{Ti}\cdot\mathbf{1}$ -ate also catalyzes the highly enantioselective addition of diethylzinc to aldehydes, but only in the presence of excess $(i\text{PrO})_4\text{Ti}$. We also developed a simple procedure for in situ preparation of other organozinc compounds, starting from lithium or XMg precursors.^[230, 248] The organometallic titanates $\text{RTi}(\text{OiPr})_3$, which are accessible by the same route, also add to aldehydes with high enantioselectivity in the presence of titanium TADDOLate (and with better stoichiometric utilization, relative to R_2Zn , of the group R that is to be introduced!).^[249] This observation is especially noteworthy because such organotitanates react with aldehydes at temperatures as low as -60°C , albeit not enantioselectively.^[27] (With respect to mechanistic studies, see Section 10.) The titanium TADDOLate catalyzed addition of carbon nucleophiles to aldehydes has proven to be the most

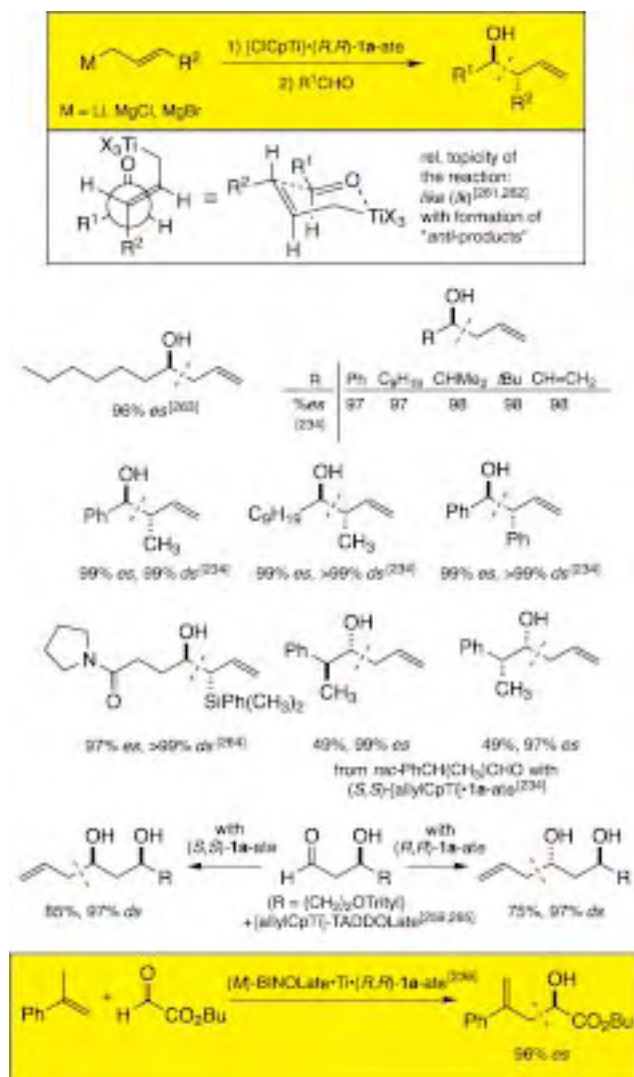
widely applicable and most highly enantioselective variant of this type of reaction, serving to some extent as a standard for comparison purposes^[250] (see Scheme 12). Often, but not always, the TADDOL bearing 2-naphthyl groups leads to record values.^[112, 230, 251] Substituents on the phenyl groups—through to 4-dimethylamino groups—have almost no effect on selectivity.^[102, 252] Carbocyclic and carbobicyclic TADDOL analogues also lead to no better results,^[44, 50, 51] and titanates other than isopropyltitanates are less well suited to the purpose.^[253] The method is applicable to all types of aldehydes so long as they contain no other functional groups capable of forming chelates with metals. In the case of chiral aldehydes the (diastereoselective) course of the reaction is dictated by the nature of the titanium TADDOLate. The structure of the nucleophile can also be varied within wide limits, again so long as there are no heteroatoms present capable of forming five- or six-membered cyclic chelates.

Tests have been conducted as well with 1:1-ate complexes composed of a titanium TADDOLate and RLi or

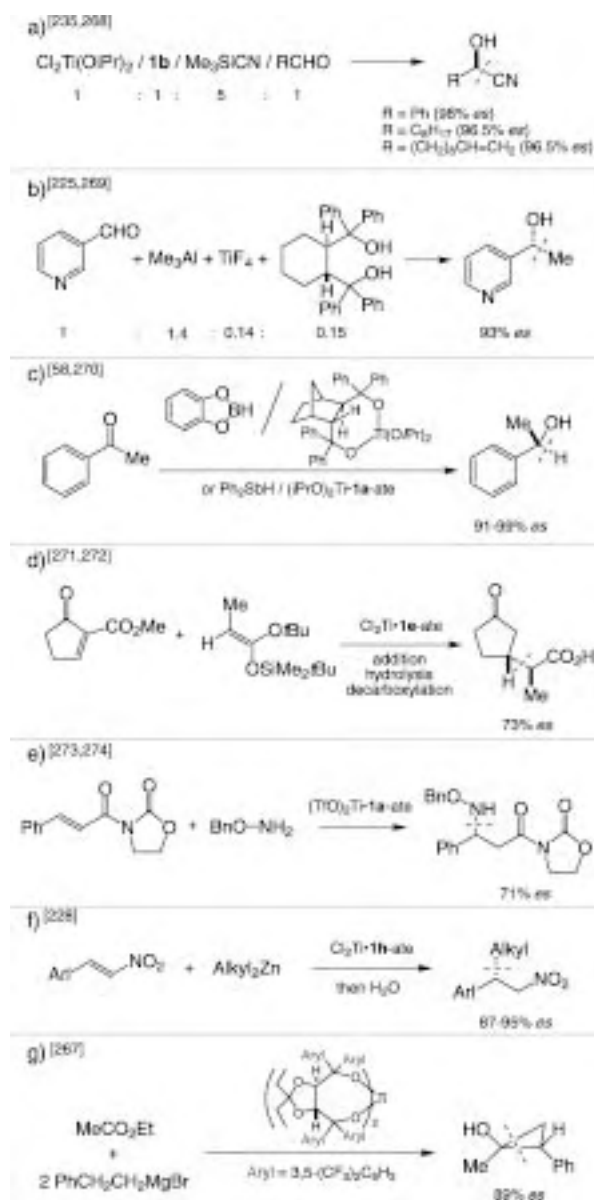


Scheme 12. Nucleophilic additions of organometallic compounds $\text{R}-\text{M}$ to aldehydes in the presence of substoichiometric amounts of $(i\text{PrO})_2\text{Ti}$ -TADDOLates, or with in situ preparation (methods B and C) of salt-free solutions of R_2Zn ^[246] and $\text{RTi}(\text{OiPr})_3$ from Grignard reagents or lithium compounds in diethyl ether, THF, hexane, or toluene. Newly formed C–C bonds are indicated by dotted lines. Addition occurs from the *Si* side of the aldehyde carbonyl group when (R,R) -TADDOL is used as the auxiliary, and from the *Re* side with (S,S) material (relative topicity *unlike* (*ul*)). In most of the examples shown here, TADDOL **1f** (with β -naphthyl groups) is utilized. The reported high selectivities are achieved only in the presence of excess $\text{Ti}(\text{OiPr})_4$. It is not necessary that there be two different types of metallic species ($\text{Ti}^{\text{IV}}/\text{Zn}^{\text{II}}$) present in the reaction mixture (in method C only titanates!). Functional groups in the reactants are tolerated so long as they cannot form 5- or 6-membered cyclic chelates with metals. With chiral aldehydes the stereochemical course of the reaction is determined by the titanium TADDOLate (“reagent control”). Note that the C–C bond forming reaction permits enantioselective preparation of secondary alcohols $\text{RCH}(\text{OH})\text{R}'$ with very similar R groups (alkyl/alkyl' or aryl/aryl'), a result that cannot be achieved by reduction of the corresponding ketones or hydroboration of olefins. TBS = *tert*-butyldimethylsilyl, MOM = methoxymethyl.

RMgX,^[231, 256] but these have rarely shown enantioselectivities exceeding 90%. The addition of allylic nucleophiles is most successful, on a stoichiometric basis, with Duthaler's CpTi-TADDOLate complexes or, catalytically, through an ene reaction with an activated aldehyde (Scheme 13). Examples of other nucleophilic additions, including reductions of ketones, are collected in Scheme 14; reactions of TADDOLato-titanium enolates are shown in Scheme 15.

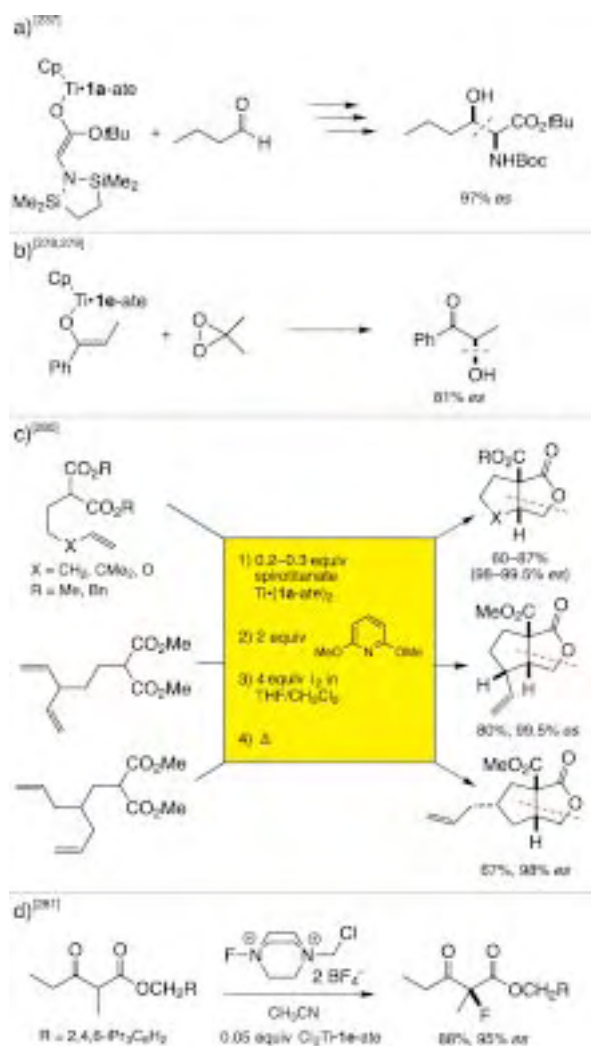


Scheme 13. Enantioselective transfer of allyl groups to aldehydes (with the formation of one or two new stereocenters) with allylcyclopentadienyltitanium TADDOLates^[237] or by a Lewis acid catalyzed ene reaction.^[236] Lower enantioselectivities are obtained with simple allyl derivatives of zinc or through ate complexes.^[231, 257] [CpTiCl₃] used to prepare the Duthaler reagent can be regenerated (to some extent recovered) at the conclusion of the reaction. Substituted allyl groups ($R^2 \neq H$) are preferentially transferred with relative topology *lk*, which is true as well of nonchiral allyltitanates^[258] (*ul* in the case of the silyl derivative illustrated because of a reversal in the CIP priority sequence). It is worth noting that the diastereoselective addition of allyl-Cp-titanate to the *unprotected* 3-hydroxyaldehyde is “dictated” by the TADDOLate.^[259] The ene reaction generally gives higher selectivities with titanium BINOLates than with titanium TADDOLates.^[236, 260] The Lewis acid employed in the example shown is a spirotitanate with the two bidentate ligands BINOLate and TADDOLate (a sort of “marriage” of two systems!). Trityl = triphenyl-methyl.



Scheme 14. Enantioselective 1,2- and 1,4-additions to carbonyl compounds and nitrostyrenes, mediated by titanium TADDOLates. a) Cyanohydrin reactions, which—depending on the type of aldehyde (aliphatic/aromatic) and the technique for preparing the reagent (with/without warming; with/without addition of molecular sieves)—result in varying yields and stereoselectivities. Under optimal conditions, alkyl-CH(OH)CN and aryl-CH(OH)CN are obtained in 80–90% yield with >97% *es*. b) Titanium fluoride catalyzed addition of Me₃Al to an aldehyde in the presence of the cyclohexane analogue of TADDOL. c) Ketone reduction with catecholborane or a stibane (radical mechanism?) occurs enantioselectively with addition of (*i*PrO)₂Ti-TADDOLate or the norbornane analogue; see also the hydrosilylations in Figure 12. d)–f) Michael additions do not show high enantioselectivities; in the case of addition of an alkylzinc compound to a nitrostyrene (f), the enantiomer purity can be increased by crystallization at the stage of the reduction product Aryl-CH₂CH₂NH₂. g) The formation of cyclopropanols from esters and Grignard reagents with β -hydrogen atoms^[266] in the presence of titanates can best be directed enantioselectively using the TADDOLate that bears four 3,5-bis(trifluoromethyl)phenyl groups (for a mechanistic suggestion, see ref. [267]).

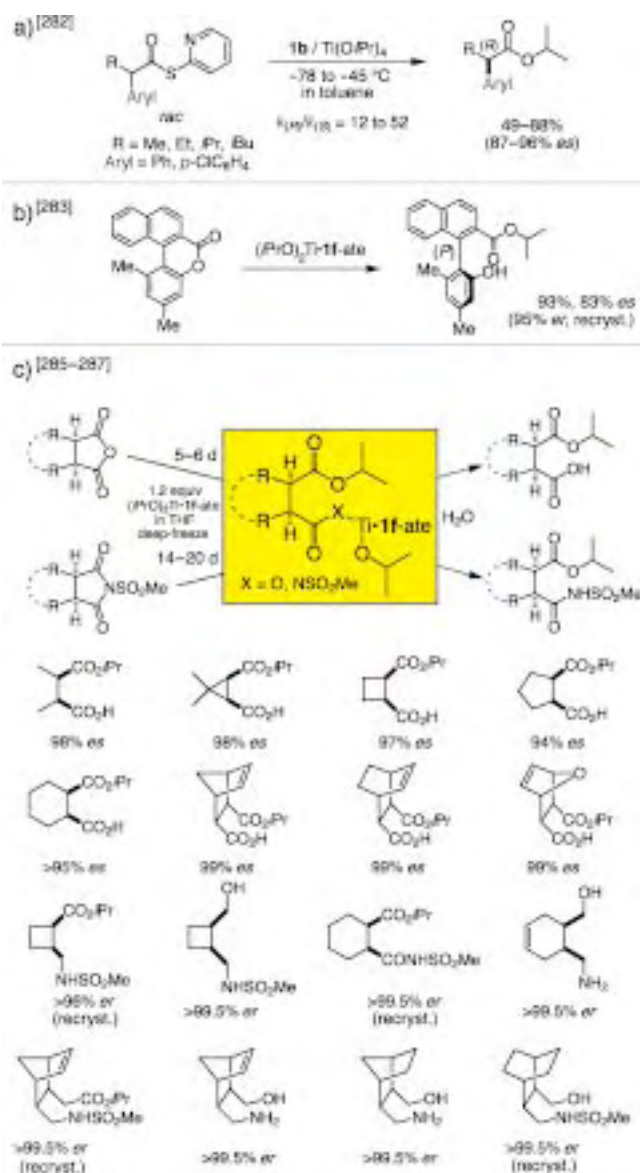
The system (*i*PrO)₂Ti-TADDOLate can also be used for transesterifications that involve differentiation between enantiomers,^[282] for ring openings of lactones^[283] and azlactones,^[284] and for the enantioselective opening of *meso* five-



Scheme 15. Reactions of TADDOLato-titanium enolates with electrophiles. a) CpTi-enolates with TADDOLate ligands generally add to aldehydes with poorer selectivity than do the corresponding allyltitanates (Scheme 13), although the example shown here is an exception;^[275, 276] in most cases, carbohydrate derivatives (diacetoneglucose, DAGO) are more effective. b) Hydroxylation with dioxirane also occurs with disappointing selectivity. c) The highly enantioselective cyclizations of ω -pentenyl malonic esters described by Taguchi et al.^[277] are a result of intramolecular alkylation of TADDOLato-titanium malonic ester enolate complexes by iodonium ions, followed by lactone formation. d) An acetoacetic ester enolate is enantioselectively fluorinated under the influence of a Cl_2Ti -TADDOLate. Boc = *tert*-butoxycarbonyl.

membered cyclic anhydrides^[285, 286] and *meso*-*N*-sulfonyl-imides.^[287] In particular, opening of an anhydride to a half ester displaying a high degree of enantiomer purity has been shown to be a generally applicable process, and should represent a real alternative to enzymatic saponification or the esterification^[288] of a dicarboxylic acid derivative, or other reactions that lead to half esters.^[289] For information regarding the conduct of such reactions and a few examples, see Scheme 16.

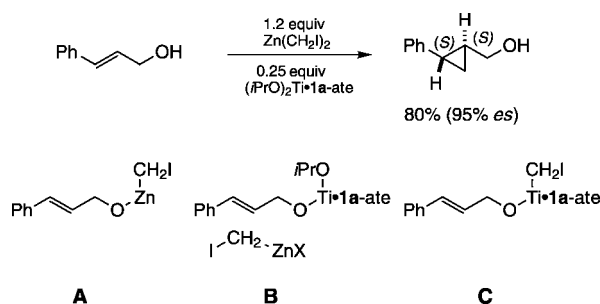
The applications illustrated with respect to titanium TADDOLates, especially nucleophilic addition, provide evidence of the versatility of this auxiliary for the enantioselective preparation of synthetic starting materials, but also for



Scheme 16. Enantioselective formation of isopropyl esters by *iPrO* transfer from $(i\text{PrO})_2\text{Ti}$ -TADDOLates. a) The illustrated racemic “active esters” of pyridinethiol are transformed (with kinetic resolution through in situ recycling) into 2-arylalkanoic acid isopropyl esters. b) Phenolic lactones can also be opened with “dynamic” racemate resolution to axial chiral biphenyl esters. c) The anhydrides of *meso*-succinic acid derivatives and the corresponding *N*-sulfonylsuccinimides are opened with diisopropoxytitanium TADDOLates containing 2-naphthyl groups to give half esters or sulfonylamido esters. The observed selectivity is largely independent of structure, and lies in the range 95–99% *ee* with anhydrides and 85–95% *ee* with imides, where the amido esters can be readily enriched further by recrystallization (hence the data in % *ee* rather than % *es*!). Separation of the products from TADDOL after hydrolysis is accomplished by extraction of the carboxylic acid or *N*-acetylsulfonamide into aqueous base. The half esters are readily transformed into γ -lactones, and hydroxysulfonamides or 4-aminoalcohols are accessible by reduction of the amidoesters (see the examples in the bottom two rows of formulae in (c)). Transformation of *meso* starting materials into chiral products by differentiation of enantiotopic groups (in the present case, with the “normal” CIP priority sequence, it is the *Re* carbonyl groups that are attacked by isopropoxide) is also referred to as “desymmetrization” (starting material with C_s symmetry is transformed into a C_1 -symmetrical product); an excellent review article on this subject has recently been published,^[290] which offers the opportunity to compare the titanium TADDOLate method of preparing half esters and their derivatives with other procedures.

carrying out diastereoselective transformations with complex synthetic intermediates. In most cases it has not been established whether—and in which of the various reactions discussed—the nucleophile is transferred directly from an Nu–TiX·TADDOLate species to the electrophilic center, or if the titanium TADDOLate behaves as a chiral Lewis acid in activating the electrophile, after which a nonchiral nucleophile carries out the actual attack (see Section 8.2.2). In fact, accomplishing such a distinction would entail complex kinetic and spectroscopic studies.

Another interesting example is provided by enantioselective Simmons–Smith cyclopropanation in the presence of 0.25 equivalents of (*i*PrO)₂Ti·**1a**-ate, an achievement that cannot be assigned unambiguously to any of the reaction categories discussed in Sections 8.2.1 and 8.2.2^[291, 292] (Scheme 17).



Scheme 17. An enantioselective Simmons–Smith reaction in the presence of a diisopropoxytitanium TADDOLate.^[291] The diastereoselectivity of Simmons–Smith cyclopropanation is usually explained in terms of the formation of a zinc alkoxide and subsequent intramolecular carbene transfer (see **A**). In the presence of titanates it could be—considering two of the many possibilities—that carbene adds to the double bond of a chiral titanium alkoxide (**B**), or else a titanium analogue of Simmons–Smith intermediate (**C**) might form. In case **B** the titanium TADDOLate would “only” provide for the trigonal centers of the allyl alcohol to have diastereotopic faces (for attack of an achiral electrophile), whereas in case **C** the titanium center could be the donor of the electrophilic carbene. Based on the current state of understanding it is not possible to classify this reaction based on reactivity criteria (Sections 8.2.1 and 8.2.2). For a lucid discussion of enantioselective Simmons–Smith reactions, including other chiral auxiliaries and a suggested mechanism, see ref. [293, 294].

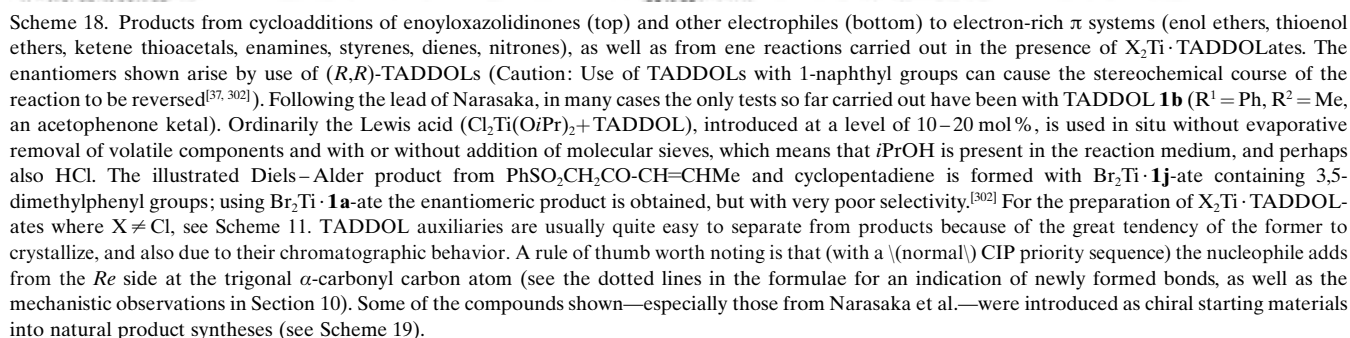
8.2.2. Enantioselective Cycloadditions^[295] with X₂Ti-TADDOLate Lewis Acids

Cycloadditions play a key role in organic synthesis, especially since they result in simultaneous formation of two new bonds and proceed according to a set of rules—first formulated empirically, and later explained, by Woodward and Hoffmann^[107]—to generate stereoselectively as many as four new stereo centers.^[295] The [4+2]-cycloaddition process (which covers “homo” and “hetero” Diels–Alder reactions) can justifiably be called one of the most valuable “work horses” in the entire synthetic repertoire. The second most important of the broadly applicable cycloaddition processes is probably 1,3-dipolar or [3+2] cycloaddition. Less synthetic attention has been directed toward [2+2] cycloaddition, although the resulting four-membered rings—like cyclopropanes and epoxides—are easily opened as a consequence of ring strain, and can thus serve as welcome precursors to

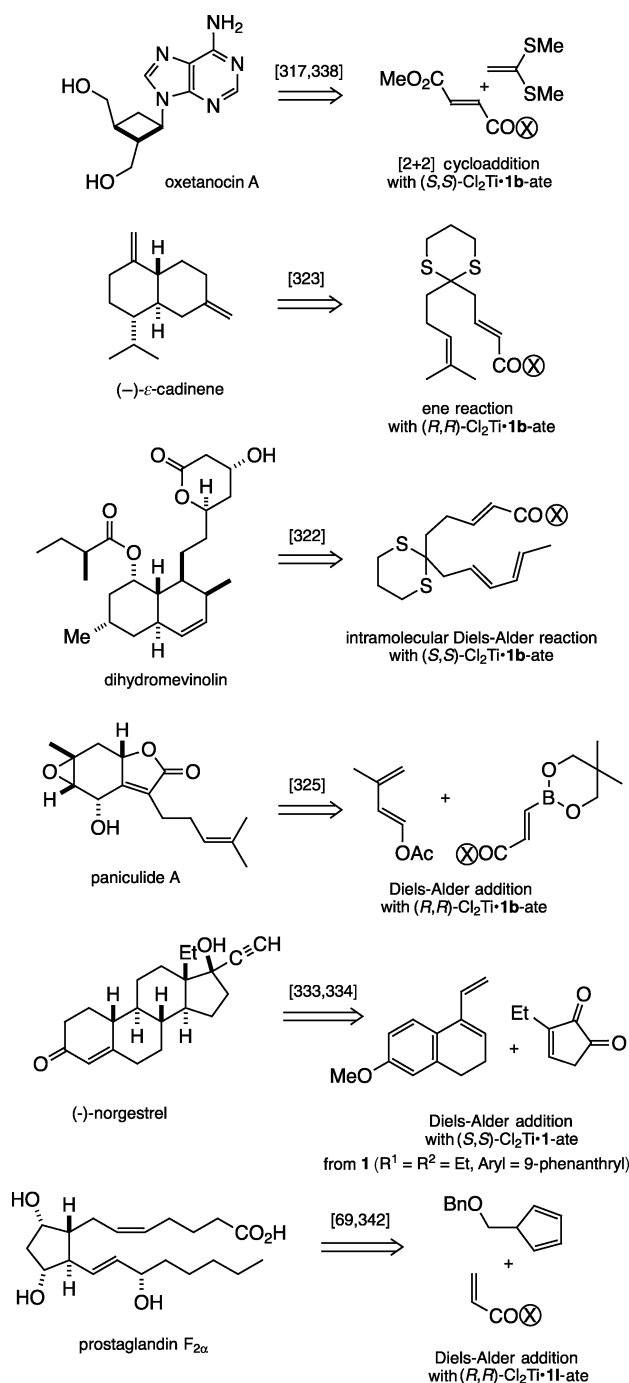
various open-chain targets.^[296] There exists therefore considerable interest in cycloaddition reactions that occur in an enantioselective way starting from achiral reactants, and many possibilities can of course be envisioned. The use of TADDOLs as auxiliaries in such transformations is the subject of the discussion that follows, which is organized on the basis of increasing ring size. Comparisons with other methods have appeared in comprehensive review articles by qualified authors dealing with enantioselective Diels–Alder^[297–299] and [3+2]-cycloaddition reactions.^[226]

Earlier attempts were made to employ titanium TADDOLates as Lewis acids for cycloaddition reactions,^[300] but Narasaka deserves the credit for having recognized that 3-enoyl-1,3-oxazolidin-2-ones^[301] are the ideal C₂ components for reactions of this type^[218] (Scheme 18, top). In a series of publications and patent applications, Narasaka’s group has reported catalytic variants demonstrating the breadth of applicability and utility of this method in the synthesis of natural products and pharmacological agents,^[338] all the reactions being carried out and optimized exclusively with the unsymmetrical TADDOL **1b** (with Me/Ph at the 2-position of the dioxolane ring). This is not to say that equally satisfactory results could not be achieved on a large scale with the more readily accessible and more easily purified C₂-symmetric TADDOLs. Indeed, careful optimization^[37] in the case of the Diels–Alder reaction between cyclopentadiene and crotonoyloxazolidinone has verified that, within the limits of error, the same enantioselectivity can be accomplished with TADDOL derivative **1f** bearing 2-naphthyl groups.^[339] It should be noted in this context, however, that the reaction conditions, the solvent employed, and especially the method of preparing the catalyst can all exert a major influence on the stereochemical course of such reactions, even to the point of reversing the observed results (see Scheme 11, and the introduction to Section 8.2).

Acyloxazolidinones of fumaric, acrylic, and crotonic acid are all subject to coupling under Lewis acid catalysis with ketenethioacetals, methylthioallenes or -acetylenes, and enamines to generate four-membered ring systems. The resulting amino and bis(methylthio)cyclobutane carboxylic acid esters can easily be cleaved to open-chain compounds that still contain a stereocenter. The corresponding addition to nitrones also depends upon Lewis acid catalysis, and investigations by Jørgensen have shown that it is subject to enantioselective control through the use of titanium TADDOLates.^[340, 341] The most extensive efforts have been dedicated to Diels–Alder reactions of enoyloxazolidinones, again involving the addition of crotonic acid derivatives to cyclopentadiene, which under appropriate conditions leads almost quantitatively to a single stereoisomer (2*R*,3*R* with (*R,R*)-TADDOLs). Narasaka and co-workers have also carried out intramolecular variants of the reaction of enoyloxazolidinone units with diene (Diels–Alder reaction) and ene groups (ene reaction, hetero-Diels–Alder addition), in which up to four new stereocenters are formed in bi- and tricyclic products with >99% enantioselectivity (Scheme 18, middle). Cycloadditions involving other α,β-unsaturated carbonyl compounds (quinones, ene-1,2-diones, phenylsulfonylmethyl enones, maleimides, amidoacrylates, pyrones) and nitrostyrenes have also been accomplished



desired configuration of the product. In the vast majority of reactions leading to the products shown in Schemes 18 and 19, the Lewis acids are prepared in 5–20 mol% quantities by mixing TiCl_4 and $\text{Ti}(\text{OiPr})_4$ (which form $\text{Cl}_2\text{Ti}(\text{OiPr})_2$) with a TADDOL in situ, although sometimes as much as a twofold stoichiometric excess of the catalyst is introduced



Scheme 19. Natural products and active substances from cycloadducts, and from the product of an ene reaction with enoxyloxazolidinones and with a cyclopentenone (⊗ = 1,3-oxazolidin-2-on-3-yl, see Scheme 18). The products initially formed (or their enantiomers) in the presence of (R,R)- or (S,S)-Cl₂Ti-TADDOLate are shown in Scheme 18. The main synthetic effort commences *after* the enantioselective step, and itself consists of numerous steps (see the comments in ref. [17]).

(200 mol%). In the case of [4+2] cycloaddition of silylenol ethers to nitrostyrenes, equally satisfactory results (if not greater selectivity) were observed when, in place of excess Cl₂Ti-TADDOLate, a mixture was instead added containing (achiral!) Cl₂Ti(OiPr)₂^[229] (see Section 10).

Titanium TADDOLates have also been tested in conjunction with Sharpless oxidation, sulfoxidations,^[343] and Baeyer–

Villiger oxidations^[210, 344] involving *t*BuOOH, as well as in ring-opening reactions of *meso*-epoxides to chlorohydrins.^[345] In most cases to date, however, the observed enantioselectivity has not been acceptable, or the processes have been found to be highly structure dependent.

The reactions discussed in this section employing titanium TADDOLates as chiral auxiliaries (reagents, mediators, substoichiometric additives, catalysts) are unquestionably of considerable synthetic value, applicable to such fundamental transformations as nucleophilic addition to carbonyl compounds and their analogues and to cycloadditions. High enantioselectivity can be anticipated, and the procedures can be optimized by simple adjustment of the structure of the TADDOL.

8.3. Use of Complexes of TADDOL Derivates with Other Metallic Centers for Enantioselective Transformations

Once TADDOLates had been successfully implemented as ligands for use with the strongly polar, oxophilic metal titanium, the question naturally arose whether derivatives might also be prepared with an affinity for the late transition metals. The simplest route would clearly be the coupling of PR₂ groups with the TADDOL oxygens to give cyclic (**A**, **B** in Figure 12) or diphosphorus esters (**C**). It is therefore not surprising that derivatives of these types appear most frequently in the literature, employed as ligands with the metals Rh, Pd, Ir, and Cu. Rhodium complexes have been utilized for hydrosilylation of ketones with enantioselectivities as high as 98%. Other illustrations of the principle include palladium complexes applied to allylation (up to 98% *es*), an iridium complex used for the enantioselective catalytic hydrogenation of styrenes (up to 95% *es*), and copper complexes of the phosphoramidites **Aa** and **Ab** that effect conjugate Et₂Zn additions to enones (Figure 12, bottom left) and the stereoselective ring opening of epoxides and aziridines by organometallic nucleophiles (Scheme 20, middle). With respect to the many TADDOL derivatives shown schematically in Scheme 5 in which one or both of the OH groups have been replaced by nitrogen, phosphorus, or sulfur substituents, few applications have so far been reported.

One would expect that the sulfur-containing compounds should be of interest, for example, with respect to nickel, silver, or copper. The monothiolato-Cu complexes **D** in fact do catalyze enantioselective 1,4-addition of Grignard reagents to enones (Figure 12). Molybdenum complexes **E** and **F** have been prepared from TADDOLs and a TADAMINE, where the former show outstanding characteristics as catalysts for ring-opening metathesis polymerization (ROMP), and the latter induces modest selectivity in reactions of benzaldehyde and styrene oxide with Me₃SiCN.

Higher valency, or more highly charged, metallic centers such as those of the lanthanides, when chelated with BINOLs, are extraordinarily successful at promoting enantioselective reactions,^[358–361] but they require ligand atoms that are more electronegative (“more strongly charged” and less vulnerable to water and protic solvents) than those available in TADDOL. It is thus not surprising that there have to date been far

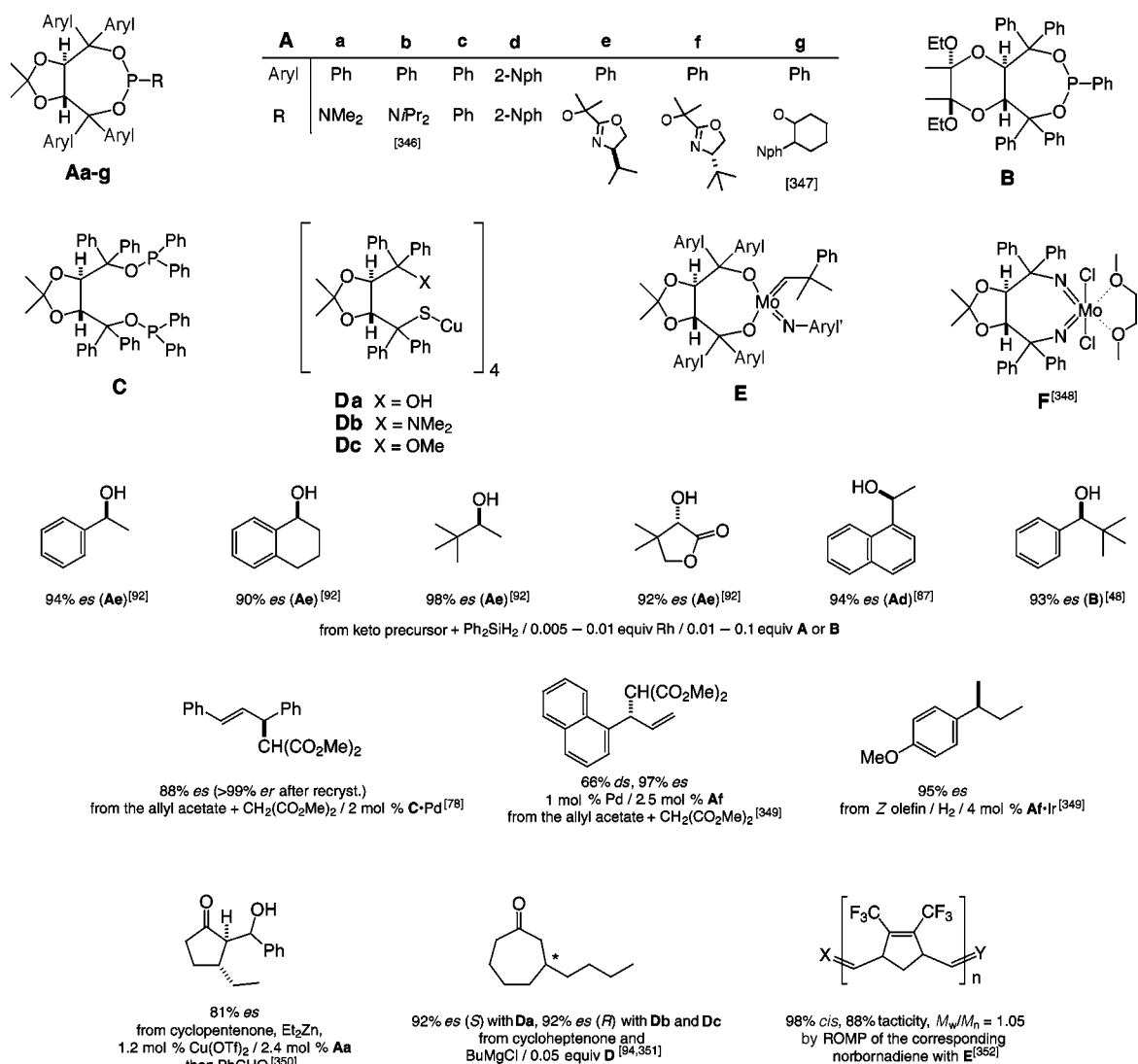


Figure 12. Phosphorus and sulfur derivatives of TADDOLs and a 1,4-dioxane analogue, copper and molybdenum complexes, as well as the products of addition reactions prepared stereoselectively with the aid of these auxiliaries. Using Cl₃P, Cl₂PR, or ClPR₂ and TADDOLs, what ultimately results is bicyclic or monocyclic phosphorus derivatives **A–C**, which may contain additional chelating units, such as oxazolinyl or 2-arylcyclohexanol groups (**Ae–Ag**). Copper complex **D** and molybdenum(vi) complexes **E** and **F** are derived from TADDOL. Rhodium, palladium, iridium, and copper complexes have been utilized for hydrosilylations, allylations, hydrogenations, Michael additions, and stereoregular polymerization (see the products in the lower part of the Figure). Enantioselectivities as high as 98% have been achieved with, in some cases, very small amounts of catalyst (as little as 0.005 of an equivalent of the metal and 0.05 of an equivalent of the chiral ligands). X-ray structures of ligands and complexes of the types shown here are illustrated in Figure 13. Two examples of copper-catalyzed nucleophilic substitution (S_N2 and S_N') conducted by employing TADDOL-phosphorus derivatives are shown in the middle of Scheme 20.

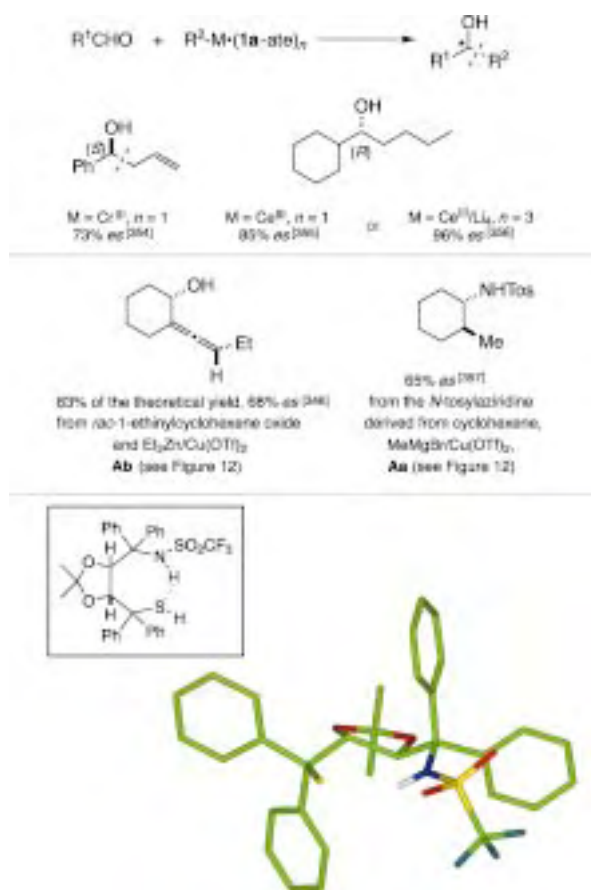
less applications of TADDOLs in this area, and the few observed have been only marginally successful (see the Cr^{III} and Ce^{III} reagents in Scheme 20, top). The large p*K*_a difference of roughly seven orders of magnitude between the phenolic BINOL and the alcoholic TADDOL sets limits we hope to overcome with compounds like the sulfanyltriflamide shown at the bottom of Scheme 20 (p*K*_a (AlkSH) approximately 10; p*K*_a (NHSO₂CF₃) approximately 6).

Numerous crystal structures have been determined for ligands derived from TADDOL and the corresponding metal complexes (Figure 5, right, and Figure 13). These will ultimately help to make the stereochemical outcomes of reactions catalyzed by such complexes more understandable (see also the mechanistic models for titanium TADDOLate mediated transformations in Section 10).

9. Macromolecular, Polymeric, and Silica Gel Bound TADDOLs

The facile separation of TADDOLs from reaction products has already been noted several times. Two particularly convenient workup procedures stem from the applications sketched in Scheme 21. Nevertheless, we thought it desirable to try to modify TADDOLs in such a way that products derived from their use could be isolated by a phase-separation protocol. In principle, four possibilities exist for modifying chiral ligands to this end, two of which permit the use of homogeneous reaction conditions whereas the other two entail heterogenic conditions.

a) The ligand can be incorporated into a macromolecule with a molecular mass high enough to permit membrane



Scheme 20. Nucleophilic additions (top) and substitutions (middle) by way of organometallic compounds of Ce^{III} , Ce^{III} , Zn^{II} , Cu^{II} , and Mg^{II} , which proceed enantioselectively in the presence of TADDOL derivatives. Below: An acidic TADDOL derivative in which the OH groups have been replaced by SH and $NHSO_2CF_3$, which should be suited to complexation with lanthanides.^[76] From the X-ray structure of the sulfonamide it is apparent that the more acidic NH group functions as a hydrogen-bond donor, with HS as acceptor. The structure of the triflamide is also present in the overlay of Figure 5 (left).

filtration, a method^[362] that has been shown to be particularly valuable in the case of enzymatic transformations.^[288] In order to ensure that the catalyst does not pass through pores in the membrane, the carrier should not be one based on a linear macromolecule or polymer, but should rather display a globular profile, rather like an enzyme. For this reason we prepared TADDOL derivatives^[63, 71] with the formulae shown in Figure 14, which, in a way, could be regarded as by-products of our work in the field of chiral dendrimers.^[363]

b) The ligand can be bonded to a polymer that is soluble under the reaction conditions but will precipitate with a change in solvent (polyethylene glycol^[364]). To our knowledge, this approach has not yet been attempted with TADDOLs.

c) An appropriate derivative of the ligand can be subjected to grafting by reaction with a suitable polymer. The desired covalent attachment is usually accomplished with an insoluble, cross-linked, chloromethylated polystyrene (Merrifield resin^[365]), one which is subject to swelling. TADDOL derivatives for this purpose are readily accessible synthetically (Scheme 22), for example bearing *para*-hydroxymethylphenyl groups at the 2-position of the dioxolane ring.^[71] Alternatively,

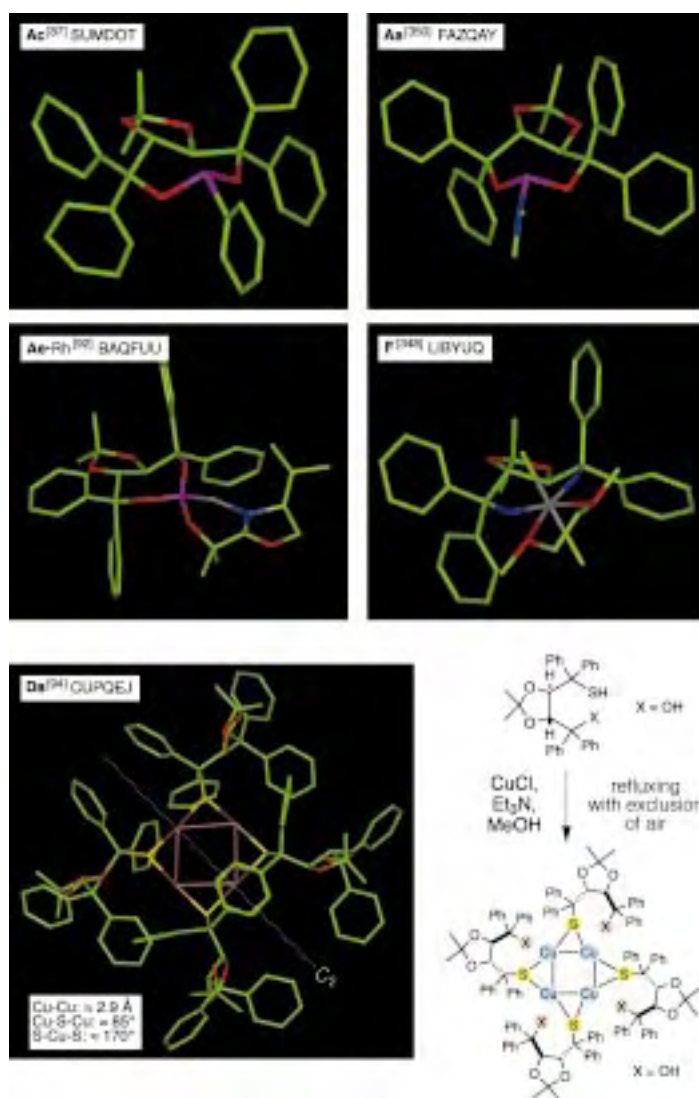
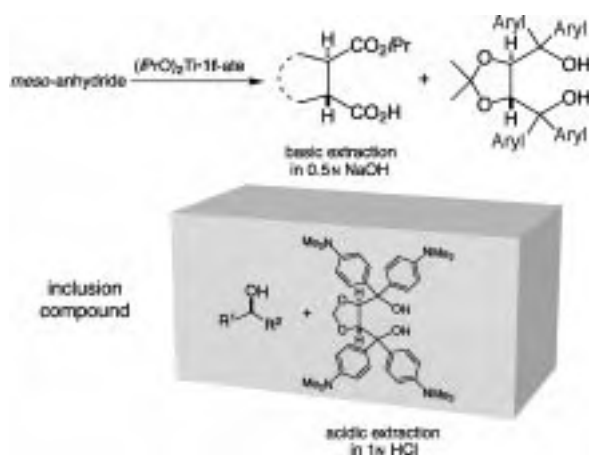


Figure 13. Crystal structures of two TADDOL-phosphorus derivatives and three metal complexes (Rh, Mo, Cu) with ligands derived from (*R,R*)-TADDOL. (For **A**, **F**, and **D**, see Figure 12). In addition to literature citations, Refcodes for the Cambridge Databank are also provided for these structures. In the case of the rhodium complex, the cod ligand has been omitted for the sake of clarity. The enclosed toluene molecule is not shown in this representation of the molybdenum complex. One sees in all cases the familiar geometrical arrangement of quasi-axial (upper right/lower left) and quasi-equatorial phenyl groups. The tetrameric copper complex with C_2 symmetry shown at the bottom is so stable that it persists even in solution and in the gaseous state (ESI-MS experiment). The sulfanylhydroxy derivative is bound in monodentate fashion. The complexes **D_b** ($X = NMe_2$) and **D_c** ($X = OMe$) with $Cu^{I[94]}$ and the corresponding **A_b** complexes are also shown in tetrameric form.^[76] The structures of **A_a** and **A_c** are included in the overlay of Figure 5 (center). The crystal structure of the $PdCl_2$ complex of the diphosphinite of TADDOL (formula **C** in Figure 12) is shown in the center of Figure 6. cod = cycloocta-1,5-diene.

TADDOL units can be synthesized directly on a polymer by first introducing aromatic aldehyde functions into phenyl groups of the resin, transforming these into acetals with tartrate esters, and subsequently treating with $ArylMgX$ ^[366–368] (see the general TADDOL synthesis shown in Scheme 2). In place of a chloromethylated polystyrene or a copolymer with polyethylene (SMOP),^[369] it is also possible to employ an inorganic carrier material for grafting purposes, the use of



Scheme 21. Two examples of especially facile separation and isolation of products from enantioselective reactions and TADDOL auxiliaries by aqueous alkaline or acidic extraction and phase separation.^[70, 102, 286] The formaldehyde acetal (no substituents in the 2-position of the dioxolane ring) was selected to assure maximum possible acid stability for the tetraamino-TADDOL. For examples of stereoselective ring openings in the case of five-membered ring anhydrides mediated by TADDOL-titanate, see Scheme 16.

which does not depend upon swelling capacity in specific solvents. To this end, porous silica-gel preparations (“controlled-pore glass”, CPG) with surface areas up to 350 m² g⁻¹ and pore diameters of 200 Å were first loaded with (CH₂)₃SH, onto which TADDOLs were then grafted.^[39, 370]

d) Finally, the ligand to be immobilized can be prepared in such a way that it contains one or more styryl substituents, permitting it to be subjected to cross-linking polymerization with styrene itself (to form a “homemade polymer”). This approach can also be exploited for the preparation of porous silica gel with ligands already built in, by way of the sol–gel process.^[373] At first glance, this procedure might appear to be the most risky, because the ligands in such a polymer could no longer be accessible for complexation, or to provide catalytic activity. On the other hand, it is known that polymers containing tailor-made cavities can be prepared in a similar fashion (“molecular imprinting”^[374]). For example, if one equips a carbohydrate unit with some polymerizable functionality by way of a labile bond, permits cross-linking polymerization to occur, and then removes the carbohydrate “template”, what results is a material with a specific affinity for the sugar derivative originally employed.

Three styryl-substituted TADDOLs we have prepared for polymerization purposes are shown in Scheme 22. The dendritic derivative with eight peripheral styryl groups is a novelty in two respects; quite apart from its TADDOL nucleus, it was the first dendritic cross-linking agent ever prepared for styrene, and this also represents the first occasion on which a chiral ligand—and thus an enantioselective catalytic agent (see below)—had been incorporated dendritically into a polymer.^[371, 376] The cross-linking suspension–copolymerization of styryl-TADDOLs with styrene under standard conditions^[375] resulted in nicely formed spheres that displayed good swelling capacity and a remarkable set of properties^[71, 371, 372] (Figure 15).

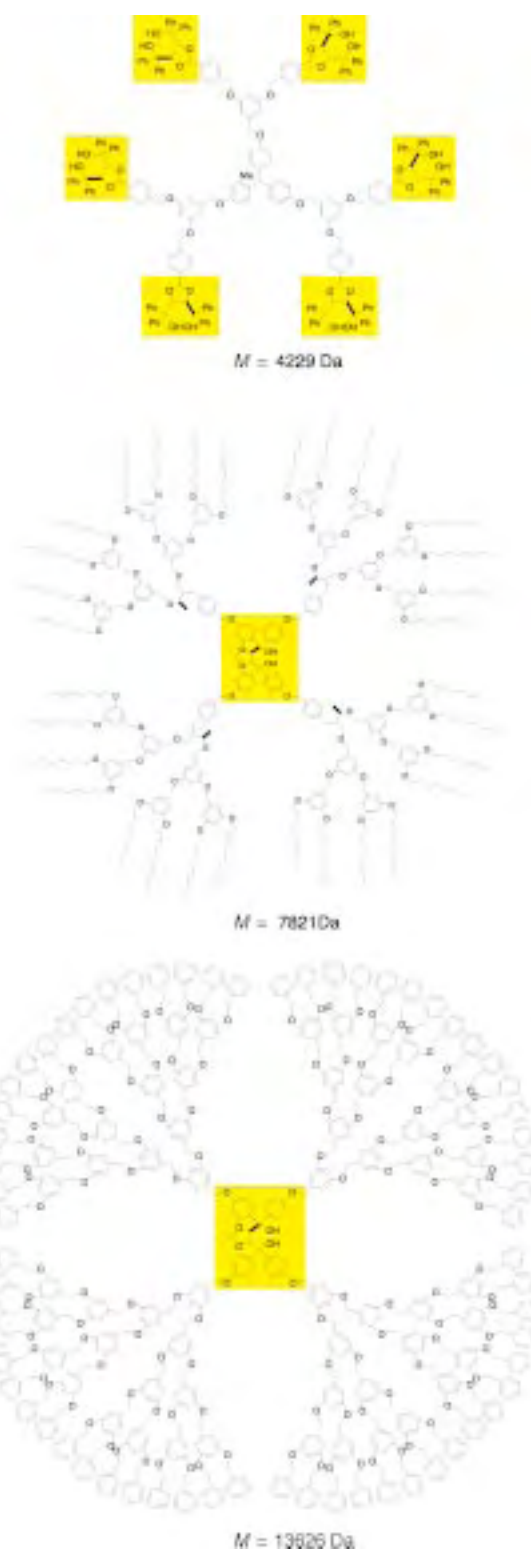
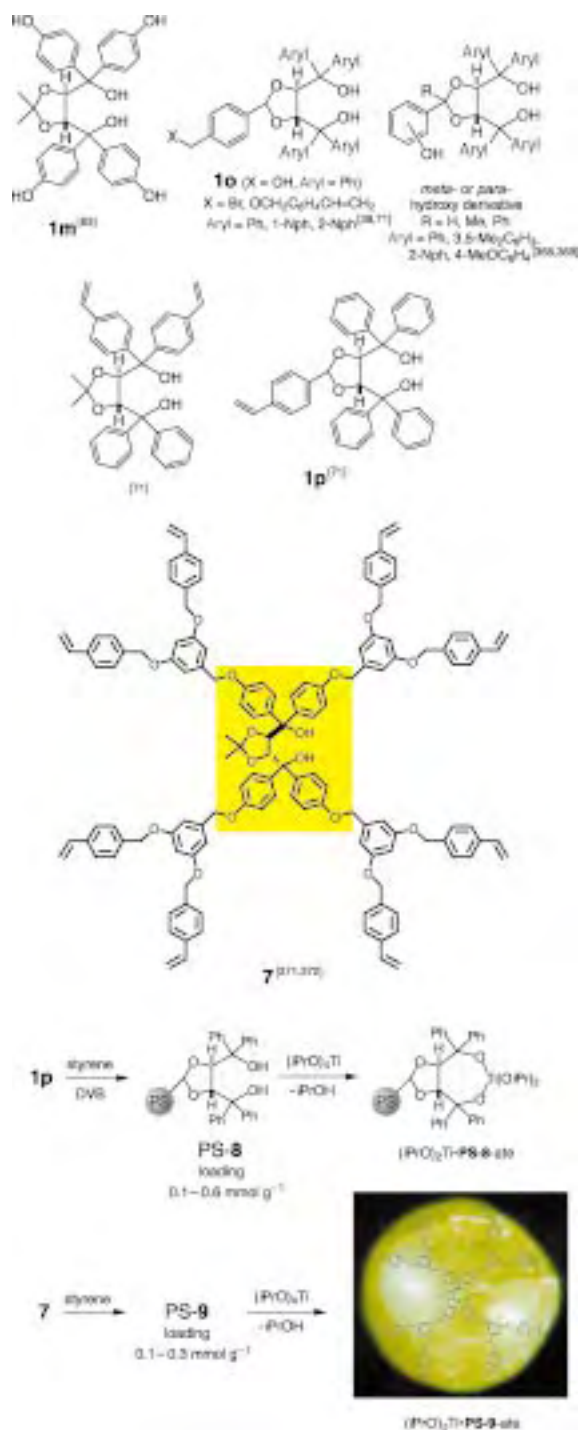


Figure 14. Three dendritic TADDOL derivatives with high molecular mass, prepared for use in the form of titanium complexes in membrane reactors.^[63, 71, 363]

Charging of the TADDOL-containing polymers with titanates was accomplished just as in the case of simple, soluble TADDOLs (see, for example, the information provided at the bottom of Scheme 22 for derivatives prepared by copolymerization). Based on elemental analysis, and espe-



Scheme 22. TADDOLs for the preparation of macromolecular titanates (see Figure 14) and polymer-bound titanates in polystyrene (PS). Top: The building blocks. Information regarding synthesis of the compounds can be obtained from the references cited. Hexol **1m** is prepared by the standard reaction (Scheme 2) with TBS protective groups; during transformation of **1m** into ethers with benzylic bromides (for example, to compound **7**), pentabenzylated products invariably form, which is an indication of the relatively high acidity of one OH group in the TADDOL nucleus.^[63] The benzylic bromides, alcohols (type **1o**), and phenols shown were used for grafting to Merrifield resins and suitably prepared SiO₂. Compound **1p** is undoubtedly the simplest derivative available for polymeric incorporation into PS. Poor results were obtained for the PS prepared from geminal distyryl substituted TADDOL.^[71] Bottom: Polymer-bound TADDOLs PS-**8** and PS-**9** obtained by suspension polymerization and subsequent charging with titanate to give the chiral Lewis acids (iPrO)₂Ti-PS-**8**-ate and (iPrO)₂Ti-PS-**9**-ate.

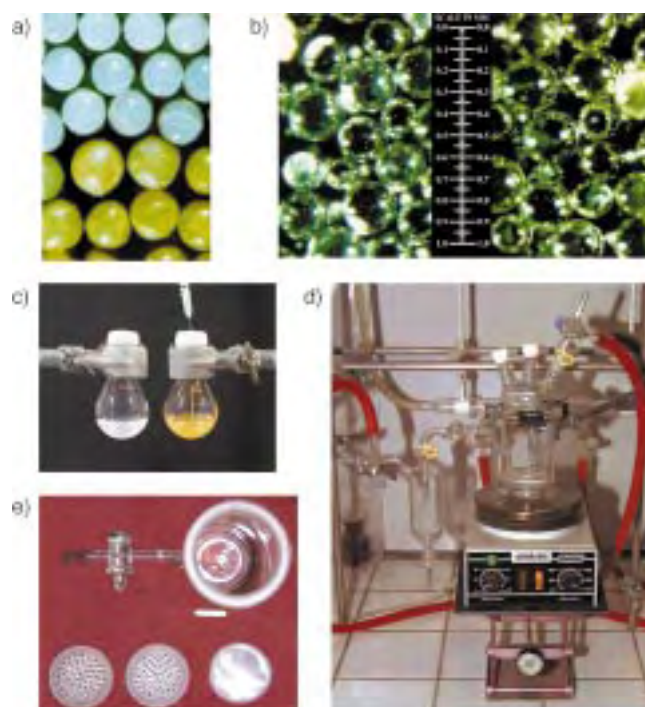


Figure 15. Polystyrene spheres (250–400 μm Ø) into which TADDOLs have been polymerized, and reaction vessels for multiple applications. a) Beads containing dendritic cross-coupled TADDOL (PS-9), which change from blue to yellow upon loading with titanate (interaction of the Lewis acid with phenol and resorcinol ether groups of the dendrimer branches?). b) Transparent beads of the monostyryl-TADDOL copolymer (iPrO)₂Ti-PS-**8**-ate before (left) and after (right) 20-fold utilization in the test reaction (Et₂Zn + PhCHO). c) As a result of high swelling capacity and low loading (0.1 mmol g⁻¹), the entire reaction volume is occupied by PS-9 spheres (before (left) and after (right) loading with titanate). Reactions with this polymer-bound catalyst are diffusion controlled; that is, they proceed equally rapidly with and without stirring. d), e) Reaction vessel (inner diameter 6.5 cm, volume approximately 250 mL) for multiple use in the addition of organometallic nucleophiles to aldehydes. The PS-**8** spheres (charge 0.6 mmol per gram of TADDOL) are sewn into a pad made of polypropylene and “immobilized” between two perforated glass plates so that they do not rub against each other during stirring (this avoids abrasion!). After loading with titanate, execution of a reaction, and syphoning off of both reaction and wash solutions, another batch can be subjected to the reaction (see Scheme 23).^[377]

cially as established by catalytic activity, 80–90% of the TADDOL units in the polymer were titanated, and the resulting Lewis acidic centers are clearly accessible to reactants.

Before discussing applications of the immobilized titanium TADDOLates, a few comments are in order regarding solid-phase synthesis, a process that has recently received increased attention due to the interest in combinatorial methodologies. Advantages provided by immobilized catalysts and reagents include not only the ease of separation from products already noted (which also applies to toxic components!) and spatial separation of reactive systems (the “wolf and lamb” principle of Patchornik^[378]), but also the applicability of large excesses of reagents and reaction partners, especially through the repeated use of catalysts or reagents. If, in order to avoid chromatographic separation of an auxiliary, the reagent or catalyst of interest needed to be modified prior to bonding to a solid phase, and if it were then to be discarded after a single

use, one might with justice inquire whether the required effort would really be worthwhile. Indeed, from this perspective many of the solid-phase bound reagents currently “marketed” could legitimately be castigated as “consumer frauds”. On the other hand, consider the case of an immobilized Lewis acid that, for chemical reasons, must necessarily be employed at the relatively high level of 5–20 mol %. A 20-fold reutilization would increase the “molar efficiency” factor to 0.25–1 %. It is for this reason that we have established as an important criterion for the utility of our immobilized TADDOL Lewis acids that they always be reusable or regenerable (that is, that they display durability). It is hardly necessary to add that the only applications worth considering are ones for which, in homogeneous solution, there are no nonlinear effects (NLE) attributable to the involvement of more than one catalyst molecule in the rate-determining step.^[379] This is a condition fulfilled by the titanium TADDOLate catalyzed addition of R_2Zn to aldehydes^[380] (Scheme 12) and the [3+2] cycloaddition of nitrones,^[71] but not by the Diels–Alder reaction of enoyloxazolidinones.^[71, 113, 381] Finally, ease of utilization requires that the particles of an immobilized catalyst not be too small, for which reason our conditions for suspension polymerization have been so adjusted that spheres with a diameter of approximately 400 μm are preferentially formed. These can easily be confined, but they are also readily removed from a reaction solution simply by filtering or decanting, or by removing the supernatant solution with fine needles (Figure 15).

As a test reaction we selected the addition of Et_2Zn to $PhCHO$ in toluene, catalyzed by $(iPrO)_2Ti$ -TADDOLate/ $(iPrO)_4Ti$. It was observed that TADDOLate incorporated into polystyrene in dendritic form possessed unique properties: at the low charge level of 0.1 $mmol\ g^{-1}$ it produced, within the limits of error, a constant enantioselectivity of 98 % under 20-fold reutilization. What prevented us from repeating the process even more times was not fatigue on the part of the catalyst, but rather fatigue displayed by the chemist (Figure 16a)! We also established that catalyst obtained from dendritically modified octasteryl-TADDOL shows, after being used 20 times, no decrease whatsoever in swelling capacity (Figure 16b/c). Finally, copolymers obtained from ordinary styryl-TADDOL **1p** led, as expected, to somewhat decreased reaction rates relative to the corresponding monomer TADDOL **7p** introduced in homogeneous solution (Figure 16b). However, we were astonished to discover that dendritic monomer **7** was associated with a lower reaction rate than the corresponding polymer (Figure 16c), although both dendritic derivatives produced slower reactions than nondendritic systems.

Using the reaction vessels illustrated in Figures 15d, e we conducted a total of 18 Et_2Zn additions to 5 different aldehydes, repeatedly employing the same packet filled with TADDOLate-charged (0.6 $mmol\ g^{-1}$) spheres. Enantioselectivities always exceeded 90 %, and we observed essentially no cross-contamination of the isolated alcohols provided the particles were thoroughly washed before each use with toluene containing $(iPrO)_4Ti$ (Scheme 23). The β -naphthyl analogue of $(iPrO)_2Ti \cdot PS-8$ -ate led to higher enantioselectivity, just as had been observed under homogeneous conditions.^[377]

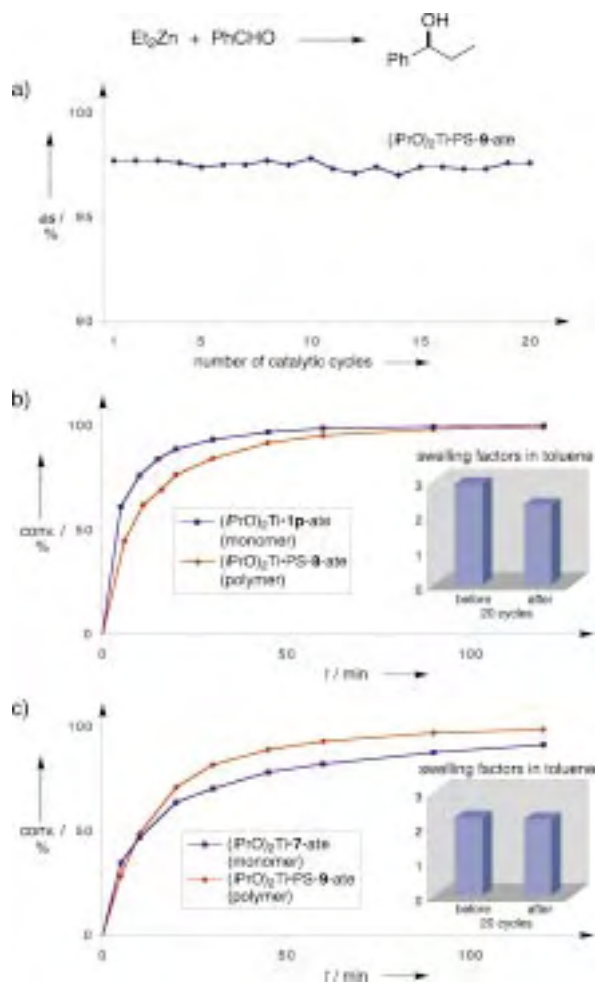
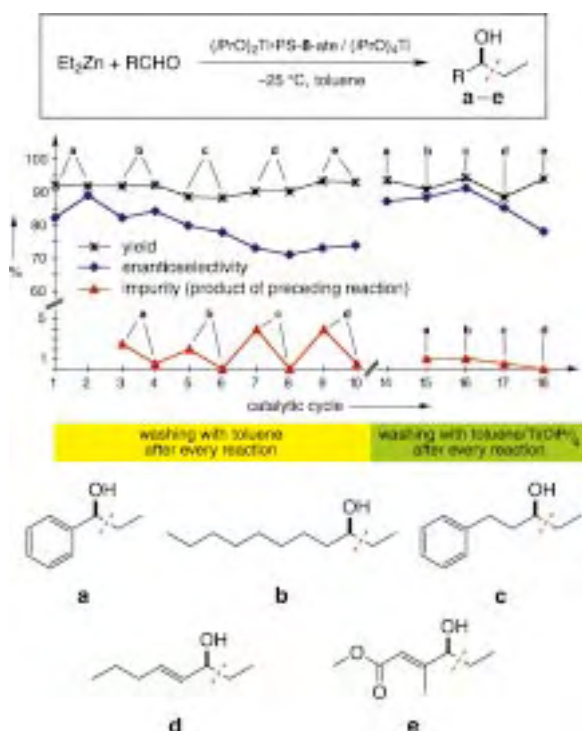


Figure 16. Reaction rates and enantioselectivities for Et_2Zn addition to benzaldehyde with the polymer-bound titanium TADDOLates $(iPrO)_2Ti \cdot PS-8$ -ate and $(iPrO)_2Ti \cdot PS-9$ -ate as well as $(iPrO)_4Ti$ in toluene at $-20^\circ C$.^[42, 372] a) Repeated utilization with essentially constant enantioselectivity of the titanium TADDOLate $(iPrO)_2Ti \cdot PS-9$ -ate (20 mol %) incorporated dendritically into polystyrene (0.1 $mmol\ g^{-1}$ loading). b) Comparison of rates of addition with monomeric $Ti-1p$ -ate and the corresponding polymer $(iPrO)_2Ti \cdot PS-8$ -ate (the monomer reaction is faster). c) Comparison of rates of addition with monomeric and polymeric dendritic titanium TADDOLate (the polymer reaction is faster!). The swelling capacity of the polymer containing “normal” titanium TADDOLate had decreased after 20 applications, but that containing dendritic TADDOLate had not.

Preliminary investigations with a TADDOL grafted onto silica gel (CPG) are equally promising. Enantioselectivities achieved in the test reaction ($Et_2Zn + PhCHO$) have been as high as 98 %, the observed loading of the CPG with TADDOL is high as well (0.3 $mmol\ g^{-1}$), the material can be washed with HCl—and thus reactivated—without loss of hydrophobicity, we have found no evidence of “fatigue” (in contrast to the simple polystyrene-bound TADDOLates where swelling capacity diminishes), and after 20-fold reuse the reaction rate appears to decline only by an insignificant extent (Scheme 24). The yields and selectivities under homogeneous reaction conditions for the addition of diphenylnitron to crotonoyloxazolidinone were, within the limits of error, also reproduced using ditosylatotitanium TADDOLate on CPG.^[370]

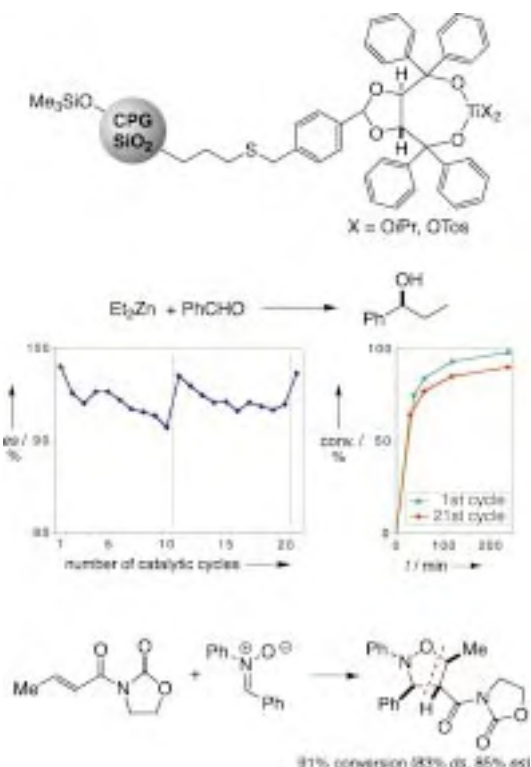


Scheme 23. Addition of Et_2Zn to various aldehydes, with formation of the alcohols **a–e** (11-mmol batches with the same pouch full of spheres at -25°C in toluene) in the presence of $(i\text{PrO})_2\text{Ti}$ -PS-**8**-ate, with the reaction vessel shown in Figure 15.^[377] Polymer loading: 0.6 mmol g^{-1} , 20 mol % titanate, and 120 mol % $(i\text{PrO})_4\text{Ti}$. If, in the case of successive reactions with different aldehydes, no cleansing measures are taken other than washing with toluene, the isolated alcohol always contains a few percent of the previously prepared alcohol; after washing with $(i\text{PrO})_4\text{Ti}$ prior to carrying out a subsequent reaction, contamination is reduced to less than 1%.

The immobilization of TADDOLs in and on polystyrene and porous silica gel increases, through repeated use, the efficiency with which titanium TADDOLates function as chiral Lewis acids. Moreover, our work in this area has brought to light an interesting “dendrimer effect” on the swelling capacity of polystyrene into which chiral ligands have been incorporated. Corresponding experiments with other popular complexing agents, such as BINOL and SALEN, have similarly led to solid-phase bound catalysts with outstanding characteristics.^[382–387]

10. Mechanistic Observations Concerning Enantioselective Lewis Acid Catalysis with Titanates

Mechanistic studies of reactions catalyzed by organometallic species are notoriously difficult to conduct because, in an extreme case, the true catalytic species may be present at such low concentration that it is virtually impossible by any available method to detect it in the presence of the chief components. A classic example of a successful mechanistic analysis is provided by Halpern's work^[388a] on the enantioselective hydrogenation of aminocinnamic acid derivatives catalyzed by rhodium diphosphine complexes. On the other



Scheme 24. Titanium TADDOLate immobilized on porous silica gel (CPG from the firm Grace), and two applications in catalysis.^[370] CPG has the advantage over PS that it is chemically inert, stable to both temperature and pressure, and not subject to swelling in applicable solvents. The particles employed have a diameter of 35–70 μm (charge: approximately 0.3 mmol g^{-1} , pore size: 200 Å, surface area: 280–350 $\text{m}^2 \text{g}^{-1}$), and OH groups not used in grafting are made hydrophobic by trimethylsilylation. Addition of Et_2Zn is carried out in the usual way with the $(i\text{PrO})_2$ derivative (20 mol % titanium TADDOLate, -20°C , toluene), and 1,3-dipolar cycloaddition is accomplished with the ditosylated derivative (50 mol % titanium TADDOLate, RT, toluene). After ten additions of $\text{Et}_2\text{Zn} + \text{PhCHO}$ (by which point the enantioselectivity has fallen from 98 % to 93 %), the material can be washed with aqueous HCl /acetone and then with H_2O /acetone, dried, and again titanated, a process that readily restores the initial enantioselectivity. In view of the observed *ee* values and reaction rates, there appears to be no basis for assuming that CPG-bound catalyst cannot be used for considerably more than 20 reactions.

hand, mechanisms for Sharpless epoxidation of allylic alcohols with *t*BuOOH in the presence of titanate and tartrate ester^[388b] or addition of Et₂Zn to aldehydes in the presence of chiral aminoalcohols^[242] still cannot be regarded as completely elucidated. The situation is no different in the present case of Lewis acid catalysis of nucleophilic additions and cycloadditions by chiral titanates. Particularly the first of these *requires* “dilution” with a large excess of achiral titanate (*i*PrO)₄Ti, even though the amount of chiral complex introduced is seldom less than 0.05 molar equivalents, and often stoichiometric quantities are added. In the case of alkylzinc addition to aldehydes, bimetallic mechanisms must be considered, and, as already noted, for cycloaddition to α,β -unsaturated carbonyl compounds a cocktail composed of a TADDOL, TiCl_{*n*}-(*Oi*Pr)_{4-*n*}, *i*PrOH, HCl, and molecular sieves is introduced as the catalyst. The Diels–Alder reaction is characterized by a nonlinear relationship between the enantiomer purity of the TADDOL and that of the product (for example, in the

reaction of enoyloxazolidinone with cyclopentadiene). Finally, the reaction site—the ligand sphere of titanium in the product-forming, enantioselective catalytic step—is far from well-defined, apart from the fact that a TADDOLate ligand must certainly be involved. The titanium might engage in trigonal, tetrahedral, trigonal-bipyramidal, or octahedral coordination, it could bear a positive or negative formal charge (in the form of an onium or ate complex), and the site might function in a bimetallic way, either with a second identical metal atom (Ti-X-Ti) or with some other metal (Ti-X-Zn). NMR spectroscopy has led to the identification of concrete titanium TADDOLate complexes present in solution, as demonstrated especially in the work of DiMare and Jørgensen, but the conclusions remain controversial,^[37, 44, 45, 69, 102, 310, 328, 389, 390] and this is not the place to delve into the matter in detail. Based on numerous X-ray structural analyses (Figures 4–6, 10, 13), one thing seems certain: TADDOL has a strong tendency to form chelates, and in every discussion it has been assumed to be present as a bidentate ligand. In the two sections that follow we wish to present a) possible reasons for ligand acceleration^[388b] of titanate catalysis through the agency of TADDOLates and other chiral complex-forming agents, and b) models and a rule describing the stereochemical course of reaction (where we deliberately avoid use of the word *mechanism*). In the process we hope to make a useful comparison of titanium TADDOLates with the titanium BINOLates and titanium CYDISates,^[386] which in general behave similarly^[391–395] (see also the structures in Figure 17).

As noted, nucleophilic additions to aldehydes—apart from allylations with CpTi-TADDOLate (Scheme 13)—proceed with maximum enantioselectivity only if excess $(i\text{PrO})_4\text{Ti}$ is added along with titanium TADDOLate^[380] (also true for use of BINOLate^[392, 393] and CYDISate;^[243, 245, 247] see the examples in Scheme 25). This means on one hand that the corresponding chiral titanates are much more active as catalysts than achiral titanate (factors of over 1000:1 have been estimated), but also that the chiral systems require the presence of the latter for optimum activity. Ligand acceleration^[388b] in the case of titanium TADDOLates has been interpreted as due to steric hindrance and therefore a rapid dynamic for the exchange of starting material/product ligands (a high “in/out” rate). “Steric pressure” from the four aryl groups leads to formation of coordinatively unsaturated or even charged species (Scheme 26a).^[44, 71, 102] When 1-naphthyl groups are present on the TADDOL, however, activity nearly disappears (too much hindrance), and the diol bearing methyl instead of aryl groups (and thus providing too little steric hindrance) gives product that is a racemic mixture (Scheme 26b). The function of excess $(i\text{PrO})_4\text{Ti}$ has been interpreted in two ways: removal of product alkoxide R^*O from the titanium TADDOLate (a sort of “clean-up effect”, Scheme 26c)^[102] and/or displacement of a charged ligand from the bulky, complexed, TADDOL-bearing titanium to the simple titanate, with formation of a chiral Lewis acid center that is cationic (Scheme 26a).^[71]

In the case of CYDISate it has also recently been shown^[387] that extremely bulky substituents ($\text{SO}_2\text{mesityl}$ instead of SO_2tolyl , SO_2alkyl , or SO_2CF_3 on the N atom) cause the

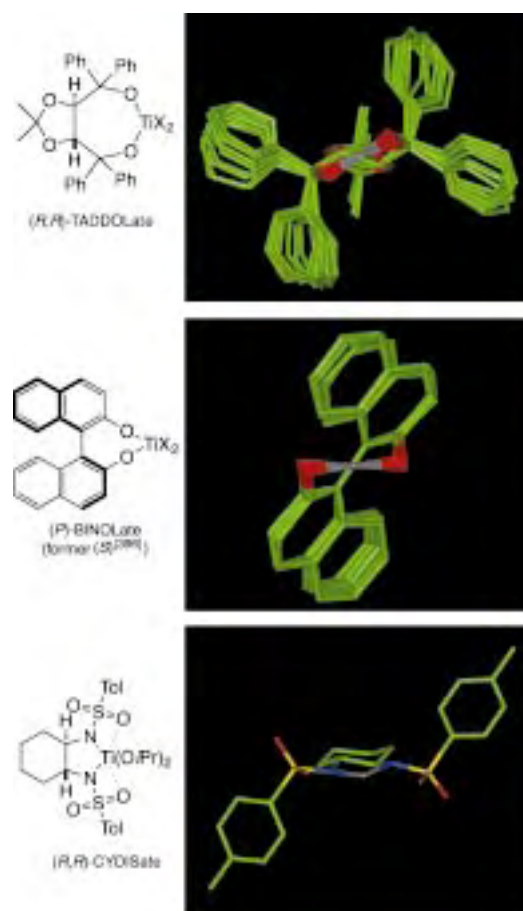
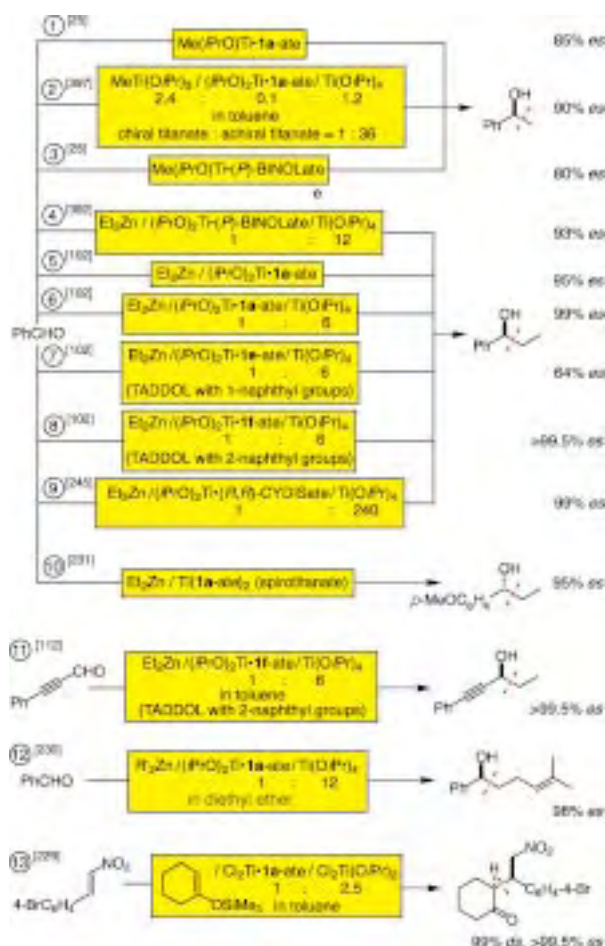


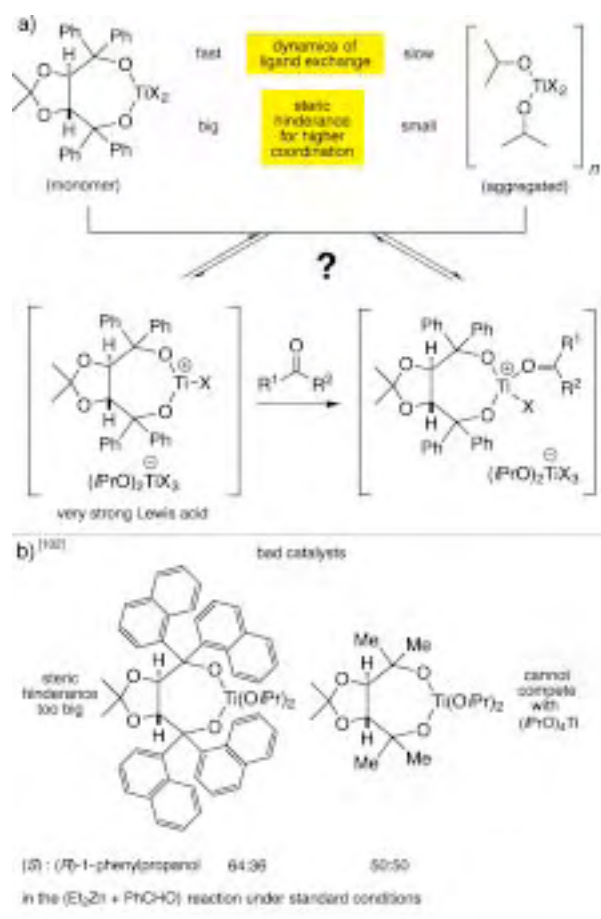
Figure 17. Formulae and crystal structures of (*R,R*)-titanium-TADDOLates, (*P*)-titanium-BINOLates, and a titanate with bis(tosylamidocyclohexane) ligands ((*R,R*)-cyclohexan-1,2-diaminedisulfonamide, CYDIS). The remaining ligands on the titanium have been omitted from the drawings. For another view of an overlay of the 11 titanium TADDOLate structures, see also Figure 5 (right). In contrast to the previous representation, C(4) and C(5) of the dioxolane ring and the titanium atom have been chosen as the fixed points in the overlay (see also Figure 4, bottom right). The eight overlaid titanium BINOLates (see ref. [37]) are registered in the Cambridge Databank under Refcodes BEYKUL, HELZIH, KOXGIN, KOXGOT, RIYDIM, VOZXAY, VOZXEN, and ZEHWOY. For purposes of clarity, substituents on the BINOL have again been omitted. When necessary, structures were recast in mirror-image form prior to overlaying. The bis(sulfonamido)diisopropyl titanate has been formulated with sixfold-coordinated titanium;^[387] for the crystal structure of a zinc CYDISate, see ref. [294]. Note the similarity of the nearly or precisely C_2 -symmetric structures (one is tempted to speak in terms of Lord Kelvin's definition^[10] of homochirality): In all three cases more steric hindrance is present “upper right and lower left” than “upper left and lower right”. During titanate-catalyzed nucleophilic addition to aldehydes, reaction with the three types of catalyst occurs from the *Si* face of the trigonal center. The relationship between the species extends considerably farther: Other reactions with (*R,R*)-TADDOL and (*P*)-BINOL derivatives also occur in the same stereochemical sense; even the HTP effect in liquid crystals (Section 5 and Figure 8) has the same sign with both (*R,R*)-TADDOL and (*P*)-BINOL!

complete collapse of enantioselective catalysis. However, the enormous ligand acceleration observed with titanium CYDISates is almost certainly not primarily a result of dynamic enhancement from steric hindrance at the titanium center, but rather of increased Lewis acidity resulting from the high electronegativity of the RSO_2N^- ligands ($\text{p}K_a$ of PhSO_2NH_2 is



Scheme 25. Enantioselective additions to aldehydes and a nitroolefin under the influence of a mixture of chiral and achiral titanates. In the absence of the achiral titanate (①, ③, ⑤) the enantioselectivity is lower than in the presence of as much as a 36-fold excess of achiral material (②, ④, ⑥–⑨, ⑪–⑬)! This applies not only to titanium TADDOLates with phenyl and 2-naphthyl groups, but also to titanium BINOLate (④) and the cyclohexandiamine derivative (CYDIS, see also Figure 17; ⑨). The reaction is slow with the TADDOLate bearing 1-naphthyl groups (just as it is with $(i\text{PrO})_2\text{Ti}$ alone!), and it is not selective (⑦), whereas the TADDOLate with 2-naphthyl groups generally gives the best *es* values (see Scheme 12). With spirotitanate $\text{Ti}(\mathbf{1a}\text{-ate})_2$ the product is the (*R*)-1-phenylpropanol, not the *S* compound (entry 10); high enantioselectivity is observed only when a 2:1 excess is employed (99% *es*). Also in the case of a [4+2] cycloaddition (formally a Michael addition after hydrolysis; see Schemes 10 and 18) of nitrostyrenes to silyl enol ethers the best enantioselectivities are achieved after “dilution” of the chiral Lewis acid with achiral material (⑬). Note that there is no need for zinc compounds to be present during the addition to aldehydes; see the pure RTiX_3 systems (①–③). The example of the titanium TADDOLate demonstrates that, under standard conditions (Et_2Zn , PhCHO , toluene, -25°C , 0.2 equiv $\text{Ti} \cdot \mathbf{1a}\text{-ate}$, 1.2 equiv $(i\text{PrO})_2\text{Ti}$), there is a linear correlation between the enantioselectivity of TADDOL and that of the product.^[71, 380]

approximately 10, that of $\text{CF}_3\text{SO}_2\text{NH}_2$ is approximately 6). With titanium BINOLate, which generally affords less selectivity in alkylzinc addition to aldehydes relative to CYDISate and TADDOLate (see also Scheme 1), the presence of excess $(i\text{PrO})_2\text{Ti}$ also leads to better results than those achieved in the absence of achiral Lewis acid.^[392–394] The ligand acceleration here may be due to the combination of a steric effect *and* the increased Lewis acidity ($\text{p}K_a$ of arylOH is approximately 10).



Scheme 26. Interpretation of ligand acceleration in titanium TADDOLates, and the role of excess $(i\text{PrO})_2\text{Ti}$ in the addition of organometallic compounds to aldehydes (see also Schemes 12, 25). a) The bulky TADDOLate ligand hinders increased coordination at titanium and leads to a high rate of exchange; for this reason, titanium TADDOLate is a much more active Lewis acid than the simple titanate. Perhaps the ligand-exchange process is even dissociative, whereby the achiral titanate could serve as a receptor for the cleaved ligand ($\text{X} = \text{OR}$ or halogen), although there is as yet no experimental evidence for the ion pair shown. If a second titanium TADDOLate functioned as an anion acceptor, nonlinear effects could result (as, for example, in the Diels–Alder addition of enoyloxazolidinones). b) Excessive steric hindrance with the 1-naphthyl derivative $(i\text{PrO})_2\text{Ti} \cdot \mathbf{1e}\text{-ate}$, on the other hand, reduces the catalytic activity in the dialkylzinc addition. The Me_4 analogue of TADDOL $\mathbf{1a}$ gives a miserable catalyst, producing racemic product; the titanium center is here much less sterically hindered. c) Excess $(i\text{PrO})_2\text{Ti}$ leads to regeneration of the “best” catalyst $(i\text{PrO})_2\text{Ti} \cdot \mathbf{1a}\text{-ate}$, whereby product alkoxide is trapped (the “purging effect”); it has been shown that the TADDOLate $(\text{RO})_2\text{Ti} \cdot \mathbf{1a}\text{-ate}$ with (*S*)-1-phenylpropoxy in place of *iPrO* groups leads to poorer enantioselectivity. With use of excess spirotitanate (see entry 10 in Scheme 25), which causes the stereochemical course of the reaction to reverse, it may be that the latter functions in the role of “purgative”.

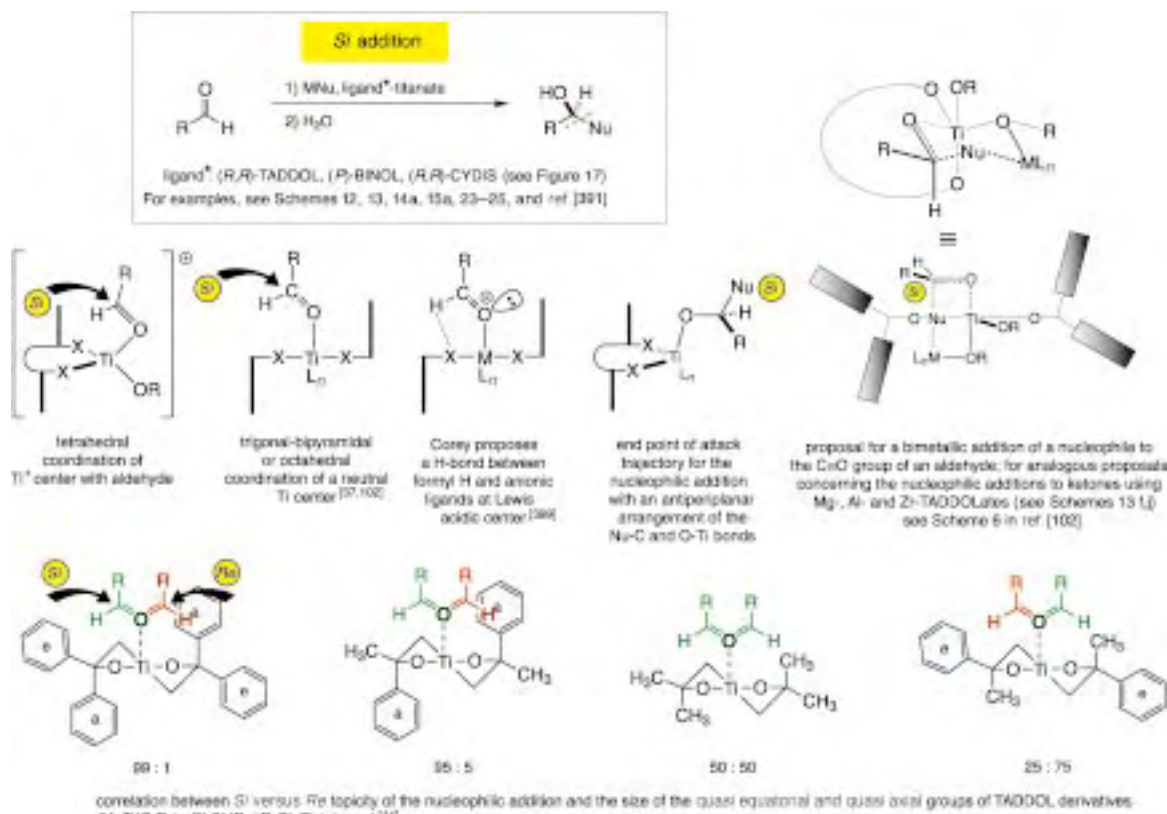
More difficult to interpret than ligand acceleration is the stereochemical course of reactions induced by the three similar chiral ligands (*P*)-BINOLate, (*R,R*)-TADDOLate, and (*R,R*)-CYDISate (Figure 17). Account must of course be taken of all the experimental data before any interpretation is

proposed, and the data in this case are very numerous—it is truly astonishing how the wildest mechanistic speculations are sometimes committed to paper on the basis of a single example!

The situation appears to be as follows for addition to “simple” carbonyl compounds RCHO (in the absence of chelating effects due to another heteroatom!): in the presence of titanates bearing one of these three ligands, a nucleophile adds consistently from the *Si*-face of the trigonal carbonyl center. If one assumes—as seems apparent from Figures 4–6, 10, 13, and 17—that “above” the TADDOLate chelate ring in these complexes there is more space to the left than to the right (for symmetry reasons, the opposite is true “below”),^[398] then an aldehyde in the *E* configuration (as illustrated in Scheme 27) could bind most readily to the Lewis acid center directed away from the quasi-axial group adjacent to the complexing heteroatom. If one further assumes that a nucleophile can approach only from the front and not from the rear (that is, from above the dioxolane ring in TADDOLates), then it is the *Si* face of the trigonal center that is open to nucleophilic attack. Whether this occurs in an intramolecular (“wandering” of an R^{Nu} group from titanium to the carbonyl

carbon atom) or an intermolecular way (via some bimetallic complex) is unknown. It is also not possible at this point to say how the titanium center is coordinated in the transition state for nucleophilic addition, or if in fact a cationic complex is present (see the contribution to the discussion in the upper part of Scheme 27). The mechanistic model shown, which is undoubtedly highly simplified, is consistent with numerous tests of the TADDOL system involving structural variations. Thus, both the stepwise substitution of phenyl groups by methyl groups in the equatorial and axial positions, and also the transition to the tetrabenzyl analogue, result in the expected loss of selectivity^[44] (Scheme 27, bottom). Simple model considerations also support the notion that coordination of an aldehyde with an *E* configuration—in the representation selected here—is most favorable to the left or outward relative to coordination to the right or inward.

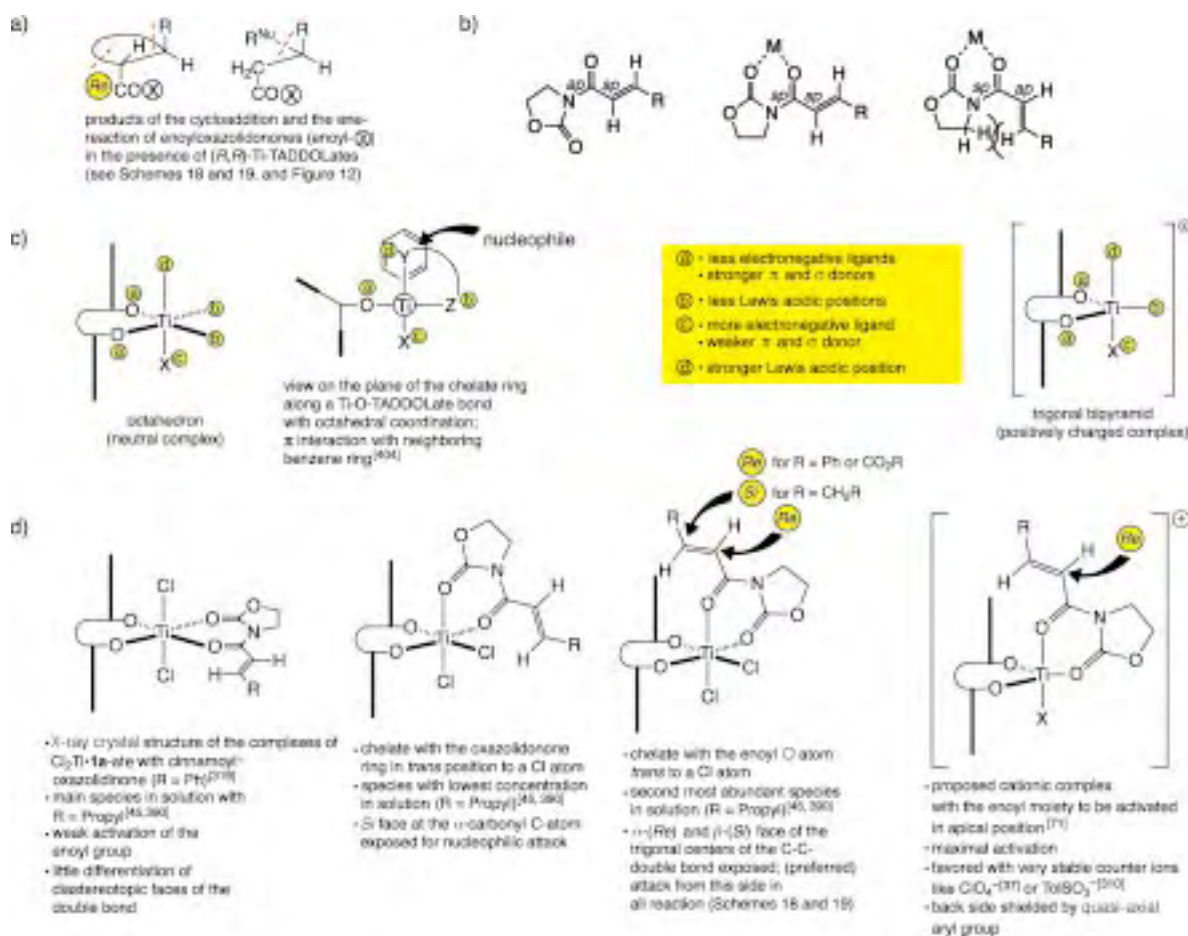
The titanium TADDOLate mediated transformations that have been investigated most thoroughly from a mechanistic standpoint (including molecular model calculations) are certainly the Diels–Alder reaction and the [3+2] cycloaddition of enoyloxazolidinones. The fact is that *all* nucleophilic additions—including the ene reaction—to the double



Scheme 27. Models for the stereochemical course of nucleophilic addition to aldehydes in the presence of titanium TADDOLates (or BINOLates or CYDISates). The two bold lines at the top represent the quasi axial phenyl groups of the TADDOL (or the benzene ring of the BINOL or SO_2R substituents on CYDIS). As the R –metal additions proceed with very high selectivity, irrespective of the nature of substituents on the formyl carbon atom (saturated, unsaturated, acetylenic, aromatic), even when we go to *p*-dimethylamino groups on the TADDOL, or when we compare between SO_2CF_3 and $\text{SO}_2\text{C}_6\text{H}_5$ on CYDIS, there is no basis for an assumption that π interactions might play an important role. In a bimetallic mechanism (for which there is neither supporting nor contradictory evidence), two identical (Ti) or two different (Ti/Zn) metallic centers might be involved. The tetrahedral complex shown, with positively charged Ti (see Scheme 26), represents a purely speculative contribution to the discussion of a pathway leading to the observed product, comparable to the suggestions made in Scheme 28 and Figure 18 for titanium TADDOLate/electrophile complexes. The Lewis acid/Lewis base complexes shown in the bottom row of formulae are intended to help rationalize the observed differences in selectivity of the various 2,2-dimethyldioxolanes with different groups on the exocyclic methanolate carbon atom (like the Me_4 analogue, the tetrabenzyl analogue of the TADDOL—a tetrakis-homoTADDOL!—is a miserable ligand, as shown by the $(\text{Et}_2\text{Zn} + \text{PhCHO})$ reaction: *Si/Re* = 54:46^[44]).

bond of these α,β -unsaturated carbonyl compounds (with retention of the *trans* configuration) mediated by (*R,R*)-titanium-TADDOLates occur from the *Re* face at the trigonal center adjacent to the carbonyl group! (In the cases investigated, this applies also to (*P*)-Ti-BINOLates.)^[399] Discussion regarding a stereochemical course for this reaction that leads to the observed result is summarized in Scheme 28. Despite the overwhelming number of known examples, no generally accepted common reaction mechanism has yet been elucidated. Certainly a decisive factor is product-forming complexation of the enoyloxazolidinone with a titanium TADDOLate (and it is to this that we limit the present discussion). Based on an X-ray structural analysis of the complex of $\text{Cl}_2\text{Ti} \cdot \mathbf{1a}$ -ate with cinnamoyloxazolidinone, an octahedron is present with *trans*-disposed chlorine atoms and a coplanar arrangement for the two TADDOLates and the two carbonyl oxygens.^[319]

NMR spectroscopy of solutions of corresponding complexes reveals in addition to this geometry another form with a carbonyl oxygen *trans* to Cl.^[45, 390] Moreover, there is evidence of π interaction between neighboring enoyl and aryl groups.^[45, 404] The sizes and polarities of polar groups (Cl, OSO_2Tol , ClO_4) on titanium can play a decisive role;^[37, 233] moving to a 1-naphthyl group on the TADDOLate can result in a reversal in the reaction's stereochemical course.^[37] Despite identical topicity in the addition, different titanium TADDOLate/enoyl complexes must be assumed to be the key to determining the nature of products from various types of reactions.^[405] Finally, it has been observed that one of the Diels–Alder additions (crotonyloxazolidinone+cyclopentadiene) shows a nonlinear effect,^[71] but a related [3+2] cycloaddition (crotonyloxazolidinone+diphenylnitrone) does not.^[71] In most cases such “details” (!) have not even been



Scheme 28. Models for the stereochemical course of cycloadditions and ene reactions of enoyloxazolidinones $\text{RCH}=\text{CH}-\text{CO} \otimes$. a) Configuration of the product formed with (*R,R*)-titanium-TADDOLate (see also (*P*)-titanium-BINOLate Lewis acids^[399]). b) Preferred conformation, as observed in numerous X-ray structures,^[400] for 3-acyloxazolidinones with synperiplanar (*sp*)/antiperiplanar (*ap*) conformations of CO–N and CO–CH bonds, respectively, as well as *sp/sp* arrangements in metal complexes^[401, 402] and destabilized *ap/sp* geometry due to 1,5-repulsion (Newman or A^{1,3} strain^[403]). c) Positions and Lewis acidities at octahedrally and trigonal-bipyramidally coordinated titanium TADDOLates; chelating complex formation with the O=C–C=C group Y (π stacking^[302, 404]) that is to be activated and the chelating ligand Z. d) Three different types of complexing for enoyloxazolidinones at $\text{Cl}_2\text{Ti} \cdot \mathbf{1a}$ -ate with an octahedral ligand sphere around Ti (theoretical TADDOLate angle O–Ti–O, ca. 90°) and a possible cationic complex (theoretical O–Ti–O angle, ca. 120°; see however the experimental values in the legend to Figure 5); for the—experimentally observed— α -(*Re*)/ β -(*Si*) approach of the nucleophilic partner, the complexes shown at the right appear probable. Corresponding structures have been demonstrated, modeled, or discussed as well for $\text{Cl}(\text{iPrO})\text{Ti}$ -TADDOLate/enoyloxazolidinone^[95] and /crotonylsuccinimide complexes.^[310] In studies that have unfortunately not yet been published,^[390] Sarko and DiMare demonstrated with low-temperature NMR spectroscopic studies, by trapping experiments with isobenzofuran, that the most stable complex (on the far left in (d), R = Bu) disappears more slowly than the isomeric complex present in smaller amount. It was pointed out in the legend to Scheme 26 that a cationic complex (with $\text{X}_2\text{Ti} \cdot \mathbf{1a}^-$ as counterion) could be responsible for nonlinear effects. For analogous complexes with other electrophiles, see also the arrangement illustrated in Figure 18.

investigated. We therefore propose a pragmatic, simple model, but one consistent with all the experimental results (Scheme 28): the electrophilic enoyl group that is to be activated sits in the reactive complex *trans* to the most polar ligand available on titanium (for example, chloride), and the chelating oxazolidinone carbonyl oxygen atom is *trans* to a TADDOLate oxide oxygen atom—so arranged that the nucleophile attacks from the side on which the TADDOLate bears an equatorial aryl group, which would be possible in either a neutral octahedral complex or in a trigonal-bipyramidal one bearing a positive charge.^[37, 71, 102] Figure 18 illustrates the arrangement based on this principle that

corresponds to the observed reaction of titanium TADDOLate and activated electrophile for a series of other transformations. Additional investigations, especially kinetic studies, will be required to confirm the overall applicability of our simple proposal.

11. Additional Diarylmethanols, and a Comparison with Other Chiral Auxiliary Systems

With additional diarylmethanols there is, to begin with, the “inverted” tetraphenylthreitol derivative in which hydroxy

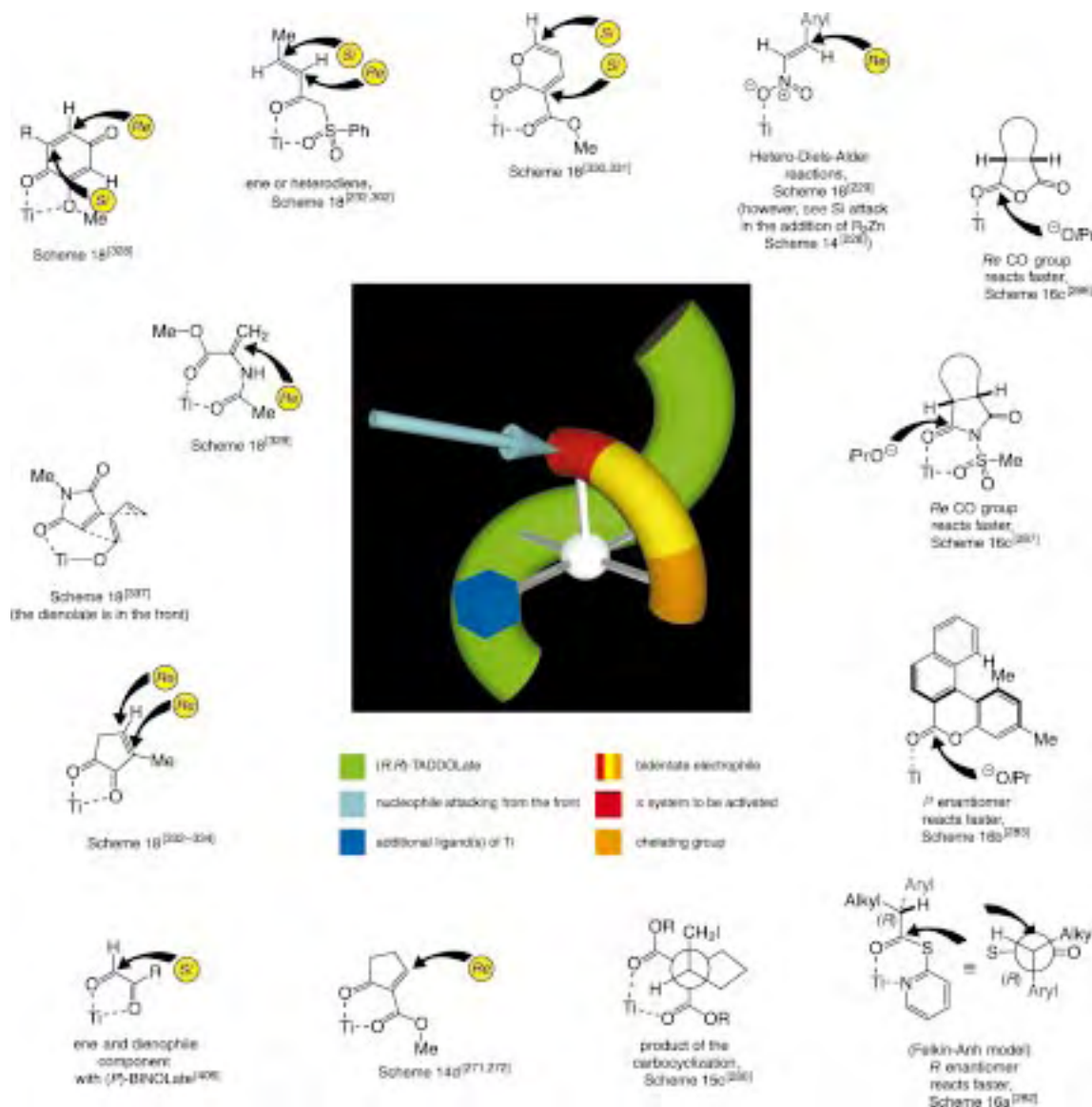
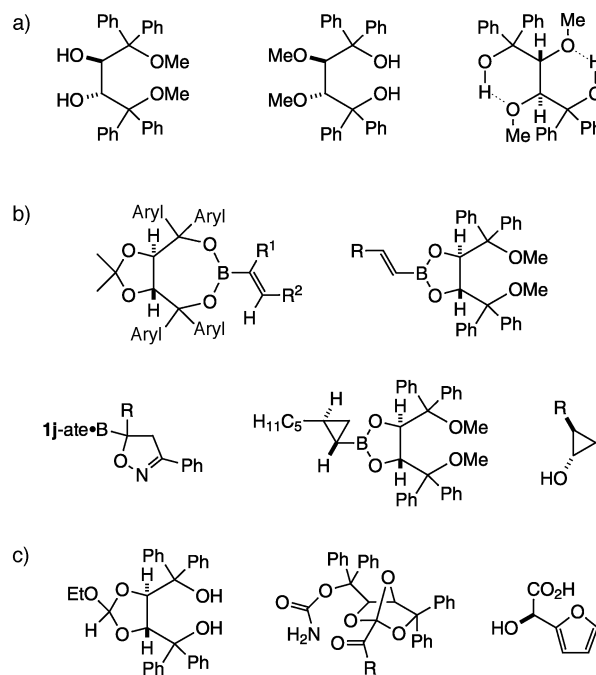


Figure 18. Schematic representation of the stereochemical course of (*R,R*)-titanium-TADDOLate mediated reactions with electrophiles other than enoyloxazolidinones (see Scheme 28). The electrophilic substrates have been so placed in the plane of the drawing that the nucleophile attacks from the side of the viewer (that is, from the front), an exception being the electrophilic attack during carbocyclization. Even in cases in which certain authors have complicated our task by putting labels like (+)-TADDOL under a structure for (–)-(*R,R*)-**1a**, we have here—to the best of our ability and conscience—summarized the reported stereochemical courses of Diels–Alder and hetero-Diels–Alder reactions, [2+2] cycloadditions, ene reactions (with (*P*)-BINOLate in place of (*R,R*)-TADDOLate), Michael additions, and enantioselective or enantiomer-differentiating *i*PrO transfers to activated carboxylic acid derivatives. In most cases the π system to be activated becomes directed “upward”, and the additional chelating group present extends to the “right” (no chelation with nitroolefins, anhydrides, and phenolic lactones?). There is thus a resemblance to the stereochemical course of the reactions of enoyloxazolidinones shown in Scheme 28, an observation (irrespective of mechanistic accuracy) that can be regarded as a rule (see the artistic rendering with octahedrally coordinated titanium in the center of the figure).

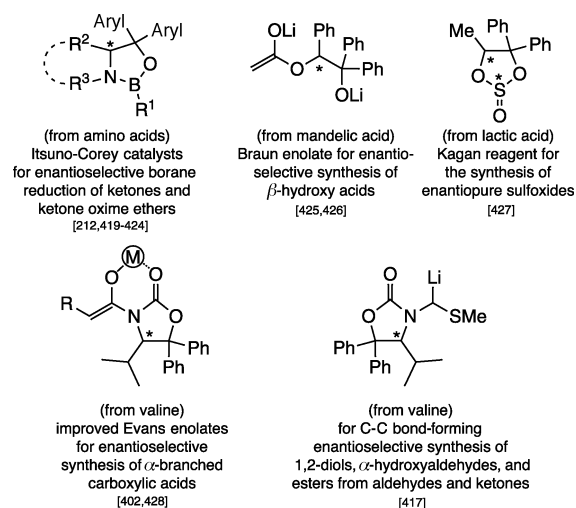
groups at the 1- and 4-positions are protected, while those in the 2- and 3-positions are not. Five-membered metallic alkoxides can form with vicinal diols of this type, as for example the alkenyl boronic acid esters shown in Scheme 29. These lead to cyclopropanols after reaction with diazomethane and subsequent oxidation. A threitol derivatized in the opposite way has also been synthesized, with free OH groups in the 1- and 4-positions, but this proved to be a poor host for inclusion compounds. Finally, there exist esters^[414] and orthoesters^[410, 415] derived from the completely unprotected tetraphenylthreitol, in which the tetrol can function as a covalently bound chiral auxiliary^[410] (see Scheme 29, bottom).



Scheme 29. Tetraphenylthreitol derivatives^[21] that have been “protected” at the OH groups in the 1- and 4-positions^[407] or the 2- and 3-positions^[408] by conversion into ethers (a), an application of the compounds (b), and of corresponding orthoester derivatives (c).^[409, 410] a) 2,3-Dimethoxy-1,4-diol is a poor host compound for the formation of inclusion compounds, probably because both OH groups are “saturated” by intramolecular hydrogen bonds, and thus not available for binding with guests.^[408] b) Cyclic alkenyl boronic acid esters,^[411–413] readily accessible through hydroboration of acetylenes, react with phenylnitrile oxides to give 1,3-dipolar cycloadducts (*dr* up to 8:1^[413]) and with diazomethane to give borylcyclopropanes (*dr* up to 13:1^[411, 412]). The latter can be used to prepare enantiomerically enriched cyclopropanols (with R = C₄H₉, *i*-C₄H₉, C₅H₁₁, and C₆H₅). Better results were achieved with the dimethoxy derivative than with the TADDOL ester! c) The orthoesters of 2-ketocarboxylic acids can be reduced with high diastereoselectivity to 2-hydroxycarboxylic acid derivatives using selectride (right).^[410]

As previously discussed (Sections 4 and 10), the introduction of two geminal diaryl groups on a C–C or C–X single bond (Aryl₂C–C, Aryl₂C–X, Aryl₂X–C) in some molecule leads mainly to the following consequences: a) the aryl groups produce a conformational fixation that formally facilitates cyclization and, on the other hand, hinders ring opening; b) two identical geminal aryl groups in a chiral molecule (quasi equatorial and quasi axial to the rings) are diastereotopic, and thus lead to more pronounced distinctions

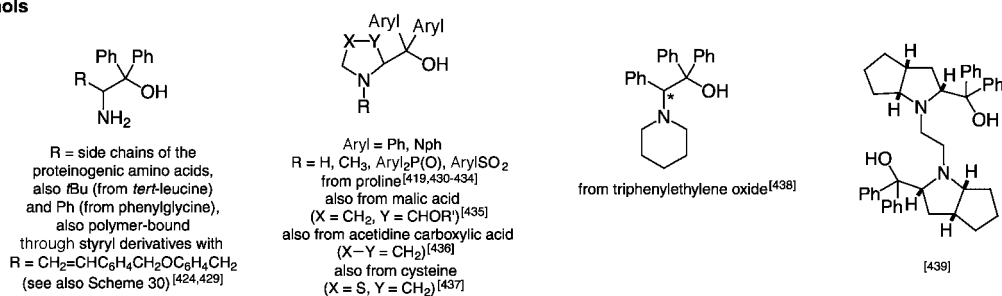
between diastereomeric transition states in comparing CH^{Re}H^{Si} with CMe^{Re}Me^{Si} and CAryl^{Re}Aryl^{Si}; c) Aryl₂C can function as a sterically effective protecting group for otherwise unprotected functionalities;^[416, 417] d) on the other hand, the presence of Aryl₂C or Aryl₂X units can sometimes cause neighboring metallic centers to dispense with a ligand (that is, become coordinatively unsaturated), thereby leading to increased rates of ligand exchange;^[418] alternatively, aggregate formation involving the participation of this metallic center may be suppressed; e) finally, experience has shown that geminal diaryl groups confer a greatly enhanced tendency toward crystallization, as well as increased melting points, relative to CH₂ and CMe₂ analogues (easier purification of intermediates and recovery of auxiliaries!).^[416] It is therefore no surprise that the use of diarylmethanol derivatives in (stereoselective) organic synthesis has proven valuable, as illustrated by the examples in Scheme 30 and Figure 19. Apart from TADDOL, the diarylmethanol derivative most frequently encountered is the aminoalcohol derived from proline and phenyl Grignard reagent (Itsuno–Corey catalyst^[451]).



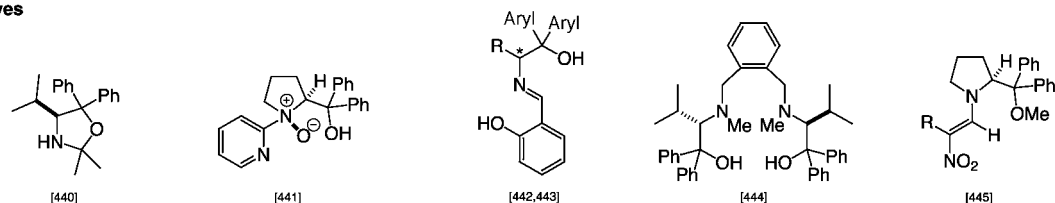
Scheme 30. A catalyst and four reagents derived from diarylmethanols for carrying out standard syntheses with enantioselectivity. For literature references and additional examples, see also Figure 19. In all cases, the two geminal aryl groups not only exert a steric effect on the course of the reaction; they also have a decisive effect in the formation and stabilization of cyclic reagents, intermediates, and complexes (see the discussion regarding the TADDOLs).

A question with wider ramifications than that directed simply toward alternative diarylmethanols is of course the search for other generally applicable auxiliary systems for the “introduction of chirality” (recall the definition specified in the Introduction). We hope we have succeeded here in showing TADDOL to be one such system, or at least that experience to date provides ample reason for dreaming that this might someday be the case. If we survey in a cursory way all the currently available—nonbiochemical—methods for EPC syntheses (Figure 20) and take note of which chiral scaffolds repeatedly turn up in reagent and ligand structures, we quickly discover that there are actually only very few indeed: vicinal aminoalcohols (from amino acids and cinchona alkaloids) and diols (primarily from tartaric acid), both

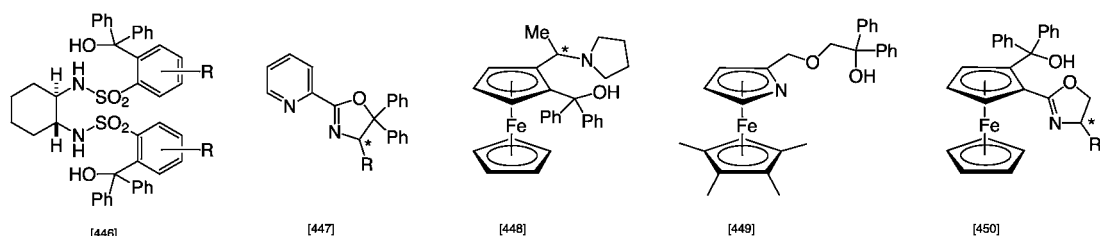
Amino Alcohols



Derivatives



"Combined" Ligands (see Figure 20)



Reactions That Can Be Made Enantioselective With These Ligands:

BH₃ reduction of ketones and oxime ethers [424,429–433,436,437,441]
R₂Zn addition to aldehydes (majority of examples) [435,439,440,446,448–450]
hydrosilylations [447]
substituting Michael additions to nitro olefins [445]
cyclopropanations [442,443]
Reformatsky reactions [434,444]

Figure 19. Chiral aminoalcohols and derivatives containing a diarylmethanol unit, together with types of standard reactions that can be carried out enantioselectively with these compounds (see also Scheme 30). It is worth noting that in the numerous applications reported so far for addition of Et₂Zn to aldehydes there is no case that offers broader applicability and generally higher enantioselectivity than has been demonstrated with titanium TADDOLates and titanium CYDISates!

derived ultimately from natural products, together with binaphthyls (occasionally biphenyls), vicinal diamines, and metallocenes, accessible by resolution of racemates or enantioselective synthesis. Much less frequently encountered—and then usually in special applications—are derivatives of terpenes or carbohydrates.

The path toward the goal^[11] of developing standard enantioselective approaches—or, even better, catalytic enantioselective approaches—to all types of chiral products from all types of achiral starting materials will undoubtedly follow an evolutionary course, and in the end only a very few “systems” will remain.^[467]

We wish to express our special gratitude to Dr. Engelbert Zass for the electronic literature search^[467a] that was of such great value to us in preparing this article, to Dr. Dietmar Plattner for his searches in the CSD database and assistance in the discussion of crystal structures, and to Silvia Sigrist for

invaluable help in preparing the manuscript. In addition, we wish to thank Felix Bangerter and Dr. Andreas Böhm for recording the NMR spectra shown in Scheme 5, Dr. Masao Aoki, Dr. Tobias Hintermann, Arkadius Pichota, Holger Sellner, and Daniel Weibel for their considerable assistance in proofreading, and all the many co-workers in the TADDOL project, and whose names appear in the various literature citations. Finally, we are appreciative of generous support from Novartis Pharma AG and the Swiss National Science Foundation (SNF).

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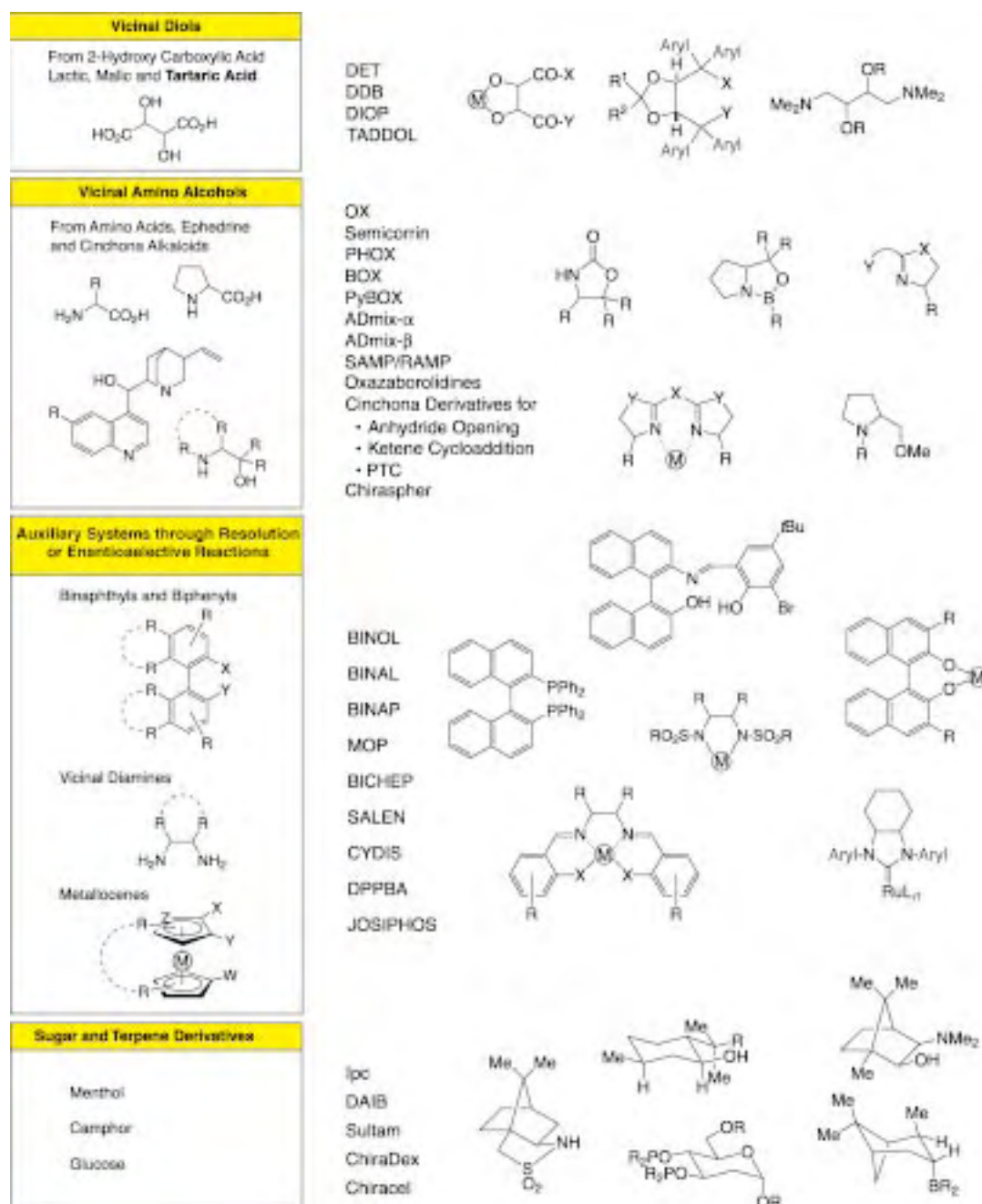


Figure 20. Leafing through reference works,^[452] books,^[453] and review articles^[454] on stereoselective syntheses, the preparation of enantiomerically pure compounds, and chiral catalysts, one repeatedly encounters the same chiral skeletons.^[452–465] Such skeletons find use not only in complexing agents for catalysts or catalyst precursors, but also as parts of reagents (including those bonded to a solid phase) introduced in stoichiometric quantities for resolution of racemates in chromatography, in analytical applications, and (as components) in materials. Were we to characterize such skeletons as “broadly applicable chiral auxiliaries”, then the category would be limited to three members: substances derived from tartaric acid (including the TADDOLs), compounds accessible through amino acids, and binaphthyl derivatives. Here we present stylized and concrete formulae and abbreviations for selected compounds that belong to these auxiliary systems. For details see the extensive secondary literature cited above. A price comparison is also of interest.^[466] It will be intriguing to see which systems prove to be most successful in the next few years, especially with respect to industrial applications.

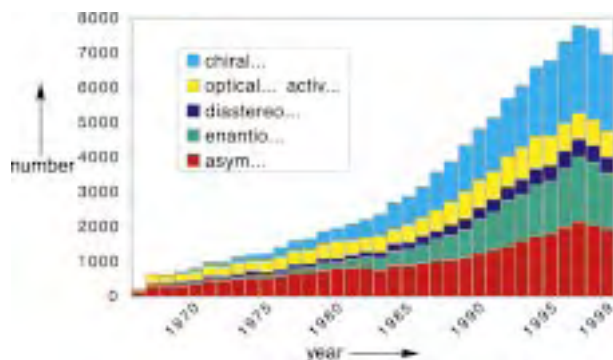
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detectability of the analytical method employed (GC, HPLC, NMR spectroscopy).

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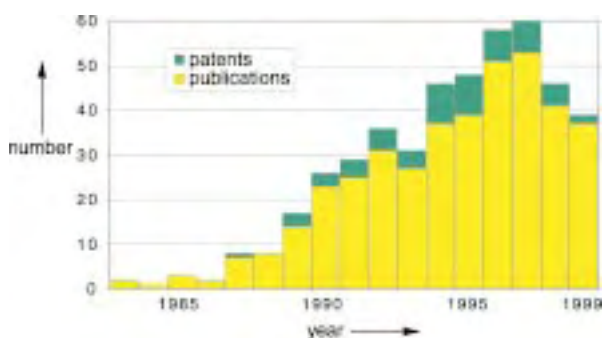


- [21] Abbreviation of the systematic name $\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol. These compounds are frequently described as acetals or ketals of 1,1,4,4-tetraaryltrithreitol, a type of

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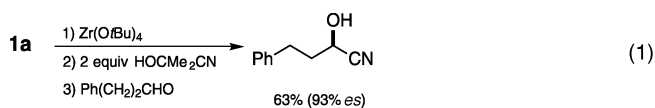
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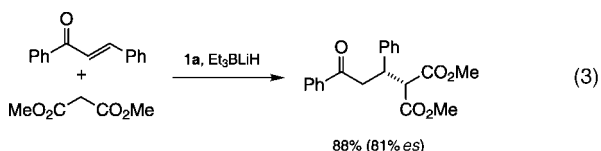
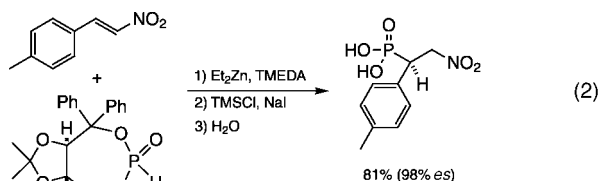
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Angewandte Chemie in Light of the Science Citation Index

Werner Marx*

Fundamental Remarks

The call for objective and understandable criteria for the evaluation of research has led to science being increasingly confronted with citation numbers for its publications taken from data in the Science Citation Index (SCI). The SCI, which is an information service comparable to the classic abstracting journals, today is mainly used as a database and has been published by the American Institute for Scientific Information (ISI) in Philadelphia since 1963. The SCI owes its exceptional position to its interdisciplinary coverage and provides access to reference data in addition to bibliographic information and author abstracts. At present the SCI covers about 5700 journals for the natural sciences including medicine. Although, this core set only comprises about 10 % of the scientific journals currently published periodically worldwide, it covers about 90 % of all publications and more than 95 % of all citations. Besides the Science Citation Index (SCI) there is the Social Sciences Citation Index (SSCI) as well as the Arts and Humanities Citation Index (A&HCI) which currently cover 3100 journals.^[1]

Metaphorically speaking the citation network is the glue that links publications containing related content. The number of citations is a direct measure for the (documented) resonance or the impact, which a publication has created among colleagues. Resonance or impact, however, cannot be equated directly with importance or quality. The latter two are mainly shaped through interest and value concepts and thus cannot be measured objectively and quantitatively. Furthermore, the citation of other publications is not exclusively determined by purely factual considerations. The question as to what extent citation numbers are suitable for the evaluation of the quality of research has been frequently debated and will therefore not be discussed any further here.^[2]

Evaluation of research through numbers of citations encompasses individual publications up to the complete sum of publications by one scientist, a research group, a research institute, or even a whole nation. Scientific journals too are

ranked according to the number of their citations in the form of the Journal Impact Factors (JIFs), which have been published yearly in the Journal Citation Reports (JCR) by ISI since 1975.^[3] *Angewandte Chemie* has been published since 1962 in the form of both a German and an International Edition, which has led to a number of problems with respect to citation analyses. Since *Angewandte Chemie* papers are contained in different volumes and appear on different page numbers in the two editions, these papers are compared and counted as if they were two completely different publications. Furthermore the way in which the two *Angewandte Chemie* editions are treated in the different literature databases is far from consistent.

One and the same publication may occur both as a citing and a cited publication in the SCI. Consequently, the name of a journal can occur saved in two different sections of the SCI: it can occur as part of the bibliographic information of the stored publications, comparable to other literature databases. Here only the selected core journals are covered, whose information has been standardized and in the case of *Angewandte Chemie* only the International Edition is considered. Furthermore, in the SCI, journal information forms part of references assigned to publications. These have been standardized with regard to authors and numerical information (publication year, volume and page numbers); however they contain the names of the journals in exactly the same form as they have been cited by the authors. References to papers in *Angewandte Chemie* relate to either one or the other edition or even both editions (double citations), as practiced, for example, for references in papers in *Angewandte Chemie* to other *Angewandte Chemie* papers.

Citations of Individual Publications

The search options available through STN International (see Fachinformationszentrum Karlsruhe), in particular the introduction of functions for carrying out statistical investigations, have made it possible to perform extensive citation analyses directly online. Such investigations were hitherto only reserved for the SCI producer and for a few research institutions specializing in this area. The findings presented herein result from using the database SCISEARCH (SCI under STN International).^[4]

Investigations in which the publications under evaluation are exclusively recorded in the SCI (standard procedure),

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

only consider the International Edition of *Angewandte Chemie* and consequently only count the citations that have been made in the form of this edition. The citations of the German Edition are only considered when they are made in addition to the citations of the International Edition as done by some authors. As an example the citations of a paper by Martin Jansen were investigated. (*Angew. Chem.* **1987**, 99, 1136–1149; *Angew. Chem. Int. Ed. Engl.* **1987**, 26, 1098–1110). The total number of citations as well as the share of those for the German and for the International Edition can be taken from the alphabetical list of all the references saved in the SCI of all the stored publications (STN EXPAND list). However, this list, which can be retrieved in the form of extracts, is only of use for investigating individual publications (with known first author), and for practical reasons is not used, for example, in the investigation of the citations of all publications of a scientist.

Accordingly, the paper by Jansen was (up to May 12, 2000) (correctly) cited 123 times in the form of the International Edition and 68 times in the form of the German Edition. The sum of 191 citations is, however, by no means the final result. Some authors cite both editions, which in this case occurred 37 times; thus, in about 20% of all citations. Consequently, 154 citations are counted in the final analysis. In an evaluation of all publications by Jansen by the standard method, this paper would be listed with 123 citations; thus lacking the number of citations exclusively in the German Edition and therefore more than 20% too low. Also a search in the Web of Science (WoS), the search platform provided by the producer of the SCI directly (i. e. not from one of the other database providers such as STN) and currently very widespread, revealed that the SCI listed 123 citations for the same paper by Jansen.

The underestimation of papers in *Angewandte Chemie* varies individually and depends generally on the timeframes of their citations. Underestimation results in a significant loss of information, since the SCI is mainly used to access contents and to investigate factual details by way of the citations. Eugene Garfield, the founder of SCI, did not so much have the evaluation of research in mind but rather the search of literature through citations rather than through the often problematic keywords.

STN International offers its customers the possibility to convert the bibliographic data of the stored publications not only of SCI, but also of most of the available literature databases in such a way that subsequently they can be searched for in the form of references in the SCI. In this way it is possible to determine the citations of all the publications of a certain author regardless of the position of his name in the authors' field. Literature entries under STN International can thus, for example, occur with inclusion of Chemical Abstracts (database clusters: CA or CAPLUS+SCISEARCH), in which at least up until 1994 (inclusive) both editions are compared (since 1995 Chemical Abstracts like the SCI has only considered the International Edition). However, in the case of a ranking the citation numbers are listed individually for each edition which results in a lower ranking. A correct summary of the citation numbers of the corresponding issues of the two editions would only be possible through a concordance list.

The Journal Impact Factor (JIF)

Without doubt *Angewandte Chemie* belongs worldwide to the top group of chemical journals, which is also demonstrated by an unusually high Journal Impact Factor (JIF). In the past the question was repeatedly asked whether the high JIF of *Angewandte Chemie* truly reflects the real impact of the journal, or as a result of double citations of both editions contains an overestimation.^[5] To establish the JIFs the publications of a journal are taken into consideration over a period of two years and their citations are then determined over the following year. The number of citations is then divided by the number of citable publications (i. e. Communications, Highlights, and Reviews) in the two preceeding years. The JIF98, for example, considers the publications from the years 1996 and 1997 and their citations in the year 1998.^[3]

The annually published JIFs in the Journal Citation Reports (JCR) from ISI are determined by "Journal Title Matching". For the determination, for example, of the JIF98 the number of citable publications in the years 1996 and 1997 was initially established. It is then investigated how often the journal name (in all the different variations in which it appears) occurs in combination with the publication years 1996 and 1997 in the reference sections of the publications of the year 1998. Finally, the quotient is derived from the counted publications and their citations. This process has the advantage that the incorrect citations are also considered since the name of the first author and the numerical data of the references are not taken into consideration.

Alternatively, the references of all stored publications can be searched to find out whether and how often each individual (previously fully recorded and not only counted) *Angewandte Chemie* paper from a two-year time interval was cited in the following year. This search is generally always carried out through only the name of the first author, the publication year, the volume number, and the first page. The journal name is not taken into account here due to a lack of standardization. This "Citation Matching" works significantly more selectively and provides distinctly lower citation numbers: only the citations of the International Edition are counted, (correctly) no multiple counting through double citations occurs, and the incorrect references are not part of the total sum. Based on the citation variants of frequently cited papers it can be shown easily that on average about 5% of all references stored in the SCI are incorrect with regard to the numerical data they contain. In the case of *Angewandte Chemie* citations an added factor is that some of the citing authors mix up the editions and attribute the numerical data (here volume number and first page) to the wrong edition. Sometimes volume numbers or page numbers of the two editions are also mixed up.

Both procedures for determining the JIF are generally also available for the investigation in the online database of the SCI available through STN International. Table 1 summarizes the data from the Journal Citation Reports (JCR) 1998 (the most recent JIFs of ISI in May 2000) and the results of the online investigation in connection with the determination of the JIF98 of *Angewandte Chemie*. The numbers in the second and fourth column have been determined through "Journal Title Matching", that is by means of the same process and can

Table 1. A comparison of the number of publications, citations, and the value of JIF98 for *Angewandte Chemie*, determined from ISI (Journal Citation Reports (JCR) 1998) and from the online database of the SCI available through STN International.^[a]

	JCR (1998) Journal Title Matching	Online (STN) Citation Matching	Online (STN) Journal Title Matching
publications (1996+1997)	1296	1299	1299
citations (1998) German Edition	–	[b]	2355
citations (1998) International Edition	–	6102	8089
citations (1998) both editions	10405	[b]	10444
JIF98 International Edition	8.03	4.70	6.23
JIF98 both editions	–	[b]	8.04

[a] The somewhat different numbers for publications and citations, respectively, in columns 2 and 4 are caused by nonidentical timeframes. [b] Not possible since the German Edition is not considered in the bibliographic section of the SCI.

thus be directly compared with each other. It is shown that the JIF98 of 8.03 determined by ISI is obviously valid for both *Angewandte Chemie* editions together and not only for the International Edition. This also largely explains the differences found by various authors when they compare the ISI data with their own results (on the basis of “Citation Matching”).^[5] They simply compare the JIFs supposedly determined by ISI for the International Edition with their own JIFs, which indeed only refer to this edition. The former are overestimated because of double citations, however, this only partly explains the differences.

For the “Citation Matching” (third column), double citations are avoided, however, at the same time the citations of only the German Edition as well as the incorrect citations (whose percentage is particularly large due to the two editions) are excluded. Accordingly, the difference between the JIFs for the International Edition (4.70 and 6.23) is caused by the consideration of inconsistencies in the “Journal Title Matching”. The difference of the JIFs of the International Edition in relation to both editions together (6.23 and 8.04) results from both (incorrect) inclusion of double citations and the additional consideration of the citations of only the German Edition in the “Journal Title Matching” for both editions.

The consequences of citation errors become evident on comparing the tables of the citations of individual papers on the basis of the two counting procedures: on the basis of “Citation Matching” the head of the table lacks in addition to other papers the two most frequently cited reviews because their first page has been saved one unit too high in the bibliographical section of the SCI. As a result the percentage of citations with the correct first page (here 140 of 163, and 108 of 135 citations, respectively, corresponding to 80 and 85%, respectively) is not included in the calculation, but merely the smaller percentage of the incorrect citations since even some citing authors cite the first page one unit too high.^[*] It remains to be investigated to what extent such errors occur for reviews in *Angewandte Chemie*. They do not influence the JIF, however for the evaluation of reviews in *Angewandte Chemie* according to the standard process they lead to an additional, this time even larger underestimation.

[*] Editorial note: Since 1996 reviews in *Angewandte Chemie* have begun with a full page picture (frontispiece). This page is always the first page of the review.

Citations of the German and International Edition

The time-dependent proportion of the publications citing the individual issues has been determined through “Journal Title Matching”. Figure 1 shows the citing publications since 1974 (first year of the database), which have at least made one citation of the German or the International Edition, respectively. A citing publication can contain several *Angewandte Chemie* references as citations (on average 1.65 *Angewandte Chemie* citations per citing publication). The numbers contain the *Angewandte Chemie* citations of papers of any given

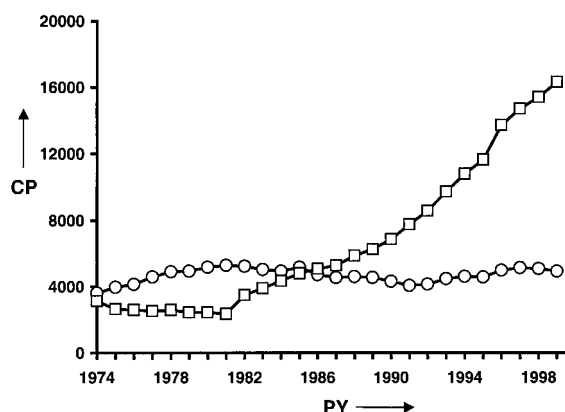


Figure 1. Number of publications (CP) that cite *Angewandte Chemie* papers as a function of the year of publication (PY) of the citing publications, separated according to citations for the German Edition (circles) and for the International Edition (squares) and determined through “Journal Title Matching” (including double citations, incorrect citations, and journal self-citations).

Angewandte Chemie volume, instead of only those of two *Angewandte Chemie* volumes as in the case of the JIF formula. Accordingly, the citations of the International Edition have increased steadily since 1981, whereas those of the German Edition have remained relatively constant. At present the International Edition contributes about 70% and the German Edition provides only 30% to the total number of citations.

Figure 2 shows how the percentage of publications that exclusively cite the German Edition (also determined through “Journal Title Matching”) has changed over time. In 1998 this percentage was only about 10% (based on *Angewandte Chemie* papers from 1996 and 1997 even as low as 5%); however, over the complete period from 1974 up to the present it averaged almost 30%. Older publications on average are underestimated by this percentage (see above). In this context it has to be taken into consideration that in addition to the impact which is documented in the form of citations there exists an impact which cannot be measured. The impact of the German Edition on numerous industrial chemists and students among the readership, for example, is hardly documented in the form of citations, however, it undoubtedly exists.

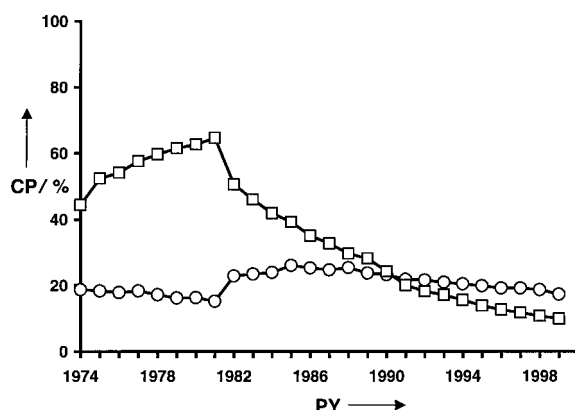


Figure 2. Percentage of the double citations (circles) among the citing publications (CP) as well as the publications exclusively citing the German Edition of *Angewandte Chemie* papers (squares) as a function of the years of publication (PY) of the citing publications, determined through "Journal Title Matching" (including incorrect citations and journal self-citations).

The Extent of Double Citations

In the determination of the JIF98 it was established that of the 5295 publications citing *Angewandte Chemie* papers 1124 (21 %) simultaneously contained at least one *Angewandte Chemie* paper in the period 1996–1997 as a citation of the German as well as one of the International Edition. However, this number also includes those publications which cite a paper in the German Edition and a totally different paper from the same period as the International Edition. The value of about 20% for double citations thus is an upper limit. Owing to the lack of a concordance list the corresponding publications of the two editions could not be exactly identified. The manual comparison of 100 of the 1124 papers with regard to real double citations (same first author, volume difference = 73, similar first page) showed a value of about 80%; that is 16 instead of 20 % double citations related to all citing publications.

Accordingly, the JIF98 of about 8.0 for both editions of *Angewandte Chemie* given by ISI (for the International Edition) and verified by an online search is about 15% too high. However, even the corrected JIF98 is still very high at a value of about 6.8 and thus changes very little regarding the positioning of the journal. This value is, for example, still higher than that of the *Journal of the American Chemical Society* (*J. Am. Chem. Soc.*) of 5.73 (JIF98). However, the two journals can hardly be compared directly with each other owing to their different composition with regard to manuscript types (percentage of Communications). Figure 2 shows how the percentage of double citations has changed over time, like in Figure 1 related to the total number of all *Angewandte Chemie* citations. For 1998 the upper limit lies again at 20%. Of the 1124 papers citing both editions 336 (30 %) were published in *Angewandte Chemie* papers (journal self-citations); however, over the whole period from 1974 up to the present the mean value is only 15 %.

To summarize: The exclusive consideration of the International Edition in the bibliographic section of the SCI in the case of an evaluation through standard processes results in an

underestimation of *Angewandte Chemie* papers by the percentage of citations which occur exclusively in the German Edition. Additionally, reviews can experience a drastic underestimation due to incorrect storage or citation of the first page. The evaluation of the journal as a whole through its Journal Impact Factor (JIF), however, leads to an overestimation by the percentage of citations from both issues of the same paper (double citation). The reason for this seeming contradiction are the different processes used for determining the citation numbers, which in one case (in the case of individual papers) compare all numerical data of the publications, whereas in other cases (in the case of the JIF determination) count the mentions of journal names.

Citations of Reviews and Communications

Since the 1950s the contributions to *Angewandte Chemie* have been divided into the two large categories Reviews and Communications. In the bibliographic section of the SCI the 1322 publications in *Angewandte Chemie* from 1996 and 1997, for example (which were used to determine the JIF98), are divided into the following document types: 1213 "Articles", 86 "General Reviews", 14 "Errata", 5 "Letters" and 4 "Editorials". Here the "Articles" correspond to the "Communications" and the "General Reviews" correspond to the Reviews. Before 1990 the larger part of the "Communications" (ca. 80 %) was categorized as the document type "Note", which, however, was not used any more after 1995. Since 1992 "Communications" have been exclusively classed as "Articles".

The separate evaluation of Reviews and Communications is only possible through "Citation Matching" because only this process generates a complete set of data for the evaluation of the publications, thus allowing a categorization according to document types. Since this process only considers citations from the International Edition and undertakes an accurate comparison of the references (incorrect references are not counted) the absolute numbers with regard to the Impact (citations and citations per publication, respectively) are too low and cannot be compared to the JIF98 data. However, the data can be used for determining the relative percentages. The separate evaluation of Reviews and Communications has been undertaken analogously to the determination of the JIF98 and is summarized in Table 2.

It is shown that in 1998 the Reviews from 1996 and 1997 were already cited almost twice as often as the Communications. A longer period (i.e. a longer timeframe for the citations than the one used for the JIF formula) results in a

Table 2. Relative impact of Reviews and Communications in *Angewandte Chemie* based on the JIF98, determined by "Citation Matching" through the online database of the SCI available through STN International.

	Publications 1996 and 1997	Citations in 1998 only	Citations per publication
<i>Angewandte Chemie</i> Reviews ^[a]	86	655	7.62
<i>Angewandte Chemie</i> Communications	1213	5447	4.49
Reviews plus Communications	1299	6102	4.70

further shift of the citation numbers in favor of Reviews. And this despite the fact that Reviews are prone to be underestimated due to the problems with their first page. However, since the number of Communications is around an order of magnitude higher than the number of Reviews the high citation numbers of the Reviews do not have a dramatic effect on the total impact.

Citation Behavior of Individual Publications as a Function of Time

The citation behavior of individual publications as a function of time reflects to what extent and how rapidly a particular publication has been received by colleagues. Figure 3 shows the development with time of citations of two

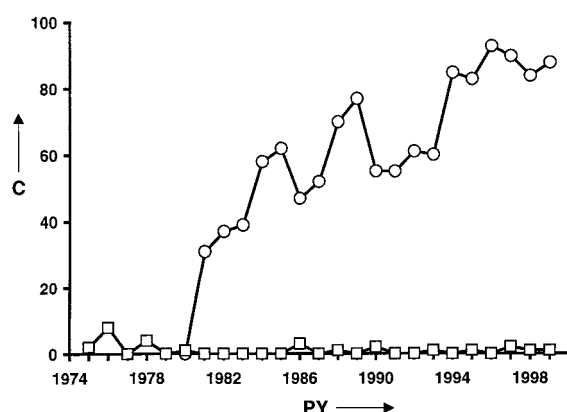


Figure 3. Number of citations (C) of a highly cited paper (*Angew. Chem.* **1980**, 92, 343–361; *Angew. Chem. Int. Ed. Engl.* **1980**, 19, 344–362) with 1245 citations (circles) and of a seldomly cited paper (*Angew. Chem.* **1974**, 86, 594–595; *Angew. Chem. Int. Ed. Engl.* **1974**, 13, 552–553) with 28 citations (squares) as a function of the year of publication of the citing publication.

publications from Wolfram Saenger, one of which is the most highly cited paper from *Angewandte Chemie* from 1980 with 1245 citations (up to May 12, 2000). Its curve is typical of many highly cited papers just as the one of the second paper can be seen as typical for the large number of the less highly cited papers.

Strictly speaking the citations of each publication develop according to their own particular characteristic time curve. However, on investigating many such time curves, some common features are evident: Noteworthy resonance for a publication in the field of chemistry or physics generally only sets in after one to two years, reaches a maximum after about three years, and can then continue for decades. Highly cited publications often reach the maximum of their citations only after decades and sometimes show an almost constant

resonance over the course of decades. Most publications, however, have a lower, often extremely oscillating effect, which can nevertheless continue for a long time. Consequently a certain period of time has to pass before the resonance of a paper (or the work of a scientist) can be realistically measured to some extent through the number of citations.

The timeframe of the citations in the determination of the JIFs by ISI permits only an average period of two years (at least one year, maximal three years). Therefore, only the first rise is calculated, which says little about the long-term impact (for example, about the one measured after one decade). JIFs thus measure more the speed of the resonance rather than its degree. The former, however, should be the reserved for the “Immediacy Index” given in the JCRs (which only considers citations within the year of publication). The narrow timeframe of the citations in the JIF formula leads to an underestimation particularly for highly cited papers (to which several of the reviews in *Angewandte Chemie* belong) because they accumulate a large percentage of their citations at a later period. The highly cited paper from Saenger, for example, had accumulated only 5 % of its total citations to date in the first three years after its appearance. In several areas of biological sciences the reaction in the form of citations occurs more rapidly, so that there the ISI formula for the determination of the JIFs is more valid. However, for chemistry (and physics) its application is questionable. It is presumably used by ISI, in an effort to be able to offer the most up to date JIFs. Apart from the possibilities for errors which lie in the nature of journals, the short timeframe of the citations demand great caution in the application and in the interpretation of JIFs.^[6]

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- [3] a) E. Garfield, *Science* **1972**, 178, 471–479; b) “*Journal Citation Reports*” (JCR), Science Edition, Institute for Scientific Information (ISI), Philadelphia, **1998**; c) URL: <http://www.isinet.com/isi/search/glossary>
- [4] a) C. F. Huber, *Database* **1995**, 18, 52–62; b) STN International: *STN Guide to Commands* **1997**; c) URL: <http://www.fiz-karlsruhe.de/stn/messenger/mc-toc.html>; d) URL: <http://www.fiz-karlsruhe.de/stn/databases/scisearch.html>
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Metal-Assisted Cleavage of a C–C Double Bond: Simple and Reversible

Helmut Werner* and Elke Bleuel

In the context of studies concerned with the mechanism of the Fischer–Tropsch synthesis, it has been speculated as to whether the generation of oxygen-containing products, formed in different amounts depending on the reaction conditions, is because of the initial coupling of a CH_2 and CO group.^[1] It appeared plausible to assume that the ketene so formed, $\text{CH}_2=\text{C}=\text{O}$ is first transformed by hydrogenation to acetaldehyde and then to ethanol. The coupling of a carbene (or a precursor thereof) with CO in the coordination sphere of a transition metal had been demonstrated for the first time in 1960 by Rüchardt and Schrauzer who attempted to prepare a diphenylcarbenenickel complex from $[\text{Ni}(\text{CO})_4]$ and Ph_2CN_2 but obtained diphenylketene.^[2]

Considering the great importance of the Fischer–Tropsch synthesis, it is not surprising that also in the years after 1960 a host of efforts were made to find evidence for the metal-assisted formation of ketenes by a C–C coupling process. For this reason, mono- as well as dinuclear complexes which contain either a terminal or a bridging carbene ligand and which react with CO to give the corresponding ketene, were chosen as model systems.^[3] However, in none of these studies had it been achieved to fragment a metal-bonded ketene into a CO and a carbene while both ligands remain coordinated to the metal center. All attempts which were undertaken in this direction led to the formation of di- or trinuclear complexes with bridging carbene units.^[4]

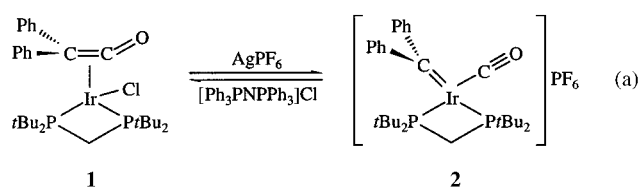
Most recently, in a paper which immediately aroused considerable attention^[5] Grotjahn et al. reported that diphenylketene linked to an iridium(III) center can be split into a CO and a diphenylcarbene ligand even at room temperature.^[6] The starting material **1** [see Eq. (a)] was prepared from the dimer $[\{\text{IrCl}(\text{C}_8\text{H}_{14})_2\}_2]$, $t\text{Bu}_2\text{PCH}_2\text{PrBu}_2$, and $\text{Ph}_2\text{C}=\text{C}=\text{O}$ in 61 % yield. The coordination of the ketene by the C=C instead

of the C=O double bond was confirmed by an X-ray crystal structure analysis. Typical structural features of **1** are the nearly orthogonal position of the C=C bond of the ketene to the $[\text{P},\text{Ir},\text{P}]$ plane and the relatively long C=C bond of 1.488(7) Å which is significantly longer than in other η^2 -(C,C)-ketene complexes.^[7, 8]

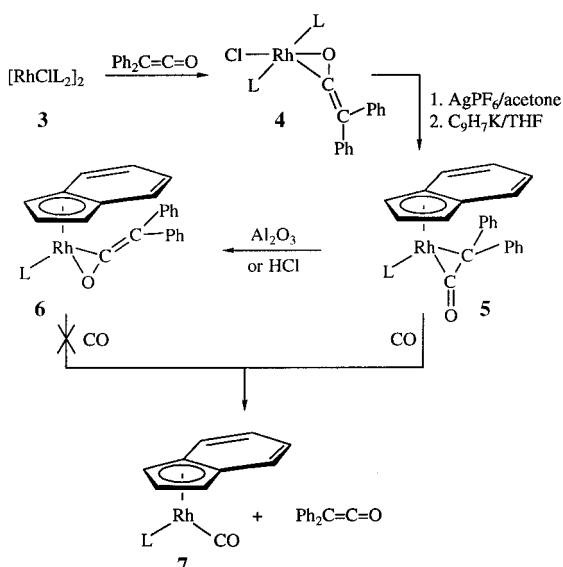
To initiate the desired cleavage of the C–C bond, the chloro ligand *cis* to the ketene of the 16-electron complex **1** was removed under mild conditions. Treatment of **1** with AgPF_6 in CH_2Cl_2 led to the elimination of chloride and the generation of a free coordination site, which allowed the C=O bond to “slide” into this position leading to the formation of the cationic carbene(carbonyl)iridium(III) complex **2**. The X-ray crystal structure analysis of **2** revealed a slightly distorted square-planar coordination geometry around the metal center, the distortion being caused both by the small bite angle of the bis(di-*tert*-butylphosphino)methane and the steric hindrance between the phenyl groups of the carbene ligand and the neighboring *tert*-butyl moieties. The Ir–C(carbene) bond of **2** is 1.996(8) Å and thus approximately 0.1 Å longer than in a recently described neutral diphenylcarbene iridium(III) complex.^[9]

However, even more interesting than the cleavage of the C–C bond is the reversibility of the reaction. Upon addition of $[\text{Ph}_3\text{P}=\text{N}=\text{PPh}_3]\text{Cl}$ to a solution of **2** in CD_2Cl_2 at -50°C and subsequent warming of the reaction mixture to room temperature, the ketene complex **2** is regenerated with 64 % yield. The carbonyl compound $[\text{IrCl}(\text{CO})(\kappa^2\text{-}t\text{Bu}_2\text{PCH}_2\text{PrBu}_2)]$ was obtained as a byproduct in 31 % yield. The authors emphasize that the conditions for the back reaction are not yet optimized.^[5] Theoretical studies by P. Hofmann and his group at Heidelberg lead to the conclusion that the activation energy for the carbene–CO coupling in the model system $[\text{Ir}(\text{CH}_2)(\text{CO})(\kappa^2\text{-H}_2\text{PCH}_2\text{PH}_2)]^+$ amounts to about 105 kJ mol⁻¹,^[10] which seems reasonable with respect to the experimental data for the real compound **3**.

Moreover, the work by Grotjahn et al. with its highlight of the reversible C–C bond cleavage has drawn attention to the renaissance of the chemistry of ketene–metal complexes and the metal-assisted activation of these ketenes.^[8, 11, 12] From the standpoint of the coordination chemist, two communications published most recently should be particularly mentioned. In both cases, rhodium plays a decisive role as the metal center. The first paper confirms with compounds **5** and **6** as an example (Scheme 1), that also in the case of ketene transition



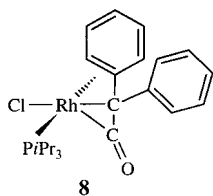
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Scheme 1. Isomerization between C,C- and C,O-bound ketene–rhodium complexes; L = $\text{P}i\text{Pr}_3$

metal complexes an isomerization by an alternating shift of the C=C and the C=O bond (e.g., the formation of bond isomers) is possible.^[13] The starting material for the preparation of **5** is compound **4**, which is obtained from **3**. As shown by an X-ray structure analysis **4** contains a C,O-bonded ketene ligand. Compound **4** is thermally remarkably stable and below its melting point of 110 °C does not rearrange into the C,C-bonded isomer. Compound **4** reacts in two steps with AgPF_6 and $\text{C}_9\text{H}_7\text{K}$ to afford the indenyl complex **5** (86% yield), the spectroscopic data of which point to the unexpected isomerization. The X-ray crystal structure analysis confirmed this assumption. The C–C bond of the diphenylketene in **5** is longer and the C–O bond shorter than in **4**. In benzene under acidic conditions **5** rearranges quickly into the thermodynamically more stable isomer **6**. The η^2 -(C,C)-bonded isomer **5** reacts spontaneously with CO to give the carbonyl complex **7** (and diphenylketene) while the η^2 -(C,O)-bonded isomer **6** is completely inert toward CO. According to the HSAB concept the “soft” C=C bond and not the “hard” C=O bond should coordinate preferentially to the “soft” metal center, thus the enhanced stability of **6** compared to **5** is noteworthy indeed.

The main goal of the second paper, which—duplication of the events—appeared only 11 months after the first,^[14] was also the synthesis and reactivity of the rhodium(I) compound **4** shown in Scheme 1. The authors prepared this compound in a one-pot procedure from $[\text{RhCl}(\text{C}_8\text{H}_{14})_2]_2$, $\text{P}i\text{Pr}_3$, and $\text{Ph}_2\text{C}=\text{C}=\text{O}$ with nearly quantitative yield. They were equally impressed by the high thermodynamic stability but in addition



observed that, in the presence of $[\text{RhCl}(\text{C}_8\text{H}_{14})_2]_2$ or CuI , **4** reacts over a few days, by elimination of a phosphane ligand, to form complex **8**. The related compounds with coordinated $\text{PMe}(\text{tBu})_2$ or PCy_3 instead of $\text{P}i\text{Pr}_3$ behave analogously. The X-ray crystal structure analysis of the $\text{PMe}(\text{tBu})_2$

derivative confirms that in the course of the reaction the metal slips from the C–O to the C–C bond of the ketene and that in the isolated product two carbon atoms of one phenyl ring weakly interact with the rhodium center. The coordination of $\text{Ph}_2\text{C}=\text{C}=\text{O}$ can thus be described as that of a chelating vinylketene. Quite unexpectedly, compound **8** shows fluxional behavior in solution which, according to the authors, could be explained by a formal migration of the metal from one side of the phenyl ring to the other.^[14]

In conclusion, there is no doubt that the work by Grotjahn et al.^[5] illustrated for the first time and in an impressive way a fundamentally important reaction for organometallic chemistry, namely the metal-assisted reversible cleavage of a C–C double bond. It is likely that this study will initiate new efforts to investigate once more the elementary steps of the Fischer-Tropsch synthesis with the aim of finding more appropriate catalysts for the selective generation of oxygen-containing products.

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NMR Quantum Computing

Steffen J. Glaser*

Nuclear magnetic resonance (NMR) is one of the most important methods for the identification of molecules and for the determination of their structure and dynamics. However, during the last few years, there has been a series of stimulating publications,^[1,2] in which the methods of NMR spectroscopy were applied to very simple and well known compounds. The goal of these projects was not to refine existing models of the structure or dynamics of these compounds but to realize experimentally the until then, purely theoretical concept of quantum computing. The idea to construct computers based on quantum-mechanical principles was first suggested in 1982 by the physicist Richard Feynman.^[3]

In order to understand why quantum computers are of interest, it is helpful to compare the ways information is stored in classical and in quantum computers, respectively. In a classical computer, the smallest unit of information, a bit, can take values represented by either 0 or 1. In a quantum computer, the smallest unit of information is a quantum bit (qubit), which corresponds to a quantum-mechanical two-level system with basis states $|0\rangle$ and $|1\rangle$. For example, such a qubit can be represented by a $\frac{1}{2}$ -spin particle, in which the states $|0\rangle$ and $|1\rangle$ correspond to a parallel or an antiparallel alignment of the spins relative to an external magnetic field (Figure 1 a). However, in contrast to its classical analogue, a

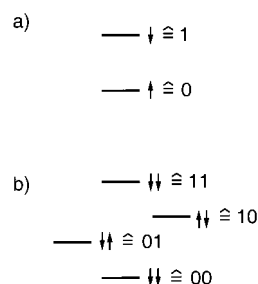


Figure 1. a) A $\frac{1}{2}$ -spin nuclei in an external magnetic field with basis states “spin up” and “spin down” is an example of a quantum-mechanical two-level system, which corresponds to a qubit with states 0 and 1, respectively. b) Two $\frac{1}{2}$ -spins in an external magnetic field form a four-level system. The basis states and the corresponding values of the two qubits are shown schematically. In contrast to classical bits, the quantum-mechanical system can also exist in a superposition of the basis states shown.

qubit can also exist in a quantum-mechanical superposition of $|0\rangle$ and $|1\rangle$ and is hence characterized by two complex numbers c_1 and c_2 , the probability amplitudes of the two basis states. The state function is $|\psi\rangle = c_1|0\rangle + c_2|1\rangle$ with the normalization condition $|c_1|^2 + |c_2|^2 = 1$. For example, in NMR the superposition states $|\psi\rangle_x = 2^{-1/2}(|0\rangle + |1\rangle)$ and

$|\psi\rangle_y = 2^{-1/2}(|0\rangle + i|1\rangle)$ correspond to transverse x and y magnetization, respectively. With every additional qubit (such as a $\frac{1}{2}$ -spin particle), the number of base states of the quantum-mechanical system doubles (Figure 1 b). Hence, the complete characterization of a register consisting of N qubits (such as N coupled $\frac{1}{2}$ -spins) requires 2^N complex numbers (probability amplitudes), whereas a register of N classical bits is, by definition, completely characterized by N integers (0 or 1). The superposition principle and the exponential growth of the size of the quantum-mechanical state space makes it possible to perform a large number of quantum computations simultaneously, that is, in parallel. However, this requires the development of appropriate computational procedures (quantum algorithms) that make the best use of the laws of quantum mechanics.^[4–6]

A quantum algorithm for prime factorization, developed by Peter Shor, is of particular interest.^[5] One of the most important methods for cryptography is based on the difficulty of prime factorization (the RSA method)^[7] because, for classical algorithms, the time required for the factorization of a given number increases exponentially with the number of digits. In contrast, the time required by Shor’s quantum algorithm grows at a significantly slower rate (only as a polynomial function of the number of digits). Hence, this quantum algorithm could be a potential threat for encrypted messages if a sufficiently large quantum computer (with hundreds or thousands of qubits) could be realized. However, as stated 1998, “Many years will pass until a computer with the necessary number of qubits will crack private keys on this planet—a quantum computer with more than four qubits in this millennium would already be a sensation”.^[8]

Current experimental approaches for the realization of quantum computers are ion traps,^[9] quantum dots,^[10] Josephson contacts,^[11] and NMR spectroscopy;^[1] the latter is, so far, most advanced in the practical implementation of quantum algorithms. NMR spectroscopy provides elegant methods for the controlled manipulation of nuclear spins, which are particularly well suited to act as qubits because of their isolation from the environment. However, a liquid NMR sample contains an ensemble of many identical spin systems and it is not possible to manipulate or to detect individual spin systems. Hence, at the beginning of a computation, NMR quantum computers are commonly prepared in a “pseudo-pure” state rather than in a pure state and, furthermore, ensemble-averaged expectation values are detected rather than the observables of individual spin systems.^[1] The basic computational steps of quantum algorithms can be realized with the help of radio-frequency pulses and can be broken down to spin-selective pulses and CNOT (conditional NOT) gates (Figure 2) between pairs of spins. The number of qubits is mainly restricted by the availability of compounds with suitable spin systems.

For the efficient implementation of an NMR quantum computer with N qubits, a molecule with N coupled $\frac{1}{2}$ -spins is

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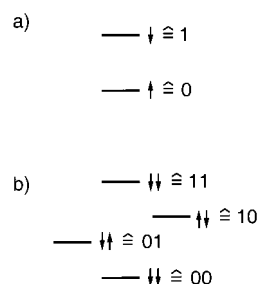


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For the efficient implementation of an NMR quantum computer with N qubits, a molecule with N coupled $\frac{1}{2}$ -spins is

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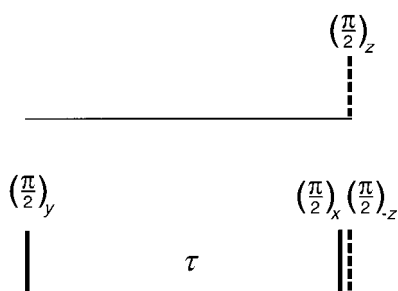


Figure 2. Schematic representation of an NMR pulse sequence to realize the logic CNOT(I,S) gate for a heteronuclear I,S spin system with coupling constant $J_{I,S}$.^[14] I - and S -spin selective radio-frequency pulses and z rotations are shown schematically on the upper and lower line, respectively. The period τ corresponds to $1/(2J_{I,S})$.

required. In order to be able to perform many basic computational steps (logic quantum gates), the time required for each quantum gate must be considerably smaller than the relaxation time of the nuclear spins. As the basic computational steps rely on the selective manipulation of individual spins, the frequency differences of nuclear spins should be as large as possible. In this respect, heteronuclear spin systems and spins with a large range of chemical shifts are advantageous. In addition, large couplings should exist between the nuclear spins because the time required for the implementation of direct logical combination of two qubits is inversely proportional to the size of the coupling between the corresponding nuclear spins. However, it is not required that all spins are mutually coupled (Figure 3a): It is sufficient if the spins form a contiguous coupling network (Figure 3b).^[12]

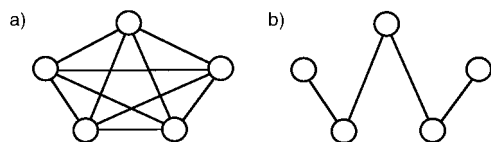
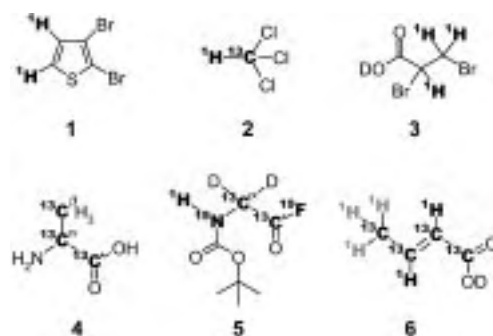


Figure 3. a) Schematic representation of a system consisting of $N=5$ pairwise-coupled spins (qubits). b) A linear coupling network is sufficient to realize all possible logic operations between arbitrary spins (qubits) in an N -spin system.^[12]

For the first NMR quantum computers with up to three qubits, readily available compounds were used, such as 2,3-dibromothiophene **1**,^[1a, 2f] [^{13}C]chloroform **2**,^[2a] 2,3-dibromopropanoic acid **3**,^[2e, 12] and [$^{13}\text{C}_3$]alanine **4**.^[13] In Scheme 1, atoms whose nuclear spins represent the individual qubits are printed in boldface. For the realization of the first NMR quantum computer with more than four qubits, compound **5** was synthesized.^[14] If the deuterium spins are decoupled, the nuclear spins of ^1H , ^{15}N , $^{13}\text{C}^\alpha$, $^{13}\text{C}^\beta$ ($=\text{CO}$), and ^{19}F form a coupled spin system consisting of five $1/2$ -spins. The ^1J coupling constants range between 13.5 Hz ($^1J_{\text{N},\text{C}^\alpha}$) and 366 Hz ($^1J_{\text{C},\text{F}}$) and, for a magnetic field of 9.4 T, the frequency differences vary between 12 kHz ($\nu_{\text{C}} - \nu_{\text{C}^\alpha}$) and 360 MHz ($\nu_{\text{H}} - \nu_{\text{N}}$). Recently, [$^{13}\text{C}_4$]crotonic acid **6** was proposed^[15] as a compound that may be suited for quantum computing with seven qubits. In a magnetic field of 9.4 T, the ^{13}C resonances are well separated with a minimal frequency difference of 2.5 kHz but the smallest frequency difference of the ^1H spins is only



Scheme 1. Compounds suitable to form the molecular basis of NMR quantum computers with up to seven qubits. The atoms of the nuclear spins, which act as qubits, are printed with boldface. In **6**, the (gray) protons of the methyl group represent just one qubit if only the $1/2$ -spin part of total spin of the methyl group is exploited.^[15]

500 Hz.^[15] The design and synthesis of molecules with suitable spin systems for 10–20 qubits is not a trivial challenge.

If the compound serving as a quantum computer is dissolved in a liquid crystal, not only scalar J couplings but also large dipolar couplings can be exploited to reduce the time required for quantum gates.^[16] Another possible approach for the realization of a molecular architecture with more than ten coupled spins is the synthesis of polymers with a repetitive unit consisting of three or more spins.^[17]

With an increasing number of qubits, not only the synthetic requirements grow but also the demands with respect to NMR instruments and pulse-sequence design, in order to keep the effects of experimental imperfections (such as the inhomogeneity of the radio-frequency fields) under control. In addition, the preparation of a pseudopure state (a prerequisite for most quantum algorithms) becomes very inefficient as the number of qubits increases.^[18] This results in a dramatic sensitivity loss of the experiments. Possible solutions could be the use of the laser-polarized ^3He or ^{129}Xe nuclei^[19] or the spin order of *para*-hydrogen^[20] or of electron spins.^[21] It is very unlikely that it will be possible to realize an NMR-based quantum computer that is large and powerful enough to surpass classical computers. However, the methods of NMR spectroscopy are almost ideally suited to experimentally realize and test theoretical quantum algorithms for small spin systems. The investigation of the limits of this approach is an exciting subject of current research.

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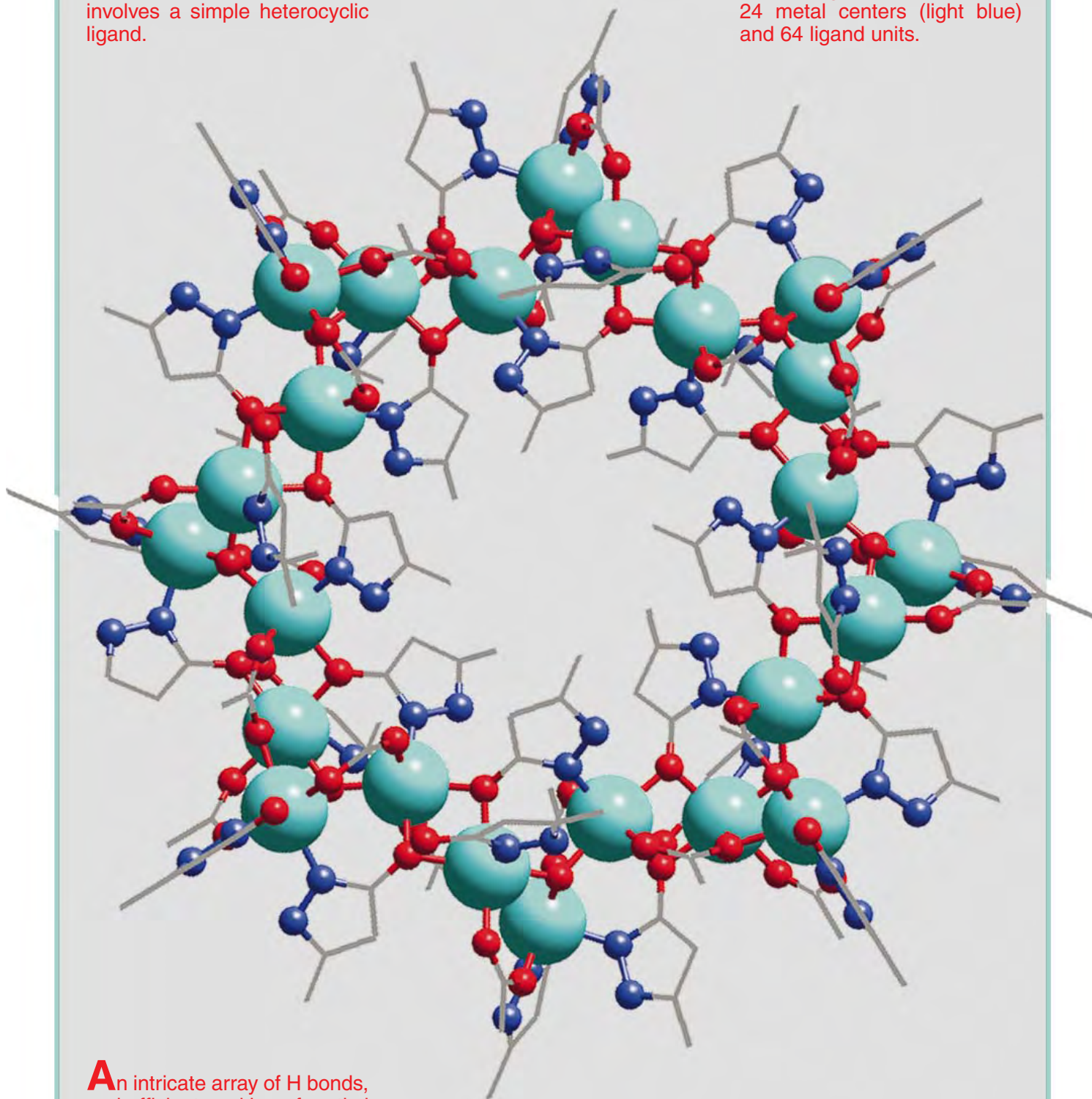

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The nickel wheel illustrated is the largest such cyclic cage known for the 3d metals, and involves a simple heterocyclic ligand.

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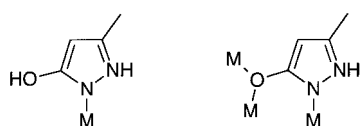
An intricate array of H bonds, and efficient packing of methyl groups within the macrocyclic cavity help stabilize this intriguing structure.

For more information see the following pages.

Synthesis, Structure, and Preliminary Magnetic Studies of a Ni₂₄ Wheel**

Angela L. Dearden, Simon Parsons, and Richard E. P. Winpenny*

Metal rings have excited mankind since mythological times.^[1] The largest cyclic structure containing exclusively paramagnetic 3d-metals is the Fe₁₈ wheel reported by Lippard and co-workers,^[2] which is an order of magnitude smaller than the giant wheels constructed from molybdate fragments by the Müller group.^[3] We have previously reported^[4] a Ni₁₂ wheel featuring acetate and 6-chloro-2-pyridonate ligands which shows ferromagnetic exchange between the metal centers, and a resulting *S* = 12 spin ground state. Herein we report initial experiments involving the heterocyclic ligand, 3-methyl-3-pyrazolin-5-one (Hmpo) (Scheme 1), which result in the formation of a cyclic Ni₂₄ cage.



(a) Hmpo binding mode (b) mpo binding mode



(c) μ₃-O₂CMe (d) μ₂-O₂CMe

Scheme 1.

Hmpo and hydrated nickel acetate were stirred together in MeOH for 24 h, during which time a pale green precipitate formed, which was removed by filtration. The solution was evaporated to dryness, the resulting powder was redissolved in MeCN and green rodlike crystals grew over two days. X-ray analysis^[5] (Figure 1) revealed a tetraicosanuclear nickel cage [Ni₂₄(OH)₈(mpo)₁₆(O₂CMe)₂₄(Hmpo)₁₆] (**1**; mpo = the mono-deprotonated anion of Hmpo).

The cage is disposed about a crystallographic fourfold axis therefore there are only six nickel centers in the asymmetric unit. However, in many ways the structure can be described as consisting of an octamer of chemically equivalent trinuclear building blocks. The first such unit contains Ni1, Ni2, and Ni3,

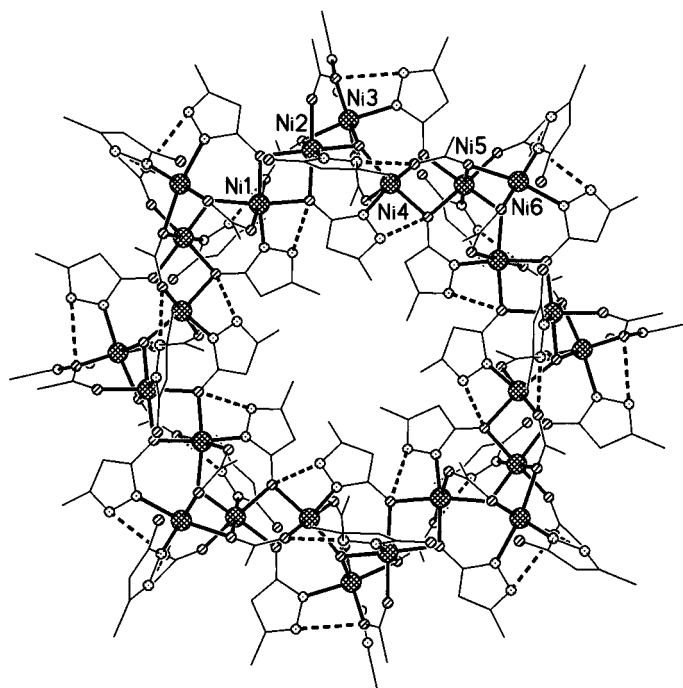


Figure 1. The structure of **1** in the crystal. Hydrogen bonds are shown as dashed lines.

while Ni4, Ni5, and Ni6 belong to the second (Figure 2). Thus the structural role and coordination environment of Ni4 is equivalent to Ni1, Ni5 equivalent to Ni2, and Ni6 to Ni3. In the following paragraph only the first trinuclear building block is discussed, with the relevant metal sites in the second fragment identified in parentheses.

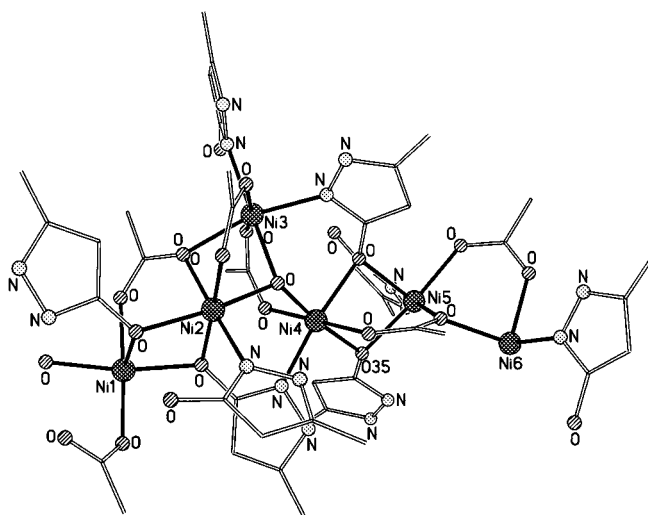


Figure 2. The asymmetric unit of **1**. Bond length ranges [Å]: Ni-O(mpo) 2.055–2.140, Ni-O(acetate) 2.034–2.137, Ni-O(OH) 2.011–2.049, Ni-N(mpo) 2.024–2.060, Ni-N(Hmpo) 2.079–2.096; (average esd 0.003 Å).

The bridging within the blocks is predominantly performed by acetate and mpo ligands (Scheme 1). One acetate bridges in a μ₃-fashion, that is, bridging Ni1 (Ni4) and Ni2 (Ni5) with the oxygen atom bound to Ni2 (Ni5) also bound to Ni3 (Ni6). The two mpo ligands within the trinuclear fragment also

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bridge the Ni1...Ni2 (Ni4...Ni5) vector through the exocyclic oxygen atom, with the ring nitrogen atom bound to a nickel center in a neighboring trimer. A second carboxylate group bridges Ni2 (Ni5) and Ni3 (Ni6) in a 1,3-fashion, with a μ_3 -hydroxide also bridging this vector and binding on to Ni4 (Ni1) in the next trinuclear fragment. Thus a 1,3-carboxylate group and two μ_2 -oxygen atoms bridge each Ni...Ni contact within the building blocks. This means of bridging M...M is found in other cyclic structures such as the Ni₁₂ cage we reported,^[4] and the decanuclear "ferric wheel" described by Lippard and co-workers.^[6] The two neutral Hmpo ligands within each trinuclear block are attached through the ring nitrogen atom to Ni2 (Ni5) and Ni3 (Ni6).

The linking between trinuclear blocks involves a μ_3 -hydroxide unit which bridges between Ni2 and Ni3 in one unit and Ni4 in the second, or Ni5, Ni6, and Ni1. The link is further supported by μ_2 -carboxylate units which bridge Ni3...Ni4 and Ni6...Ni1. Additionally the four mpo ligands each bind to two metal centers from one trinuclear block through the O-donor, while binding to a third metal center from the other fragment through the N-donor, for example, bridging Ni4 and Ni5 in the second block, while the ring nitrogen atom binds to Ni3 in the first.

This complicated set of interactions generates the Ni₂₄ structure, which is much less circular than other cyclic structures (Figure 1). The trinuclear fragments are so disposed that they point approximately at the center of the neighboring unit, rather than at the end. The angle between the lines Ni1-Ni2-Ni3 and Ni4-Ni5-Ni6 is 51.0°. This generates a structure where Ni3, Ni6 and their symmetry equivalents create distinct "points" on the wheel. In addition to the metal-ligand bonding described above, the structure is stabilized by a large quantity of H bonding. The majority of these interactions arise from the proton on the second N atom within the pyrazolinone ligands. Thus H bonds are formed between this site and O atoms from both acetate and mpo ligands (Figure 1).

All the metal centers are six-coordinate, with approximately octahedral symmetry. Four of the crystallographically independent sites (Ni1, Ni2, Ni4 and Ni5) are bound to one N- and five O-donor groups, while the remaining two sites (Ni3 and Ni6) have two N- and four O-donor groups. Magnetic measurements^[7] are consistent with twenty-four $S=1$ centers. The room-temperature value for $\chi_m T$ of approximately 30 cm³ K mol⁻¹ (χ_m = molar magnetic susceptibility) matches well with the calculated value ($\chi_m T_{\text{calcd.}}$ = 29 cm³ K mol⁻¹) for a reasonable g -value of 2.2. The $\chi_m T$ declines with temperature, however, even at 1.8 K, $\chi_m T$ is greater than 24 cm³ K mol⁻¹, which indicates that while the magnetic behavior is dominated by antiferromagnetic exchange this is rather weak and many magnetic states remain populated at even very low temperatures. The antiferromagnetic exchange suggests that, in principle, this Ni₂₄ cage should be useful for modeling the Haldane gap predicted to occur for wheels or chains of anti-ferromagnetically couple $S=1$ chains.^[8]

It is noticeable that, as with the Fe₁₈ structure,^[2] it is not possible to generate a large 3d-metal wheel with only one type of bridging interaction. Therefore while decanuclear ferric

wheels^[6,9] can be accurately described as $[\{\text{Fe}(\text{OMe})_2(\text{O}_2\text{CR})\}_{10}]$ ($\text{R} = \text{Me}, \text{CH}_2\text{Cl}, \text{CH}_2\text{CH}_2\text{C}(\text{O})\text{C}_6\text{H}_4\text{Me}$), and octanuclear chromium wheels^[10] can be described as $[\{\text{CrX}(\text{O}_2\text{CR})_2\}_8]$ ($\text{X} = \text{F}, \text{R} = \text{CMe}_3; \text{X} = \text{OH}, \text{R} = \text{Ph}$) such a description as an oligomer of a mononuclear fragment is not accurate for these larger wheels. For both the Fe₁₈ and Ni₂₄ wheels a more accurate description is as an oligomer of trinuclear building blocks. Therefore, if still larger wheels are to be constructed, a design principle might be to look for either larger oligomers of trinuclear fragments, or oligomers of higher nuclearity building blocks. This structure using 3-methyl-3-pyrazolin-5-one appears to be the first that involves this ligand; the presence of a suitable H-bond donor within this ligand might also be an important feature in generating this large cage.

The Ni₂₄ wheel appears to be the largest homometallic cage containing paramagnetic Ni^{II} centers. Previous examples of cages containing ten or more nickel centers include: Ni₁₆Na₆ which contains four Ni₄ cubanes linked by phthalate ligands,^[11] the cyclic Ni₁₂ wheel mentioned above,^[4] a [Ni₁₁Br₆(*NtBu*)₈] cage,^[12] a series of Ni₁₀, Ni₁₁, and Ni₁₂ cages containing a mixture of carboxylate and pyridonate ligands,^[13] a dimer of Ni₅ metallocrowns.^[14]

Experimental Section

1. A colorless solution of Hmpo (0.02 mol) in MeOH (100 mL) was added to a green solution of hydrated nickel acetate (0.02 mol) in MeOH (100 mL). The resulting green solution was stirred for 24 h at room temperature, during which time a pale green precipitate formed, which was removed by filtration. The solution was evaporated to dryness under reduced pressure and the resulting powder dried in vacuum. This was then redissolved in MeCN to give a saturated solution from which green rodlike crystals grew over two days; yield: 20%, elemental analysis calcd (%) for C₆₇H₇₀Cl₁₄F₁₂Ni₆O₂₀: C 35.51, H 3.24, N 6.47; found: C 35.32, H 3.13, N 6.40.

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anisotropic displacement parameters: 897 parameters, $wR2 = 0.1835$ for 18 516 unique data ($2.69 \leq \theta \leq 26.39^\circ$), $R1 = 0.0666$ for 14 232 data with $F_o > 4\sigma(F)$, max./min. residual electron density 0.789/−0.549 e Å^{−3}. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-148156. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Off-the-Shelf Colorimetric Anion Sensors**

Hidekazu Miyaji and Jonathan L. Sessler*

The recognition^[1] and sensing^[2] of anionic analytes has emerged recently as a key research theme within the generalized area of supramolecular chemistry.^[3] Of particular interest in this regard are “colorimetric anion sensors”, species that would allow the so-called “naked-eye” detection of anions without resort to any spectroscopic instrumentation. However, few such systems exist at present.^[4–7] For instance, alizarin complexone^[4a] has been used to effect the colorimetric sensing of fluoride anions in water, wet acetone, and wet acetonitrile as has 2,3-dipyrrol-2-yl-quinoxaline in dichloro-

methane.^[6b] Thiourea has also been used to sense halide, phosphate, and carboxylate ions.^[4b] Appropriately functionalized calix[4]pyrroles also show potential as naked-eye anion sensors.^[7] Separately, displacement-based strategies have been used by Lavigne and Anslyn to detect citrate anions colorimetrically^[5] and, more recently by Gale et al. to sense halide anions.^[6a] Still, there remains a cogent need for species whose changes in color could be used to signal either qualitatively or quantitatively the presence of particular anionic analytes. Such agents would be especially valuable were they to be obtained readily without resort to dedicated synthesis. Herein we report that a wide range of commercially available entities, such as 1,2-diaminoanthraquinone, 1,8-diaminoanthraquinone, 4-nitroaniline, 4-nitro-1,2-phenylenediamine, L-leucine-4-nitroanilide, 1-(4-nitrophenyl)-2-thiourea, 4-nitrophenol, alizarin, 2,2'-bi(3-hydroxy-1,4-naphthoquinone), acid blue 45, naphthol AS, 9(10*H*)-acridone, and Direct Yellow 50 may be used as “off-the-shelf” color-based anion sensors in organic solvent. We also show that some of these agents may be used in combination with a crown ether phase-transfer catalyst to extract and detect anions colorimetrically in a two-phase organic–aqueous set-up, even in those instances where the anions being detected were originally present in the aqueous phase.

Initially, we focused on 1,8-diaminoanthraquinone as a potential off-the-shelf anion sensor. We were attracted to this system because 1) it contains two aniline-like NH₂ donor groups that appeared properly positioned to bind a chloride ion by cooperative hydrogen-bonding interactions, as judged from structural analyses of previous chloride-binding^[8] and noncolorimetric sensing agents^[2c] containing a similar structural motif, 2) such binding was expected to result in a bathochromic shift in the absorption bands in the visible region,^[7b] and 3) various control compounds, with other modifications of the anthraquinone skeleton, would be readily available. In accord with the latter predicative thought, we studied the changes (if any) in the absorption spectra of anthraquinone, 1,2-, 1,4-, 1,5-, 1,8-,^[8] and 2,6-diaminoanthraquinone, as well as 1- and 2-aminoanthraquinone, induced upon the addition of various anions, namely F[−], Cl[−], Br[−], I[−], H₂PO₄[−], and HSO₄[−] in dichloromethane. Although, no change in the absorption spectrum of anthraquinone itself was found upon the addition of any of the analytes tested, the spectra of the other anthraquinone derivatives (those containing at least one hydrogen bond donor group) were all found to be modified in the presence of tetrabutylammonium fluoride. On the other hand, only the spectra of 1,2- and 1,8-anthraquinone were seen to undergo a discernable change when exposed to tetrabutylammonium chloride in this same solvent. Presumably, the fluoride ion, in contrast to the chloride ion, is a strong enough hydrogen-bond acceptor that it can interact with anthraquinone derivatives that contain only a single hydrogen-bond donor group or single accessible donor group.

Significant bathochromic shifts in the absorption spectra were also observed for 1,2- and 1,8-diaminoanthraquinone in dichloromethane in the presence of chloride, bromide, and phosphate ions. These spectral changes were particularly dramatic in the case of 1,2-diaminoanthraquinone, being

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sufficiently large that this species was found to function as an effective colorimetric anion sensor. Figure 1 shows the color changes induced upon the addition of various anions (100 equiv each) to solutions of 1,2-diaminoanthraquinone in dichloromethane. Specifically, it was found that solutions,

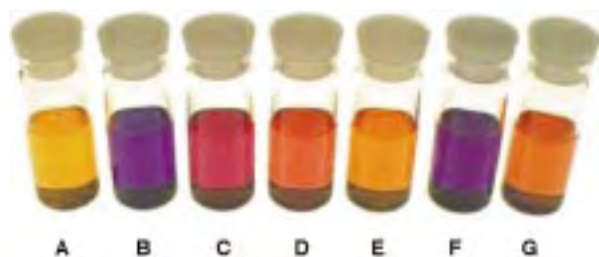
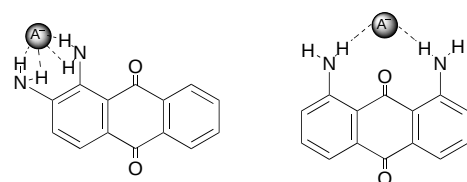


Figure 1. Photograph showing the color of dilute solutions of 1,2-diaminoanthraquinone in dichloromethane ($[\text{quinone}] = 1.0 \times 10^{-4} \text{ M}$). A) Before addition of the anion. After addition of 100 equivalents of B) fluoride, C) chloride, D) bromide, E) iodide, F) phosphate, and G) sulfate ions. All anions were added in the form of their tetrabutylammonium salts.

initially yellow in color ($\lambda_{\text{max}} = 478 \text{ nm}$), became dark purple ($\lambda_{\text{max}} = 555 \text{ nm}$), red ($\lambda_{\text{max}} = 519 \text{ nm}$), reddish orange ($\lambda_{\text{max}} = 513 \text{ nm}$), orange ($\lambda_{\text{max}} = 499 \text{ nm}$), purple ($\lambda_{\text{max}} = 548 \text{ nm}$), and orange ($\lambda_{\text{max}} = 493 \text{ nm}$) when exposed to fluoride, chloride, bromide, iodide, phosphate, and sulfate ions, respectively.^[9]

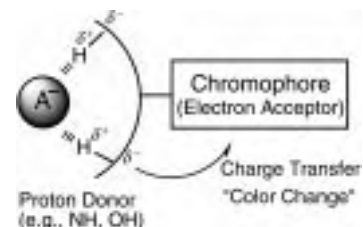
Solutions of 1,8-diaminoanthraquinone in dichloromethane were also found to change color when exposed to these anions, albeit to a lesser extent.^[10] On the other hand, no significant changes in color were observed when solutions of 1,4-, 1,5-, 2,6-diaminoanthraquinone or 1- and 2-aminoanthraquinone in dichloromethane were exposed to 100 equivalents of chloride, bromide, iodide, phosphate, or sulfate ions. Such findings are consistent with the proposal that less basic anions, such as Cl^- , Br^- , I^- , H_2PO_4^- , and HSO_4^- , are not bound to an appreciable extent by a single NH_2 site but do interact cooperatively with two appropriately spaced NH_2 donor moieties (that is, in the 1,2 and 1,8 positions of anthraquinone). Although not studied in detail, the color change itself is ascribed to the formation of a charge-transfer complex as the result of these proposed solution-phase hydrogen-bonding interactions (Scheme 1).



Scheme 1. Proposed modes of anion binding for 1,2-diaminoanthraquinone and 1,8-diaminoanthraquinone.

Although hydrogen-bonding interactions are considered key to the success of the off-the-shelf anion sensing demonstrated by 1,2- and 1,8-diaminoanthraquinone, and while the initial choice of solvent, dichloromethane, was chosen to maximize these interactions, it was found that a discernable color-based response was observed when more polar solvents, namely CH_3CN and DMSO , were used.

The results obtained with 1,2- and 1,8-diaminoanthraquinone, led to the consideration that many species should be able to function as off-the-shelf anion sensors, provided that they possess hydrogen bond donor functionality, preferably two or more -NH_2 , -C(O)NHR , or OH -derived binding sites, and a chromophore subunit whose electronic properties are modified as the result of interaction with a bound anionic substrate (through, for example, electrostatic or charge transfer effects; see Scheme 2). In accord with the above thinking,



Scheme 2. Schematic representation illustrating the origins of the generalized "off-the-shelf" approach to anion sensing being proposed here.

many commercially available compounds were screened as possible off-the-shelf anion sensors. A listing of compounds showing readily discernable changes is given as Scheme 3 while Figure 2 illustrates representative color changes observed using some of these species.

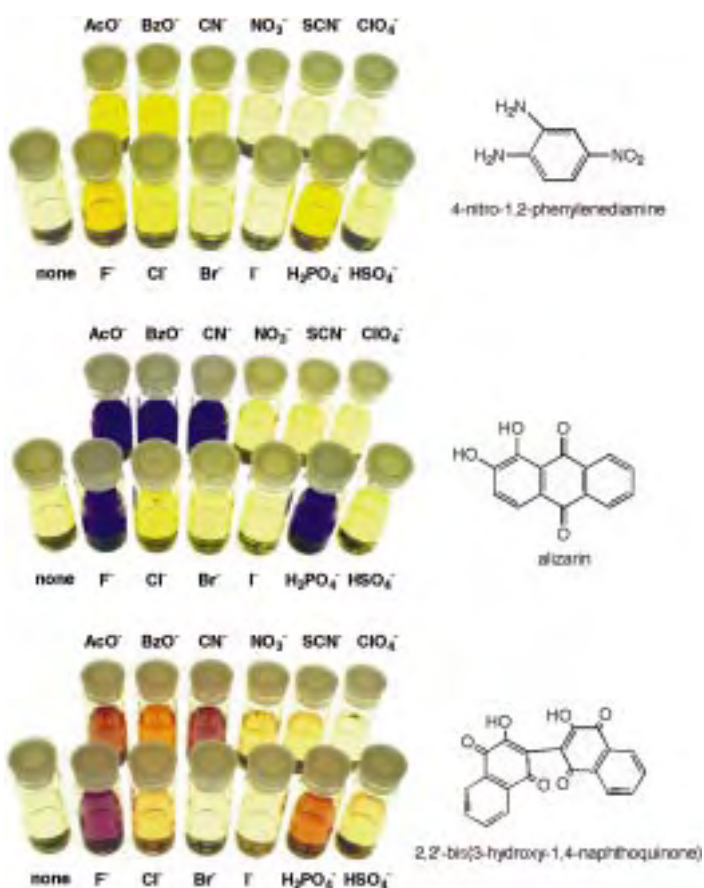


Figure 2. Color changes observed before and after dilute ($1 \times 10^{-4} \text{ M}$) solutions of 4-nitro-1,2-phenylenediamine, alizarin, and 2,2'-bis(3-hydroxy-1,4-naphthoquinone) in dichloromethane were treated with 100 equivalents of the indicated anionic analytes. All anions were added in the form of their tetrabutylammonium salts.

4-nitroaniline (Colorless → Yellow / DCM)	4-nitro-1,2-phenylenediamine (Pale Yellow → Orange ~ Yellow / DCM)	L-leucine-4-nitroanilide (Colorless → Yellow / DCM)																																																																								
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Scheme 3. Examples of commercially available colorimetric anion sensors. A checked box indicates a “naked-eye” detectable change in color is observed in the indicated solvents upon addition of 100 equivalents of the anionic analyte in question. DCM = dichloromethane; DMSO = dimethyl sulfoxide.

Based on the results summarized in Scheme 3, we believe that the use of appropriate off-the-shelf molecular entities could provide a generalized new approach to anion sensing. While lacking the specificity inherent in more sophisticated approaches to anion detection (for example, those based on specific receptor design), the fact that some inherent discrimination between anionic analytes is observed, coupled with its low cost, leads us to suggest that this new approach could find application in a variety of end-use areas, including multi-

analyte array construction,^[11] where ease of use and cost of goods are important considerations.

In support of the above contention, 2,2'-bis(3-hydroxy-1,4-naphthoquinone)^[12] was used as a potential chloride sensor under extraction-type conditions. As illustrated in Figure 3, it was found that in a two-phase, aqueous–dichloromethane system containing [15]crown-5 as a phase-transfer catalyst present in the organic phase acts as a colorimetric indicator of chloride anions originally present in the aqueous layer.^[13] This

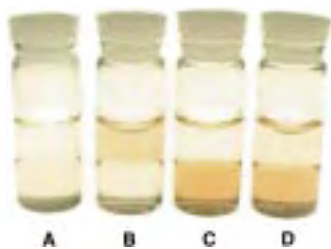


Figure 3. Color changes observed upon exposing aqueous solutions of chloride ions to dichloromethane phases containing 2,2'-bis(3-hydroxy-1,4-naphthoquinone) (1×10^{-3} M). A) Control experiment. The aqueous phase is distilled water (pH 7.41). B) The aqueous phase contains NaCl at a concentration of 1×10^{-1} M. C) The aqueous phase contains NaCl (1×10^{-1} M) and benzo[15]crown-5. D) The aqueous phase is Gulf of Mexico sea water (pH 7.34) and benzo[15]crown-5.

ability to sense qualitatively in a naked-eye-detectable fashion chloride anions is not limited to laboratory samples but was also found to work for sea water obtained from the Gulf of Mexico.^[14] This observation leads us to suggest that this particular species could prove useful as a chloride anion sensor.^[15]

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- [10] The change in color for 1,8-diaminoanthraquinone was smaller than for 1,2-diaminoanthraquinone. For example, the color of a solution of 1,8-diaminoanthraquinone in dichloromethane (1×10^{-4} M) changed from orange ($\lambda_{max} = 487$ nm) to red ($\lambda_{max} = 503$ nm) upon the addition of 500 equivalents of fluoride ions.
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- [12] As a result of a strong interaction with the crown ether and a resulting color change in the absence of anions, 1,2-diaminoanthraquinone could not be used for such extraction-type experiments.
- [13] Chloride, rather than fluoride, ions were chosen for these tests since this larger anion is less basic and less prone to modulate the pH of the aqueous phase. Since changes in pH can affect the color of the indicators in this study, rigorous efforts were made to maintain the pH (through, for example, the use of dilute samples) as well as to control any differences in color that changes in pH could induce.
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Resolution and Kinetic Stability of a Chiral Supramolecular Assembly Made of Labile Components**

Andreas J. Terpin, Marco Ziegler, Darren W. Johnson, and Kenneth N. Raymond*

The importance of chirality for recognition processes in nature is impressively exemplified by the different tastes of (*R*)- and (*S*)-asparagine,^[1] and the vastly different pharmacological effects of the two enantiomers of thalidomide.^[2] Chirality is not the exclusive domain of organic chemistry, many metals can also serve as centers of chirality.^[3] The most frequent case is an octahedral arrangement of three bidentate ligands around a metal center to form Δ or Λ absolute configurations. Chirality at metal centers has been found to play an important role in nature, for example, for the siderophore-mediated iron uptake in many organisms.^[4]

Δ/Λ Isomerization of tris-bidentate complexes of the labile high-spin ferric ion or its closely related gallium(III) analogues is rapid in aqueous solution. Tris(catecholate)gallium(III) complexes, model compounds of iron siderophores, usually racemize fast. Racemization rates of $10(1) s^{-1}$ for a mononuclear complex^[5] and $0.10(1) s^{-1}$ for a dinuclear helix^[6] were determined by NMR studies. The isomerization was found to

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[**] Coordination Number Incommensurate Cluster Formation, Part 18. Financial support of this work was provided by NSF CHE-9709621 and by NSF and NATO-NSF exchange grants INT-9603212 and SRG 951516, respectively. We thank the Alexander-von-Humboldt Foundation for a Fellowship to A.T., and a Humboldt Research Award for Senior U.S. Scientists to K.R., and the Miller Foundation for a fellowship to M.Z. The authors gratefully acknowledge the assistance of Dr. F. J. Hollander and Dr. D. L. Caulder in selecting and mounting a suitable single crystal, and Prof. Julie A. Leary, Dr. Ulla N. Andersen, and J. J. Miranda for measuring mass spectra. Part 17: M. Ziegler, J. J. Miranda, U. N. Andersen, D. W. Johnson, J. A. Leary, K. N. Raymond, *Angew. Chem.*, in press.

be unimolecular and to proceed through a Bailar twist mechanism. The combination of two chiral metal centers to form a helicate substantially slows the isomerization rate as a result of strong mechanical coupling through the rigid ligands.

Larger supramolecular clusters based on metal–ligand interactions have been designed,^[7–10] many of which are intrinsically chiral. In particular, tetrahedral $[M_4L_6]$ assemblies have been prepared from C_2 -symmetric bis-catecholate or bis-hydroxamate ligands and octahedral metal ions, which form trigonally symmetric vertices (Figure 1).^[11–15] In $[Ga_4L_6]$

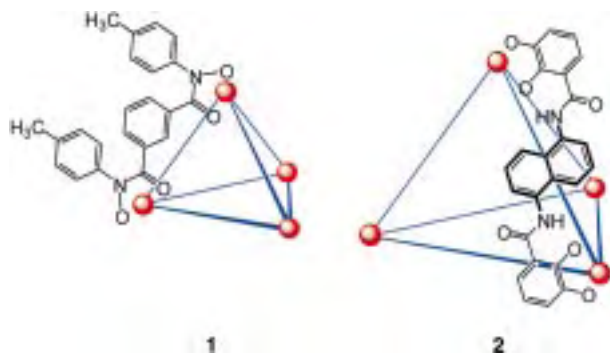


Figure 1. Tetrahedral clusters $[Ga_4L_6]$ and $[Ga_4L_6]$ formed by bis-catecholate ligands and Ga^{III} ions at the corners of a tetrahedron.

the metal vertices are bridged by a ligand that does not discriminate between the Δ - Δ or Λ - Λ configuration across an edge but does discriminate against the Bailar-twist transition state required for inversion.^[11, 12] The result is the formation in solution of all possible isomers (with point group symmetry): $\Delta\Delta\Delta\Delta$ (T), $\Delta\Delta\Delta\Delta$ (C_3), $\Delta\Delta\Delta\Delta$ (S_4), and their mirror images. In contrast, the tetrahedral complex $[Ga_4L_6]$ has strongly coupled metal centers, such that if one metal center initially has a Δ configuration, the metal center across an edge from it must necessarily also be Δ . In this case the result is the formation of a racemic mixture of homoconfigurational clusters ($\Delta\Delta\Delta\Delta$ or $\Lambda\Lambda\Lambda\Lambda$).^[13] The activation energy for interconversion of a tris(catecholate)gallium(III) center from Δ to Λ is $67(1) \text{ kJ mol}^{-1}$.^[6] If the tetrahedral structure is truly rigid and the metal centers cannot racemize independently from each other, the activation barrier for isomerizing a $[M_4L_6]$ cluster through a Bailar-twist mechanism would be expected to be much higher. Herein we report the resolution of $[Ga_4L_6]$ and show that the enantiomers are indeed exceedingly stable towards racemization.

Complete resolution of the chiral anionic cluster is accomplished in the presence of the chiral *N*-methylnicotinium cation (Nic) derived from natural (–)-nicotine and designed to interact stereospecifically with the vertices of the tetrahedron. Interestingly, the cation is encapsulated in the cavity of the

cluster $[(\text{Nic}) \subset Ga_4L_6]^{11-}$, as shown by the large upfield shift of the resonances of the cation in the ^1H spectrum (Figure 2), which is characteristic of encapsulation and has been observed previously for related clusters and guests.^[13, 16] The encapsulated chiral cation is an ideal probe to determine the diastereomeric excess (*de*) of the resolved cluster. The

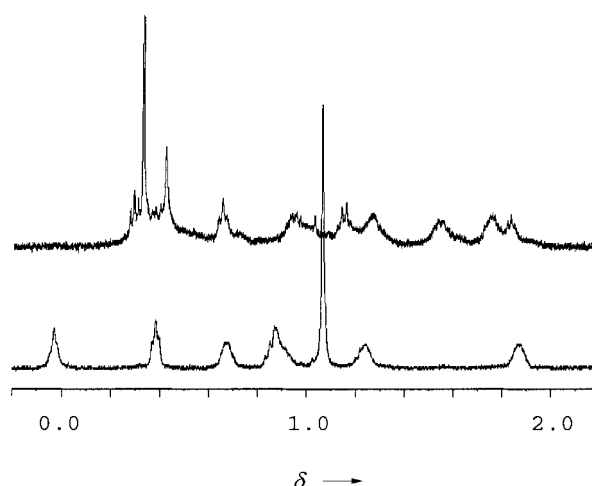
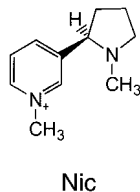


Figure 2. NMR spectra (D_2O) of the resolved tetrahedral clusters $\Delta\Delta\Delta\Delta$ - $[(\text{Nic}) \subset Ga_4L_6]^{11-}$ (bottom) and $\Lambda\Lambda\Lambda\Lambda$ - $[(\text{Nic}) \subset Ga_4L_6]^{11-}$ (top) showing the strongly upfield shifted resonances of the encapsulated chiral guest (Nic).

NEt_4^+ ion readily displaces the chiral guest to form enantiopure $\Delta\Delta\Delta\Delta$ - and $\Lambda\Lambda\Lambda\Lambda$ - $[Et_4N]_{11}[(Et_4N) \subset Ga_4L_6]$ clusters with complete retention of chirality of the metal centers. Remarkably, an alkaline, aqueous solution of $\Delta\Delta\Delta\Delta$ - $[(Et_4N) \subset Ga_4L_6]^{11-}$ retained its enantiopurity for at least eight months, and even extended boiling of the solution did not lead to racemization!^[17]

The absolute configuration and enantiopurity of the clusters was determined from their CD spectra (Figure 3): the π – π^* transitions in the catechol moiety at each metal center give rise to a strong exciton couplet from which the absolute configuration can be determined.^[18]

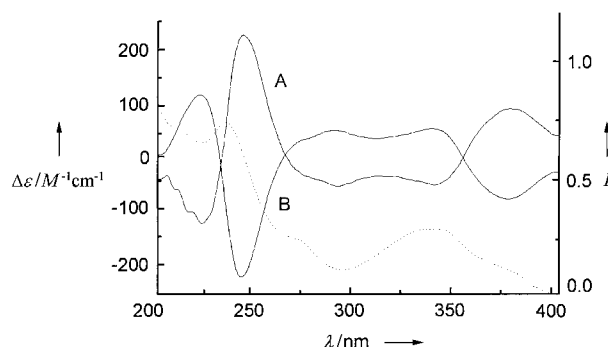


Figure 3. CD and absorption spectrum of the resolved tetranuclear cluster $[(\text{Nic}) \subset Ga_4L_6]^{11-}$: $\Delta\Delta\Delta\Delta$ (A) and $\Lambda\Lambda\Lambda\Lambda$ (B) forms.

An X-ray crystallographic analysis^[19] of $\Delta\Delta\Delta\Delta$ - $[(Et_4N) \subset Ga_4L_6]$ confirmed the absolute configuration at the metal center (Figure 4). The gallium ions are coordinated in a distorted octahedral fashion (average Ga–O bond length $1.966 \text{ \AA}$, with a twist angle at the Ga center of 40.2° and Ga...Ga distances of $12.663 \text{ \AA}$). These values are very similar to those found in the crystal structure of the same compound in racemic form.^[13]

Chirality at octahedral metal centers can be imposed by chiral ligands,^[3] and a tetrahedral bis-catecholate cluster with

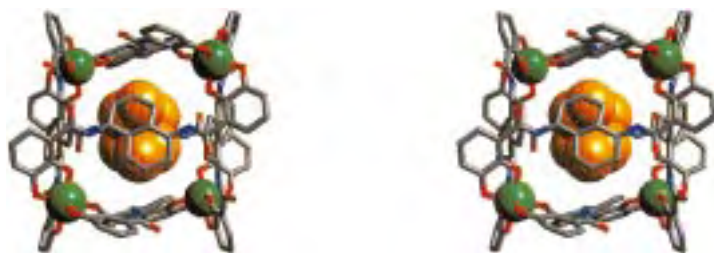


Figure 4. Crystal structure of $\Delta\Delta\Delta\Delta$ -[(Et_4N) $\subset$ $\text{Ga}_4\mathbf{2}_6$] (stereoview). View along the twofold axis of the molecule showing its overall crystallographic T -symmetry. The disorder of the naphthyl backbone and counterions have been omitted for clarity.

exclusive Δ configurations at the Ga^{III} metal centers has been reported.^[20] To the best of our knowledge, the $\Delta\Delta\Delta\Delta$ - and $\Delta\Delta\Delta\Delta$ -[Et_4N] $\subset$ [(Et_4N) $\subset$ $\text{Ga}_4\mathbf{2}_6$] clusters are the first examples of enantiopure, nonracemizing clusters formed quantitatively from achiral labile components.^[21] Like a wooden house, the rigidity of this molecular tetrahedron results from not the individual components but the way they are assembled. Dissociation of one board followed by reattachment does not change the structure.

In summary, we have shown that a racemic mixture of homoconfigurational tetrahedral clusters with labile metal ions can be resolved into its $\Delta\Delta\Delta\Delta$ and $\Delta\Delta\Delta\Delta$ enantiomers, which are stable towards racemization even though related mononuclear or dinuclear metal complexes (helicates) racemize quickly. "Mechanical stiffness" that prevents racemization is provided through the interconnection of all four labile metal centers in a rigid three-dimensional tetrahedral arrangement. We are currently investigating the use of such chiral capsules for enantioselective catalysis and diastereoselective encapsulation of other chiral molecules.

Experimental Section

General: All NMR spectra were measured with a Bruker 500 MHz spectrometer. Chemical shifts are reported as δ downfield from sodium [D_4]2,2,3,3-[3-(trimethylsilyl)]propionate. Absorption spectra were recorded on a Hewlett–Packard 8450A UV/Vis diode array spectrophotometer. Circular dichroism (CD) spectra were measured with a Jasco J-500C spectropolarimeter equipped with an IF-500 II A/D converter. Mass spectral data were acquired using a Bruker Apex II actively shielded FT-ICR mass spectrometer equipped with an Analytica electrospray source (off-axis probe). $\text{H}_2\mathbf{2}^{[13]}$ and N -methylnicotinium iodide^[24] (NicI) were synthesized according to published procedures. Solvents and commercially available reagents were used without further purification.

Enantiopure tetrahedral clusters: [$\text{Ga}(\text{acac})_3$] (37.0 mg, 0.101 mmol), $\text{H}_2\mathbf{2}$ (66.7 mg, 0.155 mmol), and NicI (94.3 mg, 0.310 mmol) were suspended in degassed, dry CH_3OH (20 mL). A 0.508 N KOH solution in CH_3OH (610 μL) was slowly added through a syringe whereupon the ligand dissolved, and a clear solution was obtained. After 1 h, an orange-yellow powder started to precipitate. The precipitate ($\Delta\Delta\Delta\Delta$ form) was collected after 24 h by centrifugation, washed with a small portion of methanol, and dried under high vacuum (55 mg, 100%, $de > 98\%$). The remaining methanolic solution was concentrated to about 1 mL and an excess of acetone (20 mL) added to quantitatively precipitate the remaining $\Delta\Delta\Delta\Delta$ -form, which was collected by centrifugation, washed with acetone, and dried under high vacuum (49 mg, 100%, $de > 98\%$). Enantiopure Al^{III} , In^{III} , and Fe^{III} complexes were obtained using the same procedure starting with the corresponding [$\text{M}(\text{acac})_3$] salts. The enantiopure [(Nic) $\subset$ $\text{Ga}_4\mathbf{2}_6$] $^{11-}$ clusters precipitated with various unstoichiometric mixtures of Nic and K^+ ions, with quantitative yields of both $\Delta\Delta\Delta\Delta$ and $\Delta\Delta\Delta\Delta$ enantiomers (50% each). The same cluster was previously found to precipitate with mixtures

of Et_4N^+ and K^+ ions.^[13] The de values were determined by NMR spectroscopy and exceeded 98% in all cases, since no trace of the other diastereomer could be found (Figure 2). The encapsulated Nic ions were exchanged quantitatively against Et_4N^+ by elution with 1 N basic Et_4NCl on a cation exchange column (Amberlite IRC-50) and precipitation of the complex by addition of acetone after elution to yield $\Delta\Delta\Delta\Delta$ -[Et_4N] $\subset$ [(Et_4N) $\subset$ $\text{Ga}_4\mathbf{2}_6$] and $\Delta\Delta\Delta\Delta$ -[Et_4N] $\subset$ [(Et_4N) $\subset$ $\text{Ga}_4\mathbf{2}_6$]. Crystals suitable for analysis by X-ray diffraction were obtained by slow vapor diffusion of acetone into an aqueous solution of $\Delta\Delta\Delta\Delta$ -[(Et_4N) $\subset$ $\text{Ga}_4\mathbf{2}_6$] $^{11-}$ with a mixture of $\text{K}^+/\text{NEt}_4^+/\text{Nic}$ ions present.

The following abbreviations have been employed: Nic_H for free nicotinium protons, Nic_E for encapsulated nicotinium protons, Ar_nH for the ligand naphthyl protons and Ar_E for the ligand catecholate protons.

$\Delta\Delta\Delta\Delta$ - $\text{K}_4[\text{Nic}]_5[(\text{Nic})\subset\text{Ga}_4\mathbf{2}_6]$: ^1H NMR (500 MHz, D_2O): δ = 13.35 (s, 12 H), 7.86 (s, 12 H, Nic_H), 7.71 (d, 5 H, Nic_H), 7.66 (d, 5 H, Nic_H), 7.55 (s, 12 H, Ar_nH), 7.35 (t, 1 H, Nic_H), 7.31 (d, 12 H, Ar_E), 7.12 (t, 5 H, Nic_H), 6.83 (t, 12 H, Ar_nH), 6.75 (d, 12 H, Ar_E), 6.61 (t, 12 H, Ar_E), 6.20 (d, 1 H, Nic_H), 5.21 (d, 1 H, Nic_H), 4.22 (s, 1 H, Nic_H), 3.77 (s, 15 H, Nic_H), 2.97 (t, 5 H, Nic_H), 2.89 (t, 5 H, Nic_H), 2.21 (dd, 5 H, Nic_H), 2.01 (d, 5 H, Nic_H), 1.88 (s, 15 H, Nic_H), 1.85 (s, 3 H, Nic_H), 1.71 (d, 5 H, Nic_H), 1.68 (dd, 5 H, Nic_H), 1.32 (m, 5 H, Nic_H), 0.02 (m, 1 H, Nic_H), -0.38 (t, 1 H, Nic_H), -0.83 (m, 1 H, Nic_H), -0.88 (m, 2 H, Nic_H), -1.07 (s, 3 H, Nic_H), -1.28 (m, 1 H, Nic_H), -1.89 (m, 1 H, Nic_H); UV/Vis (H_2O , $c = 4.85 \times 10^{-6} \text{ M}$): 229 (15500), 271 (5400, sh), 340 (12400), 365 nm (4700); CD (H_2O , $c = 4.85 \times 10^{-6} \text{ M}$): 221 (340), 242 (-680), 288 (150), 337 nm (150), 374 (-240). ESI-FTMS (410 pmol μL^{-1} in methanol, samples prepared with NaOH instead of KOH): Matching isotope distributions of $\text{Na}_8[(\text{Nic})\subset\text{Ga}_4\mathbf{2}_6]^{3-}$ and $\text{Na}_7[(\text{Nic})\subset\text{Ga}_4\mathbf{2}_6]^{4-}$ were found; m/z observed for $\text{Na}_8[(\text{Nic})\subset\text{Ga}_4\mathbf{2}_6]^{3-}$: 1065.424, 1065.759, 1066.092, 1066.425, 1066.759, 1067.094, calcd for $\text{Ga}_4\text{C}_{155}\text{H}_{101}\text{N}_{14}\text{O}_{36}\text{Na}_8$: 1065.425, 1065.759, 1066.092, 1066.426, 1066.759, 1067.093.

$\Delta\Delta\Delta\Delta$ - $\text{K}_6[\text{Nic}]_5[(\text{Nic})\subset\text{Ga}_4\mathbf{2}_6]$: ^1H NMR (500 MHz, D_2O): δ = 13.10 (s, 12 H), 7.91 (t, 1 H, Nic_H), 7.81 (d, 12 H, Ar_nH), 7.77 (s, 5 H, Nic_H), 7.61 (d, 12 H, Ar_nH), 7.55 (d, 5 H, Nic_H), 7.52 (d, 12 H, Ar_E), 7.20–7.30 (m, 3 H, Nic_H), 7.25 (t, 12 H, Ar_E), 7.08 (t, 5 H, Nic_H), 6.84 (t, 12 H, Ar_nH), 6.74 (d, 12 H, Ar_E), 6.57 (t, 12 H, Ar_E), 4.89 (d, 1 H, Nic_H), 3.64 (s, 15 H, Nic_H), 2.87 (t, 5 H, Nic_H), 2.68 (t, 5 H, Nic_H), 2.10 (dd, 5 H, Nic_H), 1.87 (s, 3 H, Nic_H), 1.86 (d, 5 H, Nic_H), 1.75 (s, 15 H, Nic_H), 1.64 (m, 10 H, Nic_H), 1.38 (m, 5 H, Nic_H), -0.39 (s, 3 H, Nic_H), -0.39 (m, 1 H, Nic_H), -0.75 (m, 1 H, Nic_H), -1.00 (m, 1 H, Nic_H), -1.29 (m, 1 H, Nic_H), -1.18 (m, 1 H, Nic_H), -1.51 (m, 1 H, Nic_H), -1.71 (m, 1 H, Nic_H).

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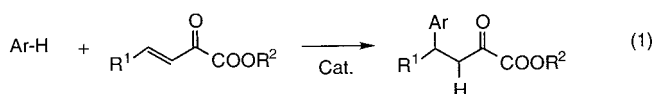
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- [19] Crystal structure of $\Delta\Delta\Delta\Delta\text{-(Et}_4\text{N)}\text{[Ga}_2\text{Zr}_2\text{]} \cdot x(\text{solvent})$: Crystal data were collected using a Siemens SMART diffractometer equipped with a CCD area detector^[25], crystal size $0.30 \times 0.20 \times 0.15$ mm, $T = -125^\circ\text{C}$, graphite-monochromated $\text{MoK}\alpha$ radiation ($\lambda = 0.71073$ Å), cubic, space group $I23$ (No. 197), $a = 22.572(1)$ Å, $V = 11500.5(9)$ Å³, $Z = 2$, $\mu = 0.528$ cm⁻¹, $F(000) = 3706$, $\rho_{\text{calc}} = 1.07$ Mg m⁻³, $2\theta_{\text{max}} = 37.64^\circ$. Of the 15524 reflections measured, 1510 were unique ($R_{\text{int}} = 0.087$). The structure was solved by direct methods and refined on F^2 using SHELXTL.^[26] Data were corrected for Lorentz and polarization effects. A semi-empirical absorption correction was applied using XPRED (ellipsoidal model, $R_{\text{int}} = 0.0486$, $T_{\text{max}} = 0.812$, $T_{\text{min}} = 0.755$).^[26] The carbonyl oxygen atom of the ligand is disordered over two positions with 1/2 occupancy, and the naphthalene backbone of the ligand is disordered across an imaginary line connecting the two carbon atoms affixed to the nitrogen atoms of the amide. This disorder was modeled as a twist of this backbone around its center with both orientations having 1/2 occupancy. A disordered NEt_4^+ ion is present in the cavity of the cluster. The nitrogen atom is located on the 23 special position, and the methylene groups are disordered over two sites with 1/2 occupancy. The methyl carbon atoms were disordered over the threefold axes and 12 sites with 1/3 occupancy. There was also a high degree of disorder among the other cations and solvent molecules present. As a result, only the encapsulated NEt_4^+ ion was found and constrained to be rigid in the disorder model described. The other 11 cations and solvent molecules are included as "x(solvent)" in the chemical formula and accounted for by a SWAT parameter. As a result of the lack of high angle data (1.2 Å resolution) only the gallium atoms, amide nitrogens, and catecholate oxygen atoms were refined anisotropically. All other atoms were refined isotropically. Hydrogen atoms were included on all appropriate atoms of the ligand that were not disordered but were not refined. Weighting scheme: $1/[\sigma^2(F_o^2) + (0.1763p)^2 + 2.7183p]$, where $p = (F_o^2 + 2F_c^2)/3$. Final $R_1 = 0.0837$ for 1022 reflections with $F_o > 4\sigma(F_o)$ (1162 Friedel unique data, 157 parameters, 6 restraints); for all 1510 data, $wR_2 = 0.269$, GOF = 1.118; Flack^[27] parameter = 0.08(8); max/min residual density +0.28/−0.27 e Å⁻³. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-145431. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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Catalytic Asymmetric Friedel–Crafts Alkylation of β,γ -Unsaturated α -Ketoesters: Enantioselective Addition of Aromatic C–H Bonds to Alkenes**

Kim B. Jensen, Jacob Thorhauge, Rita G. Hazell, and Karl Anker Jørgensen*

Aromatic compounds are very important molecules in chemistry and the addition of these compounds to alkenes in the Friedel–Crafts alkylation constitutes one of the fundamental reactions in synthetic chemistry.^[1]

The catalytic enantioselective addition of aromatic C–H bonds to alkenes leading to formation of a new C–C bond is of considerable interest and remains a long-term challenge for chemists. Such a reaction would provide a simple and attractive method for the formation of optically active aryl-substituted compounds from easily available starting materials. Recently, the first examples of catalytic enantioselective addition reactions of aromatic and heteroaromatic compounds to activated carbonyl compounds,^[2] α -dicarbonyl compounds,^[3] and imines were reported.^[4] However, the development of a catalytic enantioselective version of the corresponding Friedel–Crafts alkylation reaction has, to the best of our knowledge, not been reported, although numerous examples can be given for the non-enantioselective version of this reaction.^[1, 5] This paper presents the first catalytic highly enantioselective Friedel–Crafts alkylation, that is, the addition of aromatic C–H bonds to β,γ -unsaturated α -ketoesters catalyzed by chiral Lewis acids [Eq. (1)].



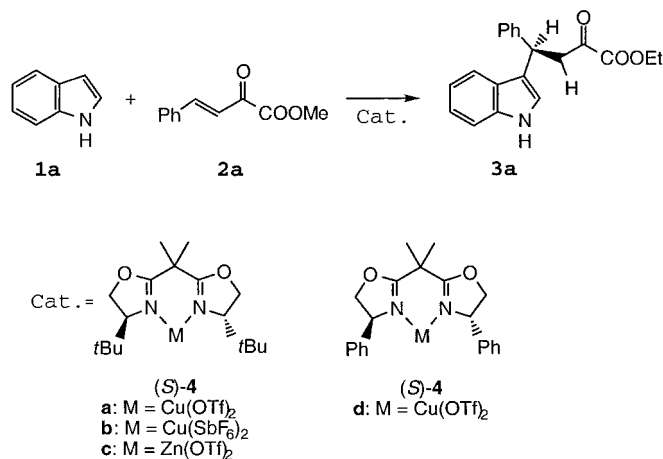
The reaction of indole (**1a**) with methyl 4-phenyl-2-oxo-3-butenolate (**2a**) can be catalyzed by various metal complexes, and the application of the chiral bisoxazoline (BOX) complexes^[6, 7] $[(S)\text{-}i\text{Bu-BOX}]\text{M}$ ($(S)\text{-4a-c}$; $\text{M} = \text{Cu}(\text{OTf})_2$, $\text{Cu}(\text{SbF}_6)_2$, and $\text{Zn}(\text{OTf})_2$, respectively) and $[(S)\text{-Ph-BOX}]\text{M}$ ($(S)\text{-4d}$; $\text{M} = \text{Cu}(\text{OTf})_2$) gives the optically active Friedel–Crafts alkylation product **3a**. Some representative screening results are presented in Table 1. The Friedel–Crafts alkylation reactions with $(S)\text{-4a-c}$ and $(S)\text{-4d}$ proceed with high conversion. For the reaction catalyzed by $(S)\text{-4a}$, product **3a** is formed with up to 88 % *ee* in CH_2Cl_2 (entry 3), while 74 % *ee* is found in THF (entry 6). In Et_2O , with 2 mol % of the catalyst,

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Table 1. Catalytic enantioselective Friedel–Crafts alkylation reaction of indole (**1a**) with methyl 4-phenyl-2-oxo-3-butenate (**2a**) under various reaction conditions.^[a]



Entry	Catalyst	Solvent	<i>T</i> [°C]	<i>t</i> [h]	Conv. [%] ^[b]	<i>ee</i> [%] ^[c]
1	–	CH ₂ Cl ₂	20	24	27	0
2	(<i>S</i>)- 4a	CH ₂ Cl ₂	0	0.5	100	36
3	(<i>S</i>)- 4a	CH ₂ Cl ₂	–78	3	100	88
4	(<i>S</i>)- 4a	Et ₂ O	0	0.5	100	88
5	(<i>S</i>)- 4a	Et ₂ O	–78	16	100	97
6	(<i>S</i>)- 4a	THF	–78	1	100	74
7	(<i>S</i>)- 4a	CH ₂ Cl ₂ /pentane 1:2	–78	16	99	89
8 ^[d]	(<i>S</i>)- 4a	Et ₂ O	–78 → –30	64	100	99.5
9	(<i>S</i>)- 4c	Et ₂ O	0 → 20	18	100	87
10	(<i>S</i>)- 4d	Et ₂ O	–78	16	100	42 ^[e]

[a] The reactions were performed on a 0.4 mmol scale with 10 mol % catalyst. Indole (**1a**) and the enone **2a** were used in a 1:1 ratio. For further details, see the Supporting Information. [b] Determined by ¹H NMR spectroscopy of the crude product. [c] Determined by HPLC. [d] The reaction was performed on a 2 mmol scale with 2 mol % catalyst. [e] The opposite enantiomer of **3a** to that shown in the scheme was obtained.

only one enantiomer of **3a** can be detected by chiral HPLC (entry 8). The reaction can also proceed with only 0.5 mol % of (*S*)-**4b** as the catalyst, to give **3a** in >95 % isolated yield and with 84 % *ee*. The reaction time required is dependent on the reaction temperature; after only 30 min the reaction of **1a** with **2a** catalyzed by (*S*)-**4a** in Et₂O at 0 °C is completed and **3a** is formed with 88 % *ee* (entry 4). Catalyst [(*S*)-*t*Bu-BOX]Zn(OTf)₂] ((*S*)-**4c**), which is a more air-stable catalyst than the corresponding copper complex (*S*)-**4a**, is also an effective catalyst for the reaction of **1a** with **2a** giving **3a** with up to 87 % *ee* (entry 9), while catalyst (*S*)-**4d** produces the opposite enantiomer of **3a** with an *ee* value of only 42 % (entry 10).^[8]

The scope of the catalytic enantioselective Friedel–Crafts alkylation reaction is shown by the reaction of various aromatic compounds **1a–g** with different β,γ-unsaturated α-ketoesters **2a–d** in the presence of (*S*)-**4a,b** as the catalysts [Eq. (2); Bn = benzyl]. The results are presented in Table 2; the compounds **2a–d** are chosen to show the span of alkene substituents in the reaction as both alkyl, aromatic, and protected alcohols can be present.

The catalytic enantioselective Friedel–Crafts alkylation reaction proceeds well for both heteroaromatic and aromatic

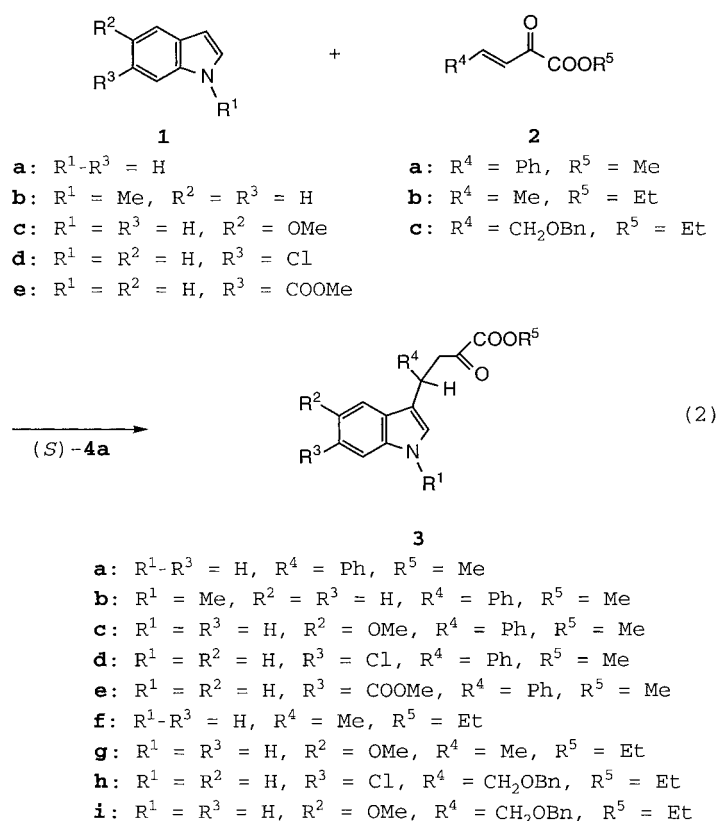


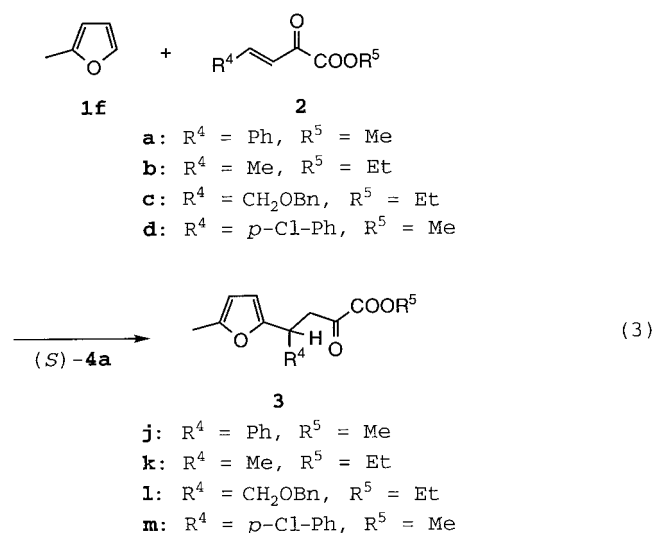
Table 2. Catalytic enantioselectivities in Friedel–Crafts alkylation reactions between different aromatic compounds and β,γ-unsaturated α-ketoesters [Eqs. (2)–(4)].^[a]

Entry	Product	Cat. [mol %]	<i>T</i> [°C]	<i>t</i> [h]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	3a	2	–78 → –30	64	77	99.5
2	3b	5	–78 → –30	48	98	96
3	3c	5	–78	1	95	>99.5
4	3d	10	–20 → 0	16	69	97 ^[d]
5	3e	10	–20 → 0	16	82	94
6	3f	5	–78	16	96	95
7	3g	5	–78	1	95	>99.5
8	3h	10	–20 → 0	16	70	80
9	3i	5	–78	1	98	95
10	3j	10	0	48	99	88
11	3k	10	0	24	93	88
12	3l	10	0	24	90	80
13	3m	10	0	18	90	79
14	3n ^[e]	10	0	2	65	89
15	3o	10	–60	28	68	60

[a] For the reactions in entries 1–13, catalyst (*S*)-**4a** was used and the aromatic compound was added in 1–1.33 equivalents. For entries 14, 15, (*S*)-**4b** was added and the aromatic compound was used in three equivalents. For further details see the Supporting Information. [b] Yield of isolated product. [c] Determined by HPLC or GC. [d] After recrystallization an *ee* value of 99 % was measured. [e] Some double-addition product is also formed.

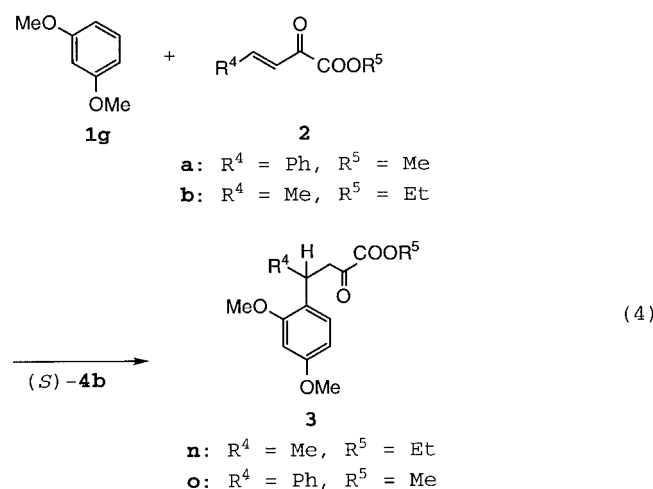
compounds. For many of the reactions reported chromatographic purification is not necessary as the optically active products can be isolated directly by filtration of the chiral catalyst followed by evaporation of the solvent. Entries 1–9 show the results for the reaction of the different indoles **1a–e** with **2a–c** giving the Friedel–Crafts alkylation products **3a–i** [Eq. (2)]^[9] in high yields and with excellent enantio-

lectivities; for example, 5-methoxy-1*H*-indole (**1c**) reacts with **2a–c** to give **3c** and **3g** as enantiopure compounds (>99.5% *ee*), while **3i** is formed with 95% *ee*. Indoles **1d** and **1e**, substituted with electron-withdrawing substituents, also react with **2a** in a highly enantioselective manner and *ee* values of 97% and 94% *ee* are obtained for **3d** and **3e**, respectively. Indoles substituted with methyl and phenyl in the 2-position give the corresponding Friedel–Crafts alkylation products in good yield (60–70%) and moderate enantioselectivity ($\approx 50\%$ *ee*; results not shown). Other heteroaromatic compounds, such as 2-methylfuran (**1f**), react with **2a–d** catalyzed by (*S*)-**4a** as shown in Equation (3) (entries 10–13 in Table 2). The Friedel–Crafts products **3j–m**^[10] are all



formed in >90% yield and with high enantiopurity (up to 88% *ee* is obtained). The enantioselective Friedel–Crafts alkylation reaction also proceeds for aromatic compounds, such as 1,3-dimethoxybenzene (**1g**) [Eq. (4)], and entries 14, 15 in Table 2 show the results for the reaction of **1g** with **2a** and **2b**. These reactions give the corresponding *o,p*-dimethoxy-substituted aromatic products and **3n** is formed in 89% *ee* at 0°C after 2 h reaction time, while **3o** is formed in 60% *ee*.

For catalytic enantioselective Friedel–Crafts alkylation reactions that take place at below -50°C with indoles, the



enol product is formed. The enol form of the product can be isolated and characterized for several of the compounds. However, treatment of the enol product with MeOH at room temperature leads to a smooth formation of the keto form of the Friedel–Crafts products.

In order to obtain insight into the mechanism for this new catalytic enantioselective Friedel–Crafts alkylation reaction, the absolute configuration of the indole-derived product **3d**, obtained by reaction of **1d** with **2a** catalyzed by (*S*)-**4a**, has been determined by X-ray analysis. The X-ray crystal structure of **3d** shown in Figure 1 leads to an assignment of the chiral center formed in the reaction as *R*.

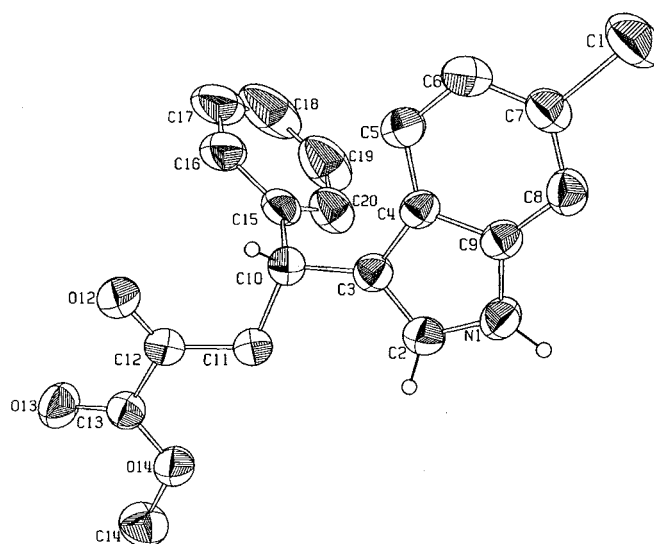


Figure 1. X-ray crystal structure of **3d** for determination of the absolute configuration of the chiral center formed during the reaction of **1d** with **2a** in the presence of (*S*)-**4a**. Only the hydrogen atoms on the chiral carbon atom and a part of the indole ring are shown, the rest are omitted for clarity.

Based on the absolute configuration of the chiral Friedel–Crafts product formed, it is postulated that the β,γ -unsaturated α -ketoester coordinates in a bidentate fashion to the (*S*)-**4a** catalyst; this leads to a square-planar intermediate.^[6b–d] Such an intermediate has the *Re* face of the reacting alkene carbon atom available for approach of the aromatic compound. In Figure 2 the approach of the indole to the β,γ -

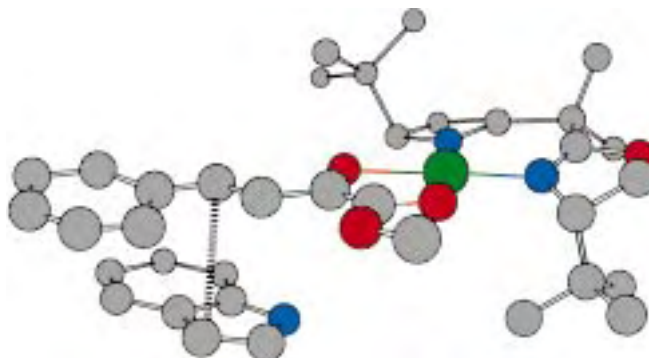


Figure 2. A model for the approach of indole to the β,γ -unsaturated α -ketoester **2a** coordinated to (*S*)-**4a** in a square-planar fashion. This model can account for the absolute configuration of the formed Friedel–Crafts product **3d**. Color scheme: gray = carbon, red = oxygen, green = copper, blue = nitrogen.

unsaturated α -ketoester coordinated to the chiral $[(S)\text{-}t\text{Bu-BOX}]\text{Cu}(\text{OTf})_2$ ($(S)\text{-}4\text{a}$) catalyst is shown. This approach can account for the absolute configuration of the product obtained, but at the present stage of investigations we do not fully understand which orientation the incoming aromatic compound has relative to the intermediate.

We have developed a highly catalytic enantioselective reaction for the addition of aromatic C–H bonds to β,γ -unsaturated α -ketoesters catalyzed by chiral bisoxazoline–copper(II) complexes. This new reaction, which is shown to be useful for the reaction of heteroaromatic and aromatic compounds with β,γ -unsaturated α -ketoesters having alkyl, aromatic, and protected alcohols as alkene substituents, is a simple and attractive method for the formation of optically active Friedel–Crafts alkylation compounds from easily available starting materials.

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Nonpeptidic $\alpha_v\beta_3$ Integrin Antagonist Libraries: On-Bead Screening and Mass Spectrometric Identification without Tagging**

Christoph Gibson, Gábor A. G. Sulyok, Diane Hahn, Simon L. Goodman, Günter Hölzemann, and Horst Kessler*

Over the past decade, combinatorial synthesis has progressed from being a little-known fringe area to an important technique in drug research.^[1] The split synthesis in particular enables comprehensive substance libraries to be produced rapidly.^[2] Such libraries also enable those resin particles with attached active compounds to be characterized by biological on-bead evaluation.^[3] However, the coding technique required for the identification of a particular selected substance usually reduces the efficiency of this approach.^[1] Herein, we describe the combinatorial solid-phase synthesis of uncoded diacylhydrazine libraries and their biological on-bead evaluation using a soluble $\alpha_v\beta_3$ integrin receptor. Orthogonal anchoring with a photolabile linker made it possible to photolytically cleave the compounds from selected beads and to identify them reliably using mass-spectrometric analysis (MSⁿ) on the basis of fragmentation patterns. The degree of affinity of the selected diacylhydrazines to the $\alpha_v\beta_3$ receptor was confirmed through receptor-binding studies carried out on the isolated compounds, which underlines the success of our strategy. To our knowledge, this is the first successful application of the “one bead–one compound” concept as applied to uncoded, nonpeptidic compound libraries.^[3]

The inhibition of the $\alpha_v\beta_3$ integrin receptor is regarded as a promising goal in the therapy of various pathophysiological processes such as tumor-induced angiogenesis, restenosis, osteoporosis, and acute renal failure.^[4] The amino acid sequence Arg-Gly-Asp (RGD), which can be recognized by the $\alpha_v\beta_3$ receptor and by at least ten additional integrins,^[5] has been used as a lead structure in the development of $\alpha_v\beta_3$ inhibitors.^[4]

In previous work, we have been able to show that the substitution of the glycine in cyclic $\alpha_v\beta_3$ -selective RGD peptides can take place with an aza-glycine whilst maintaining both affinity and selectivity.^[6] Based on these results, we developed a diacylhydrazine library that meets all require-

ments of the “one bead–one compound” concept.^[3] To achieve this, the lead structure Arg-Gly-Asp was transformed into a RGD mimetic, which could be assembled step-by-step on a solid support according to the Fmoc strategy^[7] with the building blocks **A**–**D** (see Figure 1). The RGD mimetics were anchored to the resin with a photolinker^[8] to achieve maximum orthogonality to the various reaction conditions of the solid-phase synthesis.

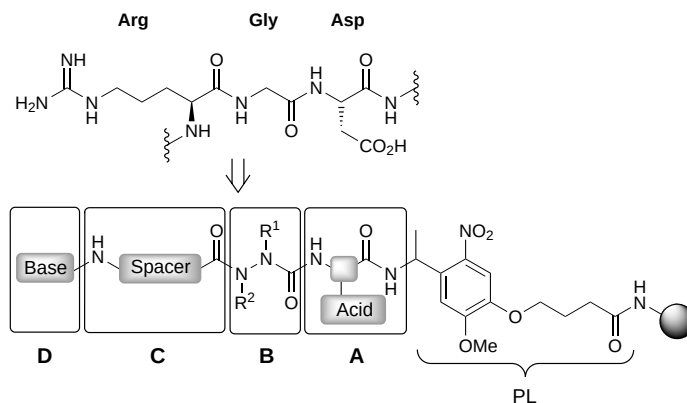


Figure 1. Transformation of the RGD sequence into a modularly assembled RGD mimetic.

The building blocks used for the synthesis of the library are shown in Figure 2.^[9] The synthesis of activated aza-substituted building blocks **B**^{1–3} and their incorporation onto the solid support has recently been described by us.^[10] The building blocks of groups **A** and **C** were selected in such a way that each molecular mass occurred only once within one group: This enabled the structure assignment of a selected RGD mimetic using MSⁿ (see below). The sequence for the synthesis of the RGD mimetics by applying the split method^[2] is shown in Scheme 1. Firstly, the building blocks **A**^{1–5} were attached to TentaGel Macrobeads under standard conditions. Building block **A**⁶ could be synthesized on the solid support using a submonomeric approach. To achieve this, TentaGel Macrobeads were acylated with 3-(chloromethyl)benzoyl chloride and the resulting resin-bound benzyl chloride was treated with *tert*-butyl-3-aminopropionate to produce the resin-bound building block **A**⁶. After removal of the Fmoc protecting group, the activated aza-building blocks **B**^{1–3} were introduced.^[10] Basic deprotection, coupling of the spacer building blocks **C**^{1–10}, and subsequent removal of the temporary and permanent protecting groups resulted in ten amino-RGD mimetic libraries, each comprising 33 compounds.^[11] Through guanylation with **D**¹ or pyrimidylation with **D**² and subsequent deprotection, two additional libraries each comprising 330 compounds were obtained.^[12]

For the quality control of the RGD mimetic libraries and after the biological on-bead evaluation, the compounds were photolytically cleaved from individual beads and characterized subsequently with LC–MS and/or ESI-MSⁿ. In order to assess the suitability of this strategy, several isolated synthesized aza-RGD mimetics were investigated by MSⁿ. Figure 3 illustrates the results of the MS² analysis of the aza-RGD mimetics **1**–**3**. The MS² spectra of the $[M+H]^+$ ions (Figure 3,

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

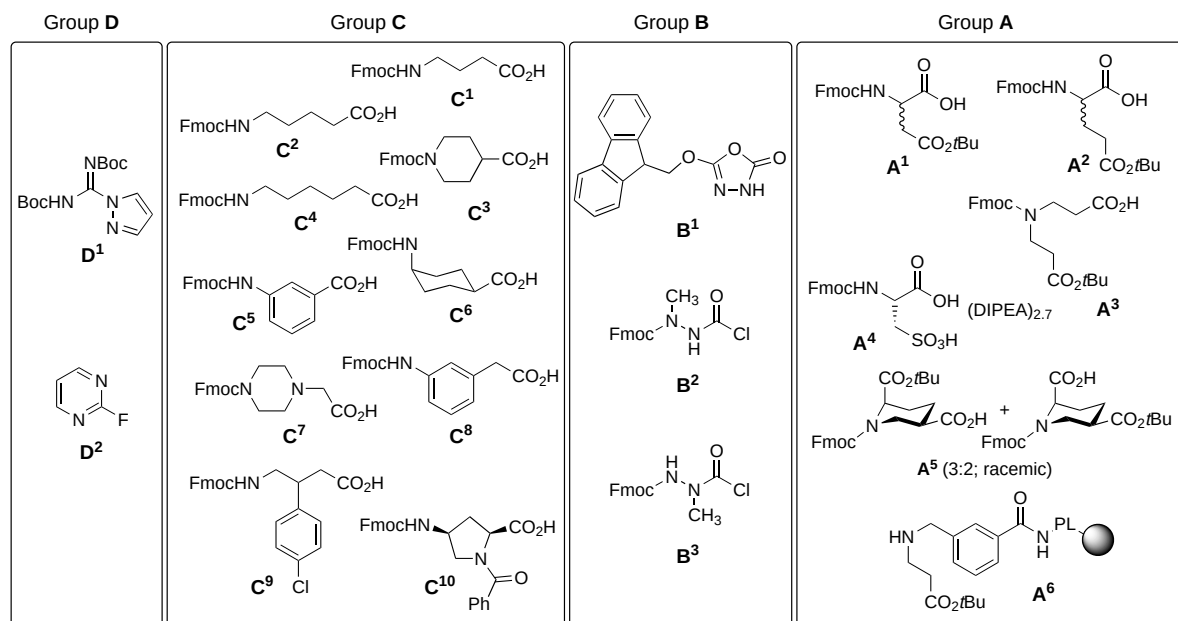
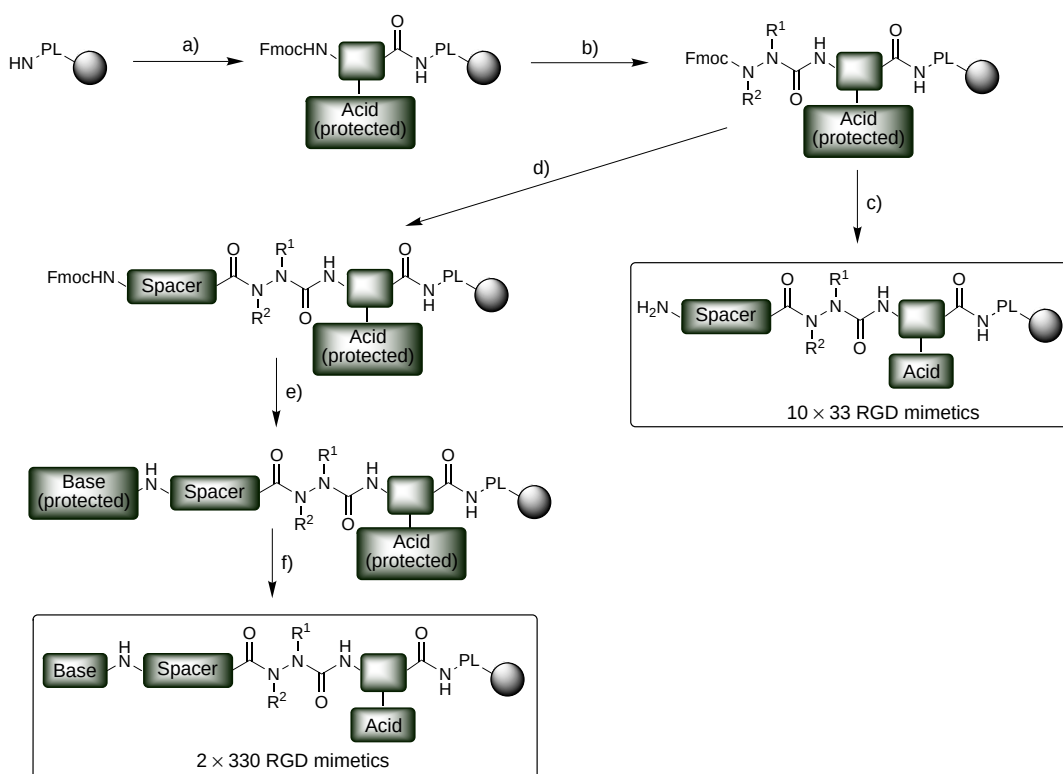


Figure 2. Building blocks used for the synthesis of the RGD mimetic libraries.



Scheme 1. a) **A**¹⁻⁵ (3.0 equiv), HATU (2.8 equiv), collidine (30 equiv), DMF, RT, 3 h; **A**⁶ 3-(chloromethyl)benzoyl chloride (6.8 equiv), DIEA (14 equiv), CH₂Cl₂, RT, 75 min; *tert*-butyl-3-aminopropionate (150 equiv), DMF, 45 °C, 12 h; b) 20% piperidine in DMF; **B**¹ (3.1 equiv), CH₂Cl₂, RT, 3 h; **B**² (5.1 equiv), DIEA (6.0 equiv), CH₂Cl₂, RT, 2.5 h; **B**³ (5.1 equiv), DIEA (5.5 equiv), DMF, RT, 15 h; c) 20% piperidine in DMF; **C**¹⁻¹⁰ (3.0 equiv), HATU (2.8 equiv), collidine (30 equiv), DMF, RT, 12 h; 20% piperidine in DMF; 50:50:5 CH₂Cl₂:TFA:TIPS, RT, 1.5 h; 20% DIEA in CH₂Cl₂; d) 20% piperidine in DMF; **C**¹⁻¹⁰ (3.0 equiv), HATU (2.8 equiv), collidine (30 equiv), DMF, RT, 12 h; e) 20% piperidine in DMF; **D**¹ (19 equiv), CHCl₃, 50 °C, 20 h or **D**² (15 equiv), DIEA (15 equiv), DMF, RT, 1 d, then **D**² (30 equiv), 5% BF₃·Et₂O in DMF, RT, 7 d; f) 50:50:5 CH₂Cl₂:TFA:TIPS, RT, 1.5 h; 20% DIEA in CH₂Cl₂. Fmoc = fluorenylmethoxycarbonyl, DMF = *N,N*-dimethylformamide, HATU = O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, DIEA = diisopropylethylamine, TIPS = triisopropylsilane.

left) and the $[M+Na]^+$ ions (Figure 3, right) show clearly defined signals of the fragment ions of B_B and/or A_B types. This information enables building block **A** to be identified. In

particular, the MS² spectra of the $[M+Na]^+$ ions of isomeric compounds **2** and **3** show clearly different intensities of the B_B and A_B fragment ions: Compound **2** containing aza-Sar

The ionization properties of the amino- as well as the guanyl-RGD mimetics were considerably improved by introduction of an "N-terminal" Boc protective group. Most of the aza-RGD mimetics investigated exhibited a high degree of purity; about one third of the LC-MS-spectra additionally contained a compound lighter by m/z 18 with a relative proportion of 30–70%.

For biological on-bead evaluation, the resin-bound RGD mimetics were first incubated with the soluble, biotinylated $\alpha_v\beta_3$ receptor and subsequently with a monoclonal antibiotin alkaline phosphatase conjugate. If a compound was recognized by the receptor, the respective bead could be stained with the well known alkyl phosphatase substrate 5-bromo-4-chloro-3-indolyl phosphate disodium salt (BCIP).^[13] No positive beads were found in the amino-libraries. Figure 4 depicts the beads of the guanylated and pyrimidylated libraries after on-bead evaluation with the $\alpha_v\beta_3$ receptor. In the guanylated library, there were four intensely stained and ten weakly stained

beads; in the pyrimidylated library, two weakly stained beads were observed.

Using LC-MS and MSⁿ, all RGD mimetics bound to the beads and designated positive could be characterized unequivocally. The four intensely stained beads all carried aromatic compound **5** (Table 1). Of the ten weakly stained beads from the same library, compound **5** was detected once, compound **6** five times, compound **7** three times, and compound **8** once. Compound **9**—analogous to RGD mimetic **5**—was detected on the two beads selected from the pyrimidylated library. For the determination of the inhibition

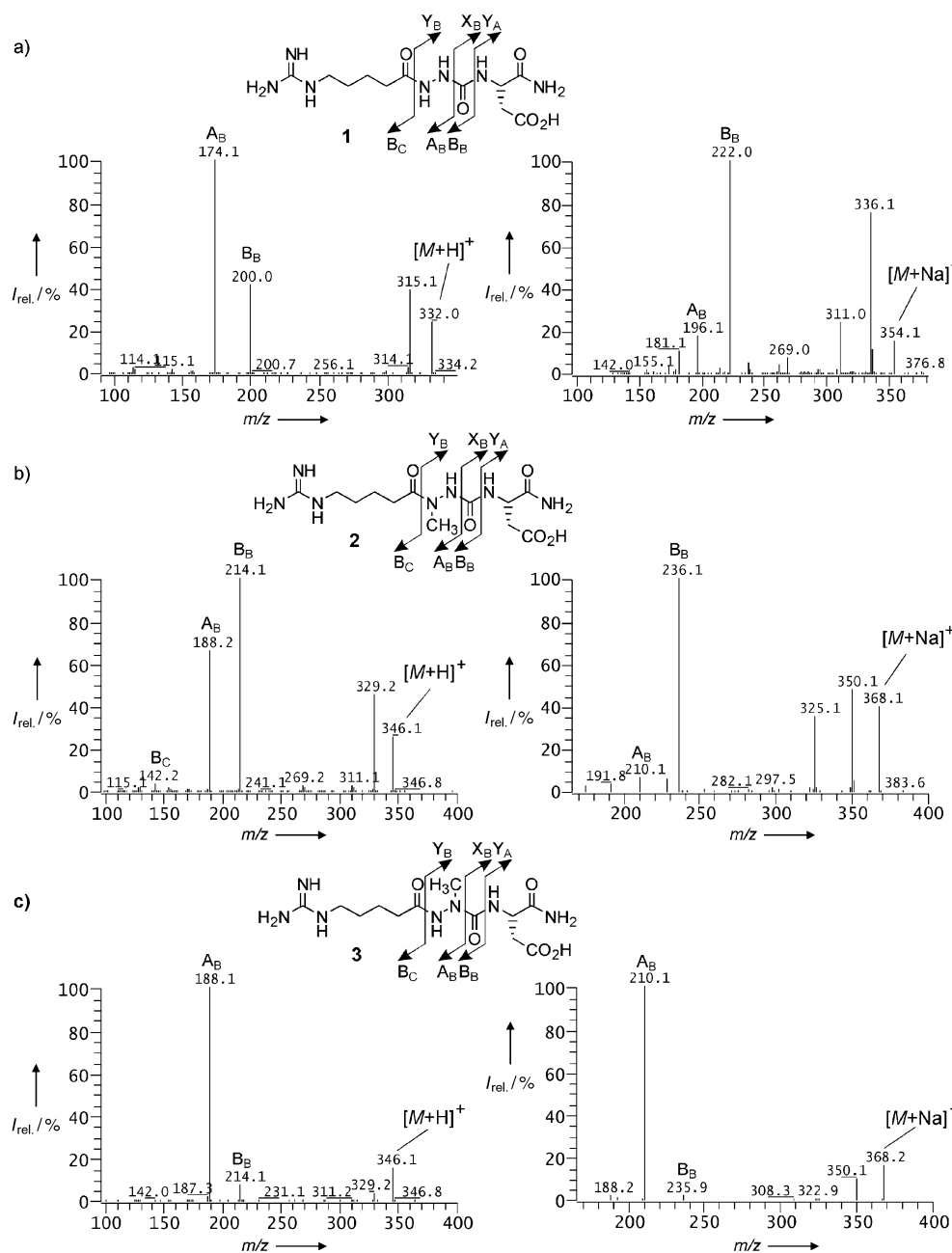


Figure 3. MS² analysis of aza-RGD mimetics containing aza-Gly (a), aza-Sar (b), and aza-Ala (c). Note that the $[M+Na]^+$ ion of the aza-Sar-containing compound **2** predominantly yields the fragment ion of the type B_B, whereas the $[M+Na]^+$ ion of the aza-Ala-containing compound **3** predominantly yields the fragment ion of the type A_B. In order to define the fragment ions unequivocally, they were subscripted with the building block, which is adjacent to the fragmentation position in the fragment ion. *RA* = relative abundance.

decomposed with 10:1 selectivity to the B_B fragment ion and compound **3** containing aza-Ala decomposed with approximately the same selectivity to the A_B fragment ion. Thus, one can differentiate clearly between regioisomeric building blocks **B** aza-Sar (**B**²) and aza-Ala (**B**³). In addition, the weak signal of the B_C fragment ion can be recognized in the MS² spectrum of the [M+H]⁺ ion of **2**. On the other hand, this fragment ion appears in all the MS³ spectra of the B_B and A_B fragment ions of protonated species **1–3** in noticeably higher intensities and, hence, enables building blocks **B** and **C** to be assigned. Consequently, our diacyl hydrazines

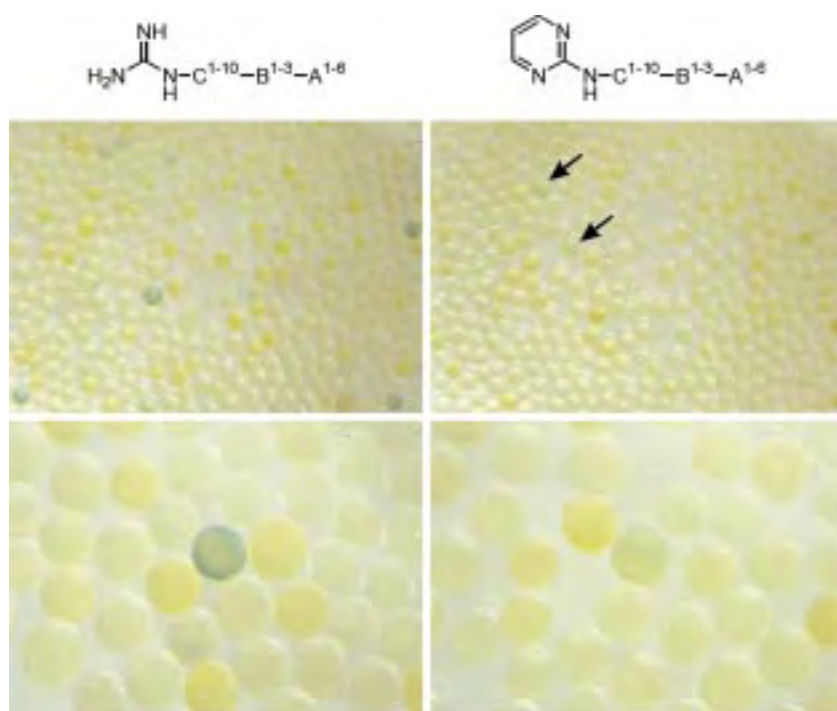


Figure 4. TentaGel Macrobeads after the on-bead receptor assay with the $\alpha_v\beta_3$ integrin. Above: fivefold enlargement, below: fifteenfold enlargement.

constants with respect to the isolated $\alpha_v\beta_3$, $\alpha_v\beta_5$,^[4b] and $\alpha_{IIb}\beta_3$ ^[14] receptors, the selected RGD mimetics were synthesized on Rink amide 4-methyl-benzhydrylamine (MBHA) resin as L- and D-enantiomers, respectively. All RGD mimetics showed a measurable activity on the $\alpha_v\beta_3$ receptor but the L-enantiomers, however, exhibited throughout a higher affinity to the $\alpha_v\beta_3$ receptor than the respective D-enantiomers. With an IC_{50} value of 150 nM, compound **5** showed, in contrast to the other selected aza-RGD mimetics, the highest affinity to the $\alpha_v\beta_3$ receptor; thus, the color intensity of the positive beads clearly correlates with the affinity of the resin-bound RGD mimetics to the receptor.

Only the L-isomers of **5** and **6** showed a weak affinity to the $\alpha_v\beta_5$ receptor, both being less pronounced when compared to the $\alpha_v\beta_3$ receptor. All selected aza-RGD mimetics inhibited the binding of the platelet receptor $\alpha_{IIb}\beta_3$ to fibrinogen with IC_{50} values of $>100 \mu\text{M}$. Thus, all the selected

Table 1. Inhibition behavior of the different RGD mimetics with regard to binding of vitronectin to the isolated $\alpha_v\beta_3$ or $\alpha_v\beta_5$ receptor, as well as the binding of fibrinogen to the isolated $\alpha_{IIb}\beta_3$ receptor. The linear peptide GRGDSPK **4** was chosen as standard.

No.	Structure and frequency	Isomer of A	IC ₅₀ [μM]			
			α _v β ₃	α _v β ₅	α _{IIb} β ₃	
4	GRGDSPK		0.40	42	1.1	
5		4 of 4; 1 of 10	L-Asp-NH ₂	0.15	7.2	> 100
			D-Asp-NH ₂	7.2	> 100	> 100
6		5 of 10	L-Asp-NH ₂	3.1	57	> 100
			D-Asp-NH ₂	50	> 100	> 100
7		3 of 10	L-Asp-NH ₂	5.0	> 100	> 100
			D-Asp-NH ₂	41	> 100	> 100
8		1 of 10	L-Asp-NH ₂	6.8	> 100	> 100
			D-Asp-NH ₂	47	> 100	> 100
9		2 of 2	L-Asp-NH ₂	15	> 100	> 100
			D-Asp-NH ₂	53	> 100	> 100
10			0.0026	0.280	8.3	

aza-RGD mimetics showed a clear preference for the $\alpha_v\beta_3$ receptor.

Lead structure **5** was found to exhibit a relatively high degree of polarity; an unfavorable pharmacokinetic profile can thus be expected for this compound. However, it has been shown in the past that a hydrophobic residue in the β -position to the carboxy group is tolerated by the $\alpha_v\beta_3$ receptor.^[4d] For this reason, we replaced the terminal carboxamide group with a phenyl residue. The less polar RGD mimetic **10** exhibited similar selectivity and considerably increased activity on the $\alpha_v\beta_3$ receptor compared to the polar mimetic **5**.

The results obtained would appear to support our concept for identifying new, low molecular weight integrin ligands through application of combinatorial solid-phase synthesis, biological on-bead evaluation, and mass spectrometry to the selected compounds.

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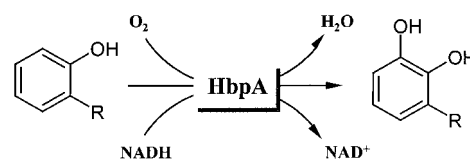
The First Synthetic Application of a Monooxygenase Employing Indirect Electrochemical NADH Regeneration**

Frank Hollmann, Andreas Schmid,* and Eberhard Steckhan†

In memory of Eberhard Steckhan

One of the most important challenges in applying monooxygenase reactions in vitro is to find an effective regeneration system for the necessary co-enzyme (mostly NAD(P)H). The well-established methods for the regeneration of the nicotinamide co-enzyme mainly consist of an enzyme-coupled approach utilizing formate dehydrogenase^[1, 4c] (for NAD(P)H) or glucose-6-phosphate dehydrogenase (for NADPH).^[2] Additionally, non-enzymatic redox catalysts have been developed and successfully applied to NAD(P)H-dependent dehydrogenases.^[3] Thus only the producing enzyme and a mediator together with the electrode, as a source of reducing equivalents, are needed.

Here we report on the first application of an isolated monooxygenase with an indirect electrochemical regeneration of NADH. The enzyme employed is the 2-hydroxybiphenyl-3-monooxygenase (HbpA, E.C. 1.14.13.44), a member the class of flavine-dependent monooxygenases, from *P. azelaica*.^[4] The homotetramer with a total mass of 256 kDa catalyzes the specific *ortho*-hydroxylation of several α -substituted phenol derivatives (Scheme 1). To the best of our knowledge no chemical counterpart with comparable specificity is known.



Scheme 1. Specific *ortho*-hydroxylation of α -substituted phenols catalyzed by 2-hydroxybiphenyl-3-monooxygenase. R = alkyl (Et, Pr, *i*Pr), aryl (Ph, 2-HOC₆H₄), Hal (F, Cl, Br).

For the regeneration of NADH we applied the [Cp*Rh(bpy)Cl]Cl complex which had been developed in our group (Cp* = C₅Me₅; bpy = 2,2'-bipyridine). The corresponding hydridorhodium complexes, which can be generated either electrochemically by cathodic reduction at –750 mV (versus Ag/AgCl_{sat.}) or chemically with formate, transform NAD(P)⁺ efficiently into the enzymatically active 1,4-NAD(P)H form^[3, 5] (Scheme 2). The conversion rates

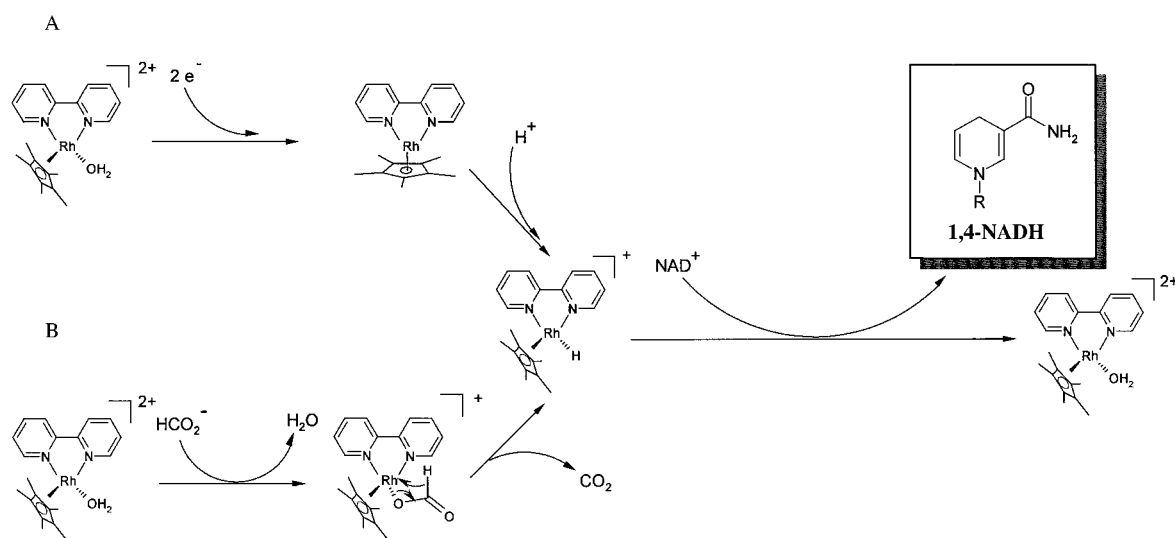
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Scheme 2. Indirect electrochemical (A) and chemical regeneration of NADH (B).

(Table 1) of the enzymatic reaction with reduced coenzyme and under indirect chemical regeneration of NADH (Scheme 2B) prove the applicability of the proposed regeneration system. Hence we advanced the enzymatic reaction to the indirect electrochemical regeneration of NADH (Scheme 2A).

Table 1. Comparison of the productivity rates (dc/dt) of 2,3-dihydroxybiphenyl with reduced coenzyme (NADH), under indirect chemical and indirect electrochemical NADH regeneration.^[a]

Regeneration	HbpA [U]	dc/dt [$\mu\text{mol min}^{-1}$]	Rel. activity ^[b] [%]
none ^[c]	2.24	2.09	93.3
chemically ^[d]	2.60	2.33	89.6
electrochemically ^[e]	19 ^[f]	1.83	9.65 ^[f]

[a] General conditions: phosphate buffer (50 mM, pH 7.5, saturated with air); $T = 25^\circ\text{C}$; $[\text{Cp}^*\text{Rh}(\text{bpy})] = 0.5 \text{ mM}$; $[\text{2-hydroxybiphenyl}] = 0.8 \text{ mM}$. [b] Productivity relative to the amount of HbpA applied. [c] $[\text{NADH}] = 1.0 \text{ mM}$. [d] $[\text{NAD}^+] = 1.09 \text{ mM}$; $[\text{HCOONa}] = 150 \text{ mM}$. [e] $[\text{NAD}^+] = 1.0 \text{ mM}$; air intake = $10 \text{ cm}^3 \text{ min}^{-1}$; $[\text{2-hydroxybiphenyl}] = 2 \text{ mM}$; $[\text{FAD}] = 20 \mu\text{M}$; $E = -750 \text{ mV}$ (versus $\text{Ag}/\text{AgCl}_{\text{sat.}}$). [f] On account of the fast HbpA inactivation (see text) large amounts of enzyme had to be applied; the air intake is rate limiting.

This approach was examined by cyclic voltammetry. Even at proton concentrations less than 10^{-8} M (pH 8) the uptake of a proton into the ligand sphere of the reduced rhodium species proceeds quite quickly so that no oxidation peak is visible. Strong increases in the peak current (catalytic effects) are detected, even at high sweep rates in the presence of NAD^+ (Figure 1). The reduction peak potential lies at -750 mV (versus $\text{Ag}/\text{AgCl}_{\text{sat.}}$), which is more positive by far than the first reduction potential of NAD^+ (-920 mV versus the saturated calomel electrode (SCE)).^[6] Thus, coenzyme inactivation by direct electron transfer becomes negligible.

The role of molecular oxygen was examined in detail. We found that it inhibits the transfer of hydride from the reduced rhodium complex to NAD^+ both in the chemical and the electrochemical regeneration. As can be clearly seen in Figure 2 the regeneration rate of NADH strictly depends on the rate of air input. For example, the rate of NADH production decreases from 1.1 (without air input) to

$0.27 \text{ mmol L}^{-1} \text{ h}^{-1}$ with an air input of $10 \text{ cm}^3 \text{ min}^{-1}$. No generation of NADH is detectable at a flow rate of $15 \text{ cm}^3 \text{ min}^{-1}$. This inhibition however is reversible: after ceasing the air input both the rate of NADH production and the concentration of NADH recover to their maximum values.

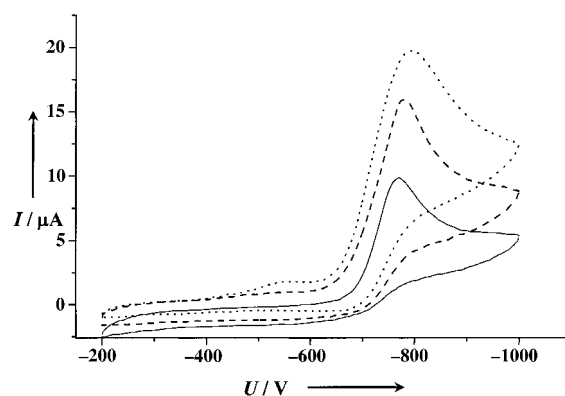


Figure 1. Catalytic effects of $[\text{Cp}^*\text{Rh}(\text{bpy})\text{Cl}]\text{Cl}$ ($5 \times 10^{-4} \text{ M}$ in 0.1 M TRIS/HCl buffer pH 7.5; TRIS = tris(hydroxymethyl)aminomethane) in the presence of various concentrations of NAD^+ (0 (—), 5×10^{-4} (---), and $1 \times 10^{-3} \text{ M}$ (·····)); $v = 81 \text{ mV s}^{-1}$; degassed buffers.

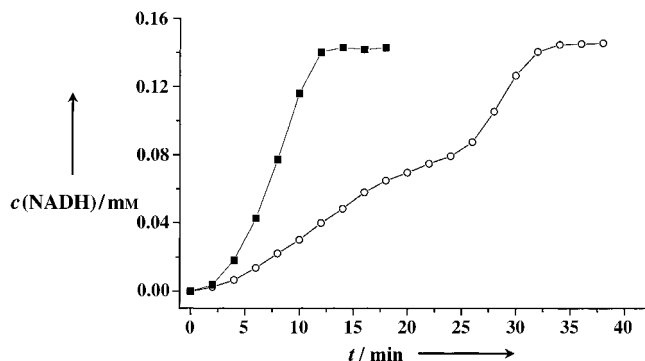
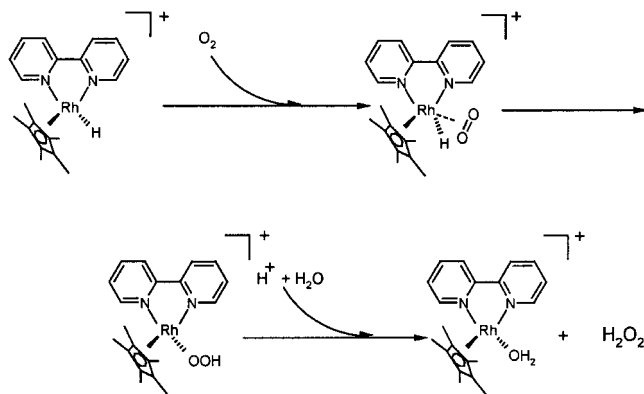


Figure 2. Influence of O_2 on the indirect electrochemical regeneration of NADH; $[\text{Cp}^*\text{Rh}(\text{bpy})\text{Cl}]\text{Cl}$ (0.1 mM in 50 mM potassium phosphate buffer pH 7.5) (■ no air insertion; ○ air input $10 \text{ cm}^3 \text{ min}^{-1}$ until $t = 25 \text{ min}$).

We characterized the product from the reaction of the hydridorhodium complex and molecular oxygen as hydrogen peroxide. We postulate its formation as depicted in Scheme 3.^[7] In addition, molecular oxygen is reduced at the applied cathode potential and also yields hydrogen peroxide. In the course of the electro-enzymatic conversion it is dismutated into O₂ and H₂O by catalase.



Scheme 3. Postulated mechanism of the reaction between the hydridorhodium complex and molecular oxygen.

During the enzymatic reaction without external input of oxygen the catechol production stops on account of a lack of molecular oxygen in the reaction medium (typically at product concentrations between 0.2 and 0.4 mM). With the active input of air into the reaction medium new product is formed. Thus productivity rates of up to 1.1 mmol L⁻¹ h⁻¹ (204 mg L⁻¹ h⁻¹) are achieved. The mediator's turnover frequency can be calculated to be 11 h⁻¹.

The rate-determining step is the inhibition of the mediator by molecular oxygen rather than the heterogeneous charge transfer at the cathode. Control experiments with homogeneous chemical regeneration of the hydridorhodium complex under otherwise comparable conditions show that the productivity rates are in the same range (for example 0.673 and 0.668 mmol L⁻¹ h⁻¹ at an air intake of 8 cm³ min⁻¹ with total conversions of 100 and 95% under electrochemical and chemical regeneration, respectively).

The poor long-term stability of the previous electro-enzymatic conversions is the result of the experimental setup: the input of heterogeneous air results in enzyme inactivation. In addition HbpA adsorbs onto the electrode surface and thus is exposed to locally high H₂O₂ concentrations that cannot be sufficiently dismutated by catalase. The half-time values for HbpA activity in phosphate buffer under the conditions of the indirect chemical regeneration are in the range of 30–40 h (depending on the speed of air input), whereas during electrolysis (depending on the amount of HbpA applied and the mass of the electrode) no enzymatic activity is detectable after about 2 h.

To overcome this stability problem we are evaluating possibilities of immobilizing the enzyme onto a solid matrix thus protecting it from the electrode. Using this division of the whole process setup into an electrochemical and an enzymatic part, the ambivalent role of molecular oxygen (substrate of the enzymatic reaction and inhibitor of the NADH regener-

ation process) can be handled better. In preliminary studies the actual production time could be enhanced by more than 2.5 fold to over 8 h.

In conclusion, we could for the first time couple a flavine-dependent monooxygenase reaction to an indirect electrochemical regeneration of NADH. The productivity rates of this not-optimized process (204 mg L⁻¹ h⁻¹) are already at about 50% of the in vivo process (390 mg L⁻¹ h⁻¹)^[8] and the in vitro process with enzymatic regeneration of the coenzyme (405 mg L⁻¹ h⁻¹).^[4c]

Experimental Section

The rhodium catalyst was prepared according to the method of Kölle and Grätzel.^[9]

HbpA was enriched from the recombinant *E. coli* JM101 [pHBP461].^[8] The raw extract was purified and enriched by expanded-bed chromatography.^[4c] Enzymatic activity was determined by a UV-spectrometric assay.^[4a]

Cyclovoltammograms were taken with a BAS-100B/W analyzer (Bioanalytical Systems) in an undivided cell employing a glassy carbon working electrode (i.d. = 3 mm), a Pt-wire counter electrode, and an Ag/AgCl_{sat.} reference electrode (Cypress Systems). Electroenzymatic conversions were performed in a thermostated electrolysis cell. A cylindrical carbon-felt electrode (*V* = 27 cm³) served as the cathode and the potential was adjusted versus a Ag/AgCl_{sat.} reference electrode. A divided cell was achieved by placing the platinum counter electrode within a dialysis membrane. The following components were dissolved in 100 mL of potassium phosphate buffer (50 mM, pH 7.5): 2-hydroxybiphenyl (2 mM), NAD⁺ (0.2 mM), [Cp*Rh(bpy)Cl]Cl (0.1 mM), FAD (20 μM), catalase (250 000 U), and HbpA (19 U). Oxygen was supplied by a heterogeneous input of air. The input rate was adjusted before each enzymatic conversion in such a way that the NAD⁺ reduction rate reached its maximum value.

The reaction was followed by HPLC analysis on a RP-18 column eluted with methanol/water (0.1% H₃PO₄) (60/40). No by-products were detected. The product was sublimated and characterized by NMR and MS analysis.

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Patterning Solid-Supported Lipid Bilayer Membranes by Lithographic Polymerization of a Diacetylene Lipid**

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Solid-supported lipid bilayers are membrane systems, in which a single lipid bilayer is adsorbed on the solid surface either by physical interactions or by chemical bonds. These systems have been studied extensively as a simple model of the biological membrane.^[1] The bilayer membrane can also incorporate proteins and provides possibilities to prepare biosensors based on electrical and optical detection.^[2] In order to mimic the sophisticated functions that real biological membranes perform, one must inevitably increase the complexity of the artificial systems. For this purpose, patterning of the membranes is a feasible approach because various components can be integrated into the membrane system with defined spatial control. The patterning of lipid bilayers has been attempted in the past either by the modification of the substrate^[3] or by the microcontact printing method.^[4]

Herein, we report a novel approach for creating patterned bilayers on solid supports. The basic idea is to imprint a pattern within the lipid bilayer by photochemical polymerization of the lipids. Two-dimensional polymerization of lipids has been studied extensively in liposomes (lipid vesicles), principally with the aim of stabilizing liposomes for drug delivery purposes.^[5] On the other hand, there have been several lines of research that exploited polymerizable thiol monolayers or fatty acid multilayers as potential photoresist materials for photolithography.^[6] One can, therefore, expect two effects from the lithographic polymerization of bilayers, namely mechanical stabilization of fluid bilayers and confinement of them in a designed region.

The general procedure is schematically illustrated in Figure 1. Firstly, a bilayer of polymerizable lipid is deposited onto a solid support (Figure 1A). The bilayer is subsequently polymerized by UV light, whereby a pattern can be imposed by using a mask (Figure 1B). The bilayer has to be kept in an aqueous solution up to this step so that the integrity of the membrane is preserved. Once the bilayer is polymerized, it becomes insoluble in organic solvents or detergent solutions. By treatment with organic solvents, monomeric lipids may be selectively removed, while the polymerized part remains on

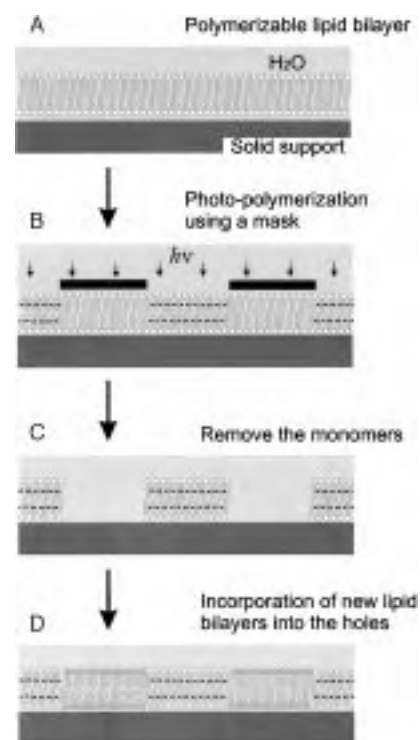
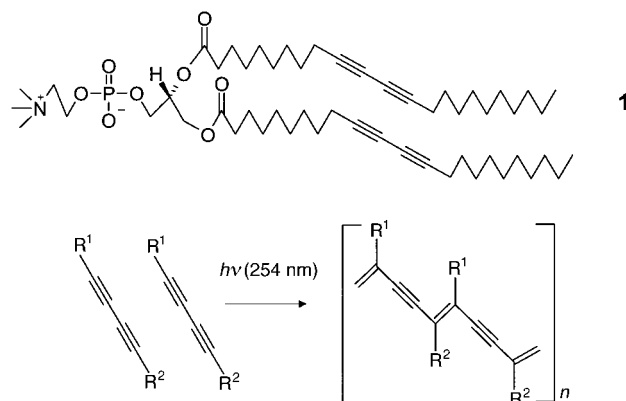


Figure 1. Schematic illustration of the bilayer patterning and introduction of new lipid bilayers.

the substrate (Figure 1C). The lipid-free areas (holes) thus created can be filled with biologically relevant lipid bilayers by the vesicle fusion technique (Figure 1D). In the case of hydrophilic surfaces, such as oxidized silicon, a lipid bilayer adsorbs spontaneously from small unilamellar lipid vesicles by the fusion and reorganization processes.^[7] The lipid bilayer is trapped in the vicinity of the surface by colloidal interactions with an estimated separation of about 10 Å^[8] and the thin water layer acts as a lubricant for the membrane. Therefore, the newly incorporated bilayers are laterally fluid and should have much of the properties that native cell membranes possess.^[1]

We have used a diacetylene phosphatidylcholine **1** as the polymerizable lipid (Scheme 1); its polymerization in liposomes has been characterized in detail.^[9] The polymerization



Scheme 1. The chemical structure of the diacetylene phospholipid **1** and its polymerization scheme.

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of **1** occurs only if the molecules are in a highly ordered state (topochemical polymerization) and the two alkyl chains react only with the same alkyl chain of adjacent molecules (α to α and β to β).^[10] Therefore, the crosslinking of two alkyl chains within a single molecule is avoided. On account of the two polymerizable chains per molecule, **1** forms crosslinked network upon polymerization and becomes insoluble in organic solvents.^[11] Such crosslinked polymers have been reported to reduce the lateral mobility of monomeric lipids drastically.^[12] The formation of a highly conjugated polymer backbone induces strong absorption and fluorescence bands in the UV/Vis range (Figure 2) and we could observe the patterned polymeric bilayers by the fluorescence microscope (Figure 3).

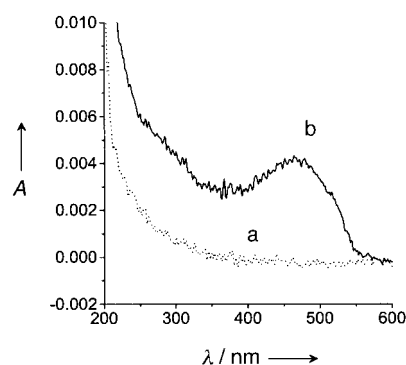


Figure 2. The UV/Vis absorption spectra of a bilayer on quartz before (a) and after (b) the photopolymerization.

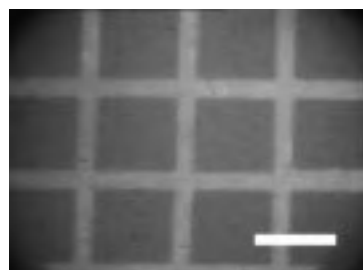


Figure 3. Fluorescence micrograph of the polymerized bilayer. The brightly fluorescent area (grid) was irradiated with UV light. The dark, square-shaped areas (wells) were protected by the mask and the lipid molecules remained monomeric. The scale bar corresponds to 200 μm .

In order to prove that new lipid bilayers can be introduced into the wells that had been created by removal of the monomeric bilayers by ethanol, we have fused small unilamellar vesicles of egg yolk phosphatidylcholine (egg PC) doped with 1 mol% of the fluorescently labeled lipid NBD-PE. Observation by the fluorescence microscope revealed that the wells were intensely fluorescent due to the incorporated lipid bilayers (Figure 4). The bilayers were fluid, as proven by fluorescence recovery after photobleaching (FRAP) experiments on a small spot (diameter 4 μm). Furthermore, if a larger area (diameter about 200 μm) in a single well was bleached by continuous illumination of UV light through a pinhole, the entire well became dark with time (Figure 5). The NBD-PE molecules in the same well obviously diffused laterally and were bleached when they came

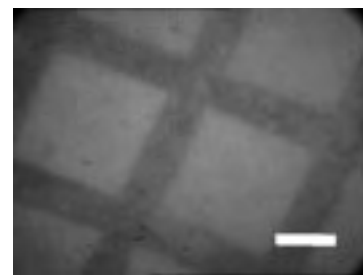


Figure 4. Fluorescence micrograph of the polymerized **1** and egg PC/NBD-PE bilayers incorporated in the wells. The contrast is inverted compared with Figure 3 because NBD-PE molecules fluoresce more strongly than the polymerized bilayer. The scale bar corresponds to 100 μm .

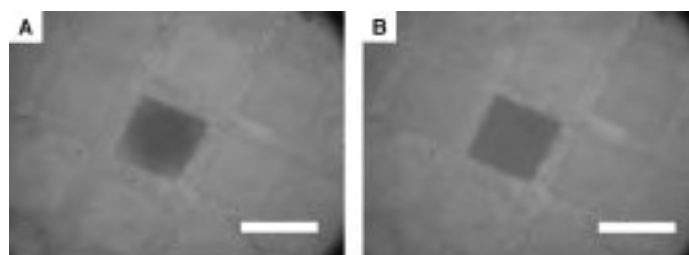


Figure 5. The egg PC/NBD-PE bilayer in a single well, bleached by UV light for 1 min, immediately (A) and 20 minutes (B) after the illumination. The illuminated spot was round (about 200 μm diameter). One can observe a slight trace of fluorescence at the edges of the bleached well in (A) that is not present in (B) due to the lateral diffusion of the lipids. The scale bars correspond to 200 μm .

into the illuminated spot. The neighboring wells separated by the polymerized bilayers retained the fluorescence. This result suggests that the polymerized bilayers act as an effective barrier that confines the lipid molecules. If one treated the sample with ethanol, the egg PC bilayers were completely removed, to leave the bare grid structure of the polymerized bilayer. The polymerized bilayer could be used repeatedly as a 2D master for the incorporation of new lipid bilayers. The bilayers were again fluid and confined in each single well.

Compared with other approaches that have been demonstrated to be effective to create patterned fluid lipid bilayers, the current method has a unique feature, in that the pattern is imprinted in the bilayer membrane as polymerized domains. This fact allows the patterned two-dimensional structure to be independent of the substrate and one could possibly construct a patterned bilayer separated from the substrate by a thin layer of soft polymeric cushion.^[13] Such polymer layers have been used as a spacer in order to accommodate membrane proteins in solid-supported bilayers in a functionally active form.^[14] It should be also possible to covalently attach the polymerized bilayer to the underlying polymer cushion by using a chemically reactive head group. The polymeric lipid bilayer might contribute to the mechanical stabilization of the membrane system, similar to cytoskeleton–transmembrane protein conjunctions.^[15]

The patterning of bilayers by lithographic polymerization described here should provide new opportunities both for the basic studies of model membrane systems and for the biomedical applications. The potential applications include incorporation of membrane proteins in order to monitor their

activities,^[16] separation of membrane proteins by 2D electrophoresis,^[17] creation of addressable arrays of modified lipid bilayer membranes for combinatorial chemistry,^[18] and controlled cell culture on designed membrane surfaces.^[19]

Experimental Section

Materials: Diacetylene lipid **1** and egg PC were purchased from Avanti Polar Lipids, Alabaster, AL, USA. NBD-PE (*N*-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)-1,2-dihexadecanoyl-*sn*-glycero-3-phosphoethanolamine) was purchased from Molecular Probes, Eugene, OR, USA.

Lithographic polymerization of bilayers: Bilayers of **1** were deposited onto glass substrates from the air/water interface by the Langmuir–Blodgett (LB) and Langmuir–Schaefer (LS) methods (surface pressure $\pi = 35 \text{ mN m}^{-1}$). Prior to the photopolymerization, oxygen was removed from the aqueous solution by an argon gas purge. After the patterned polymerization, monomeric **1** was removed by immersing the sample in ethanol and subsequently rinsing it extensively with Milli-Q water. The fluorescence microscope observation has been made using excitation and observation wavelength of 490 nm and 530 nm, respectively.

Incorporation of new lipid bilayers: Vesicle suspensions of egg PC/NBD-PE (1 mM in a 0.05 M phosphate buffer with 0.1 M NaCl (pH 7.0)) were extruded through a filter with pores of diameter $\sim 50 \text{ nm}$. A small volume of filtered suspension (100 to 200 μL) was placed onto the patterned **1** bilayer samples and sandwiched with another slide glass with a thin cover glass in between in order to avoid scratching the patterned surfaces. The sample was rinsed with the same buffer solution after 5 minutes.

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diffraction limit could possibly be overcome by use of the near-field optics, the ultimate resolution should be determined by the size of bilayer domains, within which the polymerization propagates laterally.

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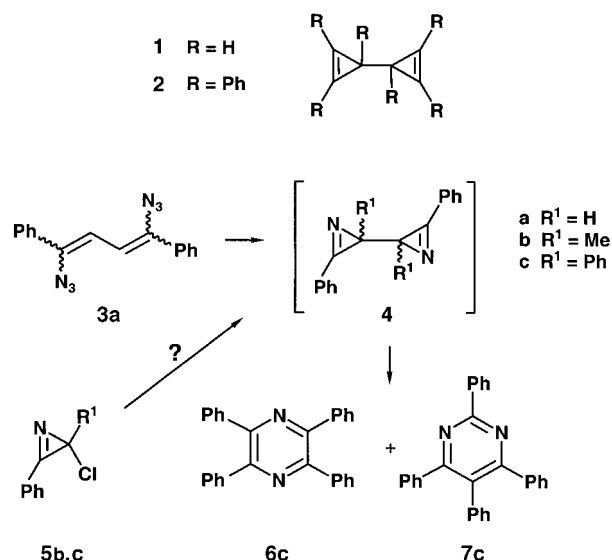
Synthesis of 1,4-Diazidobuta-1,3-dienes by Electrocyclic Ring Opening: Precursors for Bi-2*H*-azirin-2-yls and Their Valence Isomerization to Diazabenzenes**

Klaus Banert* and Frank Köhler

*Dedicated to Professor Horst Kunz
on the occasion of his 60th birthday*

Bicycloprop-2-enyl **1** was isolated first in 1989 as the last remaining valence isomer of benzene (Scheme 1).^[1] This compound, which was calculated to be the highest in energy of the $(\text{CH})_6$ species,^[2] polymerizes above -10°C ,^[1] while other bicycloprop-2-enyls, for example **2**,^[3] undergo a valence isomerization to give benzene derivatives on heating. Several

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Scheme 1. Previous unsuccessful attempts to identify the bi-2*H*-azirin-2-yls **4**.

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

mechanisms were proposed to explain these aromatization reactions.^[4] Up to now, all attempts to prepare the heterocyclic analogues **4** failed, neither the double Neber reaction nor the coupling reaction of **5b** generated these bi-2*H*-azirin-2-yls.^[5a] Later, Storr et al.^[6] reported the treatment of **5c** with lithium, which was said to lead to **6c** (10% yield) and **7c** (10%) but not to tetraphenylpyridazine (**10c**). The postulated intermediate **4c** could not be observed. Attempts to generate **4a** from the diazide **3a** failed immediately because the starting material **3a** could not be prepared.^[5] To the best of our knowledge, 1,4-diazidobuta-1,3-dienes are unknown.

Nevertheless, we consider the access via azides to be the most promising approach to investigate the highly strained heterocycles of type **4** and their valence isomerization. We describe here the synthesis of the diazides **3c–f** as well as the transformation into the biazirinyls **4c,d,f** and their aromatization.

Results in the literature^[5,7] but also of our own efforts indicated quickly that classical methods^[8] to prepare vinyl azides are unsuited for the synthesis of the diazides **3**. Thus, we generated these compounds by conrotatory ring opening of the cyclobutenes **8** ($X = N_3$; Scheme 2). Treatment of the dibromide *trans*-**8d**^[9] ($X = Br$) or the analogous diiodide^[9] with a concentrated (ca. 2 mol L⁻¹) solution of tributylhexadecylphosphonium azide (QN₃)^[10] in chloroform (20 h or 80 min/20 °C, respectively) gave in addition to small amounts of the diazide *cis*-**8d** (7% or 6%, respectively) only the diazide (*E,E*)-**3d** (89% or 62%, respectively).^[11,12] Whereas isolated *cis*-**8d** ($X = N_3$) could not subsequently be converted into **3d**, the course of the ring opening of *trans*-**8d** ($X = N_3$) was so rapid that this intermediate was not detected by NMR spectroscopic monitoring of the reaction. However, the monosubstituted products, 3-azido-4-bromocyclobut-1-ene and the analogous iodo compound, could be detected as intermediates. Evidently, the azido groups accelerate the electrocyclic ring opening as effectively as other donor substituents such as alkoxy groups.^[13] The compound **3d** could not be prepared with the aid of alternative reagents, for example, NaN₃/DMSO, or starting with less-reactive dihalides. On treatment with QN₃ at 50 °C the dichloride *cis*-**8d** gave rise to a mixture of other products, while a small amount of **10d** (10%) and the diene (*E,E*)-**11d** (62%) were formed on the reaction of *trans*-**8d**^[9] ($X = Cl$) and QN₃ at 20 °C. However, a mixture^[14] of the dibromide **8e** and the allyl

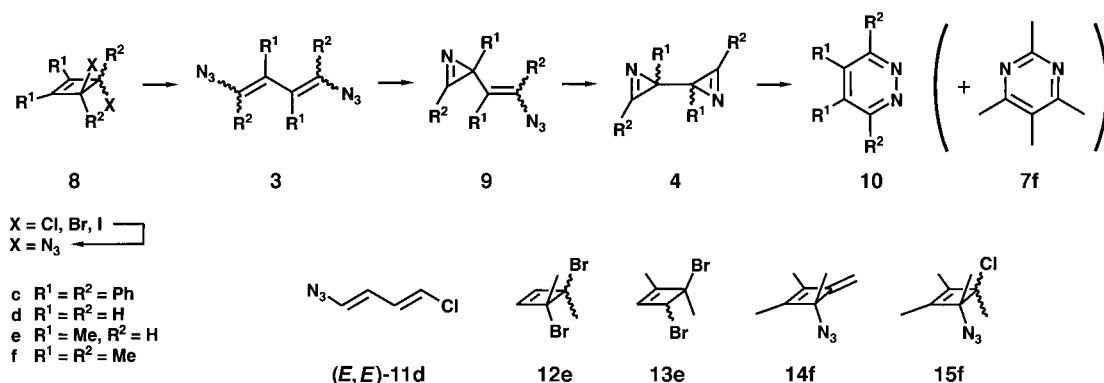
isomers **12e** and **13e** afforded the open-chain product (*E,E*)-**3e** (34–37%) in addition to *cis*-**8e** ($X = N_3$, yield ca. 16%) on treatment with either NaN₃ or LiN₃ in DMSO or with QN₃/CHCl₃.

At first, we obtained only (*E*)-**9d** (up to 59%) or (*E*)-**9e** (up to 37%) by photolysis of (*E,E*)-**3d** or (*E,E*)-**3e**, respectively (CD₂Cl₂, –85 °C, high-pressure mercury lamp). Small amounts of the very unstable compound **4d** (8% yield, 3:2 mixture of diastereomers, Table 1) could only be detected when (*E,E*)-**3d** was irradiated in the presence of the sensitizing agent 9,10-dicyanoanthracene (CDCl₃, –50 °C). On warming the mixture of products from photolysis, **4d** degraded to furnish at best only traces of **10d**. Just like compound **1**, **4d** does not tend to aromatization.

To synthesize more stable diazides and biazirinyls, we treated *trans*-**8f**^[15] ($X = Cl$) with QN₃ (CHCl₃, 20 °C) to give a mixture of diazides *trans*-**8f** (55%) and *cis*-**8f** (9%) as well as the monoazides **14f** (17%) and **15f** (2%+3%). After separation by chromatography, *trans*-**8f** ($X = N_3$) could be isolated because the electrocyclic ring opening to give (*E,E*)-**3f** is strongly decelerated by the inward rotation of the methyl groups. The target compound (*E,E*)-**3f** was generated only on warming in benzene (80 °C), whereby the secondary products (*E*)-**9f** and **10f**^[16] are also formed. Prolonged heating led exclusively to **10f** (88%). On incomplete thermolysis of *trans*-**8f** ($X = N_3$), (*E,E*)-**3f** could be isolated in 14% yield based on converted diazide (*trans*-**8f**).

The *E* configuration of (*E*)-**9e,f** was determined from two-dimensional ¹H NMR nuclear Overhauser spectroscopy (2D-NOESY) experiments and nuclear Overhauser enhancement (NOE) difference spectra. Thus the configuration of (*E,E*)-**3e,f** is also confirmed. The *trans* structure of *trans*-**8f** ($X = N_3$) was established by the signals of the ¹H NMR spectra which exhibited very small low-field shifts in the presence of [Eu(fod)₃] (tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato)europium(III)). The analogous spectra of the compounds *cis*-**8d–f** ($X = N_3$) showed changes of the chemical shifts at least 300 times greater since these diazides are able to interact with the shift reagent in a chelate-forming^[17] manner.

On thermolysis, (*E,E*)-**3f** was transformed via (*E*)-**9f** into **10f** with high yield (97%). However, the photochemical reaction of (*E,E*)-**3f** (glass equipment, CDCl₃, –60 °C), which proceeded also via (*E*)-**9f** (with a proportion of up to 61%),



Scheme 2. Synthesis and valence isomerization of the bi-2*H*-azirin-2-yls **4**.

Table 1. Selected physical data of compounds **3d–f**, **4c,d,f**, *trans*-**8f** (X = N₃), and **9c–f**.^[a]

(*E,E*)-**3d**: Yellow solid, decomposition at room temperature; IR (CDCl₃): $\tilde{\nu}$ = 2111 cm^{−1} (N₃), 1253 (N₃); UV/Vis (acetonitrile): λ_{max} (lg ϵ) = 296 nm (4.52); ¹H NMR (CDCl₃): δ = 5.87 (AA'XX', 2H), 6.12 (AA'XX', 2H), from simulation: ³J(A'X) = ³J(A'X') = 13.3 Hz, ³J(AA') = 11.5 Hz, ⁵J(XX') = 1.0 Hz, ⁴J(A'X) = ⁴J(A'X') = −0.5 Hz; ¹³C NMR (CDCl₃): δ = 116.39 (d), 127.97 (d)

(*E,E*)-**3e**: Yellow solid, m.p. 48 °C (hexane, decomp); IR (CDCl₃): $\tilde{\nu}$ = 2100 cm^{−1} (N₃), 1258 (N₃); UV/Vis (cyclohexane): λ_{max} (lg ϵ) = 300 nm (4.46); ¹H NMR (CDCl₃): δ = 1.75 (d, ⁴J = 1.1 Hz, 6H; Me), 6.26 (q, ⁴J = 1.1 Hz, 2H; 1-H/4-H); ¹³C NMR (CDCl₃): δ = 11.97 (q; Me), 123.14 (d; C-1/C-4), 125.13 (s; C-2/C-3)

(*E,E*)-**3f**: Yellow oil; IR (CDCl₃): $\tilde{\nu}$ = 2108 cm^{−1} (N₃), 1287 (N₃); UV/Vis (acetonitrile): λ_{max} (lg ϵ) = 255 nm (4.08); ¹H NMR (CDCl₃): δ = 1.66 (q, ⁵J = 1.5 Hz, 6H), 1.86 (q, ⁵J = 1.5 Hz, 6H); ¹³C NMR (CDCl₃): δ = 14.31 (q), 15.78 (q), 123.00 (s), 126.33 (s)

4c (Major (MI) and minor isomer (mi)): ¹H NMR (CDCl₃): δ = 6.80–7.80 (m); ¹³C NMR (CDCl₃): δ = 45.49 (s; C-2, MI), 45.55 (s; C-2, mi), 122.73 (s; *i*-Ph, mi), 123.14 (s; *i*-Ph, MI), 126.40 (d; *p*-Ph, mi), 126.69 (d), 126.80 (d), 127.25 (d; *o,m*-Ph, MI), 127.93 (d), 128.10 (d; *o,m*-Ph, MI), 128.80 (d), 129.12 (d; *o,m*-Ph, MI), 129.61 (d), 129.63 (d; *o,m*-Ph, MI), 132.87 (d; *p*-Ph, mi), 132.97 (d), 139.77 (s; *i*-Ph, mi), 140.70 (s; *i*-Ph, MI), 163.72 (s; C-3, MI), 163.98 (s; C-3, mi)

4d (Major isomer): ¹H NMR (−50 °C, CDCl₃): δ = 1.68 (s, 2H; 2-H), 10.09 (s, 2H; 3-H); ¹³C NMR (−50 °C, CDCl₃): δ = 28.32 (d; C-2), 165.75 (d; C-3)

4d (Minor isomer): ¹H NMR (−50 °C, CDCl₃): δ = 1.98 (s, 2H; 2-H), 9.91 (s, 2H; 3-H); ¹³C NMR (−50 °C, CDCl₃): δ = 28.70 (d; C-2), 166.89 (d; C-3)

4f (More stable isomer): IR (CDCl₃): $\tilde{\nu}$ = 1753 cm^{−1} (C=N); ¹H NMR (−50 °C, CDCl₃): δ = 1.00 (s, 6H; 2-Me), 2.44 (s, 6H; 3-Me); ¹³C NMR (−50 °C, CDCl₃): δ = 14.53 (q), 19.78 (q), 38.95 (s; C-2), 176.25 (s; C-3)

4f (Less stable isomer): ¹H NMR (−50 °C, CDCl₃): δ = 1.16 (s, 6H; 2-Me), 2.38 (s, 6H; 3-Me); ¹³C NMR (−50 °C, CDCl₃): δ = 14.71 (q), 20.25 (q), 38.92 (s; C-2), 173.75 (s; C-3)

trans-**8f** (X = N₃): Colorless oil; IR (CDCl₃): $\tilde{\nu}$ = 2093 cm^{−1} (N₃), 1251 (N₃); UV/Vis (acetonitrile): λ_{max} (lg ϵ) = 208 nm (3.74); ¹H NMR (CDCl₃): δ = 1.42 (s, 6H), 1.64 (s, 6H); ¹³C NMR (CDCl₃): δ = 8.69 (q; Me), 17.86 (q; Me), 72.67 (s; C-3/C-4), 141.28 (s; C-1/C-2)

9c: IR (CDCl₃): $\tilde{\nu}$ = 2110 cm^{−1} (N₃), 1738 (C=N), 1255 (N₃); ¹H NMR (CDCl₃): δ = 6.88–7.63 (m, 20H); ¹³C NMR (CDCl₃): δ = 44.78 (s; C-2), 123.50 (s), 126.11 (d), 126.37 (d), 127.24 (d), 127.68 (d), 127.75 (d), 128.25 (d), 128.40 (d), 128.53 (d), 128.95 (d), 129.09 (d), 129.75 (d), 131.86 (d), 133.26 (s), 137.63 (s), 139.04 (s), 142.19 (s), 165.51 (s; C-3), one signal (s) not resolved

(*E*)-**9d**: ¹H NMR (−80 °C, CD₂Cl₂): δ = 2.33 (dd, ³J = 8.9 Hz, ³J = 2.0 Hz, 1H; 2-H), 4.77 (ddd, ³J_{trans} = 13.5 Hz, ³J = 8.9 Hz, ⁴J = 0.6 Hz, 1H; 1'-H), 6.38 (d, ³J_{trans} = 13.5 Hz, 1H; 2'-H), 10.06 (dd, ³J = 2.0 Hz, ⁴J = 0.6 Hz, 1H; 3-H); ¹³C NMR (−80 °C, CD₂Cl₂): δ = 26.16 (d; C-2), 119.54 (d), 127.89 (d), 164.80 (d; C-3)

(*E*)-**9e**: ¹H NMR (−85 °C, CD₂Cl₂): δ = 1.14 (d, ⁴J = 1.3 Hz, 3H; 1'-Me), 1.31 (d, ⁴J = 1.5 Hz, 3H; 2-Me), 6.20 (qd, ⁴J = 1.3 Hz, ⁵J = 0.8 Hz, 1H; 2'-H), 10.26 (qd, ⁴J = 1.5 Hz, ⁵J = 0.8 Hz, 1H; 3-H); ¹³C NMR (−85 °C, CD₂Cl₂): δ = 13.65 (q; Me), 20.73 (q; Me), 33.65 (s; C-2), 122.48 (d; C-2'), 128.31 (s; C-1'), 172.53 (d; C-3)

(*E*)-**9f**: ¹H NMR (CDCl₃): δ = 1.28 (s, 3H; 2-Me), 1.63 (q, ⁵J = 1.5 Hz, 3H; 1'-Me), 2.12 (q, ⁵J = 1.5 Hz, 3H; 3'-H), 2.44 (s, 3H; 3-Me); ¹³C NMR (CDCl₃): δ = 12.58 (q), 13.40 (q), 14.39 (q), 22.39 (q), 36.13 (s; C-2), 124.75 (s), 127.61 (s), 174.49 (s; C-3)

[a] ¹H NMR: 300 MHz; ¹³C NMR: 75 MHz, assignments of signals by distortionless enhancement by polarization transfer (DEPT) experiments.

led quantitatively to a 1:1 mixture of *meso*-**4f** and *rac*-**4f**. On warming the irradiated solution, both stereoisomers were converted into **10f** in quantitative first-order reactions. One of these valence isomerizations occurred already with $k =$

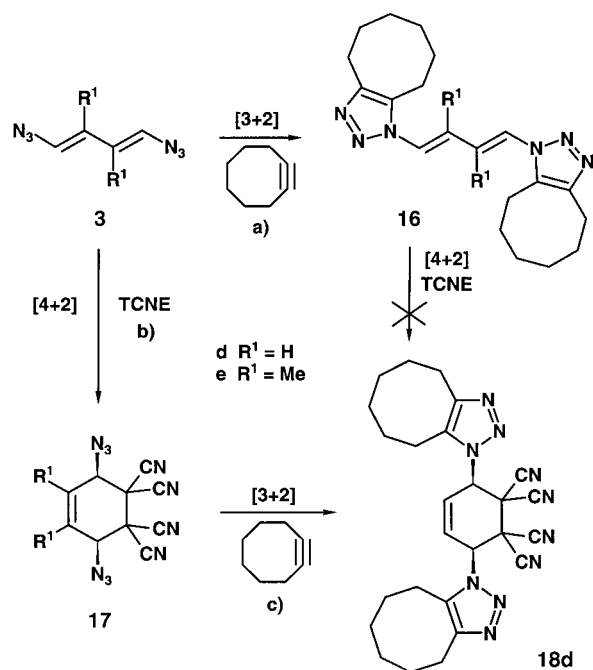
$3.65 \cdot 10^{-4} \text{ s}^{-1}$ at −25 °C, the other with $k = 1.73 \cdot 10^{-4} \text{ s}^{-1}$ at +10 °C. So far, we could not clarify which compound has the *meso* structure and which the *rac* configuration. We suppose that the new N–N bond is formed in the rate-determining step of the aromatization. For conformational reasons, this should be more difficult for *meso*-**4f** which may thus be the kinetically more stable stereoisomer. In the presence of AgBF₄, the more stable isomer of **4f** was completely transformed into **7f**^[18] at −25 °C, whereas the other stereoisomer again gave **10f**. Photolysis of (*E,E*)-**3f** in the more UV transparent CD₃CN (quartz equipment, −40 °C) furnished (*E*)-**9f** and **4f** first and then, after prolonged irradiation, a mixture of **7f** (30 %) and **10f** (22 %) as well as the fragmentation products but-2-yne (3–4 %) and acetonitrile (3–4 %).^[19] By using these conditions, prolonged photolyses of the diazides *cis*-**8f** or *trans*-**8f** proceeded via **4f** and resulted in the formation of both aromatics **7f** (13 % or 12 %, respectively) and **10f** (33 % or 41 %, respectively) as well as traces of but-2-yne and acetonitrile.

We monitored the reaction of **8c**^[20] (X = Br) with QN₃ in CDCl₃ by NMR spectroscopy at low temperature. Even at −25 °C nucleophilic substitution and electrocyclic ring opening proceeded so rapidly that only the signals of **3c** could be assigned with certainty. At +5 °C, a slow evolution of nitrogen started,^[21] in the course of which one isomer of **9c** and after that both stereoisomers of **4c** (ca. 2:1) could be detected unequivocally (Table 1). Only the aromatic compound **10c**^[22] (87 % based on dibromide **8c**) was found after prolonged reaction times or after slight warming of the reaction mixture whereas the heterocycles **6c** and **7c** could not be identified. Thus, the postulated^[6] generation of **4c** from **5c** seems to be questionable.

The 1,4-diazidobuta-1,3-dienes **3d–f** presented here could be used as synthetic building blocks for cycloaddition reactions, as shown by some examples in Scheme 3. At present, we are trying to synthesize biazirinylns **4** which bear sterically more demanding groups R¹ and exhibit a higher thermal stability. Valence isomerizations of **4** with R¹ ≠ R² may enable plausible conclusions regarding the reaction mechanism to be drawn.

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Scheme 3. Cycloaddition reactions of 1,4-diazidobuta-1,3-dienes **3d,e**. a) Chloroform, 20 °C, 30–60 min, 86 % **16d**, 99 % **16e**; b) acetone, tetracyanoethylene (TCNE) 20 °C, 2–20 h, 95 % **17d**, 91 % **17e**; c) chloroform, 20 °C, 3 h, 96 % **18d**.

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Highly Enantioselective Isomerization of 4,7-Dihydro-1,3-dioxepins Catalyzed by Me-DuPHOS-Modified Dihalogenonickel Complexes and Determination of the Absolute Configuration of the Isomerization Products**

Herbert Frauenrath,* Dirk Brethauer, Stefan Reim, Martin Maurer, and Gerhard Raabe

Dihalogenonickel complexes bearing chiral ligands have proved to be efficient catalyst precursors for the asymmetric isomerization of cyclic allyl acetals. In the isomerization of 5-methylen-1,3-dioxanes to 5-methyl-4*H*-1,3-dioxins, for example, DIOP-modified (DIOP = 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphanyl)butane) dihalogenonickel complexes activated with lithium triethylborohydride gave selectivities of up to 92 % *ee*.^[1] The enantioselectivities significantly decreased, when 4,7-dihydro-1,3-dioxepins (**1**) were used as substrates. However, we have shown previously that the selectivities depend on the relationship between the chelate-ring size of the catalyst and the ring size of the substrate.^[1, 2] Thus, isomerization of **1a** by using a five-membered CHIRAPHOS-modified (CHIRAPHOS = 2,3-bis(diphenylphosphanyl)butane) dichloronickel complex (**2a**) at room temperature in THF afforded 2-*tert*-butyl-4,5-dihydro-1,3-dioxepin (**3a**) with 67 % *ee*. In contrast, the seven-membered DIOP-modified dichloronickel complex gave **3a** under the same reaction conditions with only 38 % *ee*.^[3]

Searching for other diphosphanes that form five-membered-ring nickel chelates we found that 1,2-bis(phospholanyl)benzenes (Me-DuPHOS, Et-DuPHOS) are suitable ligands for the asymmetric nickel-catalyzed isomerization of **1**.^[4, 5] In fact, by employing Me-DuPHOS as a ligand a breakthrough was achieved in terms of enantioselectivity (Table 1). Treatment of **1a** with [NiCl₂(–)-Me-DuPHOS] (**2c**) at room temperature and activation with LiBHET₃ in toluene provided (–)-**3a** already with 85 % *ee* (Table 1, entry 5), but incomplete conversion at this temperature indicated a decreased catalytic activity of the dichloronickel complex (**2c**). However, we found that replacing the chloro by bromo or iodo ligands drastically enhanced the activity of the nickel catalysts. Thus, isomerizations of **1** with CHIRAPHOS and DuPHOS bearing NiBr₂– or NiI₂–phosphane complexes could be performed even at low temperatures yielding vinyl

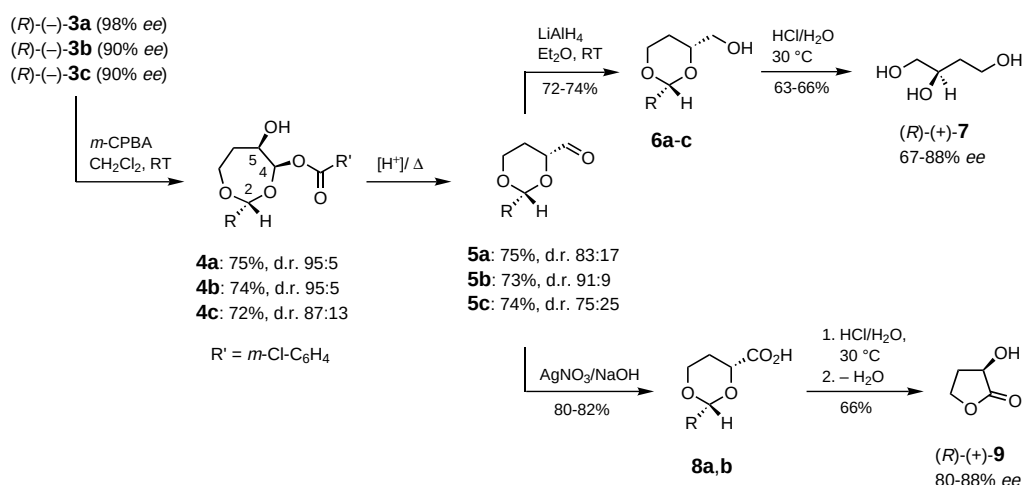
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[+] X-ray crystallographic analysis

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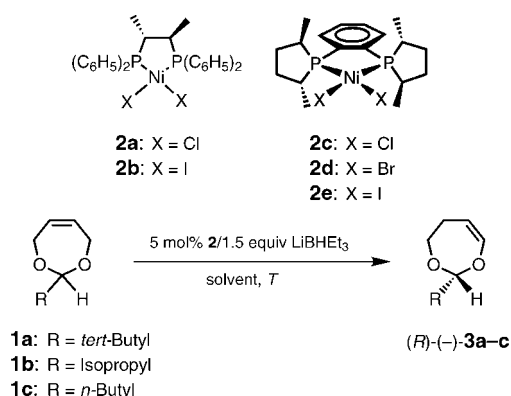
acetals (**3a–c**) in good to high enantioselectivities. Best results were achieved with $[\text{NiI}_2((-)\text{-Me-DuPHOS})]$ (**2e**) as a precatalyst and with activation by LiBHET_3 in toluene at -55°C . Under these conditions, the enantiomers $(-)\text{-3b}$ and **3c** were obtained at acceptable rates with 90% *ee*, and $(-)\text{-3a}$ with an excellent selectivity of 98% *ee* (Table 1, entries 11, 13, 15).

The absolute configuration of the isomerization products was established by the conversion of **3** into either 1,2,4-butanetriol (**7**) or 2-hydroxy- γ -butyrolactone (**9**). Both transformations proceed by a new oxidation ring-contraction sequence of **3** to give the carbaldehydes **5** (Scheme 1) according to our procedure for the synthesis of 4-methyl-1,3-dioxolan-4-carbaldehydes.^[7] Thus, treatment of $(-)\text{-3a–c}$



Scheme 1. Oxidation and rearrangement of $R(-)\text{-3}$ and the conversion of the carboxaldehydes **5** into $(R)\text{-}(+)\text{-1,2,4-butanetriol (7)}$ and $(R)\text{-}(+)\text{-2-hydroxy-}\gamma\text{-butyrolactone (9)}$, respectively.

Table 1. Asymmetric isomerization of 4,7-dihydro-1,3-dioxepins (**1a–c**) using $(R,R)\text{-}(+)\text{-CHIRAPHOS-}$ and $(R,R)\text{-}(-)\text{-Me-DuPHOS-}$ modified nickel complexes.



Entry	Product	Pre-catalyst	Solvent	T [°C]	Conversion [%] ^[a] / Time(h) ^[b]	<i>ee</i> [%] ^[c]	$[\alpha]_D^{20}$ (neat)
1	3a	2a	THF	20	100(71)/48	67	−23.6
2	3a	2a	THF	−40	0/48		
3	3a	2b	THF	20	100/48	73	
4	3a	2b	THF	−40	100(83)/72	82	−28.4
5	3a	2c	toluene	20	80/96	85	
6	3a	2c	toluene	−55	0/48		
7	3a	2d	toluene	20	100/18	80	
8	3a	2d	toluene	−55	16/72	92	
9	3a	2e	toluene	20	100/2.5	80	
10	3a	2e	toluene	−20	100/48	92	
11	3a	2e	toluene	−55	100(74)/72	98	−34.9
12	3b	2e	toluene	20	100/2.5	70	
13	3b	2e	toluene	−55	100(75)/72	90	−27.2
14	3c	2e	toluene	20	100/2.5	78	
15	3c	2e	toluene	−55	100(75)/72	90	−22.1

[a] Determined by gas chromatography (GC). Values in parentheses: yields of isolated product. [b] No further conversion on prolonged reaction times. [c] Determined by GC. Capillary column: Rt- β DEXst (30 m, internal diameter 0.32 mm);^[6] carrier gas H_2 .

with *m*-chloroperbenzoic acid and heating the resulting crude mixture in vacuo in the presence of an acid led directly to distillation of a diastereomeric mixture of carbaldehydes **5a–c**. Subsequent reduction with lithium aluminum hydride and acetal cleavage or oxidation, acetal cleavage, and lactonization by azeotropic removal of water furnished $(R)\text{-}(+)\text{-7}$ and $(R)\text{-}(+)\text{-9}$, respectively. Comparison of the specific rotation of the product with that of authentic $(R)\text{-}(+)\text{-7}$ and $(R)\text{-}(+)\text{-9}$ determined the $2R,4R$ configuration for the major diastereomers of **5a–c** and the $2S,4R$ configuration for the minor diastereomers. The absolute configuration of $(-)\text{-3a–c}$ obtained as the primary products of the *m*-chloroperbenzoic acid oxidation and isolated, by careful neutralization of the crude oxidation product, as a mixture of two diastereomers in a 95:5 to 83:17 ratio. As evidenced by NMR spectroscopic data, both diastereomers differ in the configuration at C4. In the case of *rac-4b*, the major diastereomer could be isolated in a diastereomerically pure crystalline form from pentane solution.

Crystal structure analysis of *rac-4b* unambiguously confirmed the $2RS,4RS,5RS$ configuration for both conformers in the asymmetric unit (Figure 1) indicating a preferred *trans*

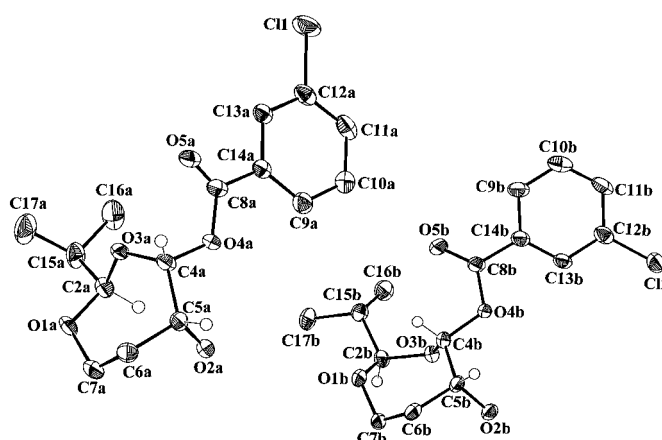


Figure 1. The symmetrically independent molecules of the asymmetric unit of *rac-4b*.

attack of *m*-chloroperbenzoic acid in the reaction with **3**.^[8] The results reveal, that (–)-**3b** and, on the basis of similar coupling constants in the ¹H NMR spectra and similar nuclear Overhauser enhancement (NOE) effects, most probably (–)-**3a, c** have the *R* configuration.

In conclusion, 4,5-dihydro-1,3-dioxepins (**3**) are readily available with high enantiomeric excess by asymmetric isomerization of **1** employing [NiI₂(Me-DuPHOS)] as a precatalyst. The conversions of **3** into 2-hydroxy-γ-butyrolactone (**9**) and 1,2,4-butanetriol (**7**) demonstrate new applications for compounds **3** as chiral synthons in asymmetric synthesis. Derivates of carbaldehydes **5** and alcohols **6**, prepared by different methods, have already been used for the synthesis of optical active α-amino acetals, α-amino acids, and 1,2- and 1,3-diols.^[9]

Experimental Section

(*R*)-(–)-**3a**: Catalyst precursor **2e** (0.20 g, 0.32 mmol) was dissolved in toluene at room temperature and activated by LiBHEt₃ (0.5 mL, 0.5 mmol, 1M in THF). After cooling to –55 °C, a solution of **1a** (1.0 g, 6.40 mmol) in toluene (5 mL) was added, and the mixture was left at this temperature for 48 h. The conversion is monitored by GC. After complete conversion the mixture was allowed to warm to room temperature and quenched with a saturated NH₄Cl solution (10 mL). The organic layer was separated, and after removal of the solvent the residue was distilled in vacuo; b.p. 55–60 °C/18 Torr; yield 0.74 g (4.7 mmol, 74%).

5a: A solution of purified *m*-chloroperbenzoic acid (3.40 g, 20 mmol)^[10] in dichloromethane (50 mL) was added dropwise at room temperature to a stirred solution of **3a** (2.34 g, 15 mmol) in dichloromethane (10 mL). After stirring for 30 min and removal of the solvent in vacuo the diastereomeric aldehydes **5a** were distilled off by heating the colorless residue to 130 °C; b.p. 75–80 °C/18 Torr; yield 1.50 g (8.70 mmol, 58%). ¹H NMR (500 MHz, CDCl₃, 22 °C, TMS); major diastereomer: δ = 0.95 (s, 9H, *t*Bu), 1.65 (dddd, 1H (eq), *J* = 13.3, 3.0, 2.7, 1.5, 0.8 Hz, OCH₂CH₂), 1.77 (dddd, 1H (ax), *J* = 13.3, 12.2, 11.8, 5.1 Hz, OCH₂CH₂), 3.75 (ddd, 1H (ax), *J* = 12.2, 11.4, 2.7 Hz, OCH₂CH₂), 4.08 (ddd, 1H (ax), *J* = 11.6, 3.0, 0.8 Hz, OCH₂CH₂), 4.19 (ddd, 1H (eq), *J* = 11.5, 4.9, 1.5 Hz, OCH₂CH₂), 4.20 (s, 1H, OCHO), 9.66 (dd, 1H, *J* = 0.8, 0.8 Hz, CHO); ¹³C NMR (125 MHz, CDCl₃, 22 °C, TMS); major diastereomer: δ = 24.6 (C(CH₃)₃), 26.0 (C(CH₃)₃), 35.0 (OCH₂CH₂), 66.0 (OCH₂CH₂), 80.0 (OCH₂CH₂), 107.2 (OCHO), 201.5 (CHO). MS (PCI): *m/z* (%) = 173 (100), 157 (13), 127 (20).

8a: A solution of AgNO₃ (2.55 g, 15 mmol) in water (70 mL) was added to a stirred solution of NaOH (1.20 g, 30 mmol) in water (70 mL). A solution of aldehyde **5a** (0.86 g, 5 mmol) in diethyl ether (15 mL) was added dropwise to the resulting suspension. After stirring for 12 h at room temperature, the mixture was filtered and the solid washed with hot water. The aqueous phase was acidified with 2M HCl, and the precipitated acid extracted with diethyl ether. After drying the combined ethereal extracts (MgSO₄) the solvent was removed, and the residue recrystallized from petroleum ether; yield 0.80 g (4.30 mmol, 85%); m.p. 95 °C. ¹H NMR (500 MHz, CDCl₃, 22 °C, TMS); major diastereomer: δ = 0.95 (s, 9H, *t*Bu), 1.91 (m, 2H, OCH₂CH₂), 3.77 (ddd, 1H (ax), *J* = 11.6, 11.5, 3.6 Hz, OCH₂CH₂), 4.21 (ddd, 1H (eq), *J* = 11.5, 4.5, 1.7 Hz, OCH₂CH₂), 4.22 (s, 1H, OCHO), 4.30 (dd, 1H (ax), *J* = 10.6, 4.3 Hz, OCH₂CH₂), 8.21 (s, 1H, COOH); ¹³C NMR (125 MHz, CDCl₃, 22 °C, TMS); major diastereomer: δ = 25.3 (C(CH₃)₃), 28.7 (C(CH₃)₃), 35.7 (OCH₂CH₂), 67.1 (OCH₂CH₂), 85.0 (OCH₂CH₂), 108.0 (OCHO), 173.4 (COOH).

(*R*)-(+)-**9**: A diastereomeric mixture of **8a** (1.88 g, 10 mmol) was stirred with 18% HCl (30 mL) at 30 °C for 12 h. After addition of CHCl₃ (100 mL) and the azeotropic removal of water the organic layer was dried (MgSO₄). The solvent was removed, and the residue distilled in high vacuum; b.p. 103–105 °C/0.1 Torr; yield 0.67 g (6.60 mmol, 66%); [α]_D²⁰ = +17.8 (*c* = 1 in H₂O) (ref. [11]); [α]_D²⁰ = +20.29 (*c* = 4 in H₂O)).

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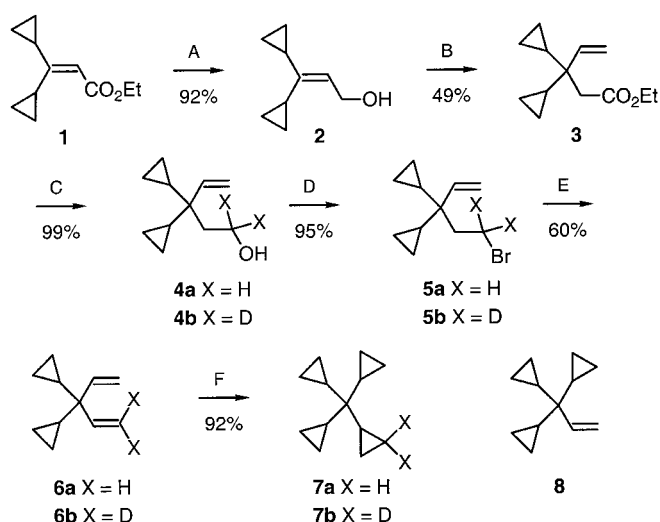
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- [8] Crystal structure analysis of *rac*-**4b**: C₁₅H₁₉O₅Cl, *M*_r = 314.77; crystals were obtained from pentane (293 K); triclinic space group *P* $\bar{1}$ (no.2), *a* = 11.716(3), *b* = 11.721(4), *c* = 12.388(3) Å, α = 73.21(2), β = 73.90(3), γ = 85.15(3)°, *V* = 1564.7 Å³, *Z* = 2 × 2, ρ_{calc} = 1.336 g cm^{–3}, 150 K. A total of 8974 reflections were collected on an Enraf-Nonius CAD4 four-circle diffractometer CAD4, graphite-monochromated Cu_{K α} radiation (λ = 1.54179 Å), μ = 11.7 cm^{–1}, no absorption correction. The structure was solved by direct methods (GENSIN^[12], GENTAN^[13] as implemented in the XTAL3.4 program package^[14]). Hydrogen atoms were fixed in idealized positions without refinement. Final full-matrix least-squares refinement of 379 parameters (involved 4855 observed reflections *I* > 4 σ (*I*)), *R*(*R*_w) = 0.091 (0.094), *w* = ($\sigma^2(F) + 0.0004F^2$)^{–1}, residual electron density –0.90/+0.86 e Å^{–3}. The asymmetric unit contains two symmetrically independent molecules of *rac*-**4b** with different conformations (Figure 1). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-134153. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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Tetracyclopropylmethane: A Unique Hydrocarbon with S_4 Symmetry**

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Dedicated to Professor Marit Tr  tteberg on the occasion of her 70th birthday

The static and dynamic stereochemistry of organoelement compounds containing the respective maximum number of geminal cyclopropyl groups, Cpr_nX (Cpr = cyclopropyl), has attracted considerable attention.^[1–4] Nevertheless, the corresponding carbon compound, tetracyclopropylmethane (**7a**), has remained elusive. Neither the two commonly used approaches to pericyclopropylated element derivatives,^[5] nor the methods for the preparation of tricyclopropylamine^[4] can be used to form **7a**. An attempted direct geminal biscyclopropylation of dicyclopropyl ketone with in situ generated $[\text{Cpr}_2\text{TiCl}_2]$ ^[6] analogous to the reported geminal bismethylation of ketones with $[\text{Me}_2\text{TiCl}_2]$ ^[7] only led to tricyclopropylmethane in a moderate yield (34%). Therefore, we considered the possibility of preparing **7a** by a twofold cyclopropanation of dicyclopropyldiethenylmethane (**6a**),^[8] and to use ethyl 3,3-dicyclopropylacrylate (**1**)^[9] as the starting material (Scheme 1).^[10] The allyl alcohol **2**, obtained by the reduction of **1**, was transformed into **6a** by the following pathway: an orthoester Claisen rearrangement,^[11] subsequent reduction of the ester **3** with LiAlH_4 to the alcohol **4**,



Scheme 1. Synthesis of **7**. A) AlH_3 , THF, 0 °C, 3 h; B) $\text{MeC}(\text{OEt})_3$, PhOH, 150 °C, 7 h; C) LiAlH_4 or LiAlD_4 , Et_2O , 34 °C, 1 h; D) $\text{Ph}_3\text{P} \cdot \text{Br}_2$, CH_2Cl_2 , –15 → 20 °C, 6 h; E) $t\text{BuOK}$, DMSO, 20 °C, 6 h; F) CH_2N_2 (10 equiv), inverse addition of $\text{Pd}(\text{OAc})_2$,^[14] –20 → 25 °C, repeated six times.

transformation to the bromide **5**, and its eventual dehydrobromination with potassium *tert*-butoxide in DMSO (Scheme 1).

The crucial step in this sequence was the cyclopropanation of **6a**. In contrast to the successful cyclopropanations of other tricyclopropylethenylelement compounds Cpr_3VinX ($\text{X} = \text{Si}$, Ge , Sn ; $\text{Vin} = \text{CH}=\text{CH}_2$),^[5b] no reaction occurred with **6a** under classical Simmons–Smith conditions,^[12a] and with $\text{Me}_3\text{Al}/\text{CH}_2\text{I}_2$ (6 equiv) or $\text{ZnEt}_2/\text{CH}_2\text{I}_2$ (12 equiv)^[12b] tricyclopropylethenylmethane (**8**) was obtained at best in 9 and 30% yield, respectively. The $\text{Pd}(\text{OAc})_2$ -catalyzed cyclopropanation of **6a** with diazomethane^[13] gave **8** in only 13% yield. The reactivity of the double bonds in **6a** is apparently retarded by the steric congestion around the quaternary carbon atom. However, the yield could be improved by the addition of the catalyst $\text{Pd}(\text{OAc})_2$, in one portion, to a solution of **6a** in ~1.9 M ethereal diazomethane.^[14] By repeating this procedure six times, tetracyclopropylmethane (**7a**) was obtained from **6a** in 92% yield. After only three repetitions, tricyclopropylethenylmethane (**8**) was isolated in 80% yield along with **6a** and **7a** (10% each). Tricyclopropyl(2,2-dideuteriocyclopropyl)methane **7b** was obtained in the same way from **6b** (which was prepared from **3** by reduction with LiAlD_4 and further transformations of the resulting **4b** as elaborated for **4a** in Scheme 1).^[15]

By looking at molecular models, it can be predicted that three of the four cyclopropyl groups in **7a** cannot have the same orientation as the corresponding three groups in tricyclopropylmethane,^[16] which in the crystal structure adopts the same C_{3v} -symmetrical conformation (Figure 1)^[17] as tricyclopropylamine.^[4a,b] According to B3LYP/6-31 + G** computations,^[18] the fourth cyclopropyl group in **7a** affects the orientation of the three others in such a way that the overall symmetry becomes S_4 (Table 1). The result of the X-ray structure analysis^[17] displays nearly S_4 symmetry for the molecules of **7a** (Figure 1). In contrast, tetracyclopropylsilane Cpr_4Si , Cpr_4Ge , and Cpr_4Sn all have D_{2d} symmetry.^[3]

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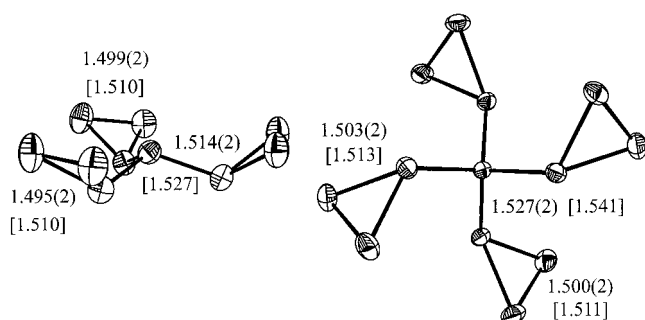


Figure 1. Molecular structures of tricyclopropylmethane and tetracyclopropylmethane (**7a**).^[17] The bond lengths [Å] are mean values based on assumed C_{3v} symmetry for tricyclopropylmethane and S_4 symmetry for **7a**; computed values at B3LYP/6-31 + G** in parentheses.

Table 1. Computed energies [kcal mol⁻¹] for tetracyclopropylmethane and tetraisopropylmethane conformations and their rotational transition structures (TS). The energies are given relative to the lowest lying geometry of the molecules **7a** and **9a**. N_{imag} = number of imaginary frequencies; ZPVE = zero-point vibrational energy.

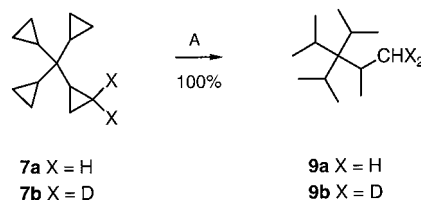
Molecule	Symmetry	N_{imag}	E	ZPVE	H_0	$G_{298\text{K}}$
7a	S_4	0	0.0	186.8	0.0	0.0
7a	D_{2d}	3	29.5	186.8	20.7	32.2
7a (TS)	C_1	1	7.6	186.7	7.0	8.2
9a	D_{2d}	0	0.0	243.4	0.0	0.0
9a	S_4	0	0.5	242.8	0.8	1.2
9a (TS)	C_1	1	4.1	243.5	3.6	4.9

For comparison, tetravinylmethane has no symmetry (C_1) in the gas phase^[19a] or the crystalline state,^[19b] tetravinyl derivatives of Si and Ge are also nonsymmetric, as are the respective Sn and Pb derivatives which differ only in their conformations.^[19b] The closest cousin to **7a**, hexacyclopropylethane, displays S_6 symmetry in the crystalline state^[20a] as well as, according to MM2^[20a] and MM3^[20b] calculations, in the gas phase. As a result of the repulsion of the cyclopropyl groups in hexacyclopropylethane, the central C–C bond length (1.636 Å) is significantly longer than an ordinary C–C σ bond.^[20a]

In accord with the computational result that the attachment of a fourth cyclopropyl group onto the central carbon in tricyclopropylmethane does not significantly enhance the overall strain, the C–CH bond length in **7a** (1.527(2) Å) is only slightly longer than that in tricyclopropylmethane (1.514(2) Å), and the CH–CH₂ and CH₂–CH₂ bond lengths in the three-membered rings are virtually the same, namely 1.503(2) and 1.500(2) Å, respectively, that is, practically identical to that in unsubstituted cyclopropane (1.499(1) Å).^[21] Yet, the computed (B3LYP/6-31 + G**) rotational barrier of the cyclopropyl groups in **7a** of 8.2 kcal mol⁻¹ (298 K) is higher than that for rotation around the central bond in hexacyclopropylethane (6.4 kcal mol⁻¹),^[20a] but comparable to the barrier for the rotation of the cyclopropyl groups in the tricyclopropylmethyl cation (~8–10 kcal mol⁻¹).^[22] However, in their ¹H, ²H, and ¹³C NMR spectra neither tetracyclopropylmethane (**7a**) nor its dideutero analogue **7b** showed any sign of nonequivalence of the sites, even at –130 °C in a CD₂Cl₂/CHCl₂F mixture. A small change in the ¹³C NMR spectra was observed upon lowering

the temperature, but this is because the deuterated carbon with a signal at $\delta = 0.91$ in **7b** loses its coupling to deuterium, and the signal becomes more intense because of the more efficient quadrupolar relaxation of deuterium nuclei at lower temperatures.

Since cyclopropane derivatives are prone to ring opening upon catalytic hydrogenation under appropriate conditions,^[23] and the opening of donor-substituted rings usually occurs selectively at the least substituted bond, tetracyclopropylmethane (**7a**) offered itself as a precursor to the previously unknown tetraisopropylmethane (**9**). In fact, hydrogenolysis of hydrocarbons **7a, b** over PtO₂ in acetic acid proceeded smoothly with fourfold selective opening of only the distal bonds to give the considerably congested^[24] tetraisopropylmethanes (**9a, b**) in quantitative yields (Scheme 2).



Scheme 2. Catalytic hydrogenation of **7a, b** to give the tetraisopropylmethanes **9a, b**. A) H₂, AcOH, PtO₂, 20 °C, 4.5 h.

The X-ray analysis of tetraisopropylmethane (**9a**) (Figure 2) shows that it has D_{2d} symmetry with the methyl groups pairwise in an eclipsed orientation with respect to an

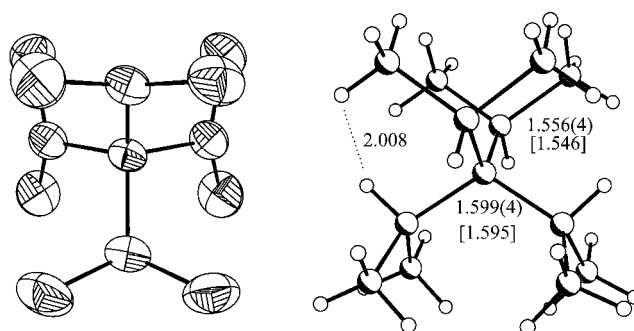


Figure 2. Molecular structure of tetraisopropylmethane (**9a**) according to X-ray structure analysis (left),^[17] and in the gas phase (right), according to B3LYP/6-31 + G** calculations (calculated bond lengths in parentheses). The experimental bond lengths [Å] are mean values based on assumed D_{2d} symmetry for **9a**.

imaginary line connecting the CH fragments of the corresponding isopropyl groups. This arrangement corresponds to the energetically most favorable conformation of each subunit in the molecule, and it is in excellent agreement with the results of B3LYP/6-31 + G** computations. Yet, the corresponding structure in S_4 symmetry differs only slightly from the D_{2d} structure, both energetically as well as geometrically (Table 1). The single bonds around the central carbon in **9a** (1.599(4) Å; computed: 1.595 Å, Figure 2) are significantly lengthened as a result of the steric interactions between the isopropyl groups. As the shortest nonbonded H...H distances in **9a** (2.008 Å; computed 1.995 Å) are between the tertiary

methyne and one hydrogen of the γ -positioned methyl group, the interaction is clearly repulsive. Thus, the arrangement of the four isopropyl groups in **9a** is a compromise between repulsive H $\cdots$ H interactions and favorable local conformations. The shortest H $\cdots$ H distances in tetracyclopropylmethane **7a** are 2.135 Å (computed 2.193 Å), and the interaction is not as repulsive as in **9a**. This is in line with the generally accepted notion that an isopropyl is considerably more sterically demanding than a cyclopropyl substituent.^[27]

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- [15] All new compounds were fully characterized by spectroscopic methods (¹H NMR, ¹³C NMR, MS), elemental analyses and, in part, crystal structure analyses. **7a**: Colorless liquid, m.p. ca. –15 °C; ¹H NMR (250 MHz, CDCl₃): δ = 0.15–0.23 (m, 8H, $\frac{1}{2}$ from 8CH₂), 0.36–0.46 (m, 12H, $\frac{1}{2}$ from 8CH₂+4CH); ¹³C NMR (62.9 MHz, CDCl₃, additional DEPT): δ = –0.72 (8CH₂), 15.61 (4CH), 32.65 (C). **7b**: Colorless liquid, m.p. ca. –20 °C; ¹H NMR: δ = 0.12–0.22 (m, 7H, $\frac{1}{2}$ from 7CH₂), 0.33–0.50 (m, 11H, $\frac{1}{2}$ from 7CH₂+4CH); ²H NMR (CD₂Cl₂/CHCl₂F): δ = 0.09 (s), 0.35 (s); ¹³C NMR: δ = –1.35 (p, J = 24.3 Hz, CD₂), –0.94 (CH₂), –0.72 (6CH₂), 15.41 (CH), 15.64 (3CH), 32.65 (C). **6a**: Colorless liquid, b.p. 58–60 °C (12 mbar); ¹H NMR: δ = 0.27–0.37 (m, 8H, 4CH₂), 0.78–0.87 (m, 2H, 2CH), 5.09 (dd, J = 10.8, 1.9 Hz, 2H, =CH₂), 5.18 (dd, J = 17.8, 1.9 Hz, 2H, =CH₂), 5.59 (dd, J = 17.8, 10.8 Hz, 2H, =CH); ¹³C NMR: δ = –0.22 (4CH₂), 17.17 (2CH), 44.65 (C), 114.81 (2CH₂), 141.36 (2CH). **6b**: Colorless liquid, b.p. 65–67 °C (15 mbar); ¹H NMR: δ = 0.27–0.37 (m, 8H, 4CH₂), 0.78–0.85 (m, 2H, 2CH), 5.09 (dd, J = 10.5, 2.0 Hz, 1H, =CH₂), 5.18 (dd, J = 17.5, 2.0 Hz, 1H, =CH₂), 5.57 (brs, 1H, =CH), 5.59 (dd, J = 17.5, 10.5 Hz, 1H, =CH); ¹³C NMR: δ = –0.22 (4CH₂), 17.19 (2CH), 44.59 (C), 114.27 (quint, J = 23.9 Hz, CD₂), 114.78 (CH₂), 141.10 (CH), 141.33 (CH). **8**: Colorless liquid; ¹H NMR: δ = 0.25–0.36 (m, 12H, 6CH₂), 0.54–0.60 (m, 3H, 3CH), 5.04 (dd, J = 10.5, 2.5 Hz, 1H, =CH₂), 5.29 (dd, J = 17.5, 2.5 Hz, 1H, =CH₂), 5.47 (dd, J = 17.5, 10.5 Hz, 1H, =CH); ¹³C NMR: δ = –0.41 (6CH₂), 16.32 (3CH), 38.89 (C), 114.66 (CH₂), 141.50 (CH). **9a**: Colorless solid, m.p. 74–76 °C; ¹H NMR: δ = 1.04 (d, J = 7.2 Hz, 24H, 8CH₃), 2.23 (sept, J = 7.2 Hz, 4H, 4CH); ¹³C NMR: δ = 20.87 (8CH₃), 31.94 (4CH), 45.58 (C). **9b**: Colorless solid, m.p. 58–60 °C; ¹H NMR: δ = 1.05 (d, J = 7.2 Hz, 21H, 7CH₃), 1.08 (m, 1H, CD₂H), 2.18–2.30 (m, 1H, CH), 2.24 (sept, J = 7.2 Hz, 3H, 3CH); ²H NMR (CD₂Cl₂/CHCl₂F): δ = 1.04 (dd, J = 1.2, 2.0 Hz); ¹³C NMR: δ = 20.31 (quint, J = 19.0 Hz, CD₂H), 20.89 (7CH₃), 31.81 (CH), 31.96 (3CH), 45.59 (C).
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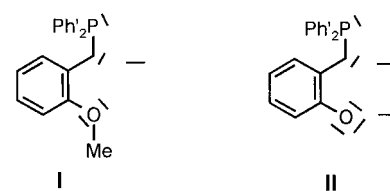
Cyclopentadienyl-Free Calcium Alkyls with Heteroelement-Substituted Anionic Phosphane Ligands: Synthesis and Structure of a Trialkyl Calcate(II) and of an Organocalcium Heterocubane**

Volker Knapp and Gerhard Müller*

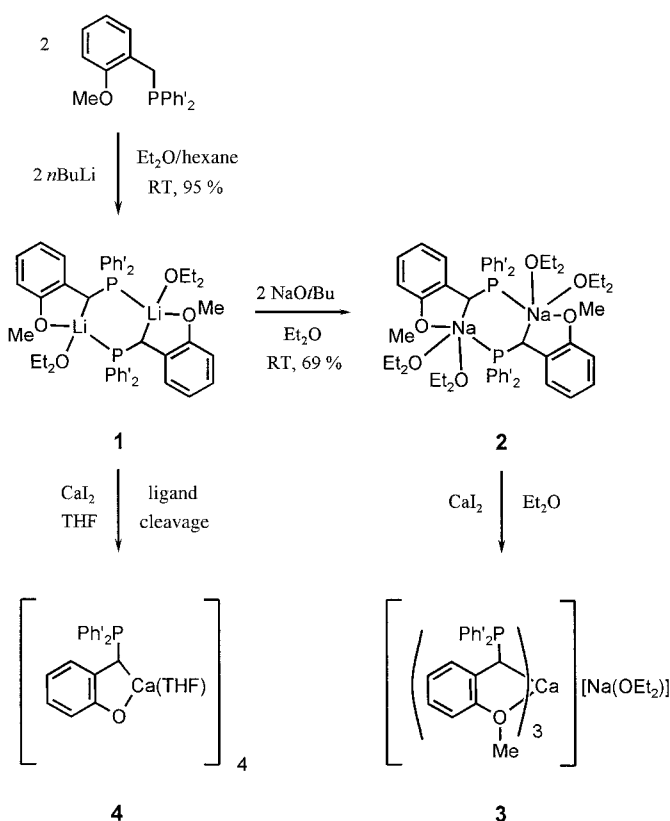
Characteristic for organocalcium chemistry is the predominant use of cyclopentadienyl^[1] and related ligands.^[2] Their bulk and electronic properties serve in an ideal way to solubilize the highly polar calcium organyls in organic solvents, to control their degree of association, and to kinetically stabilize otherwise highly reactive calcium species. In contrast, the number of cyclopentadienyl-free organocalcium complexes is very limited,^[3] particularly noteworthy being $[\text{Ca}\{\text{C}(\text{SiMe}_3)_3\}_2]$.^[4] Because of the extreme steric bulk and electron-donating properties of the tris(trimethylsilyl)-methyl ligand, this compound is monomeric with a bent coordination geometry at the two-coordinate calcium center.^[4]

By employing the moderately bulky, multidentate, oxygen-substituted anionic phosphanes **I** and **II**, we were able to synthesize and structurally characterize a sodium trialkyl calcate(II) (with the monoanionic ligand **I**) and a calcium organyl with a heterocubane structure (with the dianionic ligand **II**). Soft ligands (such as phosphanes) have been shown

to be best suited for complex formation with the hard alkali and alkaline earth metals when they are anionic.^[5]



As starting materials for the novel calcium alkyls the lithium and sodium complexes of **I** were used. They are prepared in good yields by lithiation of 2-MeO-C₆H₄CH₂PPh₂ (Ph' = *p*-tolyl) with *n*BuLi to give **1** (Scheme 1) which reacts by metathesis with NaO*t*Bu to give the sodium



Scheme 1. Synthesis of complexes **1**–**4**. Ph' = *p*-tolyl.

complex **2** (see Experimental Section). The constitution and structural details of **1** and **2** are based on crystal structure determinations.^[6] The reaction of isolated **2** with CaI₂ (Scheme 1) is not the only way to prepare the trialkyl calcate(II) **3**, it may also be prepared in a one-pot synthesis starting from 2-MeOC₆H₄CH₂PPh₂; the overall product yield is still 40%.

Although the good solubility of **3** in aromatic solvents permits the recording of NMR spectra, (see Experimental Section), details of its composition and structure could only be obtained from a crystal structure determination.^[7, 12] As Figure 1 shows, calcium is coordinated by the carbanionoid

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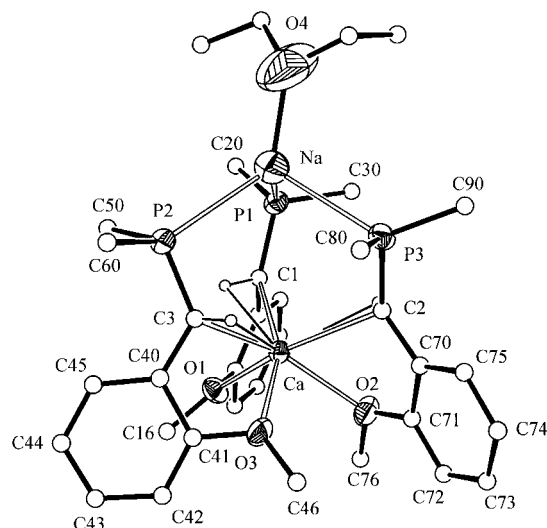


Figure 1. Molecular structure of **3** and numbering scheme (ORTEP-III; thermal ellipsoids at the 50 % level. C atoms with arbitrary radii. For clarity, only the C_{ipso} atoms of the *p*-tolyl substituents are shown and the H atoms are omitted except those at the carbanionoid C atoms. Of the disordered ether C atoms only one alternative is shown). Important distances [Å] and angles [°]: Ca–C1 2.573(4), Ca–C2 2.554(4), Ca–C3 2.532(4), Ca–H11 2.41(4), Ca–H21 2.40(3), Ca–H31 2.43(3), Ca–O1 2.438(3), Ca–O2 2.441(3), Ca–O3 2.423(3), Na–P1 2.851(2), Na–P2 2.934(2), Na–P3 2.871(2), Na–O4 2.150(7), P1–C1 1.761(4), C1–C10 1.457(5), C1–H11 0.90(4), P2–C2 1.764(4), C2–C40 1.455(5), C2–H21 0.85(3), P3–C3 1.774(4), C3–C70 1.458(5), C3–H31 1.04(3); C1–Ca–O1 66.4(1), C2–Ca–O2 66.7(1), C3–Ca–O3 66.2(1), C1–Ca–O2 159.7(1), C2–Ca–O3 152.1(1), C3–Ca–O1 153.5(1); O4–Na–P1 109.5(3), O4–Na–P2 128.1(3), O4–Na–P3 111.2(2), P1–Na–P2 102.5(1), P1–Na–P3 96.6(1), P2–Na–P3 104.2(1), Na–P1–C1 105.3(1), P1–C1–Ca 122.6(2), C10–C1–Ca 103.6(2), H11–C1–Ca 69(3), P2–C2–Ca 127.8(2), C40–C2–Ca 98.3(2), H21–C2–Ca 70(2), P3–C3–Ca 117.2(2), C70–C3–Ca 105.0(2), H31–C3–Ca 73(2).

carbon atoms and the ether oxygen atoms of three ligands **I**, resulting in the coordination number six and a coordination geometry almost exactly between octahedral and trigonal prismatic. Thereby the triangular faces of the coordination polyhedron are formed by three carbon atoms (C1, C2, C3) and three oxygen atoms (O1, O2, O3). They are not strictly parallel but tilted by 4.5° with respect to each other. The twist angle τ between the planes is 31.3°. [13] A noteworthy feature in the ligand coordination of **3** is that the calcium atom is not situated directly above the triangular planes of the coordinating carbon atoms C1–C3 but rather tilted towards the H atoms (H atoms refined). This results in short Ca–H distances of 2.41 Å (av). This bonding situation closely resembles agostic metal–hydrogen interactions as known from transition metal chemistry (Figure 1). We also attribute the noticeable pyramidalization of C1–C3 (sum of the angles at C1, C2, C3 excluding Ca: 345.2, 347.0, and 349.0°, respectively) to this peculiar coordination mode. The Ca–O bonds in **3** (av 2.43 Å) are noticeably shorter than the Ca–C bonds (av 2.55 Å). Because of the metal coordination number of six and the special ligand coordination mode in **3**, not many reference compounds are at hand for comparison. In $[\text{Ca}\{\text{C}(\text{SiMe}_3)_3\}_2]$, containing a two-coordinate calcium center, the Ca–C bond distances are 2.459(9) Å, [4] while in the four-coordinate calcium complex $[\text{Ca}\{\text{CH}(\text{SiMe}_3)_2(1,4\text{-dioxane})_2\}]$ they are 2.483(5) Å. [3e] In the 2,3-dimethyl-1,4-diphenylbutadiene complex $[\text{Ca}(\text{PhCH}=\text{CMe}=\text{CMe}=\text{CHPh})(\text{thf})_4]$ [3d] both the

Ca–C bond distances (2.574(7), 2.588(7) Å; terminal butadiene C atoms) as well as the Ca–O bonds (2.397–2.445 Å) are very similar to those in **3**.

The phosphanyl groups in **3** are not coordinated to calcium but rather to the sodium counterion, resulting in a mixed-metal complex with a relatively short (nonbonding) Ca...Na distance of 4.11 Å. A distorted tetrahedral coordination geometry at the sodium atom is completed by one molecule of Et₂O. The Na–P distances are rather short (av. 2.885 Å) for Na–PR₃ bonds, although not many such interactions have been reported before. [5, 14, 15] We are not aware of any other example of a coordination environment at sodium comprising three phosphane and one ether donor. The calcatenine **3** is the first structurally characterized trialkyl ate complex [16] of calcium. [17, 18]

Complex **4** was prepared during attempts to synthesize **3** from the lithium compound **1** in THF (Scheme 1). As is evident, the formation of the alkoxo phosphane ligand **II** results from an unexpected ligand cleavage reaction of **1** involving the loss of the methoxy methyl group. Consequently, the yields of **4** were low. As the starting complex **1** was pure (NMR spectroscopy), **II** must have been formed by ether cleavage during the prolonged reaction times of **1** with CaI₂ in THF. In contrast to the synthesis of **3**, in Et₂O under heterogeneous conditions, that of **4** is homogeneous in THF. Furthermore, the reaction and crystallization times for **4** were much longer than those for **3** (see Experimental Section). Therefore, it seems plausible that the ligand fragmentation occurs by nucleophilic attack of the iodide ion at the carbon atom of the calcium-coordinated methoxy group. [19]

In the solid state **4** is tetrameric with a cuboidal Ca₄O₄ core, [12, 20] the oxygen atoms belong to the μ_3 -aryloxide groups (Figure 2). Although the structural motif of a cube with metal

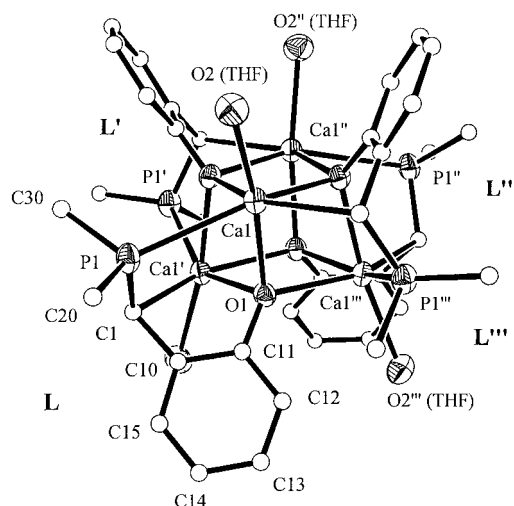


Figure 2. Molecular structure of **4** (ORTEP-III, thermal ellipsoids at the 50 % level. C atoms with arbitrary radii. For clarity, only the C_{ipso} atoms of the *p*-tolyl substituents and the O atoms of the THF molecules are shown. All H atoms are omitted). Selected distances [Å] and angles [°]: Ca–O1 2.346(4), Ca–O1' 2.430(3), Ca–O1'' 2.360(3), Ca–O2 2.387(4), Ca–C1'' 2.591(5), Ca–P1 2.985(2), P1–C1 1.772(6), C1–C10 1.484(7), C1–H11 0.96(4); O1'–Ca–O1'' 76.8(1), Ca'–O1–Ca'' 103.2(1); Ca–P1–C1 99.7(2), P1–C1–C10 113.0(4), P1–C1–H11 114(2), C10–C1–H11 106(3), P1–C1–Ca' 111.6(3), C10–C1–Ca' 88.7(3), H11–C1–Ca' 121(2). Symmetry: $L' = 1/4 - y, 1/4 + x, 1/4 - z$; $L'' = -x, 1/2 - y, z$; $L''' = -1/4 + y, 1/4 - x, 1/4 - z$.

and oxygen atoms at alternate corners has precedent in calcium chemistry,^[21] to our knowledge it has not been observed in organocalcium compounds.

In **4** each individual calcium atom (compare Ca1 in Figure 1) is coordinated by the oxygen and the phosphanyl phosphorus atoms of one ligand (L), the oxygen and the carbanionoid carbon of a second ligand (L'), and the oxygen atom of a third ligand (L''). The hexacoordination is completed by the oxygen atom of the coordinated THF molecule. The molecular structure has crystallographic $\bar{4}$ (S_4) symmetry. As compared to **3**, the Ca–O(ligand) bonds in **4** are slightly shorter while the Ca–C bonds are slightly longer. The Ca–P bond length of 2.986(3) Å in **4** can only be compared with those in the calcium diphosphanylmethanide complex $[\text{Ca}(\text{P-Me}_2)_2\text{C}(\text{SiMe}_3)_2(\text{thf})_3]$ (av $d(\text{Ca}-\text{P}) = 3.043$ Å), which is the only other example of crystallographically characterized Ca–PR₃ bonds.^[22, 23] The carbanionoid carbon C1 in **4** is pyramidalized as the sum of the angles excluding calcium of 333.0° shows. However, in contrast to **3**, in **4** no agostic-type interaction between calcium and the hydrogen atom at C1 is observed.

In summary, our results show that ligands of type **I** and **II** are particularly suitable for complex formation to calcium (and presumably to other hard and large metal centers). These ligands combine three donor sites consisting of two soft (P, C) and one hard (O) donor atom suitably located for chelate formation and thus producing a coordinatively saturated, shielded calcium center.

Experimental Section

Synthesis of 1: A solution of *n*BuLi in hexane (2.5 M; 2.78 mL) was added dropwise to 2.32 g (6.93 mmol) of 2-MeOC₆H₄CH₂PPh₂ dissolved in Et₂O (40 mL) whereupon the reaction mixture turned from yellow to dark orange. Stirring was continued for 3 h at room temperature. After evaporating the solvent under reduced pressure, the residue was washed twice with toluene (20 mL) and dried in vacuo; yield: 2.74 g (6.6 mmol, 95 %); m.p. 192 °C (sealed capillary, decomp); elemental analysis calcd for C₂₂H₂₂LiOP · C₄H₁₀O (%): C 75.7, H 7.3; found: C 74.2, H 7.0; ¹H NMR (400 MHz, [D₈]toluene/[D₈]THF (9/1), 25 °C, TMS): δ = 7.49 (dd, ³J(H-H) = 6.2 Hz, ³J(H-P) = 6.2 Hz; *o*-H, *p*-tol), 6.89 (d, ³J(H-H) = 7.7 Hz; *m*-H, *p*-tol), 7.25 (m, *o*-H, benzyl), 6.69 (t, ³J(H-H) = 7.4 Hz; *m*-H, benzyl), 6.45 (d, ³J(H-H) = 7.8 Hz; *m*-HCCOMe), 6.22 (t, ³J(H-H) = 5.9 Hz; *p*-H, benzyl), 3.49 (s, OMe), 3.24 (q, CH₂, OEt₂), 2.55 (d, ²J(H-P) = 5.5 Hz; PCH), 2.12 (s, Me, *p*-tol), 1.05 (t, Me, OEt₂); ¹³C {¹H} NMR (101 MHz, [D₈]toluene/[D₈]THF (9/1), 25 °C, TMS): δ = 151.18 (d, ³J(C-P) = 7.3 Hz; COMe), 145.45 (d, ¹J(C-P) = 9.6 Hz, *ipso*-C, *p*-tol), 144.89 (d, ²J(C-P) = 20.3 Hz; *ipso*-C, benzyl), 134.81 (s, *p*-C, *p*-tol), 132.83 (d, ²J(C-P) = 11.9 Hz; *o*-C, *p*-tol), 128.40 (d, ³J(C-P) = 3.6 Hz; *m*-C, *p*-tol), 123.83 (s, *m*-C, benzyl), 120.05 (d, ³J(C-P) = 17.8 Hz; *o*-C, benzyl), 110.63 (s, *p*-C, benzyl), 110.24 (s, *m*-CCOMe), 55.54 (s, OMe), 36.52 (s, PCH), 21.08 (s, Me, *p*-tol); ³¹P {¹H} NMR (162 MHz, [D₈]toluene/[D₈]THF (9/1), 25 °C, ext. 85 % H₃PO₄): δ = -15.97 (br. s); ⁷Li {¹H} NMR (155 MHz, [D₈]toluene/[D₈]THF (9/1), 25 °C, ext. 1 M LiBr in [D₈]THF): δ = 0.07 (s).

Synthesis of 2: NaOtBu (1.03 g, 9.35 mmol) was added to a solution of **1** (2.97 g, 7.21 mmol) in Et₂O (60 mL). The solution turned deep-red and after 30 min a yellow solid started to precipitate. Centrifugation and subsequent washing with Et₂O (2 x 10 mL) yielded **2** (2.51 g, 4.97 mmol, 69 %) as yellow powder. M.p. 202 °C (sealed capillary, decomp); elemental analysis calcd for C₂₂H₂₂NaOP · C₈H₂₀O₂ (%): C 71.4, H 8.4; found: C 69.8, H 6.7; ¹H NMR (400 MHz, C₆D₆/[D₈]THF (9/1), 25 °C, TMS): δ = 7.72 (dd, ³J(H-H) = 6.6 Hz, ³J(H-P) = 6.6 Hz; *o*-H, *p*-tol), 7.38 (m, *o*-H, benzyl), 6.97 (d, ³J(H-H) = 7.6 Hz; *m*-H, *p*-tol), 6.74 (t, ³J(H-H) = 7.1 Hz; *m*-H, benzyl), 6.54 (d, ³J(H-H) = 7.7 Hz; *m*-HCCOMe), 6.19 (t, ³J(H-H) = 7.2 Hz; *p*-H, benzyl), 3.56 (s, OMe), 3.25 (q, CH₂, OEt₂), 3.03 (d, ²J(H-P) = 7.3 Hz;

PCH), 2.15 (s, Me, *p*-tol), 1.08 (t, Me, OEt₂); ¹³C {¹H} NMR (101 MHz, C₆D₆/[D₈]THF (9/1), 25 °C, TMS): δ = 149.94 (d, ³J(C-P) = 10.0 Hz; COMe), 144.46 (d, ²J(C-P) = 17.68 Hz; *ipso*-C, benzyl), 144.19 (d, ¹J(C-P) = 11.5 Hz; *ipso*-C, *p*-tol), 135.13 (s, *p*-C, *p*-tol), 133.41 (d, ²J(C-P) = 19.2 Hz; *o*-C, *p*-tol), 128.63 (d, ³J(C-P) = 6.2 Hz; *m*-C, *p*-tol), 123.68 (s, *m*-C, benzyl), 117.14 (d, ³J(C-P) = 23.1 Hz; *o*-C, benzyl), 110.70 (s, *m*-CCOMe), 107.90 (s, *p*-C, benzyl), 56.14 (s, OMe), 37.22 (br. s, PCH), 21.13 (s, Me, *p*-tol); ³¹P {¹H} NMR (162 MHz, C₆D₆/[D₈]THF (9/1), 25 °C, ext. 85 % H₃PO₄): δ = -18.87 (br. s).

Synthesis of 3: a solution of *n*BuLi in hexane (2.5 M; 2.5 mL) was added dropwise to 2-MeOC₆H₄CH₂PPh₂ (2.12 g, 6.34 mmol) dissolved in Et₂O (30 mL). The reaction mixture was stirred for 3 h at room temperature then NaOtBu (0.69 g, 6.34 mmol) was added. A yellow precipitate formed which was separated by centrifugation. It was washed twice with hexane and dried in vacuo. After it had been suspended in Et₂O (40 mL), anhydrous CaI₂ (0.72 g, 2.46 mmol) was added and the reaction mixture was stirred for 3 d. The precipitated NaI was separated by centrifugation and to the resulting clear red solution was carefully layered with hexane (3 mL). Yellow crystals suitable for X-ray analysis formed at 4 °C; yield: 2.88 g (40 %); m.p. 131 °C (sealed capillary); elemental analysis calcd for C₇₀H₇₆CaNaO₄P₃ (%): C 73.9, H 6.7; found: C 73.6, H 6.5; ¹H NMR (400 MHz, C₆D₆, 25 °C, TMS): δ = 7.78/7.03 (br. s, *o*-H, *p*-tol), 7.10/6.89 (br. s, *m*-H, *p*-tol), 6.94 (d, ³J(H-H) = 7.0 Hz; *o*-H, benzyl), 6.60 (m, *m*-H, benzyl), 6.36 (t, ³J(H-H) = 6.9 Hz; *p*-H, benzyl), 3.26 (q, CH₂, OEt₂), 2.40 (m, PCH), 2.23/2.13 (s, Me, *p*-tol), 1.08 (t, Me, OEt₂); ¹³C {¹H} NMR (101 MHz, C₆D₆, 25 °C, TMS): δ = 152.29 (s, COMe), 139.61 (s, *ipso*-C, benzyl), 136.67 (s, *p*-C, *p*-tol), 135.28 (s, *ipso*-C, *p*-tol), 133.83 (s, *o*-C, *p*-tol), 131.79 (s, *m*-C, *p*-tol), 124.21 (s, *m*-C, benzyl), 115.45 (s, *p*-C, benzyl), 112.38 (s, *m*-CCOMe), 57.68 (s, OMe), 34.6 (s, PCH), 21.21 (s, Me, *p*-tol); ³¹P {¹H} NMR (162 MHz, C₆D₆, 25 °C, ext. 85 % H₃PO₄): δ = -22.34 (br. s).

Synthesis of 4: a solution of *n*BuLi in hexane (2.5 M; 1.4 mL) was added dropwise to a solution of 2-MeOC₆H₄CH₂PPh₂ (1.16 g, 3.47 mmol) in THF (20 mL). The reaction mixture was stirred for 3 h at room temperature and CaI₂ (0.34 g, 1.17 mmol) was added. Stirring was continued for 2 d at room temperature. Yellow crystals suitable for X-ray analysis formed at 4 °C over a period of 4 weeks; yield: 0.06 g (0.035 mmol, 12 % based on CaI₂). The small amount of isolated substance allowed only the recording of the following preliminary NMR data: ¹H NMR (400 MHz, C₆D₆, 25 °C, TMS): δ = 7.64 (m, *o*-H, *p*-tol), 7.29 (t, ³J(H-H) = 7.9 Hz; *m*-H, benzyl), 6.98 (m, *m*-H, *p*-tol), 6.86 (t, ³J(H-H) = 6.6 Hz; *p*-H, benzyl), 6.76 (d, ³J(H-H) = 7.6 Hz; *o*-H, benzyl), 6.45 (d, ³J(H-H) = 8.1 Hz; *m*-HCCO⁻, benzyl), 3.23 (s, PCH), 2.06/1.93 (s, Me, *p*-tol); ³¹P {¹H} NMR (162 MHz, C₆D₆, 25 °C, ext. 85 % H₃PO₄): δ = 1.64 (s).

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- Crystal structure data of **3** · 2 hexane: C₇₀H₇₆CaNaO₄P₃ · C₁₂H₂₈, *M*_r = 1309.71 g mol⁻¹, monoclinic, space group C2/c (No. 15), *a* = 31.462(3), *b* = 15.958(1), *c* = 33.396(4) Å, β = 117.395(5)°, *V* = 14887(3) Å³, *Z* = 8, ρ_{calcd} = 1.169 g cm⁻³, μ(MoKα) = 0.203 cm⁻¹, *F*(000) = 5632, *T* =

- 183(2) K. Enraf-Nonius CAD4, graphite monochromatized $\text{MoK}\alpha$ radiation, $\lambda = 0.71069 \text{ \AA}$, ω scans, $\Delta\omega = 0.8^\circ$, $((\sin \theta)/\lambda)_{\text{max}} = 0.592 \text{ \AA}^{-1}$, hkl range: $+37, +18, -39 - +35$. Of a total of 13282 measured reflexions, 13008 were unique ($R_{\text{int}} = 0.027$) and 7920 were "observed" with $I > 2\sigma(I)$. Refinement of 797 parameters was done on F^2 of all unique reflexions leading to $R(F)/wR(F^2) = 0.064/0.190$, $GoF = 1.06$, $w = 1/(\sigma^2(F_o^2) + (0.1086 P)^2)$, $P = (\max(F_o^2, 0) + 2F_c^2)/3$. $\Delta\rho_{\text{fin}}$ (max/min) = $0.62/-0.69 \text{ e \AA}^{-3}$. In the refinement all non-H atoms were refined anisotropically, except the C atoms of the coordinated molecule Et_2O which were treated in a split atom model. H11, H21, H31 were refined freely with individual isotropic displacement parameters. While one of the interstitial hexane molecules could be refined satisfactorily, the second one was found to be severely disordered, thereby impeding any meaningful refinement. Therefore, it was excluded from structure factor calculations with the routine SQUEEZE^[8] as included in PLATON.^[9] Restraints were applied to the bonds between the disordered ether and hexane atoms. Programs used: SHELXS-97 (structure solution),^[10] SHELXL-97 (structure refinement),^[10] ORTEP-III (molecular drawings).^[11]
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$F(000) = 3648$, $T = 183(2) \text{ K}$. Enraf-Nonius CAD4, graphite monochromatized $\text{MoK}\alpha$ radiation, $\lambda = 0.71069 \text{ \AA}$, ω -scans, $\Delta\omega = 0.8^\circ$, $((\sin \theta)/\lambda)_{\text{max}} = 0.50 \text{ \AA}^{-1}$, hkl range: $\pm 25, \pm 25, +14$. Of a total of 10451 measured reflexions, 2369 were unique ($R_{\text{int}} = 0.122$) and 1380 were "observed" with $I > 2\sigma(I)$. Refinement of 302 parameters on F^2 of all unique reflexions leading to $R(F)/wR(F^2) = 0.046/0.104$, $GoF = 1.01$, $w = 1/(\sigma^2(F_o^2) + (0.0456 P)^2 + (10.2187 P))$, $P = (\max(F_o^2, 0) + 2F_c^2)/3$. $\Delta\rho_{\text{fin}}$ (max/min) = $0.22/-0.26 \text{ e \AA}^{-3}$. In the refinement all non-H atoms were refined anisotropically. Some of the H atoms including that at C1 were refined freely with individual isotropic displacement parameters.

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The Unusual Photochemistry of Dendrimers with an Anthracene Core**

Derong Cao and Herbert Meier*

Monodisperse dendrimers represent a link between organic compounds with low molecular masses and polymers, and are distinguished by a number of special properties.^[1] The objective of the present work was to study the photochemistry and the photophysics of anthracene when used as a core of a dendritic structure. Thus, dendrons of the Fréchet type^[2] were attached in the 9 and 10 positions of anthracene. The nucleophilic substitution of the halogen atoms in 9,10-bis(chloromethyl)- or 9,10-bis(bromomethyl)anthracene (**2**) with 3,5-dialkoxy-substituted benzyl alcohols **1a–c** in an alkaline medium under phase-transfer conditions provided yields between 66 and 30 % (Scheme 1). An increase in the branching makes the reaction less effective.^[3] For comparative purposes the methoxy compound **3d** was prepared by an analogous procedure.

The ^1H and ^{13}C NMR data of the dendrimers **3a–c** are summarized in Table 1; they differ little from the model compound **3d**, apart from the presence of methoxy groups in

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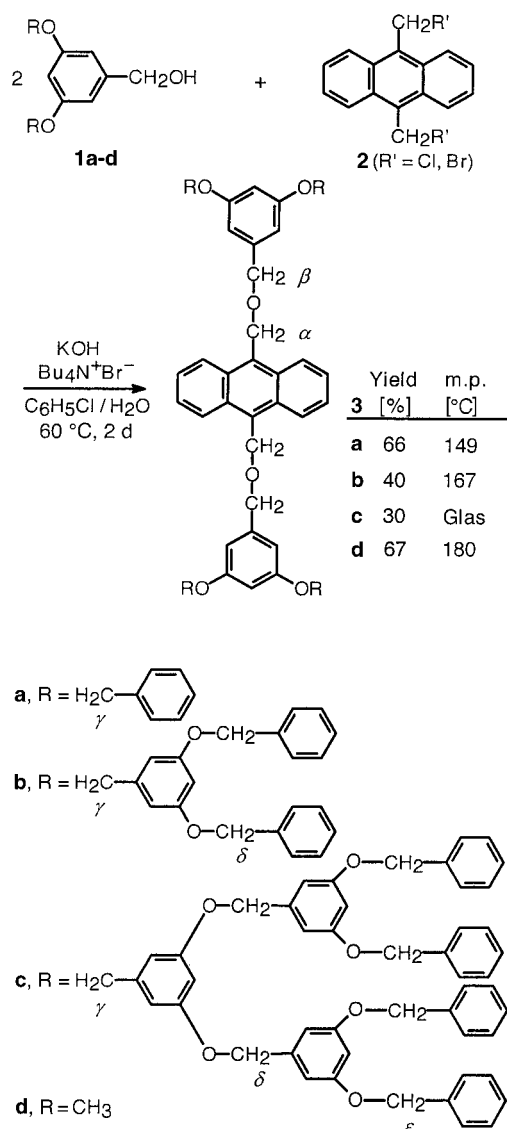
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 Scheme 1. Synthesis of the dendrimers **3a–c** and the model compound **3d**.

the latter. The chemical shifts of the OCH_2 groups (α to ϵ , Scheme 1 and Table 1) are most characteristic. Their chemical shifts $\delta(^1\text{H})$ follow the sequence: $\alpha > \epsilon > \delta > \gamma > \beta$; however, contrary to this, the $\beta\text{-OCH}_2$ group has the highest and the $\alpha\text{-OCH}_2$ group the lowest chemical shift in the ^{13}C NMR spectra, with the sequence being: $\beta > \epsilon \approx \delta \approx \gamma > \alpha$.

The Fréchet-type dendrons were selected so that the “antenna effect” could be studied.^[4,5] The electronic transitions in the dendrons **3a–c** can be localized, to a first approximation, in separated molecular regions: in the anthracene core A, in the middle benzene rings B_m bearing

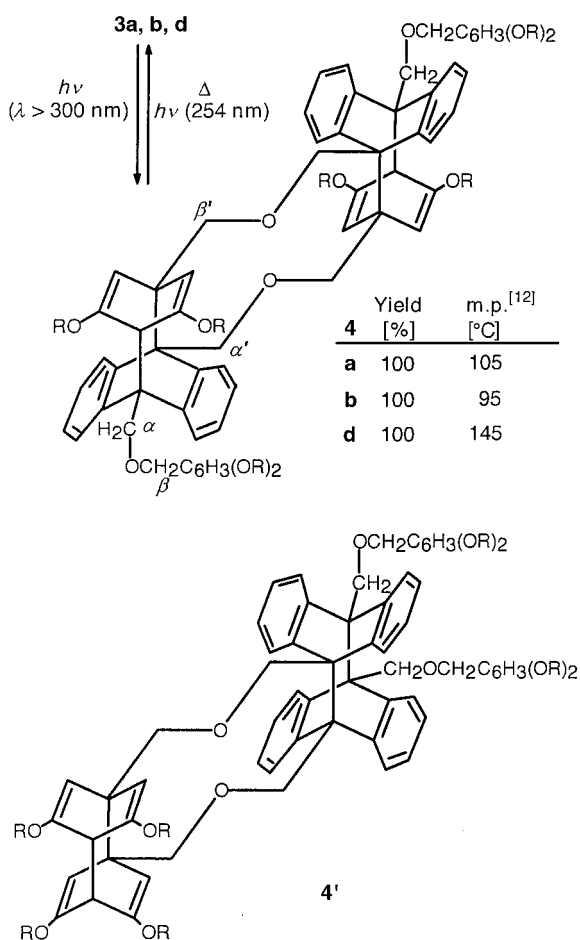
alkoxy groups, and in the peripheral benzene rings B_p . The corresponding excitation energies $[E(\text{S}_1) - E(\text{S}_0)]$ decrease from the outside to the inside, and an effective singlet energy transfer $\text{B}_p \rightarrow \text{B}_m \rightarrow \text{A}$ should, therefore, be possible. An impressive proof of this hypothesis was provided by the fluorescence quantum yields: Φ_F increases by a factor of 2.24 for **3a** and by a factor of 2.57 for **3b** relative to unsubstituted anthracene when solutions of the compounds in dichloromethane at room temperature are excited at $\lambda = 260 \text{ nm}$.^[6] Solutions containing equal molar concentrations of anthracene and the “arms” **1a** or **1b** the probes of **3a** and **3b**, respectively, do not indicate an amplification effect at all. Thus, an intermolecular energy transfer under the conditions described can be ruled out.

The photochemistry of anthracene and its derivatives is distinguished by wavelength-dependent dimerization reactions. Apart from the $[4\pi+4\pi]$ cyclodimerization of the central rings, some examples of $[4\pi+4\pi]$, $[4\pi+2\pi]$, and $[2\pi+2\pi]$ cyclodimerization reactions are known in which the outer rings are involved.^[7,8] Irradiation in the near-UV region ($\lambda \geq 300 \text{ nm}$) of an approximately 10^{-3} M solution of **3a**, **b** or **3d** in benzene leads to the quantitative formation of similar dimerization products; the ^1H and ^{13}C NMR spectra of the crude products do not reveal any side reactions occurred. The structures of the photodimers do not fit into the known reaction schemes.^[7–9] We established that in each case a benzene ring at the $\beta\text{-OCH}_2$ group is involved in the dimerization. This finding points to structures **4** and **4'** (Scheme 2). Photocycloadditions between two benzene rings^[10] or between an anthracene and a benzene ring system^[11] are extremely rare; up to now they were only observed in intramolecular reactions of a few rigid structures.

Provided that the inversion of the central 1,6-dioxacyclodecane ring in **4** and **4'** is fast, **4** will show a C_{2h} and **4'** a C_{2v} symmetry; accordingly one can not distinguish between these two structures on the basis of the number and the splitting of the signals in the ^1H and ^{13}C NMR spectra. A decision in favor of **4a**, **b**, **d** was possible with the help of nuclear Overhauser effect (NOE) measurements. Irradiation into the signal of the methine protons on the cyclohexadiene rings produces a positive NOE in the signal corresponding to the $\alpha\text{-OCH}_2$ groups (and simultaneously an INDOR effect in the signal of the olefinic protons). This result is compatible with structure **4** but not with **4'**. The photodimerization **3** $\rightarrow$ **4** consists of an intermolecular and an intramolecular $[4\pi+4\pi]$ process. The UV spectra measured during the reaction do not reveal an intermediate. Whereas aggregation seems to be relevant for the intermolecular step, the two 4π components of the intramolecular step are already fixed in a spatial proximity.

 Table 1. ^1H and ^{13}C NMR data of **3a–c** (δ values in CDCl_3 , TMS as an internal standard).

Anthracene core				Benzene rings				Oxymethylene groups							
AA'	BB'			A ₂	B		AA'	BB'	C			$\alpha\text{-H}$	$\beta\text{-H}$	$\gamma\text{-H}$	$\delta\text{-H}$
C-1	C-2	C-4a	C-9	CH	CH	C _q	C _q O	CH	CH	CH	C _q	$\alpha\text{-CH}_2$	$\beta\text{-CH}_2$	$\gamma\text{-CH}_2$	$\delta\text{-CH}_2$
8.35	7.47	–	–	6.64	6.55	–	–	7.32	7.32	7.32	–	5.47	4.62	4.91	4.95
± 0.02	± 0.02			± 0.01	± 0.02			± 0.04	± 0.04	± 0.04		± 0.02	± 0.03	± 0.06	± 0.05
125.1	125.7	130.9	130.4	106.6	101.7	140.1	160.1	127.5	128.6	128.0	136.8	64.1	72.3	70.0	70.1
± 0.1	± 0.1	± 0.1	± 0.1	± 0.2	± 0.1	± 0.9	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1



Scheme 2. Reversible photodimerization of **3a, b, d**.

As a result of the loss of aromaticity in the central ring of the anthracene and in the benzene ring which is involved in the cycloaddition the ¹H NMR spectra of **4a, b, d** show numerous changes relative to those of the starting compounds **3a, b, d**.^[13] The methylene groups in the ten-membered ring give singlet signals at $\delta = 4.75 \pm 0.05$ (α') and $\delta = 3.84 \pm 0.05$ (β') in CD₂Cl₂. The protons on the cyclohexadiene ring resonate at very high field, namely at $\delta = 4.37 \pm 0.10$ (olefinic H) and $\delta = 2.19 \pm 0.20$ (methine group). The AA'BB' spin system of the original anthracene unit is also shifted to high field: $\delta = 7.29 \pm 0.10$ and 7.12 ± 0.05 . Even the signals of the side chains, which are not involved in the dimerization, are affected and have δ values of 4.29 ± 0.15 (α H), 4.60 ± 0.05 (β H), 6.53 ± 0.15 (aromatic H), 7.35 ± 0.10 and 5.02 ± 0.04 (benzyloxy), and 3.77 (methoxy). The AB spin pattern of the benzyloxy groups attached to the cyclohexadiene rings ($\delta = 4.18 \pm 0.03$ and 3.55 ± 0.03 , $^2J = -(10.8 \pm 0.3)$ Hz) are particularly striking in the ¹H NMR spectra of **4a, b**; the corresponding methoxy groups in **4d** lead to a singlet at $\delta = 2.86$.

The molecular ions $[M+H]^+$ of the monomeric and the dimeric structures can be obtained in the mass spectra using field-desorption (FD) conditions. Electron-impact measurements induce a dissociation of the photodimers in the ionization chamber.

The unusual photodimerization of **3a, b, d** can be explained by an aggregation of the dendrimers and the model compound

in solution. Presumably, a π - π interaction of the anthracene unit and the electron-rich, alkoxy-substituted benzene rings is more favorable than the anthracene-anthracene interaction. Until now, cycloadducts of anthracene and benzene rings could only be obtained by multistep procedures.^[14, 15] Irradiation of **4a, b, d** with UV light of short wavelengths^[16] or heating above 100 °C leads to a quantitative reverse reaction.

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A Silyl Substituent Can Dictate a Concerted Electrocyclic Pathway: Inward Torquoselectivity in the Ring Opening of 3-Silyl-1-cyclobutene

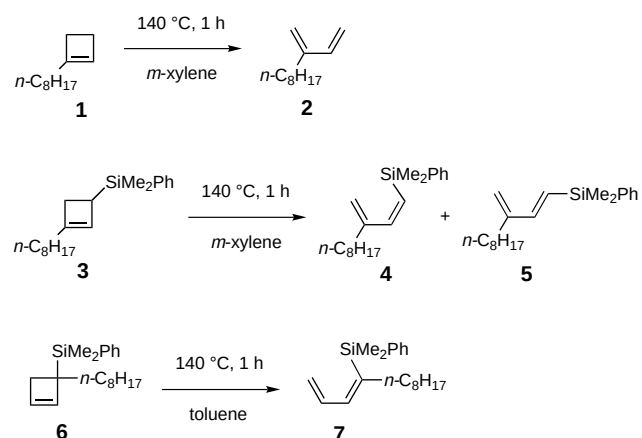
Masahiro Murakami,* Yasufumi Miyamoto, and Yoshihiko Ito*

A thermal conrotatory ring-opening reaction of cyclobutenes to produce 1,3-butadienes has been a source of continuing interest from the viewpoints of both organic and theoretical chemistry. The substituent effects on this reaction have been well studied in terms of torquoselectivity, namely, inward versus outward rotation.^[1] Theoretical studies proved that the stereochemical trend is subject to electronic control rather than steric control. For example, outward rotation is preferred by electron-donating substituents, such as a hydroxy group at the 3-position. In contrast, it was predicted that an electron-accepting substituent at the 3-position would prefer inward rotation.^[2] However, experimentally verified examples of this phenomenon have been limited to the CHO,^[3] COCl,^[3] and CF₃^[4] substituents. Even CO₂Et^[5] and CN^[6] groups favor outward rotation. On the other hand, it is known that, while the silicon atom in a Si–C linkage is depleted of its negative charge, silicon can accommodate electron density from a neighboring p orbital in its low lying σ^* orbital.^[7] The HOMO of the transition state of the ring-opening reaction of 1-cyclobutene is primarily concentrated on the cleaving C3–C4 σ orbital, which is a good electron donor. Thus, we anticipated that a silyl substituent at the 3-position would possibly accept the HOMO electron of the transition state, to result in its stabilization. Here, we report the interesting effects of the silyl substitution on a concerted thermal ring-opening reaction of 1-cyclobutene.

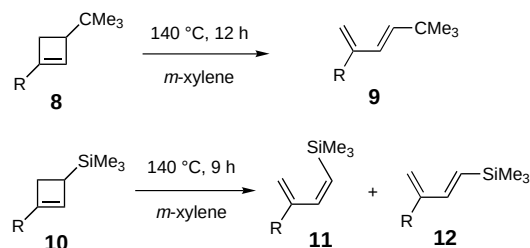
First, the reactions of 1-octyl-1-cyclobutene (**1**) and its silyl-substituted analogues **3** and **6** were examined (Scheme 1). After heating a solution of **1** at 140 °C for 1 h, only 12% of **1** underwent a ring-opening reaction to produce 1,3-diene **2**. In contrast, when a mixture of **3** and **6** (58:42)^[8] was heated under the same conditions, complete conversion to the corresponding 1,3-dienes (**4**, **5**, and **7**; 96% overall yield) was observed. An NMR analysis of the product mixture revealed that the ratio (**4** + **5**):**7** was identical with that of **3**:**6**, to confirm that the 1,3-dienes **4** and **5** arose from **3**, and the 1,3-diene **7** from **6**, in a specific manner. The reactions of **3** and **6** are therefore described separately in Scheme 1.

Interestingly, the *cis* isomer **4**, formed by inward rotation, was favored over the *trans* isomer **5**, formed by outward rotation (**4**:**5** = 83:17). The ratio **4**:**5** was constant through the reaction and even after heating for a longer period, which

suggests that the ratio was kinetically determined. The preference for inward rotation was opposed to what might be expected on steric grounds. Moreover, only the *cis* isomer **7** was produced by inward rotation of **6**.^[9] The inward-selective ring opening reaction of **6** also took place at 110 °C in toluene and completed in 1 h.^[10] These results suggested that a silyl substituent at the 3-position of 1-cyclobutene accelerates the ring-opening reaction and prefers inward, rather than outward, rotation.



Scheme 1. Ring-opening reactions of cyclobutenes **1**, **3**, and **6**.



Scheme 2. Ring-opening reactions of cyclobutenes **8** and **10**. R = PhMe₂C.

To get further experimental verification of this effect, cyclobutenes **8** and **10** were prepared and their reactivities compared. Cyclobutenes **8** and **10** have an identical structure except the tertiary element, that is, a carbon atom of a tertiary butyl group versus a silicon atom of a trimethylsilyl group. When heated at 140 °C, **8** underwent ring opening with outward rotation to give exclusively the *trans* isomer **9** (92%),^[9] which is in agreement with the result of 3-methyl-1-cyclobutene.^[11] On the other hand, **10** furnished a mixture of *cis* isomer **11** and *trans* isomer **12**, with the former predominating (**11**:**12** = 69:31; 95% overall yield). The reaction of **10** ($k = 0.53 \text{ h}^{-1}$ at 140 °C) was faster than that of **8** ($k = 0.32 \text{ h}^{-1}$ at 140 °C). The proportion of *cis* and *trans* isomers **11**:**12** was again opposite to what would be predicted as a result of simple steric argument. The contrasting results of **8** and **10** confirm that a silyl substituent prefers inward rotation.

For density functional theory calculations, 3-silyl-1-cyclobutene (**13**) was taken as a model and the transition states for outward and inward rotations were computationally located.^[12] The potential-energy diagram is shown in Figure 1. The activation energy for inward rotation to *cis* product **15** is 1.67 kcal mol⁻¹ lower than that of outward rotation to *trans*

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product **14**. In the case of 3-methyl-1-cyclobutene, the carbon counterpart of **13**, the calculated preference is just the opposite, that is, the outward rotation is favored by 5.3 kcal mol⁻¹.^[13]

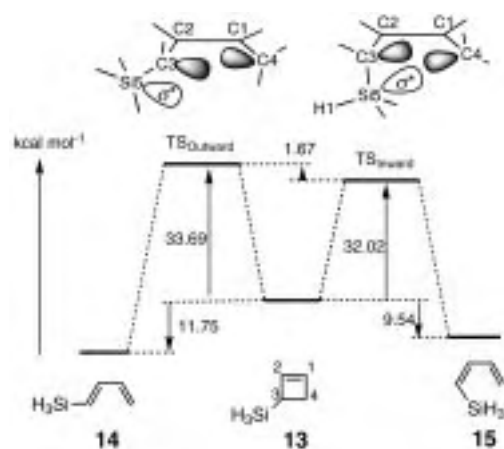


Figure 1. Potential-energy diagram of ring opening reactions of 3-silyl-1-cyclobutene **13**.

For the inward transition state of **13**, the angle C4-C3-Si5 is 92° and the dihedral angle C4-C3-Si5-H1 is 170°. These structural features indicate that the Si5-H1 σ^* orbital eclipses well with the breaking C3-C4 σ orbital, where the HOMO electron is primarily concentrated, and thus accommodates some of the HOMO electron density. For the outward transition structure, in which the angle C4-C3-Si5 is as much as 132°, an analogous stabilizing interaction of the silicon σ^* orbital with the HOMO is smaller. Thus, the observed inward preference and accelerating effect of a silyl substituent can be explained by assuming electron-accepting interactions of the rather low lying σ^* orbital of the silicon atom with the HOMO orbital of the inward transition state.^[14]

The substitution effects of silicon are now widely utilized in a variety of organic reactions.^[15] The stabilization of β -cations in electrophilic reactions of organosilicon compounds is one of the most exploited. The present study discloses an interesting influence of silyl substituents on a concerted electrocyclic reaction. Further investigations of the effects of silyl substituents on other concerted electrocyclic reactions are underway.

Experimental Section

11 and **12**: A solution **10** (30.0 mg, 0.10 mmol) in *m*-xylene (2 mL) was heated at 140 °C for 9 h under an argon atmosphere. The cooled reaction mixture was filtered through a pad of florisil and the filtrate was purified by preparative thin-layer chromatography (silica gel, *n*-hexane) to afford **11** and **12** (69:31, 28.6 mg, 95 %) as a colorless oil. **11**: ¹H NMR (200 MHz, CDCl₃): δ = 0.12 (s, 9H), 1.42 (s, 6H), 5.09 (d, *J* = 1.4 Hz, 1H), 5.15 (d, *J* = 1.4 Hz, 1H), 5.43 (d, *J* = 14.8 Hz, 1H), 6.36 (d, *J* = 14.8 Hz, 1H), 7.18–7.38 (m, 5H); ¹³C NMR (75 MHz, CDCl₃): δ = 0.3, 28.4, 42.8, 111.3, 125.9, 126.3, 128.1, 131.3, 147.2, 148.0, 156.2; elemental analysis: calcd for C₁₆H₂₄Si: C 78.62, H 9.90; found: C 78.86, H 10.14. **12**: ¹H NMR (300 MHz, CDCl₃): δ = 0.07 (s, 9H), 1.44 (s, 6H), 5.09 (s, 1H), 5.35 (s, 1H), 5.90 (d, *J* = 18.6 Hz, 1H), 6.09 (d, *J* = 18.6 Hz, 1H), 7.11–7.30 (m, 5H); ¹³C NMR (75 MHz, CDCl₃): δ = -1.5, 28.9, 42.9, 109.8, 125.7, 126.3, 128.1, 130.9, 144.1, 148.3, 156.0; elemental analysis: calcd for C₁₆H₂₄Si: C 78.62, H 9.90; found: C 79.01, H 10.22.

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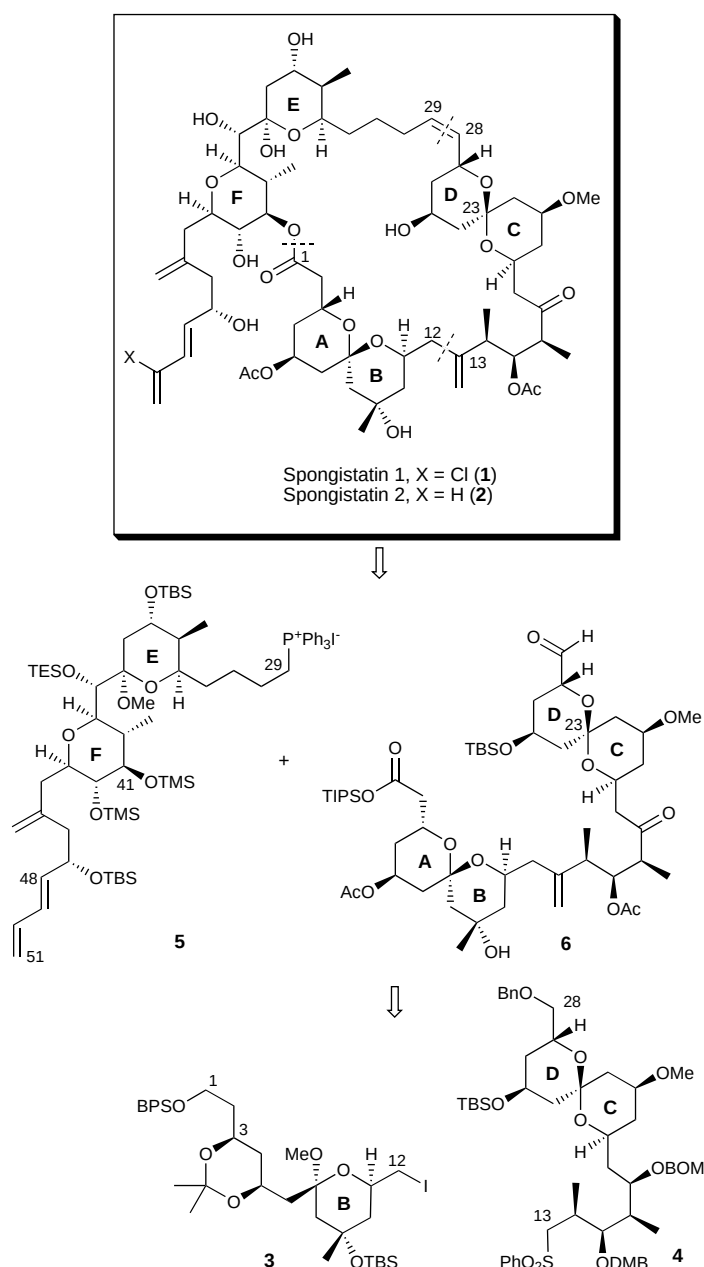
The Spongistatins: Architecturally Complex Natural Products—Part One: A Formal Synthesis of (+)-Spongistatin 1 by Construction of an Advanced ABCD Fragment**

Amos B. Smith III,* Victoria A. Doughty, Qiyang Lin, Linghang Zhuang, Mark D. McBriar, Armen M. Boldi, William H. Moser, Noriaki Murase, Kiyoshi Nakayama, and Masao Sobukawa

The spongipyranes comprise an important family of architecturally unique bis-spiroketal macrolides that display extraordinary (subnanomolar) antitumor activities against a wide variety of human cancer cell lines, including melanoma, lung, colon, and brain.^[1] Three research groups (those of Pettit,^[1a, 2] Fusetani,^[3] and Kitagawa^[4]) independently isolated members of the spongipyran family in minute amounts, naming them in turn the spongistatins, cinachyrolide, and the altohyrtins.^[5] Whereas the carbon skeleton was common to all three families, the structures differed in the assignment of the relative stereochemical relationships. Kitagawa and co-workers assigned the correct relative and absolute stereochemistries based on extensive Mosher analysis and circular dichroism studies.^[4c] These assignments were subsequently confirmed by the total syntheses of (+)-altohyrtin C [spongistatin 2 (**2**)] by Evans et al.^[6] and (+)-altohyrtin A [spongistatin 1 (**1**)] by Kishi and co-workers.^[7] The elegant syntheses at Harvard University demonstrated unequivocally that the altohyrtins and spongistatins were indeed identical.

The spongistatins have attracted wide interest^[8] as a result of their architectural complexity, which includes two [6,6] spiroketal moieties,^[9] two highly substituted tetrahydropyran rings encased in a 42 membered macrolide framework, 24 stereogenic centers, and a delicate triene side chain. Particularly intriguing is the CD spiroketal possessing only a single anomeric interaction in conjunction with an intramolecular hydrogen bond that stabilizes the axial–equatorial configuration.

To assemble the complex spongipyran skeleton, we envisioned Wittig union of **5** with **6** (Scheme 1), followed by regioselective macrolactonization at C(41), first demonstrated



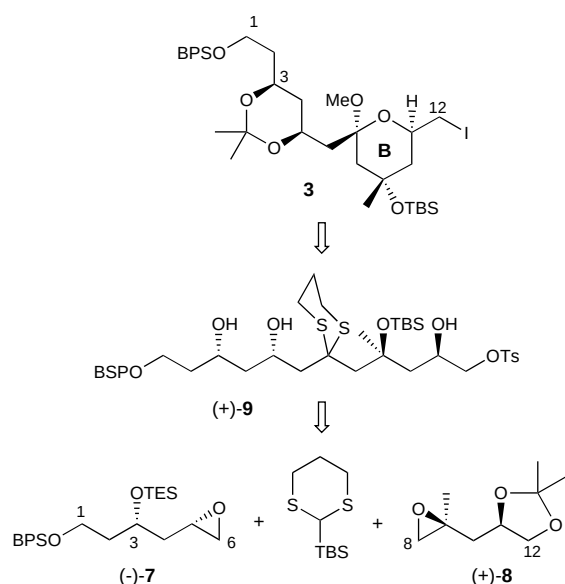
Scheme 1. Retrosynthetic analysis of spongistatin 2 (see ref. [20] for abbreviations).

by Evans et al.^[6] Advanced intermediate **6** would in turn arise from a sulfone-mediated coupling of subunits **3** and **4** followed by Julia methylenation,^[10] elaboration of the AB spiroketal, and oxidation at C(1) and C(28). Herein we report the synthesis of an advanced C(1–28) subunit for the spongistatins. Central to this venture was the development of epimerization conditions to control the C(23) configuration of the CD spiroketal. In conjunction with this effort we achieved a formal synthesis of spongistatin 1 (**1**). In the following communication we describe the synthesis of **5**, fragment assembly, and final elaboration to (+)-spongistatin 2 (**2**).

Continuing with the synthetic analysis, disconnection of methylketal **3** (Scheme 2) revealed the opportunity to exploit a one-pot unsymmetrical bisalkylation of 2-TBS-1,3-dithiane

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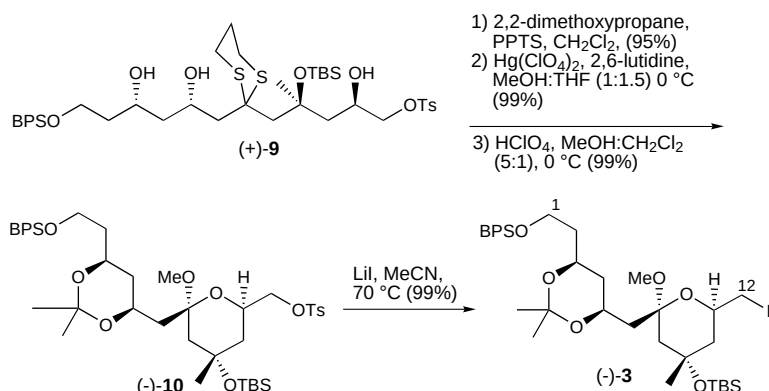
[**] Financial support was provided by the National Institutes of Health (National Cancer Institute) through Grant CA-70329, NIH Postdoctoral Fellowships to A.M.B. and W.H.M., a Japan Society for Promotion of Science Fellowship to N.M., and a Royal Society Fulbright Fellowship to V.A.D. We also thank the Daiichi Pharmaceutical Co., Ltd, and the Tanabe Seiyaku Co., Ltd for financial support. Finally we thank Dr. George T. Furst, Dr. Patrick J. Carroll, Dr. Rakesh Kohli, and Mr John Dykins of the University of Pennsylvania Spectroscopic Service Center for assistance in securing and interpreting high-field NMR spectra, X-ray crystal structures, and mass spectra.



Scheme 2. Retrosynthetic analysis of the AB subunit revealing a one-pot unsymmetrical bis-alkylation disconnection (see ref. [20] for abbreviations).

with Brook rearrangement recently reported by our laboratory.^[11] The development of this route and the synthesis of fragments (–)-7, (+)-8, and (+)-9 were disclosed earlier.^[8b]

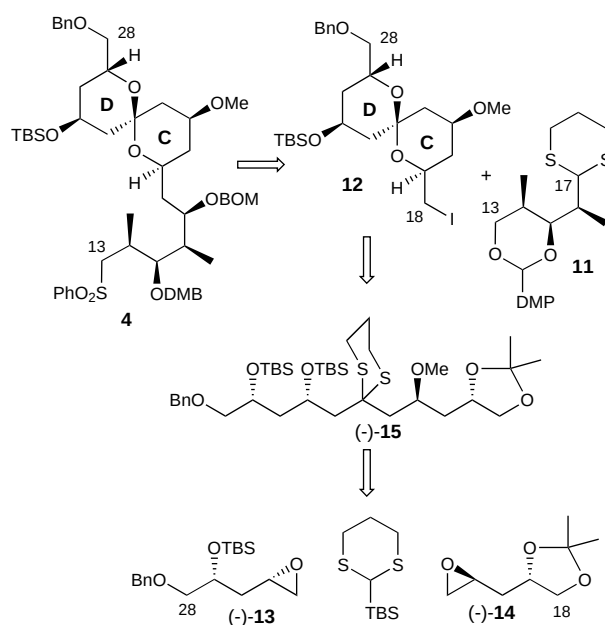
Completion of subunit (–)-3^[12] required four steps beginning with (+)-9^[8b] (Scheme 3). Protection of the 1,3-diol as the



Scheme 3. Synthesis of the AB subunit (–)-3 (see ref. [20] for abbreviations).

acetone, mercury perchlorate mediated removal of the dithiane^[13] in the presence of methanol to furnish a mixture of methyl ketals, and acid-catalyzed equilibration led to the thermodynamically more stable ketal (–)-10 (d.r. > 10:1). Treatment with lithium iodide completed the construction of the AB fragment (–)-3; the overall yield was 92% (four steps).

The CD fragment (4) was envisioned to arise through the coupling of dithiane 11 with iodide 12 (Scheme 4). Disconnection of 12 at the spiroketal provided another opportunity to employ the one-pot bis-alkylation tactic.^[11] Indeed, the coupling of (–)-13 and (–)-14 with the lithium anion of 2-TBS-1,3-dithiane followed by methylation furnished (–)-15 in 68% yield (two steps).^[8m]

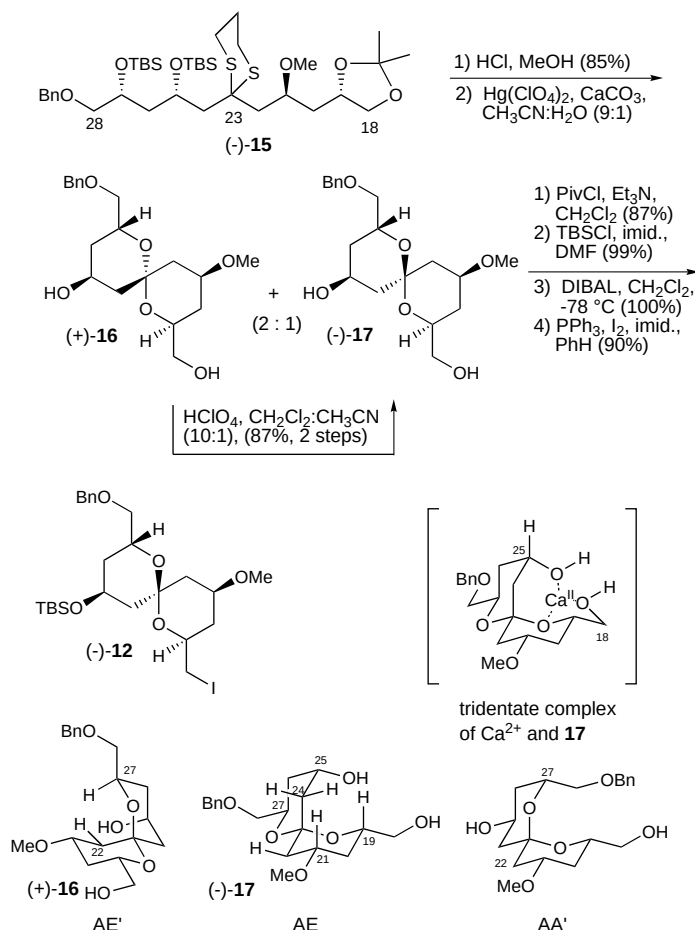


Scheme 4. Retrosynthesis of the CD spiroketal 4 revealing a one-pot unsymmetrical bis-alkylation disconnection (see ref. [20] for abbreviations).

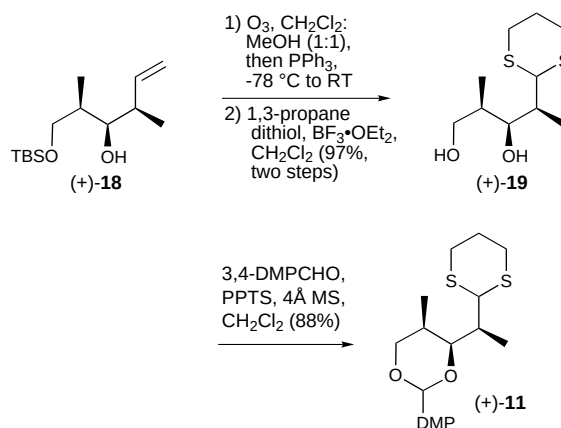
Assembly of the CD spiroketal required removal of both the TBS and acetonide groups (HCl/MeOH) in (–)-15 (Scheme 5), followed by treatment with mercury perchlorate buffered with calcium carbonate; the result was a mixture of spiroketals (+)-16 and (–)-17 (2:1). After separation, NOE experiments revealed that both spiroketals possessed an “axial–equatorial (AE)” configuration;^[14] the “axial–axial (AA)” congener was not observed. Importantly, treatment of the mixture with perchloric acid prior to purification furnished only the desired spiroketal (–)-17 (87%, two steps). Subsequent experiments^[15] demonstrated that the calcium ion, a remnant of dithiane removal, stabilizes spiroketal (–)-17, presumably through coordination with the hydroxyl groups at C(18) and C(25) as well as the C-ring pyran oxygen atom. This observation would prove critical late in the synthesis (see below). Conversion of (–)-17 into iodide (–)-12 was then achieved in four steps: pivaloylation of the primary hydroxyl group, protection of the secondary hydroxyl group (TBSCl), reductive removal of the pivaloyl (DIBAL), and conversion of the primary hydroxyl group into the iodide completed the synthesis of (–)-12.

Construction of dithiane (+)-11 (Scheme 6) required three steps, beginning with (+)-18;^[8b] ozonolysis, introduction of the dithiane with concomitant loss of the TBS group, and protection of the diol (+)-19 as the DMP acetal furnished (+)-11 in 85% yield (three steps).

The coupling of (+)-11 and (–)-12 proceeded with high efficiency (95%) to furnish (+)-20 (Scheme 7). Removal of the dithiane followed by reduction of the resultant ketone (NaBH₄) then led to a mixture of alcohols (3.5:1; 97% yield), favoring the C(17) β-epimer 21. After protection of the



Scheme 5. Synthesis of the CD spiroketal iodide (–)12 (see ref. [20] for abbreviations).

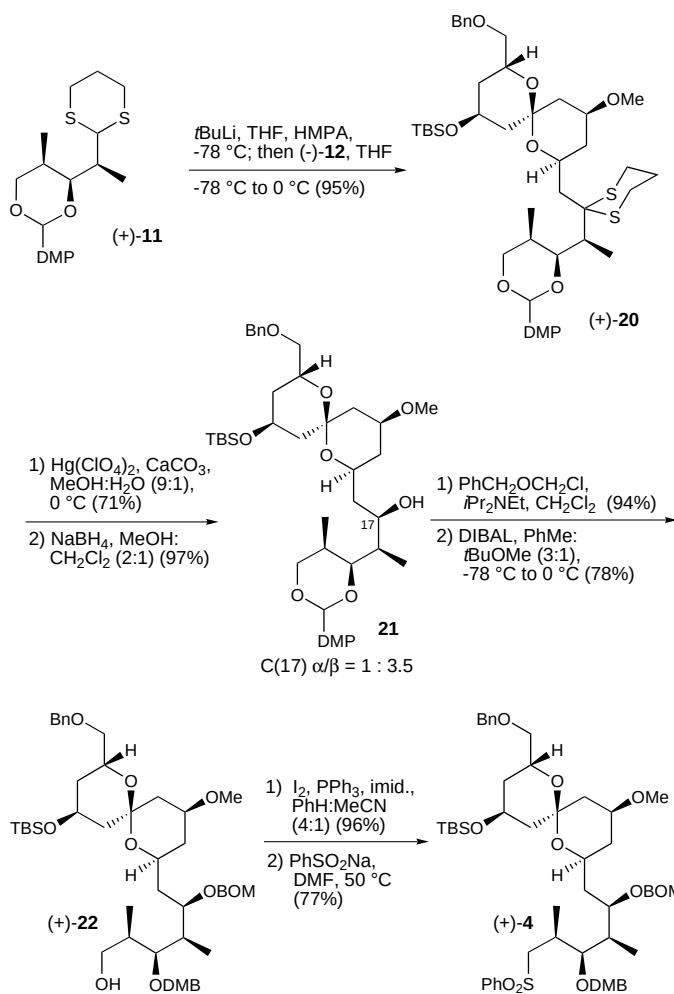


Scheme 6. Synthesis of dithiane (+)-11 (see ref. [20] for abbreviations).

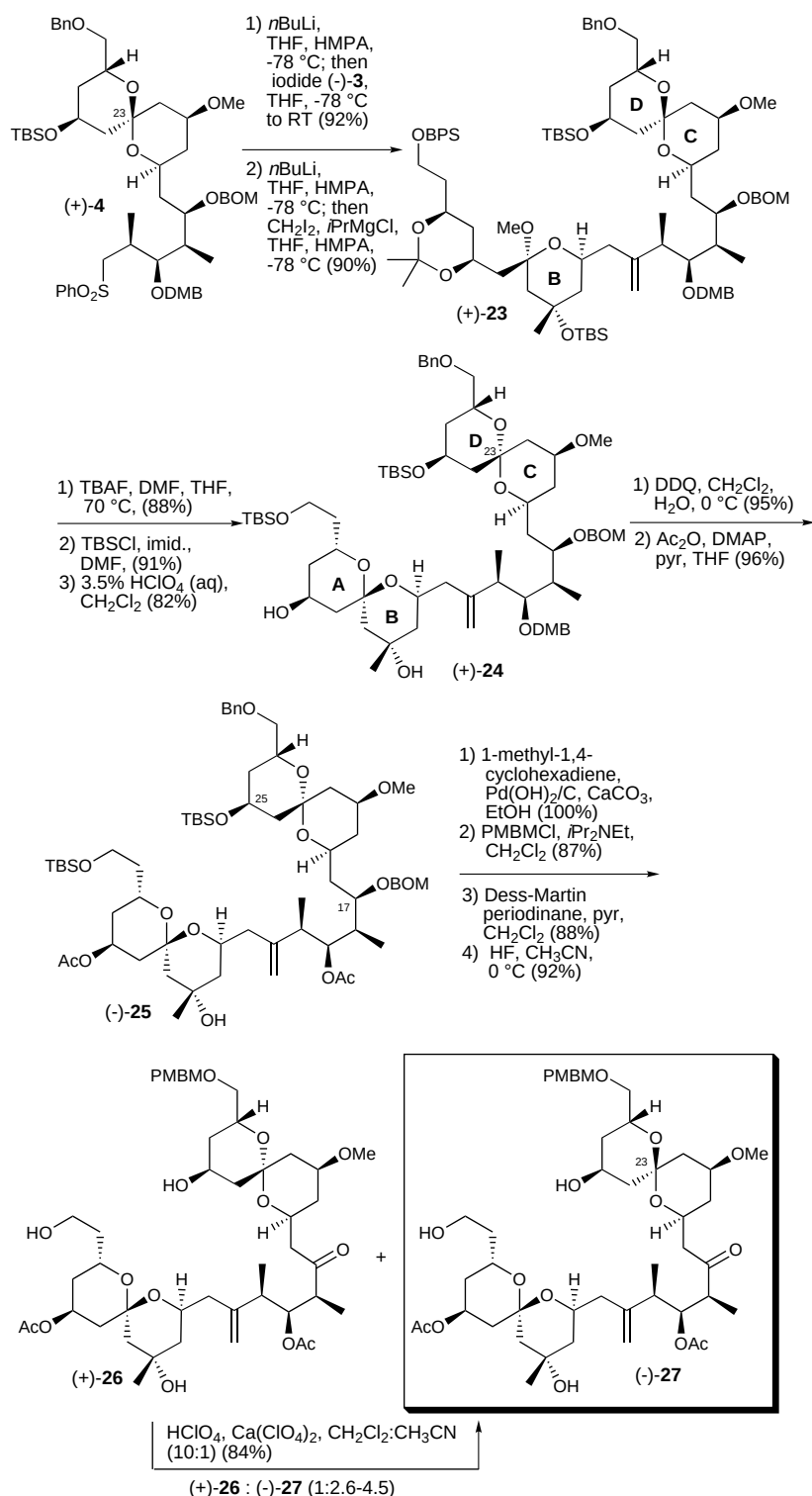
secondary hydroxyl group (BOMCl), the mixture was separated, and although both epimers were potentially useful, only the major β -epimer was carried forward. Regioselective reduction (DIBAL) of the acetal led to (+)-22. The weakly coordinating co-solvent, *tert*-butylmethyl ether, proved essential to minimize reduction of the spiroketal. Conversion of (+)-22 into the iodide and subsequent introduction of the phenyl sulfone completed the assembly of the CD fragment (+)-4.

The coupling of (+)-4 with iodide (–)-3 also proceeded in excellent yield to furnish an inconsequential mixture of sulfone epimers (Scheme 8). In contrast to a system explored earlier, which possessed a fully elaborated AB spiroketal,^[16] Julia methylenation^[10] in this case proceeded smoothly to furnish (+)-23 (90%). Removal of the silicon protecting groups with TBAF, followed in turn by reprotection of both the primary and secondary hydroxyl groups as TBS ethers and hydrolysis of the acetonide with concomitant spiroketalization then furnished spiroketal (+)-24. Although not surprising in the retrospect that epimerization of the CD spiroketal had occurred under the acidic conditions, this fact went undetected until the spectroscopic properties of the fully elaborated 23-*epi*-spongistatin was compared with those of an authentic sample of (+)-spongistatin 2 (1). Undaunted, we reasoned that it should be possible to correct the CD spiroketal stereochemistry by epimerization (for example, with HClO₄/Ca²⁺) at a late stage in the synthesis.

To confirm rigorously the stereochemistry of (+)-24, we prepared (–)-27, an advanced intermediate employed in the total synthesis of (+)-spongistatin 1 (1) by Kishi and co-workers.^[7] Toward this end, oxidative removal of the DMB ether (DDQ), followed by bis-acylation of the triol gave diacetate (–)-25. Removal of the C(25) TBS group (HF/CH₃CN) set



Scheme 7. Synthesis of sulfone (+)-4 (see ref. [20] for abbreviations).



Scheme 8. C(23) Epimerization attempts: Completion of a formal synthesis of (+)-spongistatin 1 (**1**) (see ref. [20] for abbreviations).

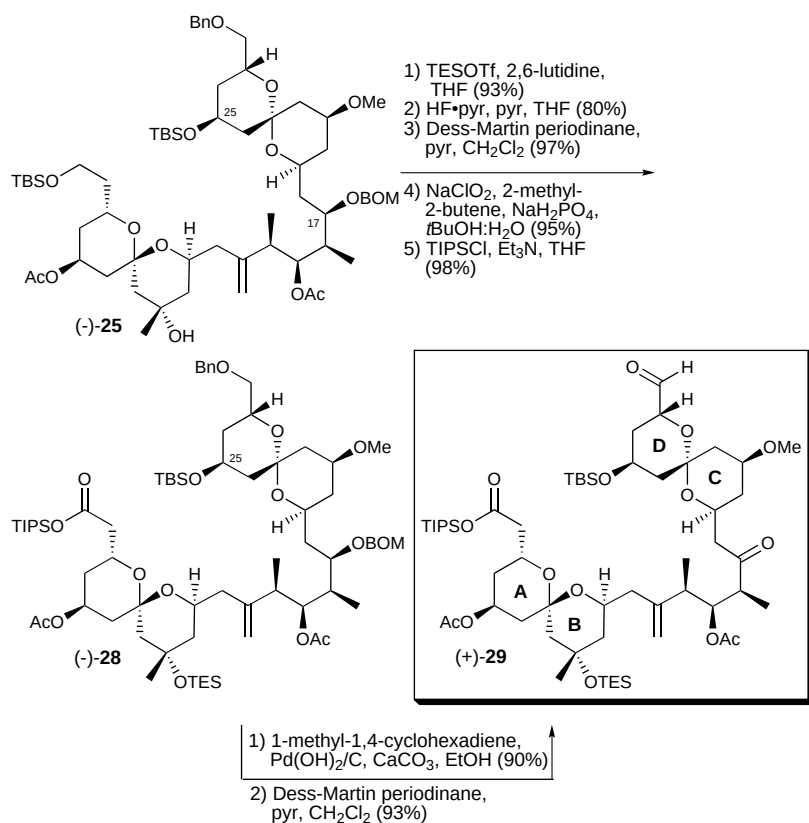
the stage for spiroketal correction. Unfortunately, all attempts to effect epimerization at C(23) employing our previously optimized conditions failed. We reasoned that the bulky C(17) BOM group precluded epimerization. Accordingly, the BOM and benzyl groups were removed (transfer hydrogenolysis). Selective protection of the primary hydroxyl group with PMBMCl, oxidation of the secondary hydroxyl group, and

treatment with HF/CH₃CN then afforded the desired spiroketal (–)-**27** along with the epimer (+)-**26** (ca. 1:1.3) in 92 % yield. Importantly, epimerization of (+)-**26** (HClO₄/Ca²⁺) proceeded consistently with high mass recovery (ca. 80–84 %), although the ratio of spiroketals was variable (2.6–4.5:1). In this fashion (–)-**27** could be obtained in approximately 75 % yield. Treatment of (+)-**26** with only HClO₄ established the critical requirement for a calcium ion; both (+)-**26** and (–)-**27** (6.1:1, 81 %) were obtained. The synthesis of (–)-**27**, which was identical to that prepared by Kishi and co-workers, constitutes both a formal total synthesis of (+)-spongistatin 1 (**1**) and confirms our stereochemical assignments.^[7, 17]

Continuing with the synthesis of the advanced ABCD fragment (+)-**29** (Scheme 9) for spongistatin 2 (**2**; see accompanying communication), protection of the tertiary hydroxyl group as a TES ether^[18] was followed by selective removal of the primary TBS group in the presence of both the secondary TBS and tertiary TES ethers. A two-step oxidation (Dess–Martin periodinane^[19] and buffered NaClO₂), followed by silylation of the resulting carboxylic acid led to (–)-**28** (67 %, five steps). Removal of the benzyl and benzyloxymethyl groups in the presence of the exo-methylene group (transfer hydrogenolysis) then proceeded smoothly. Finally, Dess–Martin oxidation furnished aldehyde (+)-**29**. In the following communication we describe the synthesis of the C(29–51) subunit (**5**), its coupling with (+)-**29**, and final elaboration to afford (+)-spongistatin 2 (**2**).

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Scheme 9. Synthesis of (+)-**29** (see ref. [20] for abbreviations).

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- [15] Treatment of a purified mixture of (+)-**16** and (–)-**17** (2:1) with HClO₄ afforded a 1:1 mixture of spiroketals. Addition of Ca(ClO₄)₂ to the reaction provided a 9:1 mixture favoring the desired spiroketal (–)-**17**.
- [16] See ref. [8b]. With the fully formed spiroketal in place, only modest yields for the installation of the exo-methylene group could be obtained.
- [17] We thank Prof. Y. Kishi for providing the ¹H NMR spectra of advanced intermediates **26** and **27**.
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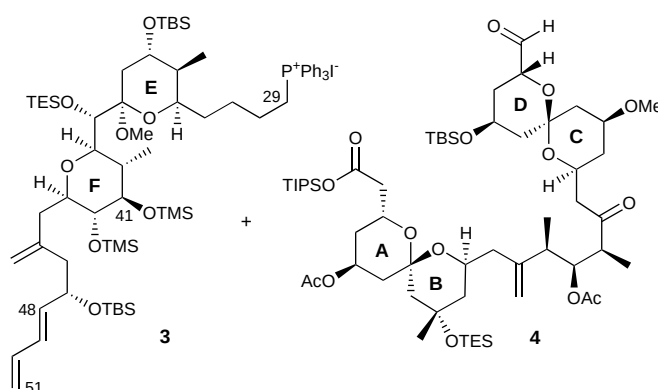
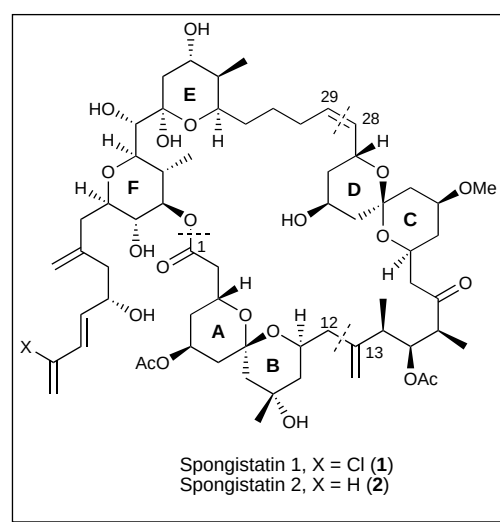
The Spongistatins: Architecturally Complex Natural Products—Part Two: Synthesis of the C(29–51) Subunit, Fragment Assembly, and Final Elaboration to (+)-Spongistatin 2**

Amos B. Smith III,* Qiyang Lin, Victoria A. Doughty, Linghang Zhuang, Mark D. McBriar, Jeffrey K. Kerns, Christopher S. Brook, Noriaki Murase, and Kiyoshi Nakayama

The spongistatins comprise an architecturally unique family of macrolides that have attracted wide interest in both the chemical and biomedical communities^[1] as a consequence of their extraordinary cytotoxicity against several highly chemo-resistant tumor cell lines. In the preceding communication^[2] we described a formal total synthesis of (+)-spongistatin 1 (**1**), based on the epimerization of the CD spiroketal in an advanced ABCD fragment. We now report the synthesis of the C(29–51) subunit **3** (Scheme 1) incorporating both the E and F tetrahydropyran rings and the triene side chain, fragment assembly, and final elaboration to spongistatin 2 (**2**). Central to this achievement was the stereocontrolled epimerization of 23-*epi*-spongistatin 2 to **2**.

Synthetic analysis of the EF fragment **3** led to the side chain fragment **5** and bis(tetrahydropyran) **6** (Scheme 2). Further disconnections of **6** suggested the union of aldehyde **7** with dithiane **8**, prepared respectively from Brown crotylboration^[3] products **9** and **10**. The synthesis of (+)-**7** employing a Sharpless asymmetric epoxidation,^[4] the construction of (–)-**8** utilizing our IBr modification^[5] of the Bartlett iodocarbonate cyclization,^[6] and their union to give (+)-**11** (Scheme 3) were disclosed in an earlier communication.^[7]

Elaboration of the E-ring pyran entailed acidic hydrolysis of the acetonide groups in (+)-**11** (Scheme 3), followed by removal of the dithiane (buffered mercury perchlorate/MeOH) with concomitant cyclization to the methyl ketal, and masking the primary hydroxyl group as a pivaloate (PivCl, pyr., stoichiometric DMAP) to furnish methyl ketal (+)-**12**^[8] (45 %, three steps). Protection of the least hindered-secondary hydroxyl group at C(35) as a TBS ether, removal of the two benzyl groups (hydrogenolysis), and re-protection of both the newly liberated primary hydroxyl group as a BPS



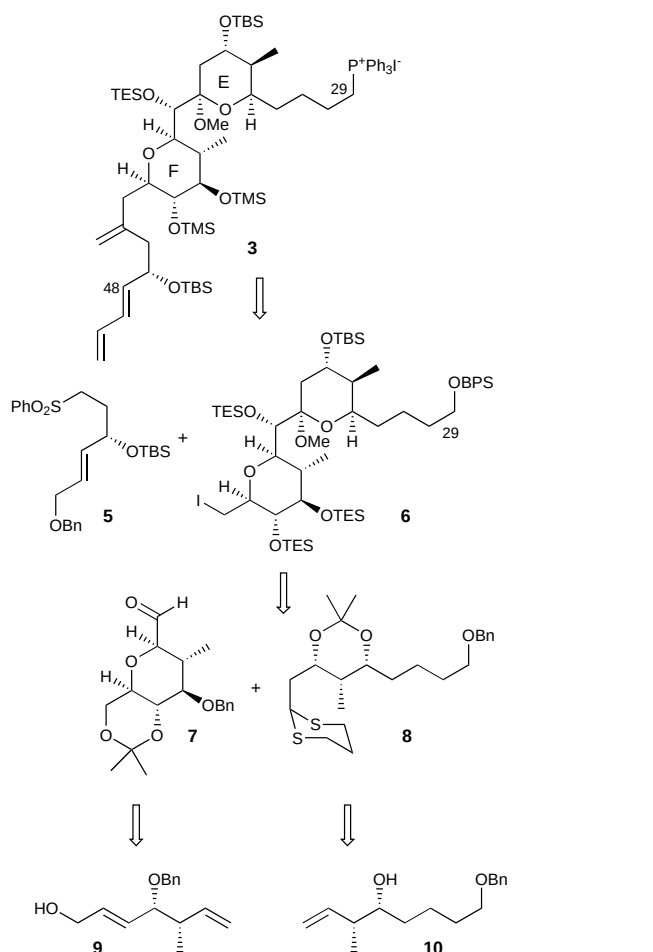
Scheme 1. Retrosynthetic analysis of spongistatin 2.

ether and the three secondary hydroxyl groups as TES ethers^[9] then afforded (+)-**13** (70 %, four steps). Reductive removal of the pivaloate (DIBAL) afforded the primary hydroxyl (81 %). The use of a strongly coordinating solvent (namely, THF) was vital for a clean transformation; non-coordinating solvents led to competitive formation of the E-ring glycan, presumably through coordination of the methylketal to the electrophilic aluminum reagent. The resulting primary hydroxyl group was then converted into iodide (+)-**6** in excellent yield (95 %).

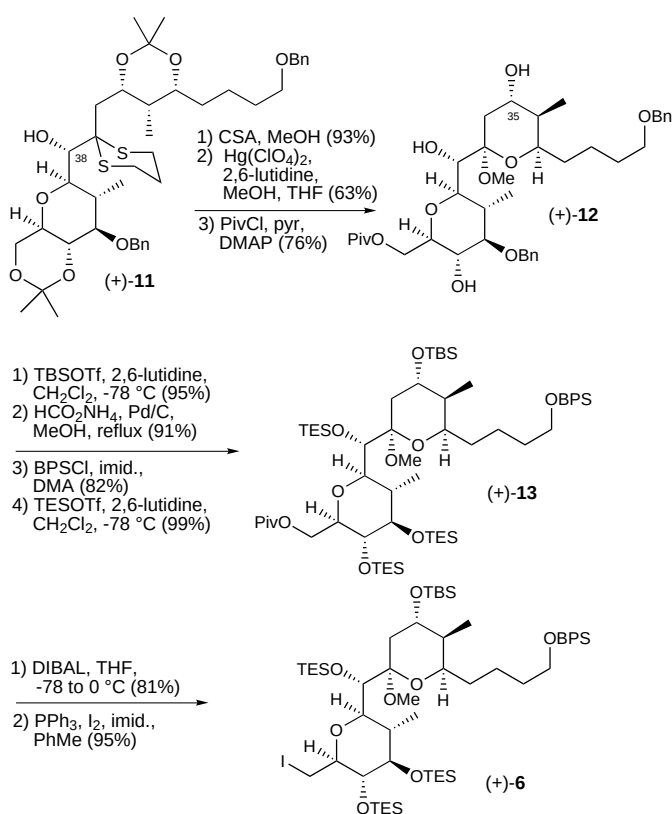
Our point of departure for the side chain was sulfone (–)-**14**, previously prepared in connection with the synthesis of spongistatin analogues (Scheme 4).^[10] Removal of the PMB ether and Dess–Martin oxidation^[11] furnished the corresponding aldehyde which was subjected to Wittig olefination ($\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$). Reduction of the ester, benzylation of the resulting alcohol, and coupling with iodide (+)-**6** then provided **15** as an inconsequential mixture of C(45) epimers in excellent yield (80 %), with the balance of the material recovered being the product of elimination of the iodide. In contrast to the high yield observed in an earlier model system,^[10] Julia methylenation^[12] of **15** furnished (+)-**16** in only 25 % yield (50 % based on recovered starting material). Reductive removal of the benzyl ether (LiDBB) to unmask the primary hydroxyl group, followed by Dess–Martin

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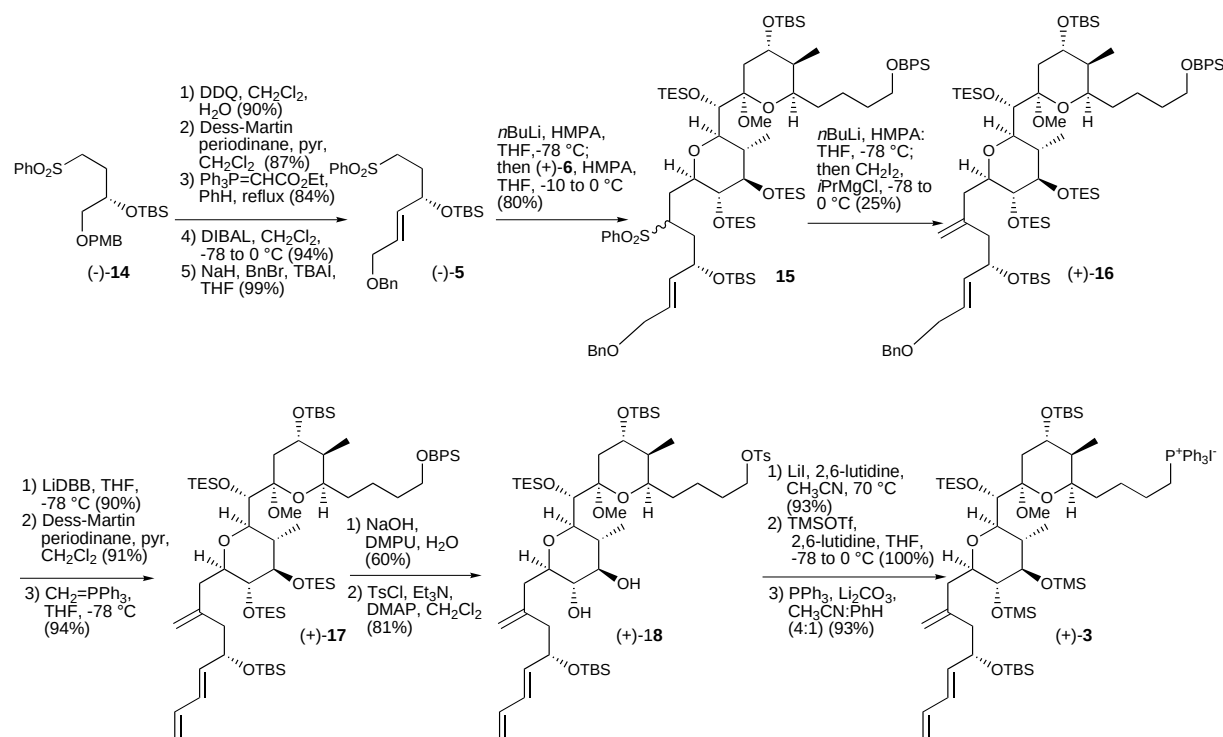


Scheme 2. Retrosynthetic analysis of the EF subunit **3** (see ref. [18] for abbreviations).



Scheme 3. Synthesis of EF iodide **(+)-6** (see ref. [18] for abbreviations).

oxidation and olefination with CH₂=PPh₃ then led to **(+)-17**. At this point, removal of the BPS and the two sterically unencumbered TES groups (NaOH, DMPU/H₂O), followed by selective tosylation of the resultant primary hydroxyl group

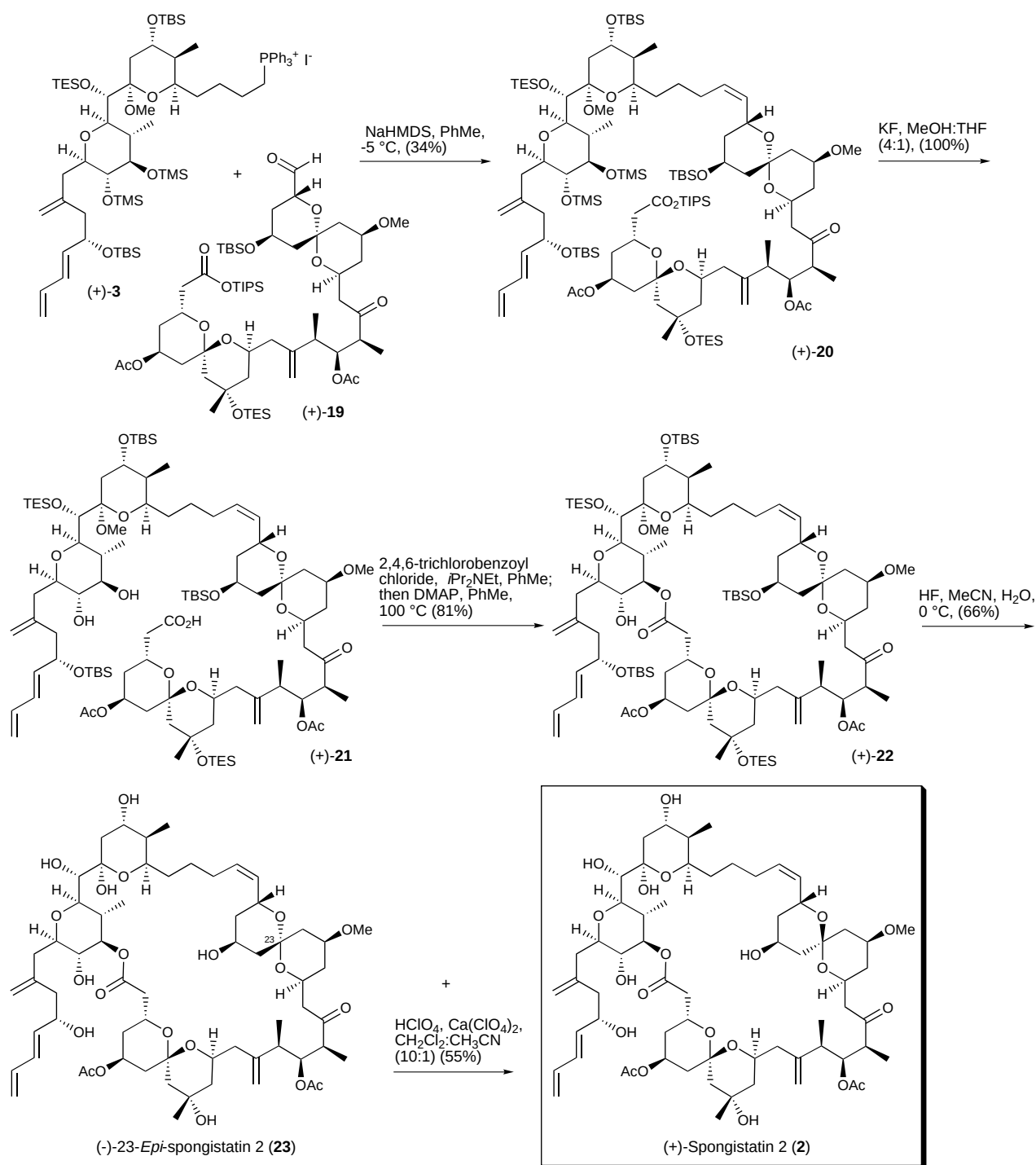


Scheme 4. Synthesis of EF subunit **(+)-3** (see ref. [18] for abbreviations).

furnished (+)-**18**. Conversion to the iodide (LiI), reprotection of the two secondary hydroxyl groups (TMSOTf), and formation of the phosphonium salt (PPh₃) completed the assembly of the EF Wittig salt (+)-**3**.

Fragment assembly entailed Wittig coupling^[13] of (+)-**3** with advanced aldehyde (+)-**19** possessing the *epi*-spiroketal configuration described in the preceding communication: (+)-**20** was obtained in 34% yield (Scheme 5). Selective removal of the TMS and TIPS groups (KF/methanol) then afforded seco-acid (+)-**21**. Regioselective macrolactonization^[14] (Yamaguchi protocol)^[15] afforded only (+)-**22**, the

desired 42-membered macrocycle. While Evans et al. had previously reported the successful regioselective macrocyclization of a spongistatin seco-acid, it is intriguing to note that the 23-*epi*-seco acid also displays the same ring size preference. Global deprotection (HF/CH₃CN/H₂O)^[14a] then furnished both (+)-spongistatin 2 (**2**) and the C(23) epimer (**23**) in 60–66% yield, with the unnatural congener predominating (3:1).^[16] Acid-mediated epimerization of **23** in the presence of Ca²⁺ ions led to a mixture of (+)-spongistatin 2 (**2**) and (–)-*epi*-spongistatin 2 (**23**) in a ratio of 3.9–2.3:1 (ca. 55%), along with some degradation products. The synthetic (+)-spongis-



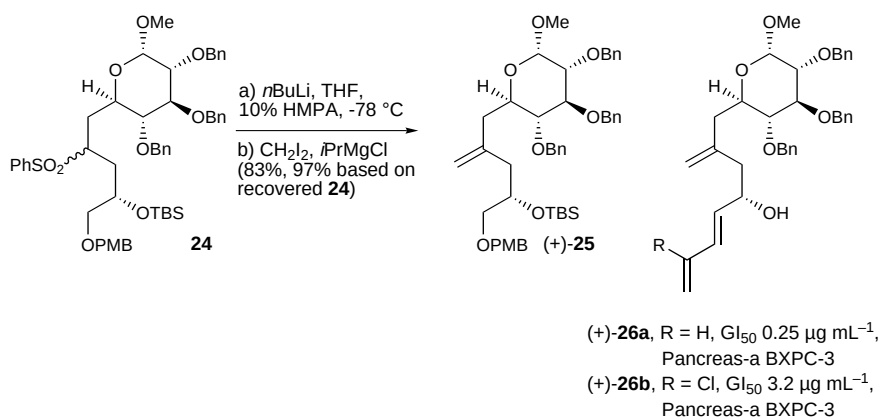
Scheme 5. Completion of the total synthesis of spongistatin 2 (+)-**2** and *epi*-spongistatin (–)-**23** (see ref. [18] for abbreviations).

tatin 2 (**2**) was identical in all respects (500 MHz ^1H NMR, LR-MS, HR-MS, $[\alpha]_D^{25}$, TLC (3 solvent systems), and HPLC) with an authentic sample kindly provided by Professor Evans.^[17]

In summary, the total synthesis of (+)-spongistatin 2 (**2**) has been achieved. Highlights of the synthesis include the stereocontrolled synthesis of the E and F bis(tetrahydropyran) subunit, Wittig coupling with an advanced ABCD fragment, and acid-mediated epimerization in the presence of a Ca^{2+} ion of (–)-*epi*-spongistatin (**23**) to (+)-spongistatin 2 (**2**).

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- [17] We thank Professor Evans for supplying an authentic sample of (+)-spongistatin 2 (**2**).
- [18] Abbreviations used: Ac = acetyl; Bn = benzyl; TES = triethylsilyl; TBS = *tert*-butyldimethylsilyl; TMS = trimethylsilyl; BPS = *tert*-butyl-biphenyllithium; CSA = 10-camphorsulfonic acid; LiDBB = di-*tert*-butyl-biphenyllithium; Piv, pivaloyl = 2,2-dimethylpropanoyl; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone; TBAI = tetrabutyl-ammonium iodide; Tf = triflate = trifluoromethanesulfonyl; imid. = imidazole; DMA = *N,N*-dimethylacetamide; DIBAL = diisobutylaluminum hydride; DMAP = 4-dimethylaminopyridine; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; Ts = tosyl; pyr = pyridine; HMPA = hexamethylphosphoramide; THF = tetrahydrofuran; HR-MS = high-resolution mass spectrometry; LR-MS = low-resolution mass spectrometry; TLC = thin-layer chromatography; HPLC = high-performance liquid chromatography.

A Chemical Model of Homeostasis**

Helmut H. Zepik, Eveline Blöchliger, and
Pier Luigi Luisi*

The experimental realization of self-replication systems^[1–3] has permitted the representation of one of the key mechanisms of life in simple chemical terms. The chemical rendering of other main cellular mechanisms remains, however, elusive. One of these is homeostasis. There are different forms of homeostasis, and in quite general terms one may envisage that the chemical rendering of such a cellular feature might be constituted by a spherical bilayer structure which hosts chemical reactions and which is self-maintaining, because these reactions regenerate all components of the system that disappear in the reactions. One simple possible working unit of this kind, based on the structure of liposomes and on the notion of chemical autopoiesis,^[4–7] was proposed a few years ago^[8] and is shown in Figure 1a.

This represents a spherical system with a semipermeable boundary formed by one single component S, into which the reagent

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A can permeate. Owing to the particular

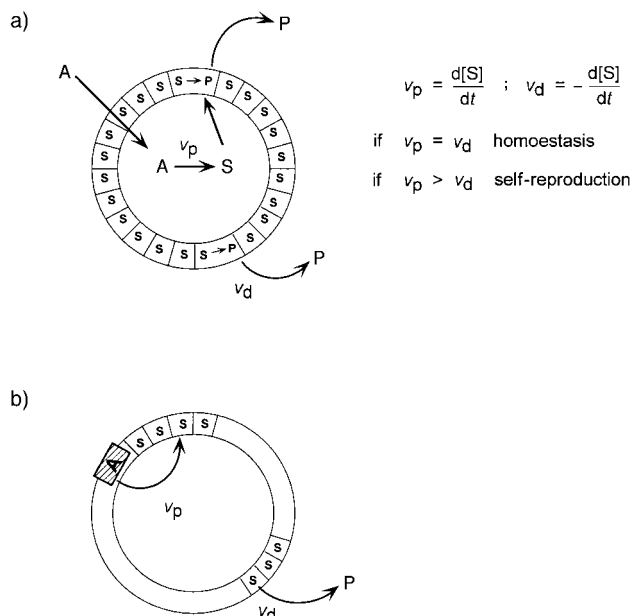


Figure 1. The simplest possible chemical rendering of the overall cell behavior (autopoietic unit), characterized by only two competitive reactions of anabolism and catabolism. The boundary is built by only one component S, which is continuously regenerated on the boundary with velocity v_p from the nutrient A. A competitive reaction destroys S, transforming it into P with velocity v_d . Depending upon the relative values of the two velocities, the autopoietic unit can undergo various kinetic destinies, namely, homeostasis, growth, or death.^[7] a) The ideal case in which the bilayer is permeable to the precursor A. b) The case in which the precursor A is water-insoluble and binds to the bilayer membrane, where it is transformed in situ into the surfactant S.

conditions inside the boundary, A is transformed by a single chemical reaction with velocity v_p into the surfactant S, which is then sequestered into the membrane. A concurrent reaction destroys S, transforming it into P with velocity v_d . It is clear that this system permits various kinetic conditions (modes) which may simulate, although at the most primitive level, the overall behavior of a minimal cell. In fact, if the two velocities are numerically equal, the autopoietic unit is in homeostasis; that is, it maintains its identity and its concentration, despite and in force of the two concurrent reactions. If v_d is larger than v_p , the autopoietic unit will be destroyed (simulating death). Finally, if the velocity of formation is larger than the velocity of decay, the system will tend to grow due to accumulation of the product S on the membrane. Self-reproduction may then occur if conditions of monodispersity of the spherical structures are imposed.

The question is now, how to transpose this model into experimental chemical terms. Spherically closed structures such as those represented in Figure 1 call to mind vesicles, and in fact liposomes (lipid vesicles) have been regarded as protocells, as prebiotic cellular shell structures.^[9, 10] More recently, conditions have been described under which vesicles,^[11, 12] as well as micelles,^[3] are able to self-reproduce. It must be added that in all these systems the experimental implementation was based on a slight variation of the model in Figure 1 a, which is shown in Figure 1 b: In this case, the

precursor of the surfactant S is a water-insoluble substance which does not penetrate into the aqueous core of the vesicle, but remains bound on the surface. Reactions are still confined within the boundary of the spherical aggregate and are determined by the properties of the aggregate itself, so that the conditions of autopoiesis^[4–7] still hold.

Whereas self-reproduction based on the model in Figure 1 could be realized, the implementation of the homeostatic mode proved to be much more difficult and has not been described to date. We present here a simple system which is able to perform this task. This is a system which, depending on the initial parameters, is in principle capable of performing all the three modes represented in Figure 1, namely, homeostasis, self-reproduction, and “death”. To this aim, we have utilized the vesicular system oleic acid/oleate under the conditions of self-reproduction,^[13, 14] but modified it by adding a reaction which destroys the vesicles by oxidizing the oleate double bond. At variance with previous systems, we will be dealing now with a continuously doubly fed system, in which both the oleic anhydride (feeding) and the oxidizing medium (destroying) are added separately by continuous injection. The whole system can be seen as a continuous reactor (Figure 2).

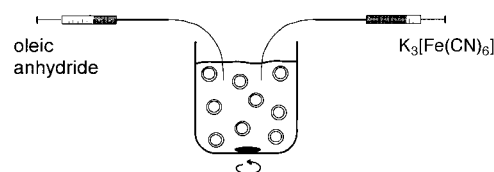


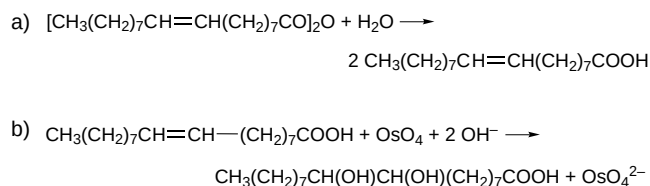
Figure 2. Schematic representation of the chemical bioreactor forming the experimental autopoietic model. The macroscopic system consists of the two injection syringes, each driven by a step motor (Bioblock Scientific KDS 100) to add oleic anhydride ($2 \mu\text{L h}^{-1}$) and $0.93 \text{ M K}_3[\text{Fe}(\text{CN})_6]$ ($50 \mu\text{L h}^{-1}$) to a stirred suspension (20 mL, borate buffer (100 mM), pH 8.8) of oleate vesicles (10 mM oleic acid/oleate) charged with dihydroquinidine (0.5 mM) and OsO_4 (0.2 mM) at 40°C .

Let us analyze in more detail the chemistry. As mentioned above, the feeding element is the water-insoluble oleic anhydride. This is dissolved into the preformed vesicles, and hydrolyzed on or in the bilayer, following the chemical scheme represented by Figure 1 b. The surfactant produced in this way partly induces the growth of the host vesicles and partly induces the formation of new vesicles.^[11, 12, 14] This increase of active surface facilitates further solubilization and hydrolysis of the anhydride: The more vesicles are produced, the more the anhydride is solubilized and hydrolyzed, in a typical autocatalytic process.

At the same time, the presence of oxidizing agents brings about a partial destruction of the vesicles. The oxidation reaction that we have used is the well-known OsO_4 -catalyzed *cis* hydroxylation of olefins^[15] with the hexacyanoiron(III) ion as a cooxidant.^[16] Osmium tetroxide reacts first with the olefin to give a cyclic diester, which is then hydrolyzed to the diol and osmate (OsO_4^{2-}). The latter is continuously regenerated to OsO_4 by an excess of $\text{K}_3[\text{Fe}(\text{CN})_6]$. The oxidation affords 9,10-dihydroxystearic acid, which does not form vesicles (data not shown).

The osmium tetroxide/ferrocyanide system is per se water-soluble. To ensure that also the oxidation reaction takes place on the bilayer, dihydroquinidine was added to the liposome suspension. This base is known to form strong complexes with OsO_4 ,^[17, 18] and in fact it has been used in an aqueous–organic two-phase system, whereby the osmium tetroxide was kept in the organic phase.^[19] We could show in a series of ultra-filtration experiments that when dihydroquinidine (0.5 mM) is added to a vesicle suspension (10 mM oleic acid/oleate) it is completely bound to the bilayers. As with the aqueous–organic two-phase system, the actual osmylation of the olefin occurs on the bilayer. The resulting osmium(vi) monoglycolate ester undergoes hydrolysis at the interface, releasing ligand to the bilayer, and diol and OsO_4^{2-} to the aqueous pool.

The two competitive reactions are shown in Scheme 1. The reaction was carried out in a reaction vial that was fed continuously with anhydride and hexacyanoiron(III) (Figure 2). The two reactions were first studied individually in



Scheme 1. The two basic reactions of the autopoietic system: a) Hydrolysis of oleic acid anhydride in borate buffer (pH 8.8). b) Oxidation of oleic acid to 9,10-dihydroxystearic acid with cat. $\text{OsO}_4/\text{K}_3[\text{Fe}(\text{CN})_6]$.

order to calibrate their individual rates (data not shown). Once conditions had been found under which the two rates were numerically equal, the oleate concentration was monitored as a function of time. In a typical experiment (Figure 3,

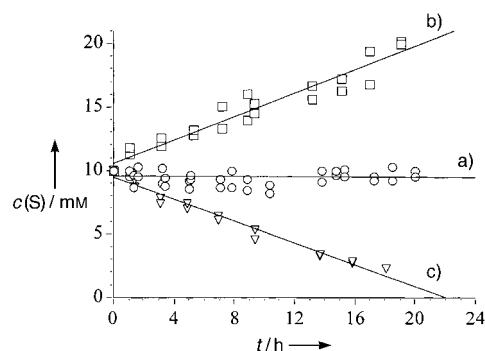


Figure 3. The time course of oleic acid generation in the system of Figure 2. a) Hydrolysis and oxidation ($\circ$); the velocity of hydrolysis and the velocity of oxidation (see Scheme 1) are numerically equal. b) Only hydrolysis ($\square$); the velocity of oleate production (and therefore the formation of vesicles) is predominant. c) Only oxidation (∇); the decay velocity (the rate of oleate oxidation and breakdown) is predominant, which leads to the destruction of the whole system. The oleic acid concentration $c(S)$ was determined by GC analysis (Hewlett Packard 5890A, capillary Nukol column (Supleco)) after addition of 1M HCl and extraction into isooctane.

curve a) a constant concentration of oleic acid/oleate could be kept for 20 h. This means that the concentration of vesicles

remains constant, and in fact the turbidity of the vesicles suspension remains also constant (data not shown). Our earlier results^[11, 12] indicate that under similar conditions, but without catalytic $\text{OsO}_4/\text{K}_3[\text{Fe}(\text{CN})_6]$ and in the presence of preadded vesicles, the concentration of fatty acids and correspondingly the optical density increases by a factor of two within two hours. In principle, homeostasis conditions could be maintained for a much longer period of time.

Curve b in Figure 3 shows the increase of oleic acid/oleate concentration and qualitatively illustrates the case in which the velocity of production of S is much larger than the velocity of oleic acid/oleate oxidation. Conversely, curve c shows the oxidation rate of oleic acid/oleate and illustrates qualitatively the case in which the velocity of vesicle destruction is much larger than the velocity of vesicle regeneration. Eventually the concentration of oleic acid/oleate decreases to zero (the solution becomes transparent).

In conclusion, we have realized the system of Figure 1, in the modification illustrated by Figure 1b. In fact, depending upon the conditions, either one of the three kinetic patterns of the minimal autopoietic system can prevail.

The model cannot be but very primitive, considering that it has been achieved on the basis of very simple chemical means, that is, hydrophobic forces and one hydrolysis and one oxidation reaction. Also, as a further limitation of this work, the model represented here corresponds to only one particular type of homeostasis. On the other hand, one can argue that the force of this model resides precisely in the simplicity of the used means: It is actually surprising that by such simple chemical means a homeostasis model can be realized.

The relevance of this simple model lies also in the fact that, based on these chemical principles, one can conceive more complex and more biologically relevant homeostatic systems (e.g., with internalized genetic material), which may permit one to get closer to a metabolic model of a cell. This does not appear out of reach, considering that biologically active ribosomes have been entrapped into liposomes,^[20] and that quite complex molecular biological reactions do take place in vesicles.^[21]

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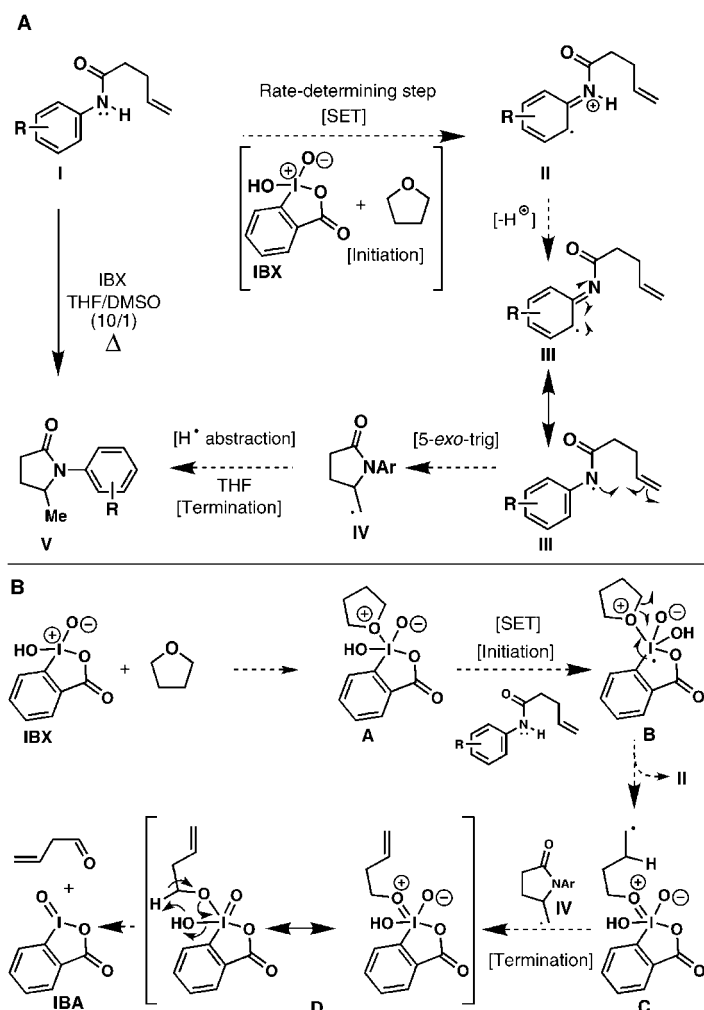
Mechanistic Studies of Periodinane-Mediated Reactions of Anilides and Related Systems**

K. C. Nicolaou,* Phil S. Baran, Remo Kranich, Yong-Li Zhong, Kazuyuki Sugita, and Ning Zou

We have recently reported a series of novel synthetic technologies for the facile construction of complex polycycles,^[1] diverse heterocycles,^[2] amino-sugars,^[3] and α,β -unsaturated carbonyl compounds^[4] induced by hypervalent iodine reagents (*o*-iodoxybenzoic acid (1-hydroxy-1,2-benziodoxol-3(1*H*)-one-1-oxide, IBX) and Dess–Martin periodinate (DMP)). This spate of reactions, which arose from a discovery made during the total synthesis of the CP molecules,^[5] necessitated an in-depth mechanistic investigation to gain further understanding of the sequence of processes involved. Herein we present divergent mechanistic pathways for these IBX- and DMP-mediated reactions based on isotope

labeling, kinetic studies, cyclic voltammetry measurements, NMR spectroscopic analysis, and designed cascade reactions.

For the IBX-mediated ring closures of anilides and related systems to N-heterocycles, we had previously proposed a pathway predicated on single electron transfer (SET) as shown in Scheme 1 (**I** $\rightarrow$ **II** $\rightarrow$ **III** $\rightarrow$ **IV** $\rightarrow$ **V**).^[3] To confirm this

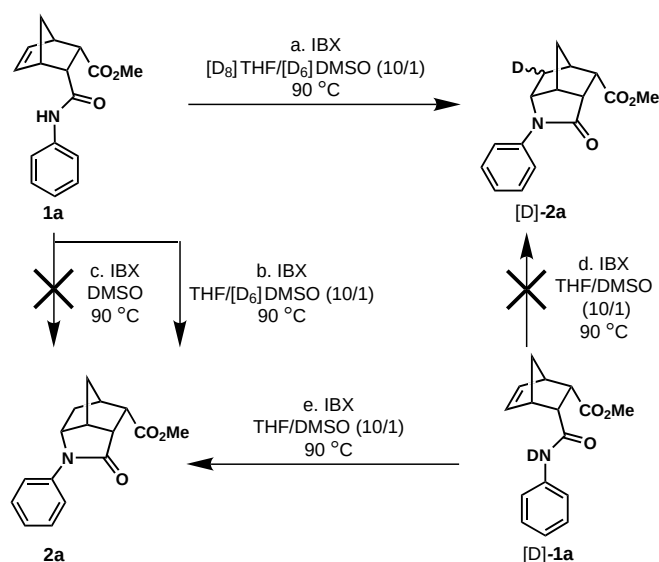


Scheme 1. Proposed mechanism of the IBX-mediated ring closure of anilides and related systems to N-heterocycles (**I** $\rightarrow$ **V**). SET = single electron transfer, IBX = *o*-iodoxybenzoic acid.

hypothesis it was critical to first determine whether the hydrogen atom which must quench the proposed radical that would result from cyclization (**IV** $\rightarrow$ **V**, Scheme 1) originated from the substrate itself, IBX, or the solvent. Thus, when the reaction of **1a** (Scheme 2) with IBX was performed in $[D_8]$ THF/ $[D_6]$ DMSO (10/1), deuterium was detected (NMR) in product **[D]-2a** at the carbon atom as predicted from the proposed mechanism. Carrying out the reaction of **1a** in THF/ $[D_6]$ DMSO (10/1) or of **[D]-1a** (see Scheme 2) in THF/DMSO (10/1) led to **2a** containing no deuterium. When the experiment was carried out without a hydrogen-donating solvent (such as THF or dioxane) present (for example, in neat DMSO), no reaction was observed.^[6] This peculiar solvent dependence led us to conclude that the solvent actually plays a role in this reaction, besides being a source of

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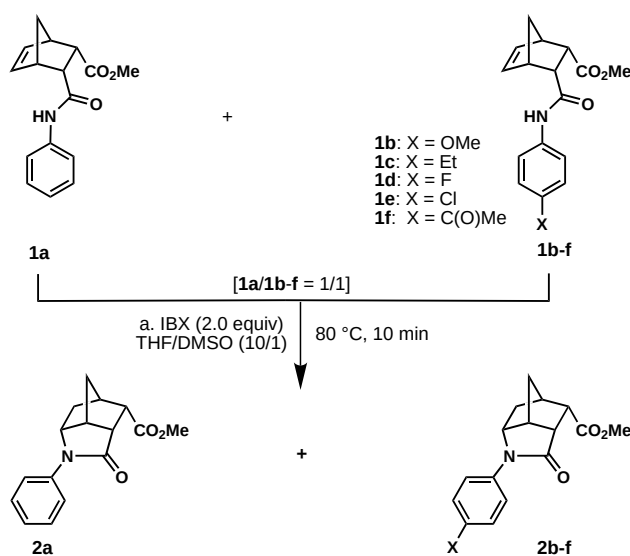
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Scheme 2. The role of THF as a hydrogen atom donor in the IBX-mediated cyclization of amides. Reagents and conditions: a) IBX (4.0 equiv), $[D_8]THF/[D_6]DMSO$ (10/1), 90 °C, 24 h, 24%; b) IBX (1.0 equiv), THF/ $[D_6]DMSO$ (10/1), 80 °C, 10 min, 15% conversion (NMR); c) IBX (4.0 equiv), DMSO, 90 °C, 24 h; d) and e) IBX (4.0 equiv), THF/DMSO (10/1), 90 °C, 24 h, 40% (**2a**).

hydrogen as shown in Scheme 1 B. A viable scenario might involve coordination of THF to IBX, which would lead to intermediate **A** (Scheme 1 B). This intermediate would act as an extraordinary oxidant which could then initiate the cyclization by SET to furnish intermediates **II** (Scheme 1 A) and **B** (Scheme 1 B). Rearrangement of **B** to **C** followed by hydrogen abstraction by **IV** would lead to product **V** in addition to **D**, which should rapidly lead to IBA and 3-butenal. Notably, treatment of THF with only IBX at 90 °C for 24 h led to the isolation of 2-iodobenzoic acid along with polymeric material and compounds containing aldehyde residues, as judged by ^1H NMR spectroscopy. In addition, when IBA was employed in the cyclization (**I** $\rightarrow$ **V**) no reaction was observed.

Further support of the proposed mechanism (Scheme 1) was gained upon a systematic evaluation of the kinetics of the reaction with substrates designed to probe the electronic effects of aromatic substituents on the rates of the entire process (**I** $\rightarrow$ **V**) and of step **III** $\rightarrow$ **IV** (see below). Thus, by synthesizing a series of aromatic amides differing in substitution at the *para* position (**1b–f**, Scheme 3)^[7] the stage was set to compare the different overall reaction rates and to arrive at a Hammett plot. Competing equimolar mixtures of **1a** and **1b**, **1c**, **1d**, **1e**, or **1f** were heated with two equivalents of IBX in THF/DMSO (10/1) at 80 °C for 10 min (Scheme 3). The ratios between the unsubstituted product **2a** and the *para*-substituted products **2b–f** were determined by ^1H NMR spectroscopy. Electron-donating substituents [namely, X = OMe (**1b**) and Et (**1c**)] resulted in an increase in the rate of the cyclization, whereas electron-withdrawing substituents caused a decrease in the reaction rate [namely, X = Cl (**1e**) and C(O)Me (**1f**)] or had no significant effect on the rate [X = F (**1d**)] relative to that of the unsubstituted substrate. For amides of type **1** with X = NO₂ or CF₃, no reaction occurred under the conditions described in Scheme 3.



Scheme 3. Competition reactions of equimolar mixtures of **1a** and **1b–f**. Reagents and conditions: a) IBX (2.0 equiv), THF/DMSO (10/1), 80 °C, 10 min.

The Hammett plot,^[8] based on the ratio of the reaction rate constants (k_s/k_u) and σ_p^+ parameters,^[9] gave a linear graph with a negative slope ($\rho = -1.4$, $R^2 = 0.97$; Figure 1).^[10] This ρ value is typical for a radical reaction^[8] and indicates a lower electron density in the transition state relative to the initial

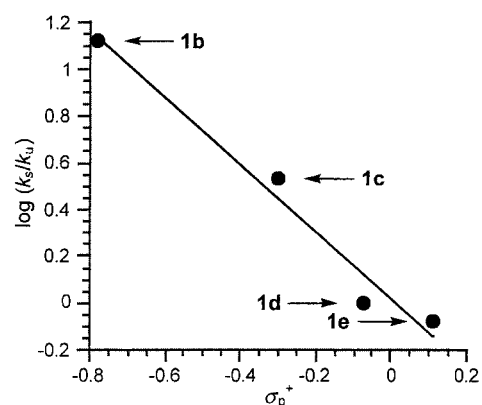
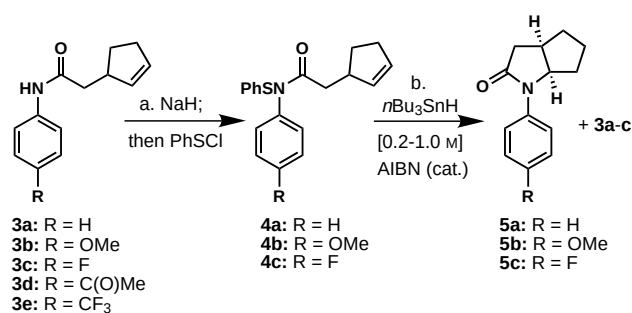


Figure 1. Hammett plot for the reaction shown in Scheme 3 (**1** $\rightarrow$ **2**). See ref. [9] for more details.

ground state of the substrate. It supports the assumption that the first step of the reaction involves SET from the aromatic ring of the amide to IBX to form a radical anion/radical cation pair as shown in Scheme 1. After loss of a proton, radical cation **II** is converted into radical **III** as shown in Scheme 1. The latter amidyl radical (**III**) then cyclizes onto the double bond in a 5-*exo-trig* fashion, to furnish carbon-centered radical species **IV** which is quenched by the transfer of a hydrogen radical from THF (see above).

Based on the pioneering work of Newcomb and co-workers in the area of amide-centered radicals,^[11–13] we were able to use *N*-(phenylthio)amides^[12] **4a–c** derived from **3a–c**^[7] (Scheme 4) to deduce whether the rate-limiting step of the reaction was **I** $\rightarrow$ **II** or **III** $\rightarrow$ **IV**. Three reactions for each amide



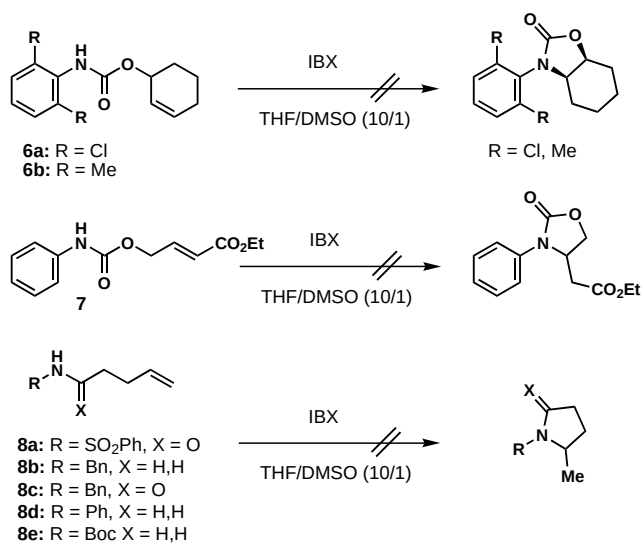
Scheme 4. Synthesis of *N*-(phenylthio)amides **4a–c** and their tin hydride-mediated conversion into cyclized (**5a–c**) and uncyclized (**3a–c**) amides. Reagents and conditions: a) NaH (1.3 equiv), THF, reflux, 4 h; then PhSCl (ca. 1 equiv, added until yellow color of PhSCl persists), –78 °C, 1 h, 74–86%; b) *n*Bu₃SnH (0.2–1.0 M), toluene, 65 °C, 2–5 h, 85–92% total yield of cyclized and uncyclized anilide.

were conducted at 65 °C in toluene in the presence of excess *n*Bu₃SnH at concentrations ranging from 0.2 to 1.0 M. The relative yields of cyclized product (**C**, **5a–c**) and acyclic amide (**A**, **3a–c**) were determined by HPLC. From the ratio of **C**:**A** and by assuming that the rate of trapping of tin hydride is the same for all of the radicals^[11–13] the relative rate constants for cyclization of the amide centered radicals could be inferred. The relative rates of cyclization were determined to be (0.66 ± 0.1), (0.30 ± 0.1), and (0.40 ± 0.1) M for **4a**, **4b**, and **4c**, respectively. Since the opposite trend is observed when the overall rate (see above) is evaluated, and because the amidyl radical cyclization is quite rapid in all cases (**4a–c**), we conclude that SET from the aromatic nucleus of the anilide to IBX/THF (**I** → **II**) is the rate-determining step of the reaction.

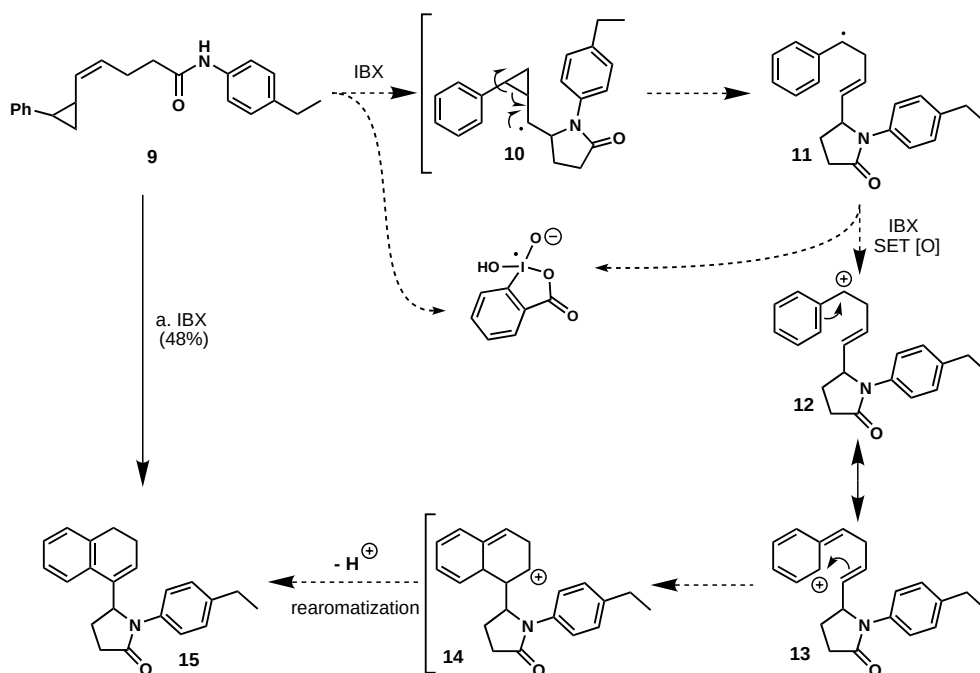
Since the first SET step (**I** → **II**) is likely irreversible, we gauged the oxidation potentials of a series of anilides (**3a–e**, Scheme 4). By performing cyclic voltammetry on CH₂Cl₂

solutions, the *p*-substituted anilides were determined to be more difficult to oxidize than ferrocene by the following amounts: 1.20 V (**3a**), 0.82 V (**3b**), 1.23 V (**3c**), 1.48 V (**3d**), and ≥ 1.57 V (**3e**).^[14] A direct correlation of the measured oxidation potentials with the observed relative rates of the reactions (see above) was immediately apparent. Thus, anilides with lower oxidation potentials (**3a–c**) proceeded rapidly while anilides with higher oxidation potentials proceeded only sluggishly (**3d**) or not at all (**3e**).^[15]

Scheme 5 illustrates a number of unexplained failures of this IBX reaction previously encountered in our laboratories which can now be rationalized in light of these new findings. The need for an open position *ortho* to the nitrogen atom is evident since substrates **6a** and **6b** do not undergo reaction. This could be explained by an increase in the oxidation



Scheme 5. Nonparticipating substrates for the IBX-mediated cyclization which supports the proposed mechanism of Scheme 1.

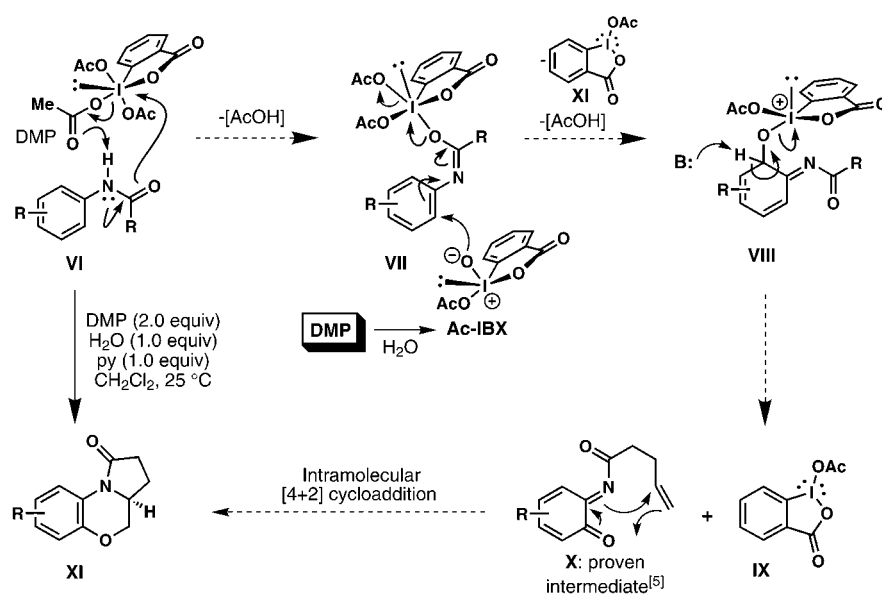


Scheme 6. Cascade cyclization of **9** to **15**. Reagents and conditions: a) IBX (4.0 equiv every 24 h), THF/DMSO (10/1), 90 °C, 48 h, 48%.

potential caused by deconjugation of the lone pair on the nitrogen atom from the arene ring,^[16] a decreased rate of 5-*exo-trig* cyclization, or simply a lack of deprotonation of the radical cation (**II** $\rightarrow$ **III**). The mildly electrophilic nature of the nitrogen-centered radical^[11, 13] is evident since α,β -unsaturated ester **7** failed to react (Scheme 5). The notion that only anilides can react with IBX in this manner is supported by the fact that substrates **8a**, **8c**, and **8e** are unresponsive to the conditions, while **8b** and **8d** lead rapidly only to decomposition products.

Additional evidence pointing to a radical-based mechanism for this process is provided by the designed cascade reaction depicted in Scheme 6. Thus, when cyclopropyl-anilide **9**^[11] was treated with IBX in the usual manner^[2] for 48 h the novel tetracycle **15** was obtained in 48% yield. This striking transformation can be explained by invoking a radical mechanism involving formation of species **10**, as predicted by Scheme 1, and which initiates rupture of the adjacent cyclopropyl ring to give the benzylic radical **11**. Oxidation of this radical (**11**) leads to cation **12** which is then followed by cationic cyclization to **14** via resonance structure **13**. Finally, re-aromatization and loss of a proton leads to the observed product **15** (Table 1).

Our present investigation into the mechanism of the DMP-induced cyclization of anilides and related substrates to N,O-heterocycles led us to revise our original proposals^[11] to the one depicted in Scheme 7. Indeed, upon addition of freshly prepared DMP to a solution of *N*-phenylacetamide in CDCl₃ a dark brown coloration appeared along with new ¹H NMR



Scheme 7. Proposed mechanistic aspects of the DMP-cascade reaction of anilides (**VI**) to polycycles (**XI**).

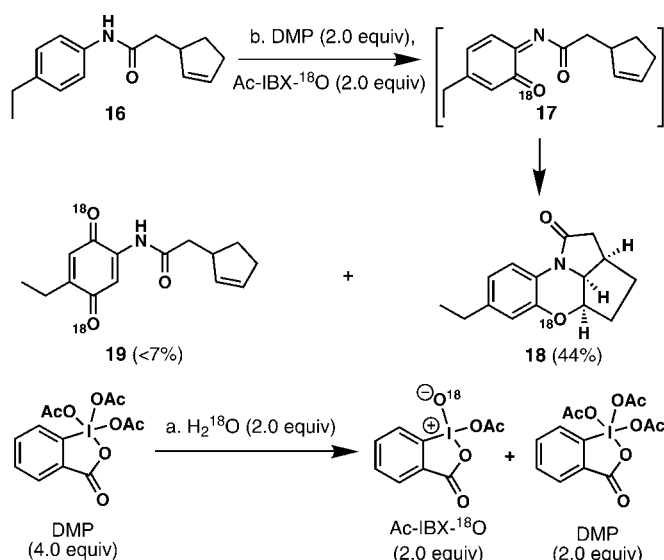
signals, whereas TLC analysis revealed only starting materials and minor decomposition products, which indicate the formation of a transient intermediate (presumably a complex of type **VII**, Scheme 7). Furthermore, the participation of two periodinane species (DMP and Ac-IBX) as postulated in the proposed mechanism was supported by the observation that no product was formed in the presence of 1–3 equivalents of DMP alone (strictly anhydrous conditions) or Ac-IBX alone (freshly prepared).^[17] Recognition of the key synergy between DMP and Ac-IBX in this cascade led to the proposition that enough water was needed to convert half of the DMP to Ac-IBX, and prompted the use of pyridine as a facilitator of the reaction. These mechanistic insights inspired further modifications of the reaction conditions leading to a refined process requiring room temperature, dichloromethane as solvent, and a minimum of 2.0 equivalents of DMP (optimally 4.0 equivalents), 1.0 equivalent of H₂O (optimally 2.0 equivalents), and 1.0 equivalent of pyridine, the latter accelerating the reaction but not essential.^[18]

Further compelling evidence of the participation of Ac-IBX in the process as a nucleophile that attacks intermediate **VII** (Scheme 7) was gathered by preparing Ac-IBX-¹⁸O (DMP + H₂¹⁸O) and employing it in the reaction of substrate **16** (Scheme 8). Thus, treatment of anilide derivative **16** with DMP and Ac-IBX-¹⁸O (1.0 equivalent of each) in dichloromethane at 25 °C led to ¹⁸O-labeled polycycle **18** (44% yield) as confirmed by mass spectrometric analysis. This observation supports the notion that the newly installed oxygen atom arises from Ac-IBX, rather than from H₂O, air, or the substrate itself. Initial attempts to intercept the postulated *o*-azaquinone intermediate **17** were unsuccessful; however, we were able to isolate and characterize a minor product in this reaction, the *p*-quinone structure **19** (Table 1) containing two ¹⁸O atoms (mass spectrometry analysis). This intriguing observation and the understanding of the relation between the fleeting *o*-azaquinone **17** and quinone **19** led to the design of

Table 1. Selected data for compounds **15** and **19**.

15: *R*_f = 0.42 [silica gel, ethyl acetate:hexane (1:2)]; IR (film): $\tilde{\nu}_{\text{max}}$ = 2966, 2923, 2869, 1695, 1609, 1512, 1453, 1394, 1362, 1292, 1217, 1131, 1104, 836 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 7.49 (d, *J* = 8.5 Hz, 2H), 7.27–7.24 (m, 3H), 7.21–7.18 (m, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 5.88 (d, *J* = 4.6 Hz, 1H), 5.22 (d, *J* = 8.1 Hz, 1H), 2.75–2.66 (m, 3H), 2.58 (q, *J* = 7.5 Hz, 2H), 2.51–2.42 (m, 1H), 2.23 (m, 2H), 1.99 (brt, *J* = 10.6 Hz, 1H), 1.18 (t, *J* = 7.5, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 174.9, 137.2, 133.7, 132.7, 129.0, 128.1 (2C), 128.0 (2C), 127.3 (2C), 126.6 (2C), 121.9, 120.7, 60.5, 31.2, 28.2, 28.0, 25.8, 22.7, 15.5; HR-MS (matrix-assisted laser desorption/ionization (MALDI)-FTMS): calcd for C₂₂H₂₃NONa [*M*+H]⁺: 318.1858, found: 318.1857.

19: yellow needles; *R*_f = 0.61 [silica gel, ethyl acetate:hexane (1:2)] m.p. 77–79 °C (CHCl₃); IR (film) $\tilde{\nu}_{\text{max}}$ = 3330, 2934, 1710, 1692, 1665, 1644, 1609, 1503, 1464, 1454, 1328, 1174, 1096, 898, 723 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz): δ = 8.03 (brs, 1H), 7.55 (s, 1H), 6.54 (t, *J* = 1.5 Hz, 1H), 5.84–5.80 (m, 1H), 5.70–5.65 (m, 1H), 3.25–3.12 (m, 1H), 2.57–2.31 (m, 6H), 2.25–2.08 (m, 1H), 1.60–1.41 (m, 1H), 1.13 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ = 187.9, 183.2, 171.5, 153.2, 137.8, 133.0, 132.3, 128.2, 114.9, 43.9, 42.1, 31.8, 29.5, 22.3, 11.6; HR-MS (MALDI) calcd for C₁₅H₁₇NO(¹⁸O)₂ [*M*+H]⁺: 264.1366, found: 264.1487.



Scheme 8. ^{18}O -labeling studies with the DMP-cascade reaction. Isolation of labeled polycycle **18** and quinone **19** from anilide **16**. Reagents and conditions: a) H_2^{18}O (2.0 equiv), CH_2Cl_2 , 25 °C, ultrasound, 1 min; then 25 °C, 10 min; b) solution of Ac-IBX- ^{18}O /DMP, **16** (1.0 equiv), CH_2Cl_2 , 25 °C, 4 h.

a series of new reactions which will be described in the following communication.^[19]

In conclusion, through this study we have provided supporting evidence for a mechanistic rationale of the previously reported unique interactions^[1–4] of periodinane reagents (DMP, IBX, and Ac-IBX) with anilide and related substrates. The mechanistic understanding of these intriguing processes is expected to lead to the design of new reactions for the construction of novel molecular diversity and to enrich the enabling technologies for combinatorial chemistry, chemical biology, and medicine.

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p. 230. For a discussion of Hammett plots, see T. H. Lowry, S. K. Richardson, *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper & Row, New York, **1987**.

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Structure and Base Catalysis of Supercritical Water in the Nuncatalytic Benzaldehyde Disproportionation Using Water at High Temperatures and Pressures**

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The physicochemical characteristics of water are greatly changeable by varying the pressure or temperature under supercritical conditions,^[1] and supercritical water (scH₂O)

offers exiting possibilities for the development of new chemical processes.^[2] Furthermore, scH₂O is a suitable medium in connection with “green” (environmentally friendly) technology because water is the most environmentally acceptable and naturally abundant solvent. However, the microscopic characteristics of scH₂O, including the structure which is closely related to chemical reactivity in scH₂O, are not sufficiently well understood. Hence a better understanding of the structure and nature of scH₂O leads to marked improvements in practical applications such as in the mechanical, chemical, and geothermal industries.

Currently in organic synthesis, a matter of primary interest is the promotion of reaction rates by more “green” chemical processes. Recently we reported an interesting finding that scH₂O itself successfully functions as an acid in accelerating pinacol/Beckmann rearrangements.^[3] Bröll et al. have briefly reported a base-catalyzed Cannizzaro-type disproportionation of formaldehyde in scH₂O carried out without a base catalyst.^[4] In addition, our in situ Raman spectroscopy measurements have indicated that the extent and strength of hydrogen bonding of scH₂O are very different to those in heated and ambient H₂O.^[5] This suggests a pronounced stimulation of the breakdown of monomeric water molecules under supercritical conditions, which would account for the acid and base difunctionality of scH₂O. We have further studied the base function of scH₂O by conducting a base-catalyzed disproportionation of benzaldehyde in the absence of any base catalysts. The rate of such a noncatalytic disproportionation in scH₂O has been found to be several-hundred-fold larger than in the conventional catalytic reactions, whereas the rates of these reactions in hot water (below 300 °C), even at high pressures, are extremely small. In addition, the participation of the OH[−] ion, the not OH[•] radical, in the reaction is strongly suggested from GC-MS and NMR spectroscopic analysis of the benzyl alcohol product in the disproportionation using [D₆]benzaldehyde as a reactant.

We first demonstrate that the reaction of benzaldehyde to benzyl alcohol and benzoic acid proceeds in scH₂O even in the absence of any base catalysts. Figure 1 shows the background corrected IR spectra for reaction mixtures in scH₂O (397 °C) and hot water (277 °C) at a constant pressure of 25 MPa along with those for ordinary benzyl alcohol and benzaldehyde aqueous solutions. These measurements were performed by real time, in situ FT-IR spectroscopy for benzaldehyde in H₂O introduced into a high-pressure, high-temperature, flow reactor at a constant residence time of 105.0 s. The spectrum obtained in scH₂O (trace D), shows a new intense band at 1002 cm^{−1}, not present in that of the benzaldehyde solution (trace A). This strong band can be assigned to the CO stretching vibration(ν_1) of the benzyl alcohol formed, and is not observed in the hot water (trace C) or ordinary water (trace A) phases. We have further analyzed the absorption bands around 1700 cm^{−1} (not shown) can be assigned to the CO stretching vibrations of benzaldehyde and benzoic acid, in which the ν_1 frequency of benzoic acid is somewhat higher than that of benzaldehyde. In the scH₂O an intense band at 1702 cm^{−1} nearly coincides with that of the authentic benzoic acid sample, showing unambiguously that benzoic acid is produced in addition to benzyl alcohol. Detailed analysis of

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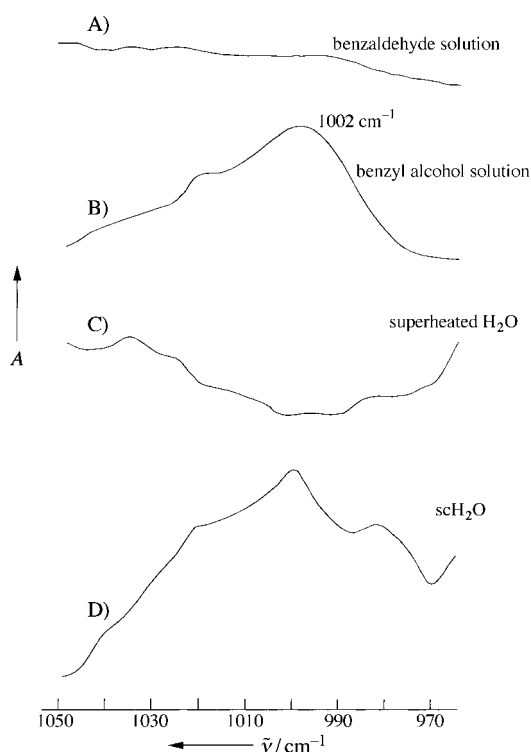


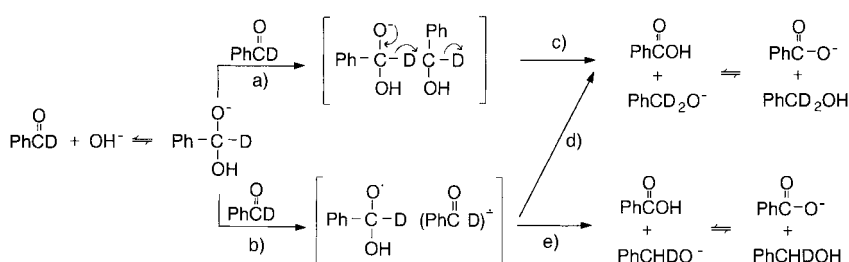
Figure 1. Infrared spectra of aqueous solutions of A) benzaldehyde 20 °C, 0.1 MPa, B) benzyl alcohol 20 °C, 0.1 MPa; and of reaction mixtures in the aqueous, noncatalytic disproportionation of benzaldehyde C) superheated H₂O, 277 °C, 25 MPa, D) scH₂O, 397 °C, 25 MPa. The band at 1002 cm⁻¹ is assigned to CO stretching vibration (ν_1) of benzyl alcohol.

the reaction mixture by GC-MS and NMR spectroscopy at the end of the reaction supported the formation of benzyl alcohol and benzoic acid in scH₂O. Hence this in situ observation has first demonstrated the disproportionation of benzaldehyde to benzyl alcohol and benzoic acid in scH₂O without base catalysts.

To explore what kind of species causes the “noncatalytic” disproportionation in scH₂O, we attempted the disproportionation of [D₆]benzaldehyde in scH₂O at 397 °C and 25 MPa. The benzyl alcohol product in the disproportionation was analyzed by GC-MS of the product mixture containing benzaldehyde and the alcohol, and also by ¹H NMR spectroscopy of the isolated alcohol product. We observed well-defined fragment ions such as C₆D₅CD₂OH⁺ (m/z 115), C₆D₅CDOH⁺ (m/z 113), C₆D₅CDO⁺ (m/z 112), C₆D₅CO⁺ (m/z 110), C₆D₅CD₂⁺ (m/z 98), C₆D₅CD⁺ (m/z 96), and C₆D₅C⁺ (m/z 94) characteristic of [α -²H₂]benzyl alcohol according to the reported analysis,^[6] whereas signals from the fragments corresponding to the ionized products of [α -²H]benzyl alcohol were negligible. In addition, the identification by ¹H NMR supports the result from the GC-MS analysis. A generally postulated mechanism for the disproportionation involves a pre-equilibrium addition of OH⁻ to the [α -²H]benzaldehyde and a rate-determining intermolecular hydride transfer, followed by the production of [α -²H₂]benzyl alcohol (Scheme 1, pathway

a–c),^[7a,f] or an intervention of radical intermediates leading to the formation of [α -²H₂]benzyl alcohol (Scheme 1, pathway b–d)^[7b,e] or the formation of [α -²H]benzyl alcohol (Scheme 1, pathway b–e).^[7d,e] The OH⁻ ion and/or OH[•] radical species are thus expected to cause this disproportionation using scH₂O alone, and undoubtedly arise from the H₂O molecule itself although H₂O at ambient conditions does not provide the benzylic hydrogen of the product.^[8] The OH⁻ ion is required to form the product alcohol in any reaction mechanisms,^[7] and the participation of the OH⁻ ion in the disproportionation using scH₂O has been clearly demonstrated. On the other hand, the formation of [α -²H]benzyl alcohol was not identified in this experiment, and one can eliminate completely the possibility of participation of the OH[•] radical, that is, the breakdown of the H₂O molecule to H[•] and OH[•] radicals under supercritical conditions on the assumption that the disproportionation using scH₂O follows reported mechanisms.^[7]

Our in situ FT-IR measurements enable us to carry out a kinetic analysis. The extent of the conversion of benzaldehyde in the disproportionation reaction changes in proportion to an increase in the absorbance of the benzyl alcohol formed. In this study pseudo second-order rate constants have been determined at temperatures of 20–427 °C and pressures of 0.1–25 MPa by assuming that excess OH⁻ is evolved.^[9] The extinction coefficient of the ν_1 band of benzyl alcohol determined through the Lambert–Beer law was assumed to be independent of temperature. Pressure differences did not influence the absorbance at temperatures of 20–200 °C.



Scheme 1. A postulated mechanism for the disproportionation of [D₆]benzaldehyde in scH₂O; d) D⁺ transfer; e) H⁺ transfer.

Figure 2 shows the pseudo second-order rate constants (k_{p2}) under various conditions: scH₂O, hot water, and concentrated aqueous NaOH solution. A dramatic enhancement in the reaction rate is seen on carrying out the reaction in scH₂O in the absence of any base catalysts. The reaction in scH₂O at 25 MPa and 427 °C (Figure 2g) is about 600 times faster than in 2M NaOH at 60 °C (Figure 2a).^[9] The reaction is greatly accelerated by raising the temperature in the scH₂O region; however, in hot water below 300 °C even at such high pressures the reaction was not observed to occur for residence time from 12 to 360 s. The change in the molecular extinction coefficient of benzyl alcohol with water density might influence the rate constants. Recent experimental data show that the extinction coefficient of triplet anthracene in scH₂O decreases with increasing density, by a factor of about 3–4 in the density range of 0.12 to 0.62 g cm⁻³ (ref [10]); however, we

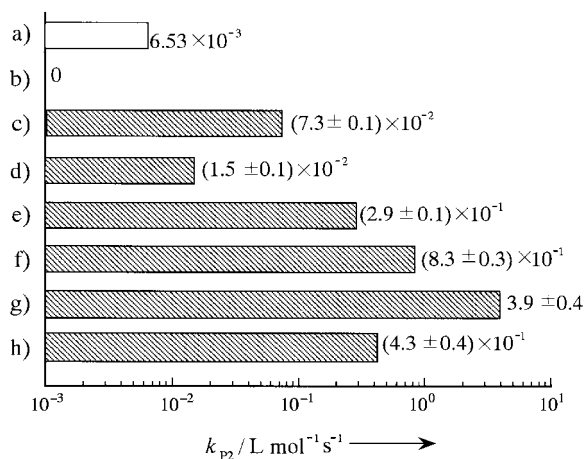


Figure 2. The pseudo second-order rate constants (k_{p2}) of the disproportionation of benzaldehyde. The base catalyst and its concentration, solvent, pressure, and temperature are a) 2M NaOH aq. solution, 60 °C;^[9] b) no catalyst, hot water, 25 MPa, 300 °C; c) no catalyst, hot water, 25 MPa, 352 °C; d) no catalyst, hot water, 19.1 MPa, 377 °C; e) no catalyst, scH₂O, 25 MPa, 377 °C; f) no catalyst, scH₂O, 25 MPa, 397 °C; g) no catalyst, scH₂O, 25 MPa, 427 °C; h) no catalyst, scH₂O, 22.1 MPa, 377 °C. For our data 95 % confidence limits are provided.

think that this change is not so large when compared with the marked enhancement of the rate of reaction, by one or two orders of magnitude, when using scH₂O, and does not prevent us from concluding that the use of scH₂O can significantly promote the rate of organic synthesis. Under the conditions used, the substrate can be soluble in the solvent at high pressures and temperatures. Increasing the pressure and temperature increases the density of H₂O and so decreases the concentration of substrate in the constant volume of reaction mixture. This will have a negative effect on the rate of reaction and so the enhanced reactivity of scH₂O is of great significance.

The change in hydrogen bonding is presumed to be a key factor for clarifying the temperature and/or pressure dependence of the rate of the disproportionation. It was demonstrated that the extent of hydrogen bonding is reducing uniquely near the critical point (critical pressure), where dimers and/or monomers are predominant,^[11] but monomers, in part, are further broken into H⁺ and OH⁻ ions by the large fluctuations in the water structure.^[5, 11d] That is, the “local” H⁺ or OH⁻ ion concentration would be extremely high when the transferring ion species cannot escape, leading to the maximized rate near the critical pressure. Hence such an acceleration of the disproportionation is quite peculiar to the supercritical state, and it is highly possible that the “specific breakdown” of H₂O to H⁺ and OH⁻ ions under supercritical conditions occurs.

Figure 3 shows the change in the rate constant with temperature at a fixed pressure of 25 MPa, together with the extent of the disappearance of hydrogen bonding ($1-\eta$) of water determined by our Raman spectroscopic data.^[5] The rate constant increases with increasing temperature above the near-critical region despite the loss in OH⁻ ion activity anticipated from the Raman data.^[5] The significant increase in the rate constant with increasing temperature from 397 to

427 °C at 25 MPa is because of an increase in thermal energy; however, hot water did not show any reactivity below 320 °C, whereas a marked increase in the rate with increasing temperature was observed in the near-critical region. Thus, the rate of reaction did not show a monotonous temperature dependence, being in agreement with the $1-\eta$ values up to approximately 400 °C. Furthermore, even though such a specific breakdown really occurs near the critical point, extensive spectroscopic data^[5, 11] suggest that the dispersed phase beyond the critical point contains low aggregates including monomeric water molecules. Hence, the excellent performance of the base-catalyzed disproportionation from the near-critical to supercritical region might be related not only to the thermal energy contribution but also to monomer-like water molecules that do not break completely into H⁺ and OH⁻ ions but polarize extremely in the supercritical state. There is still a possibility that the reaction mechanisms using scH₂O might be different from those reported.^[7] Microscopic dynamic behavior of water molecules in a shorter time domain is in any event more important when discussing the specific reactivities. We have successfully used the $1-\eta$ value to correlate the acid/base reactivity of scH₂O. Another possible

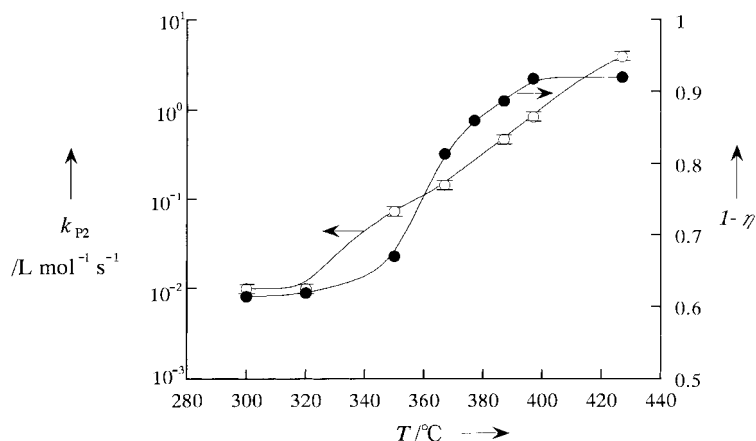


Figure 3. Relationship between the extent of disappearance of hydrogen bonding, $1-\eta$ (●) and the pseudo second-order rate constant, k_{p2} (○) for the benzaldehyde disproportionation as a function of temperature at a fixed pressure of 25 MPa. For k_{p2} values, 95 % confidence limits are given by bars.

parameter is the ion product of water (K_w) value; however, detailed measurements have not yet been made for scH₂O near the critical region, where interesting reaction results have been obtained.

Experimental Section

The reactions were performed under ambient to scH₂O conditions using a high-pressure, high-temperature flow-reaction system with a short-path-length (20 μm) FT-IR cell operable at 500 °C and 50 MPa. Details of the FT-IR system used are described elsewhere.^[3b] An aqueous solution of benzaldehyde (0.05 M) was introduced into the system in the range of flow rates of 0.07 to 0.7 mL min⁻¹ (the residence time from 12 to 360 s) using a high-pressure liquid pump. Pressure control was achieved by a back-pressure regulator. The temperature was then raised to the desired value. Once stabilized, 50 spectra (4 cm⁻¹ resolution) were accumulated in one destination file. Each file was rationed against the spectrum of pure H₂O under the same conditions. Furthermore, all of the products were

qualitatively identified by using ^1H NMR spectroscopy and GC-mass spectrometry.

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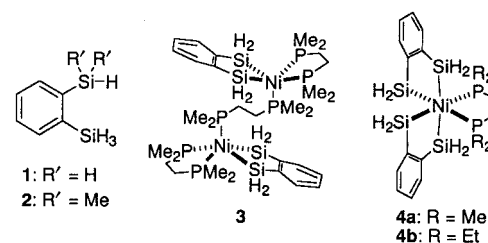
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Isolation of Dinuclear (μ -Silylene)(silyl)nickel Complexes and Si–Si Bond Formation on a Dinuclear Nickel Framework**

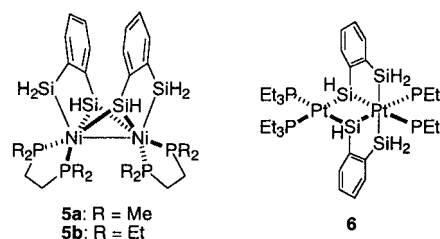
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Palladium and platinum complexes are versatile catalysts for the transformation of organosilicon compounds.^[1] However, the utility of nickel complexes has not been as well

established.^[2] The understanding of the structure and the reactivity of silylnickel species^[3] is indispensable for the development of new catalytic methodologies. Although a number of mononuclear silylmethyl complexes are known for all Group 10 metals, structurally characterized silylene-bridged dinuclear complexes have been reported only for platinum^[4] and palladium.^[5, 6] These dinuclear species are considered to play important roles in catalytic processes. For example, silylene-bridged Pt_2Si_2 rings are potential key intermediates in the platinum-catalyzed dehydrocoupling of hydrosilanes.^[4b–d] Here we report on the reaction of 1,2-disilylbenzene (**1**) with nickel(0) complexes, which led to the isolation of the dinuclear (μ -silylene)(silyl)nickel(III) complexes $[\{1,2\text{-C}_6\text{H}_4(\text{SiH}_2)(\text{SiH})\}_2\text{Ni}_2(\text{R}_2\text{PCH}_2\text{CH}_2\text{PR}_2)_2]$ ($\text{R} = \text{Me}$ or Et), which contain the first structurally characterized four-membered Ni_2Si_2 rings. The short contact between the SiH_2 and $\mu\text{-SiH}$ moieties revealed by X-ray crystallography suggests the possibility of Si–Si bond formation, which indeed takes place in a similar reaction of 1-(dimethylsilyl)-2-silylbenzene (**2**) with $[\text{Ni}(\text{dmpe})_2]$ ($\text{dmpe} = 1,2\text{-bis}(\text{dimethylphosphanyl})\text{ethane}$).



Previously, we reported that treatment of **1** with $[\text{Ni}(\text{dmpe})_2]$ results in the dimeric bis(silyl)nickel(II) complex **3** and the first tetrakis(silyl)nickel(IV) complex **4a**.^[7] A similar reaction under somewhat different conditions led to the formation of a new dimeric Ni^{III} complex. While studying **3** by variable-temperature NMR spectroscopy in $[\text{D}_8]\text{toluene}$, we observed, upon heating the solution to 80°C , a color change from pale yellow to orange and the emergence of new weak signals in the ^1H and ^{31}P NMR spectra. Further heating at 110°C for 30 min gave a new complex **5a**, which could be isolated as orange crystals (34%) by crystallization from benzene. The similar complex **5b**, ligated by 1,2-bis(diethylphosphanyl)ethane (depe), was also obtained directly from **1** and $[\text{Ni}(\text{PEt}_3)_2(\text{depe})]$ ($1:\text{Ni} = 1:1.05$); the reaction proceeded even at room temperature and gave **5b** as the main product (49% yield). The ^{29}Si NMR spectrum of the crude mixture showed the presence of the tetrakis(silyl)nickel(IV) complex **4b** as a side product [$\delta = -2.11$ (dd, $^2J(\text{Si}, \text{P}_{\text{cis}}) = 20$, $^2J(\text{Si}, \text{P}_{\text{trans}}) = 101$ Hz), 3.03 (t, $^2J(\text{Si}, \text{P}) = 16$ Hz)].



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The structures of **5a** and **5b** were established by X-ray diffraction as dinuclear (μ -silylene)(silyl)nickel complexes (Figure 1).^[8] In sharp contrast to the case of platinum, which forms complex **6** with a mixed valent $\text{Pt}^{\text{II}}\text{Pt}^{\text{IV}}\text{Si}_2$ four-membered ring,^[4f] **5a** and **5b** have symmetric structures with

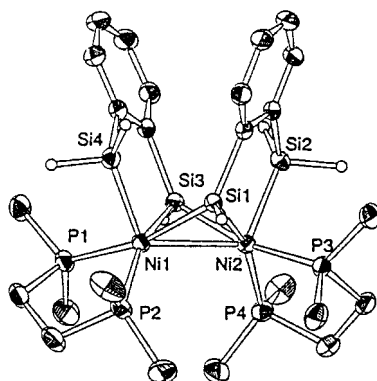
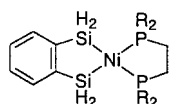


Figure 1. Molecular structure of **5a** (30% probability thermal ellipsoids).

$\text{Ni}^{\text{II}}\text{Si}_2$ four-membered rings. Most of the complexes containing four-membered Pt_2Si_2 rings so far reported have short diagonal $\text{Si}\cdots\text{Si}$ distances (2.55–2.88 Å) and long $\text{Pt}\cdots\text{Pt}$ distances (3.66–4.05 Å).^[4b–f] In contrast, **5a** and **5b** have long diagonal $\text{Si}\cdots\text{Si}$ distances (2.980(1) Å for **5a** and 2.998(1) Å for **5b**) and short $\text{Ni}\cdots\text{Ni}$ distances (2.6658(7) Å for **5a** and 2.7201(7) Å for **5b**). The $\text{Ni}\cdots\text{Ni}$ distances are longer than the usual Ni – Ni single bonds but still within the range of known Ni – Ni bond lengths; this suggests a bonding interaction.^[9] The Ni – Si distances range from 2.210(1) to 2.304(1) Å for **5a** and from 2.2098(6) to 2.2976(6) Å for **5b**, and 2.304(1) Å is the longest Ni – Si bond so far reported. In contrast to the diagonal $\text{Si}\cdots\text{Si}$ distances, the $\text{Si1}\cdots\text{Si4}$ and $\text{Si2}\cdots\text{Si3}$ distances (2.693(2) Å and 2.685(1) Å for **5a** and 2.7049(9) for **5b**) are short and nearly the same as the value for the longest Si – Si single bond.^[10] Complexes **5a** and **5b** are envisioned to be



7a: R = Me
7b: R = Et

formed by the dehydrogenative dimerization of bis(silyl)nickel(II) complexes **7a** and **7b**, respectively. In the reaction of **1** with $[\text{Ni}(\text{dmpe})_2]$, the sterically less demanding dmpe easily intercepts **7a** to form stable pentacoordinate species such as **3**, while in the reaction of **1** with $[\text{Ni}(\text{PET}_3)_2(\text{depe})]$, the bulkier depe and PET_3 ligands probably prevent the formation of analogous pentacoordinate nickel species and allow **7b** to dimerize even at room temperature.

Solid-state CP/MAS NMR spectra of **5b** displayed ^{31}P signals at $\delta = 48.6$ and 52.0, reasonable for the structure, and ^{29}Si signals at $\delta = -48.5$ and 79.9, which can be assigned to SiH_2 and μ - SiH , respectively. A solution of **5b** in $[\text{D}_8]\text{THF}$ at -40°C also displayed signals similar to those found in the solid-state NMR spectrum; a pair of triplets at $\delta = 47.4$ and 50.1 in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum and two signals at $\delta = -52.0$ (ddd, $J = 6, 13, 55$ Hz, SiH_2) and 92.2 (quasi dt, $J = 6, 67$ Hz, SiH) in the $^{29}\text{Si}\{^1\text{H}\}$ spectrum.^[11] However, these signals became broad and/or weak at higher temperatures,

and a number of other signals were observed.^[12] These results suggest that **5b** is in equilibrium between several species in solution, although their structures are unknown at the moment.

The short $\text{Si1}\cdots\text{Si4}$ and $\text{Si2}\cdots\text{Si3}$ distances in **5a** and **5b** suggest that and Si – Si bond-forming reaction can possibly take place in these complexes to form an eight-membered cyclic dimer of **1**. Attempted thermal reactions of **5a** or **5b** did not provide any clear evidence for Si – Si bond formation. However, Si – Si bond formation did take place upon treatment of **2**^[13] with $[\text{Ni}(\text{dmpe})_2]$ to generate the dimeric complex **8**. Heating a mixture of **2** and $[\text{Ni}(\text{dmpe})_2]$ ($2:[\text{Ni}(\text{dmpe})_2] = 2:1$) in benzene at 55 – 80°C for 4 d resulted in the spontaneous separation of yellow crystals of **8** (21% yield) from the solution. ^1H , ^{31}P , and ^{29}Si NMR spectroscopy on the solution part of the reaction mixture revealed that a large amount of $[\text{Ni}(\text{dmpe})_2]$ still remained, while **2** was completely consumed to give a mixture of silicon-containing compounds. Crystalline **8** is virtually insoluble in benzene. The structure determined by X-ray diffraction unequivocally verifies that the silyl ligand originated from Si – Si bond formation through dehydrocoupling (Figure 2).^[8]

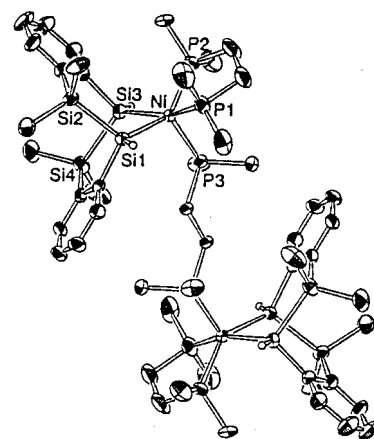
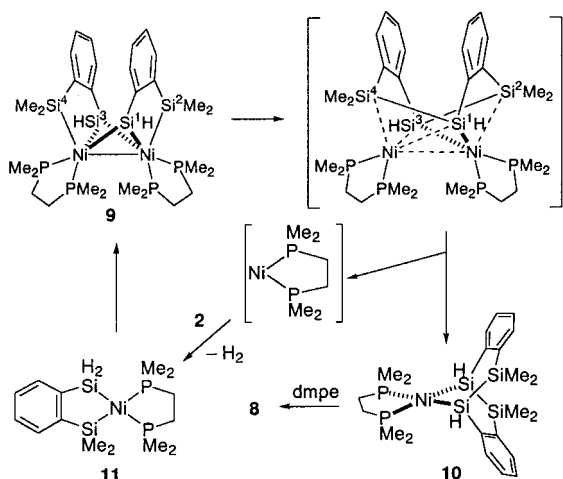


Figure 2. Molecular structure of **8** (30% probability thermal ellipsoids). Selected bond lengths [Å] and angles [$^\circ$]: Ni1 – Si1 2.263(2), Ni1 – Si3 2.257(2), Ni1 – P1 2.160(2), Ni1 – P2 2.182(2), Ni1 – P3 2.236(2), Si1 – Si2 2.357(2), Si3 – Si4 2.361(2); Si1 – Ni1 – Si3 76.83(6), P1 – Ni1 – P2 86.81(8), P1 – Ni1 – Si1 90.24(7), P2 – Ni1 – Si3 90.89(7), P1 – Ni1 – P3 103.53(8), Ni1 – Si1 – Si2 116.48(8), Ni1 – Si1 – C1 124.1(2), Si2 – Si1 – C1 102.3(2), Ni1 – Si3 – Si4 119.82(8), Ni1 – Si3 – C2 121.5(2), Si4 – Si3 – C2 101.1(2).

Although further studies are necessary to clarify the reaction mechanism, an assumption of the intermediacy of a dinuclear species **9** similar to **5** appears to rationalize the formation of **8** (Scheme 1). Formation of Si^1 – Si^4 and Si^2 – Si^3 bonds on the dimeric nickel framework in **9** and the release of a $[\text{Ni}(\text{dmpe})]$ fragment generate a monomeric product **10**, which readily dimerizes by coordination of dmpe to form **8**. The release of $\text{Ni}(\text{dmpe})$ fragment is likely to be assisted by the simultaneous attack of **2** to regenerate **11**. The successful Si – Si bond formation observed for **2**, but not for **1**, is presumably



Scheme 1. A possible mechanism for the formation of **8**.

associated with the low stability of organosilicon to transition metal bonds relative to that of hydridosilicon to transition metal bonds.^[14] Further mechanistic studies and catalytic dimerization of **1** and **2**^[15] are now underway.

Experimental Section

5a: A solution of **3** (160 mg, 0.19 mmol) in toluene (8 mL) was heated at 110 °C for 30 min under N₂. During heating, the color of the mixture turned from yellow to red. After removal of volatile substances under vacuum (10^{−4} Torr), the residue was dissolved in hot benzene (2 mL), from which remaining **3** crystallized (10 mg). After collection of the crystals by filtration, the filtrate was concentrated and the residue was dissolved in hot benzene (1 mL). A few seed crystals of **5a** were added, and the hot benzene solution was slowly cooled to room temperature. During the cooling process, orange prismatic crystals of **5a** grew initially, and then a small amount of crystalline **3** precipitated. After removal of the liquid portion with a syringe, washing the solid with benzene (1 mL) and diethyl ether (2 × 2 mL), and drying under vacuum, the solids were manually separated under a microscope to give pure **5a** (50 mg, 34% yield) and a mixture of **3** and **5a** (18 mg). **5a**: M.p. 134–152 °C (decomp); IR (KBr): $\tilde{\nu}$ = 3088, 3033, 2962, 2896, 2799, 2022, 1989, 1415, 1293, 1278, 1123, 1097, 931, 891, 819, 745, 701, 673, 632, 478, 459 cm^{−1}. X-ray diffraction showed the presence of one molecule of benzene per molecule of **5a** in the crystal; elemental analysis calcd for C₂₄H₄₆Ni₂P₄Si₄ · C₆H₆: C 47.02, H 6.84; found: C 46.78, H 6.85.

5b: [Ni(PET₃)₄] (505 mg, 0.95 mmol) was dissolved in toluene (3 mL) and depe (222 μ L, 0.95 mmol) added at room temperature. After 20 min of stirring, volatile substances were removed under vacuum to give [Ni(PET₃)₂(depe)] (³¹P NMR ([D₈]toluene, 202 MHz): δ = 16.25 (t, *J* = 28 Hz), 30.98 (t, *J* = 28 Hz)). **1** (124 mg, 0.90 mmol) was added to a solution of crude [Ni(PET₃)₂(depe)] in hexane (4 mL) at 0 °C. During the addition of **1**, the color of the mixture changed from light purple to light brown with evolution of a small amount of H₂. After the addition of **1**, the mixture was stirred at 30 °C for 44 h and then at 50 °C for 9 h to give a deep brown solution. Removal of volatile substances under vacuum left a brown oil, from which **5b** crystallized. Washing the solid with diethyl ether (1 × 15 mL, 2 × 3 mL) followed by drying under vacuum afforded analytically pure **5b** as orange crystals (120 mg). Another crop (55 mg) of **5b** was obtained by evaporation of the diethyl ether washings and crystallization of the residue from diethyl ether/hexane. Total yield based on **1** was 49%. M.p. 150–157 °C (decomp); ³¹P CP/MAS NMR (121.5 MHz): δ = 48.6, 52.0; ²⁹Si CP/MAS NMR (59.6 MHz): δ = −48.5, 79.8; IR (KBr): $\tilde{\nu}$ = 3034, 2961, 2932, 2902, 2028, 1456, 1416, 1376, 1240, 1097, 1026, 950, 867, 816, 762, 677, 622 cm^{−1}; elemental analysis calcd for C₃₂H₆₂Ni₂P₄Si₄: C 48.02, H 7.81; found: C 48.33, H 7.75.

8: A solution of **2** (0.332 g, 2 mmol) and [Ni(dmpe)₂] (0.358 g, 1 mmol) in benzene (4 mL) was heated at 55 °C for 24 h and at 80 °C for 3 d. Yellow

crystals precipitated and were collected by filtration, washed with benzene (3 × 1 mL), and dried under vacuum to give **8** (125 mg, 20.5%). M.p. 178–183 °C (decomp); IR (KBr): $\tilde{\nu}$ = 3033, 2963, 2903, 1958, 1637, 1420, 1295, 1248, 1139, 933, 892, 830, 804, 746, 717, 657, 635, 440 cm^{−1}; elemental analysis calcd for C₃₀H₉₂Ni₂P₆Si₈: C 49.18, H 7.59; found: C 48.95, H 7.77.

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A Mass Spectrometric Labeling Strategy for High-Throughput Reaction Evaluation and Optimization: Exploring C–H Activation**

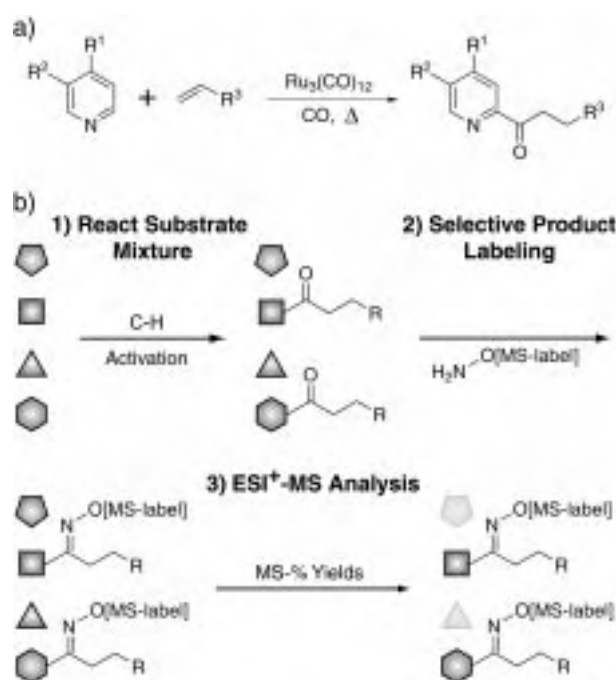
Jason W. Szewczyk, Rebecca L. Zuckerman, Robert G. Bergman,* and Jonathan A. Ellman*

Chemical transformations that combine C–H activation^[1] and olefin insertion^[2] present attractive opportunities for the rapid assembly of complex structures from unexploited classes of building blocks through carbon–carbon bond formation (Scheme 1).^[3] Controlling the site of activation is



Scheme 1. The generality of C–H activation allows, in principle, the combination of aromatic heterocycles with alkenes to rapidly assemble diverse structures using unexploited classes of building blocks.

one of the key challenges of this chemistry. Moore et al. first demonstrated that $[\text{Ru}_3(\text{CO})_{12}]$ catalytically activates the *ortho* positions of pyridine toward acylation with CO and olefins (Scheme 2a).^[4] They proposed that the aromatic



Scheme 2. a) A mixture of diverse pyridines is C–H activated to provide a mixture of products each bearing a ketone group. b) A schematic representation summarizing the high-throughput strategy for the optimization of the reaction and discovery of new products.

nitrogen atom coordinates the ruthenium catalyst, and directs activation specifically to the *ortho* sp^2 C–H bonds. More recently, Murai and co-workers have extended this reaction to several different aromatic heterocycles and olefin substrates.^[5] A better understanding of the rules for functional group compatibility and substrate generality demands that a large number of heterocyclic classes be investigated, yet current approaches cannot efficiently provide this information because of the large number of compounds that require testing.

Combinatorial methods have made a major impact on new catalyst discovery, but the development of rapid and efficient analyses remains a challenge.^[7] Several recent high-throughput methods monitor reactions through the catalyst turnover and/or reaction conversion by IR thermography,^[8] the formation of UV-active products,^[9] or the production of acid^[10] or carbon dioxide.^[11] Although, these techniques are powerful, they cannot distinguish between products, by-products, and decomposition. Alternatively, serial methods (TLC, GC, and HPLC) have been employed to identify products and/or quantify yields,^[12] but these methods severely limit the number of reactions that can be analyzed in a short period of time. In addition, fluorescent-labeled substrates have been used in the rapid monitoring of reactions.^[13] Unfortunately, each substrate under investigation must be individually synthesized as a specifically labeled compound prior to reaction and analysis; thus experimental effort increases linearly with the number of different substrates to be evaluated. We report here the first optimization strategy that enables efficient quantitation of product yields at multiple time points for large numbers of substrates, thereby establishing structure–reactivity relationships and reaction compatibility of functional groups (Scheme 2b).

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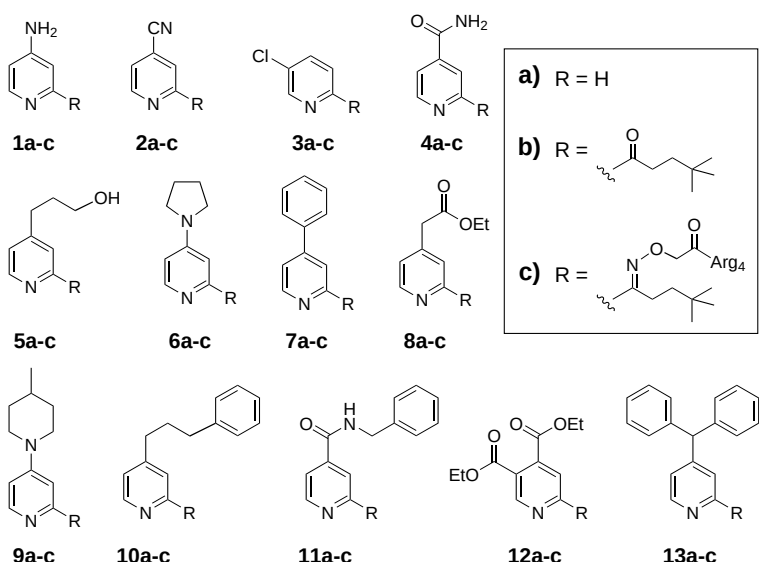
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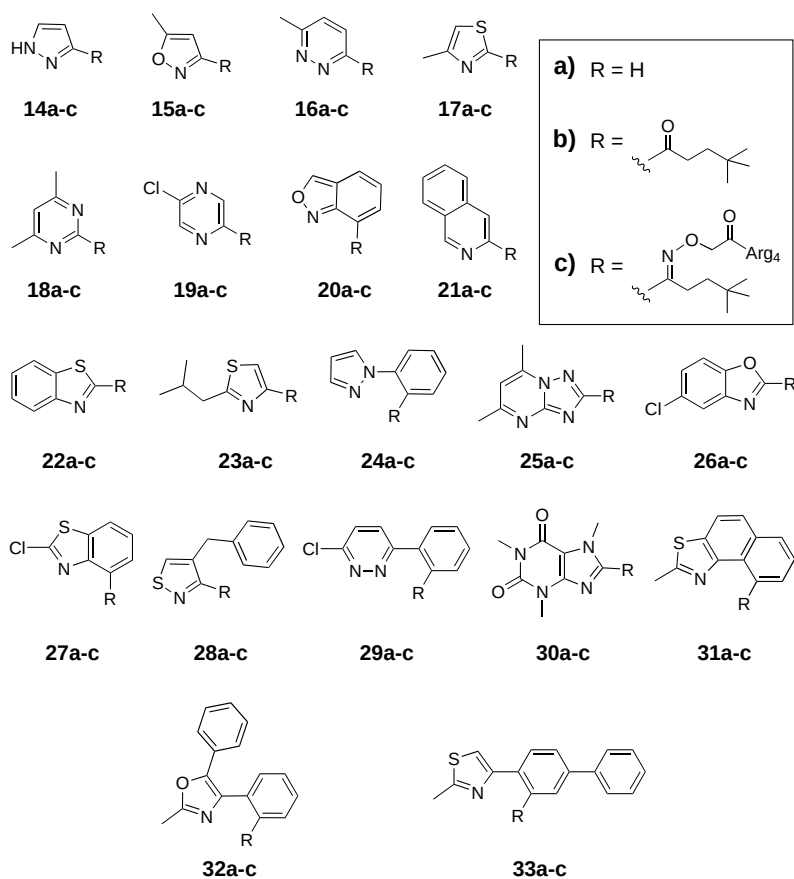
Electrospray ionization mass spectrometry (ESI-MS) has drawn increasing attention for the analysis of combinatorial libraries as a consequence of its mild ionization conditions, rapid data acquisition, and the recent availability of affordable equipment.^[14] However, all previous combinatorial approaches employ only a single substrate or a few substrates to optimize reaction parameters.^[15] Since a typical mass spectrum surveys a window of thousands of Daltons simultaneously, mass spectrometry can theoretically be used to evaluate hundreds of substrates in a single experiment. In our strategy a mixture consisting of aromatic heterocycles and a single alkene was subjected to catalytic C–H activation with $[\text{Ru}_3(\text{CO})_{12}]$ and CO (Scheme 2). Next, products bearing a ketone group were selectively labeled.^[16] This step silences remaining starting materials and/or decomposition products and allows the yields of the desired products to be determined directly by positive-ion ESI-MS ($\text{ESI}^+\text{-MS}$). As proof of principle, a small library of functionalized pyridines was treated with $[\text{Ru}_3(\text{CO})_{12}]$, alkene, and CO to determine the compatibility of functional groups and substrate generality (Scheme 3). In addition, a second array of diverse heterocycles was investigated using this combinatorial method to further expand the number of heterocyclic classes that were compatible with this chemistry (Scheme 4).

A quantitative mass spectrometric assay requires uniform ionization and negligible fragmentation of all analytes so that the yields can be determined by peak integration. As a control, a simple peptide label composed of four arginine residues and an N-terminal alkoxyamine ($\text{H}_2\text{NOGlyArg}_4$) was treated with an equimolar mixture of 13 purified pyridylketone products prepared individually in the C–H activation reaction. The resulting oximes were then analyzed by $\text{ESI}^+\text{-MS}$. Complete conversion into the oxime products was always observed as a result of the high efficiency of this labeling reaction. Notably, this labeling strategy allows a wide range of functional groups to be present in the starting heterocycle. The MS label ($\text{H}_2\text{NOGlyArg}_4$) was sufficient to dominate the ionization of all 13 oximes and provided a uniform response for all the substrates within experimental error ($< \pm 10\%$, Figure 1), which permits for the accurate determination of yields by the direct integration of peak areas relative to that of an external standard. Also, the high molecular weight of the labeled products (> 700 Da) ensures that ions of the product oximes are not obscured by ions from residual reactants and decomposed material.

In a typical timed run the pyridine mixture (1 mmol/substrate) was placed in a stainless steel bomb and allowed to react



Scheme 3. The library of pyridine substrates used to investigate the functional group compatibility of directed C–H activation.



Scheme 4. The library of diverse heterocycles used to investigate the substrate generality of directed C–H activation.

with $[\text{Ru}_3(\text{CO})_{12}]$ (40 mol %) and neohexene (5 equiv) in toluene under CO (300 psi, 160°C). A 40 mol % catalyst loading was chosen to ensure that the yield and relative rate data obtained were accurate and not biased by catalyst availability. The product mixture was then cooled, concentrated, dissolved in acetonitrile, and an external standard (2-pyridinecarboxalde-

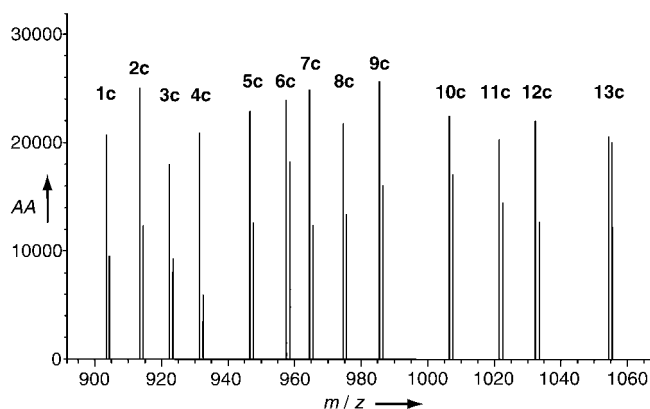


Figure 1. A control positive-ion ESI mass spectrum demonstrating that the mass spectrometric label (-GlyArg₄) ionizes the product oximes uniformly regardless of the functional group present (AA = absolute abundance of the ion).

hyde, 1 mmol) added that reacted efficiently with the MS label. With no purification required, a sample of the product mixture was treated with a fourfold excess of the MS label (H₂NOGlyArg₄) overnight to ensure complete conversion. This solution was diluted with 5 % trifluoroacetic acid (TFA) in MeCN (30 μ M/substrate) and analyzed by ESI⁺-MS. The yields of the products relative to the standard were found to be independent of concentration.

Data from the library of 13 pyridine derivatives shows the scope of the functional group compatibility of [Ru₃(CO)₁₂]. Directed C–H bond activation occurs in good yield for pyridine substrates bearing nitriles, amides, alcohols, esters, biaryls, benzhydryls, and amines (Table 1). Surprisingly, aromatic chlorides **3a** react in good yield, which suggests that the acylation reaction may be combined with palladium-mediated chemistry^[17] to enable more highly functionalized structures to be built rapidly. Furthermore, by executing a series of timed runs, the relative rates of product formation from all 13 pyridine substrates could be monitored simultaneously to provide optimized reaction conditions for each substrate (Figure 2). Trends in the rate data demonstrate that electron-withdrawing substituents slow the rate of reaction,

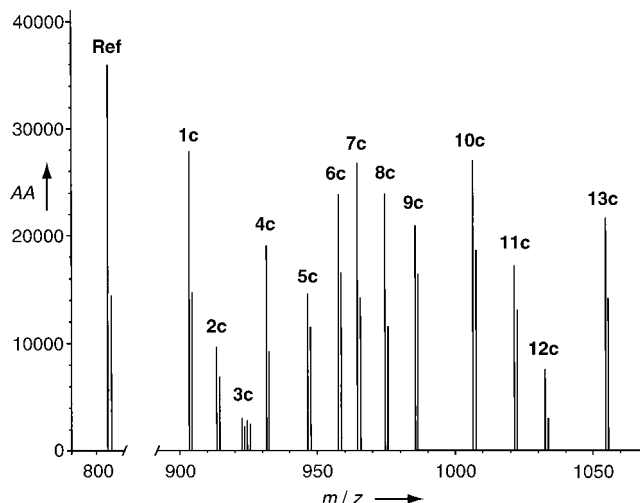


Figure 2. A typical positive-ion ESI mass spectrum obtained for the timed run (over 5 h) from the unpurified pyridine reaction mixture using 2-pyridinecarboxaldehyde as the reference (Ref).

while electron-donating groups increase the rate. The success of this high-throughput strategy for the challenging case of substrate mixtures elegantly demonstrates the deconvolution power of an analytical strategy based on mass spectrometry.

A series of control experiments were performed to test the accuracy of the yields determined by MS and the effect of catalyst loading. Two products (**4b** and **7b**) were synthesized individually under conditions identical to those employed in the mixture and the yields determined by mass balance (57 and 95 %, respectively). The yields for the individual runs are in excellent agreement with those measured by ESI⁺-MS for the same compounds when run in the library format. Additionally, the yields determined by MS compare favorably with previous experiments in which lower catalyst loadings and extended reactions times were employed to prepare the 13 authentic pyridine standards.

To assess the generality of the reaction a mixture of 20 diverse heterocyclic substrates was investigated using the same C–H activation conditions as those employed for the pyridine library (Scheme 4). Labeling and ESI⁺-MS analysis revealed a number of new substrate classes for activation (pyridazines, thiazoles, isoquinolines, and benzothiazoles) which proceeded in good yield and with rates of reaction comparable to that of pyridine (Table 2). Further investigation of the unreactive substrates at an elevated temperature (180 °C) did not increase product yields. Intriguingly, the two thiazole substrates **17a** and **23a** both present C–H bonds for activation; however reactivity at C2 (**17a**) is accelerated nearly sixfold over that at C4 (**23a**). The observed reactivity trend was independently confirmed by the C–H activation of unsubstituted thiazole, where the C2 and C4 activated products were produced in a 9:1 ratio. This additional level of selectivity could allow for the efficient elaboration of multicomponent structures through a series of controlled C–H activations where different olefin building blocks are introduced regioselectively without the need for blocking groups. After the completion of these studies, Murai and co-workers published an independent report on a subset of the

Table 1. Yields obtained by mass spectrometry for the C–H activation of the pyridine library.

Compound	Calcd <i>m/z</i>	Found <i>m/z</i>	Yields [%] ^[a]			
			3 h ^[b]	5 h ^[b]	10 h ^[b]	20 h ^[b]
1c	903.59	903.50	65(±5)	80(±6)	54(±14)	32(±2)
2c	913.57	913.45	25(±3)	30(±5)	48(±3)	63(±4)
3c	922.54	922.43	26(±3)	27(±10)	54(±13)	57(±7)
4c	931.58	931.48	43(±1)	48(±6)	56(±7)	31(±3)
5c	946.62	946.56	48(±12)	48(±5)	46(±2)	9(±1)
6c	957.63	957.55	50(±6)	68(±5)	38(±3)	18(±2)
7c	964.61	964.50	71(±4)	83(±10)	86(±11)	66(±3)
8c	974.61	974.54	71(±6)	66(±8)	84(±10)	64(±5)
9c	985.66	985.61	45(±6)	71(±12)	54(±8)	26(±2)
10c	1006.65	1006.58	63(±5)	79(±6)	71(±5)	56(±1)
11c	1021.63	1021.55	42(±1)	56(±6)	63(±6)	55(±4)
12c	1032.62	1032.48	15(±1)	20(±3)	37(±8)	43(±1)
13c	1054.65	1054.58	57(±4)	69(±5)	66(±2)	50(±2)

[a] The reported yields are the mean values measured from at least three experiments. [b] Standard deviations are shown in parentheses.

Table 2. Yields determined by mass spectrometry for the C–H activation of the heterocyclic library.

Compound	Calcd <i>m/z</i>	Found <i>m/z</i>	Yields [%] ^[a]			
			3 h ^[b]	6 h ^[b]	20 h ^[b]	40 h ^[b]
14c	877.57	877.56	3(±1)	3(±2)	2(±1)	5(±1)
15c	892.57	892.43	2(±1)	3(±1)	2(±1)	2(±1)
16c	903.59	903.51	38(±6)	16(±4)	13(±9)	7(±3)
17c	908.55	908.49	36(±5)	46(±3)	65(±4)	91(±2)
18c	917.60	917.55	4(±1)	5(±1)	4(±2)	7(±3)
19c	923.53	923.50	3(±1)	3(±1)	5(±2)	4(±4)
20c	928.57	928.63	2(±1)	2(±1)	2(±1)	4(±2)
21c	938.59	938.52	35(±4)	32(±5)	49(±10)	22(±4)
22c	944.55	944.54	42(±4)	59(±6)	95(±5)	78(±6)
23c	950.59	950.56	6(±1)	8(±2)	16(±1)	32(±5)
24c	953.60	953.51	4(±2)	3(±2)	5(±1)	7(±3)
25c	957.61	957.51	2(±1)	2(±1)	2(±2)	3(±1)
26c	962.53	962.35	3(±3)	4(±2)	3(±2)	4(±1)
27c	978.51	978.39	1(±1)	1(±2)	1(±1)	4(±1)
28c	984.58	984.55	2(±1)	2(±1)	2(±1)	7(±1)
29c	999.56	999.55	1(±1)	1(±1)	1(±1)	3(±2)
30c	1003.61	1003.59	2(±1)	2(±1)	3(±2)	3(±2)
31c	1008.58	1008.56	2(±1)	2(±2)	4(±1)	3(±1)
32c	1044.63	1044.65	1(±1)	1(±1)	4(±3)	3(±2)
33c	1060.61	1060.54	1(±1)	1(±1)	2(±1)	3(±2)

[a] The reported yields are the mean values measured from at least three experiments. [b] Standard deviations are shown in parentheses.

heterocycles described here, which completely supports our results for the small number of compounds investigated in both studies.^[18]

In summary, a rapid method to evaluate large numbers of substrates was developed which defines structure–reactivity relationships and the reaction compatibility of functional groups. Additionally, no purification and only a structurally simple mass spectrometric label are required to directly determine the desired products and their yields. In three simple experiments 33 different substrates were submitted to C–H activation conditions and analyzed over time to provide more than 170 determinations of yield. This information identifies acceptable and unacceptable substrates, relative rates of product formation, and optimal reaction times for achieving high yields. While substrate mixtures were appropriate for these investigations, the method is applicable to spatially separate reactions, which may simply be sampled, pooled, and assayed as described. Notably, this approach can be directly applied to any reaction where a carbonyl group is introduced into the product. Furthermore, simple modification of the attachment functionality and linking group allows the mass spectrometric labeling strategy to be applied, in principle, to a broad range of transformations.^[19]

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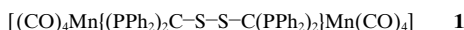
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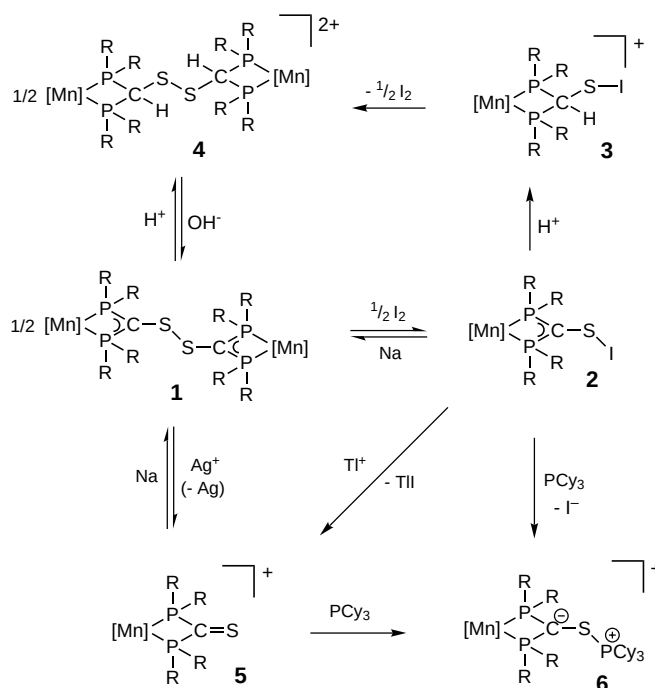
Reversible S–S Bond Breaking and Bond Formation in Disulfide-Containing Dinuclear Complexes of Mn^I**

Javier Ruiz,* Mario Ceroni, Oscar V. Quinzani, Víctor Riera, and Oscar E. Piro

Disulfide-containing compounds are of considerable biological^[1] and technological relevance,^[2] and the mechanisms by which the sulfur–sulfur bond in these compounds can be reversibly broken and formed has attracted a great deal of interest.^[3] We have recently reported that nucleophilic degradation of cyclooctasulfur by the diphosphanymethanide complex of manganese(I) [Mn(CO)₄{(PPh₂)₂CH}] allows the formation of the hexasulfur-bridged bis(diphosphanymethanide) dimetallic derivative [(CO)₄Mn{(PPh₂)₂C–S₆–C(PPh₂)₂–Mn(CO)₄}.^[4] In this complex the polysulfur chain can be progressively shortened by treatment with PPh₃ leading finally to the disulfide compound **1**, which does not undergo further sulfur extrusion processes.^[5] We have now explored the chemistry of this disulfide derivative with regard to the controlled scission and formation of the sulfur–sulfur bond, promoted either by redox processes or by combined redox and acid–base treatments. This has led to a number of scarce functionalities such as diphosphanylthioketone, sulfenyl iodide, and thioxophosphorane ylide, as parts of the corresponding carbonyl complex of manganese(I).



The treatment of **1** with one equivalent of I₂ in dichloromethane led instantaneously to the formation of **2** (Scheme 1), which was isolated as a red solid. The spectroscopic and analytical data for **2** (see Experimental Section), as well as further reactivity studies (see below), strongly support the proposed formulation for this complex as the sulfenyl iodide derivative [Mn(CO)₄{(PPh₂)₂C–S–I}]. The Raman spectrum of **2** is in agreement with the scission of the S–S bond upon oxidation with iodine, since it shows the complete disappearance of the strong S–S stretching band at 321 cm^{–1} which corresponds to the disulfide moiety in the starting complex **1**. Reduction of **2** with Na in THF quantitatively



Scheme 1. Reversible scission and formation of the S–S bond in **1**, and synthesis of the ylide derivative **6**. [Mn] = Mn(CO)₄⁺. R = Ph.

regenerates the disulfide **1**. The sulfur–sulfur bond formation to give **1** is also accomplished by passing **2** through an alumina column and, partially, by heating a solid sample of **2** under vacuum at about 200 °C. In spite of their biochemical interest (e.g., as intermediates in the iodination of tyrosine), thermally stable sulfenyl iodides are scarce owing to their very favored disproportionation [Eq. (1)].^[6] For this reason, they had never



been prepared by direct reaction of a disulfide with iodine. In our case, the noteworthy stability of **2** could be due to the anionic character of the diphosphanyl methanide ligand {(PPh₂)₂C–S–I}[–] in which the sulfenyl iodide functionality is included. In fact, when **2** was protonated at the methanide carbon atom (using HBF₄), the opposite reaction was immediately observed (even at low temperature) yielding the dication **4** and I₂, instead of the mononuclear species **3** (Scheme 1). This means that the sulfur–sulfur bond is once again easily regenerated by treatment with acids. Naturally, the cationic derivative **4** is transformed into **1** by simple reaction with KOH.

The sulfur–sulfur bond in **1** can also be broken by oxidation by using two equivalents of AgBF₄. This led to **5**, which, on reduction with Na in THF, readily regenerated **1**. The cationic complex **5** can also be prepared through iodide abstraction from **2**, by using either TIPF₆ or an excess of I₂, which abstract iodide as TI and I₃[–], respectively. To the best of our knowledge, diphosphanylthioketones are unknown, although the related carbodiphosphorane thiolate and selenolate zwitterions PPh₃C(X)PPh₃ (X = S, Se) have been described,^[7] as has the coupling of two selenolate functions upon oxidation to afford the cation [(PPh₃)₂C–Se–Se–C(PPh₃)₂]²⁺.^[8] Notably,

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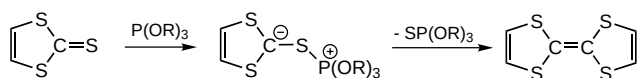
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the well-known processes of S–S bond formation from thiol functionalities, which stabilize the tertiary structure of many proteins, take place by oxidative coupling,^[9] whereas in our case oxidation of **1** (either with I₂ or Ag⁺) results in the scission of the S–S bond.

The thione in **5** undergoes thiophilic addition by treatment with phosphanes, such as PCy₃, to afford **6**, a complex in which the diphosphane ligand contains a unique thioxophosphorane ylide functionality (Scheme 1). The same behavior is shown by complex **2**, which readily reacts with PCy₃ by nucleophilic substitution of I[−] to give **6**. Similar types of 1,3-dipolar molecules are assumed to be reaction intermediates in the well-known desulfurization and coupling reactions of 1,3-dithiole-2-thiones by trialkylphosphites, which led to tetrathiafulvalene derivatives (constituents of organic conductors, Scheme 2),^[10] as well as in the formation of phosphorus ylides



Scheme 2. Schematic representation of the desulfurization of 1,3-dithiole-2-thiones by thiophilic addition of phosphites to give tetrathiafulvalene derivatives.

from thiones.^[11] However, this is the first time that such a derivative has been isolated and fully structurally characterized. The structure of **6**·BF₄, which has been elucidated by X-ray crystallography (Figure 1),^[12] clearly shows the presence of the modified diphosphane ligand [(PPh₂)₂CSPCy₃] η^2 (P, P′)-coordinated to the Mn(CO)₄ moiety. The P1–P2–C5–S skeleton departs appreciably from the expected planar conformation (the sulfur atom is at 0.644(2) Å from the P1–P2–C5 plane), probably due to the

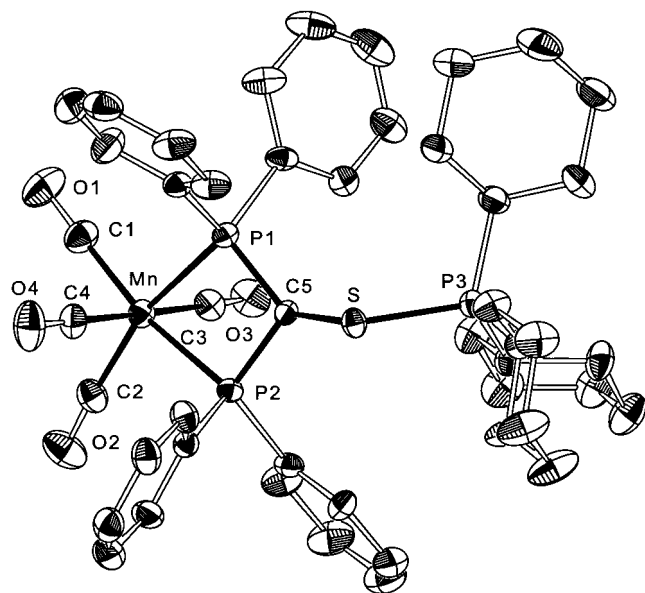


Figure 1. Structure of the cationic complex **6** in the crystal (30% probability ellipsoids; hydrogen atoms are omitted for clarity). Selected bond lengths [Å] and angles [°]: Mn–P1 2.342(2), Mn–P2 2.318(2), P1–C5 1.756(7), P2–C5 1.744(7), C5–S 1.760(7), S–P3 2.107(3); P1–Mn–P2 70.39(7), Mn–P1–C5 93.4(2), Mn–P2–C5 94.5(2), P1–C5–P2 100.3(3), P1–C5–S 131.2(4), P2–C5–S 121.9(4), C5–S–P3 116.0(2).

steric hindrance of the cyclohexyl groups. The three bond lengths around the ylide carbon atom are slightly shorter than expected for single bonds (P1–C5 1.756(7), P2–C5 1.744(7), C5–S 1.760(7) Å). The P1–P2–C5 and C5–S–P3 planes are almost mutually perpendicular (dihedral angle 79.0(3)°, which minimizes the steric repulsions between the cyclohexyl and phenyl rings. In the S–PCy₃ moiety the phosphorus atom has a distorted tetrahedral coordination geometry, and the P–S distance (2.107 (3) Å) is typical of a single bond.

The gentle warming of **6** in THF readily liberates SPCy₃, thus completing the sulfur extrusion process from **5**. However, the transient diphosphanycarbene complex [Mn(CO)₄–{(PPh₂)₂C:}]⁺ which should remain in the reaction mixture was not detected; instead a complex mixture of manganese(I) derivatives is found that still requires characterization.

In summary, the approach presented allows the reversible scission and formation of the S–S bond in the dinuclear complex **1**, which, in parallel, enables the generation of unusual functionalities at the central carbon atom of the diphosphane moiety. Preliminary results show that **2** and **5** undergo nucleophilic attack on the sulfur atom not only with tertiary phosphanes, but also with a wide variety of nucleophilic reagents such as KCN, MgRCl, and NaSR. Thus these complexes show great promise for synthetic applications.

Experimental Section

2: I₂ (0.022 g, 0.087 mmol) was added to a solution of **1** (0.1 g, 0.086 mmol) in CH₂Cl₂. After the mixture had been stirred for 5 min at room temperature, the solvent was evaporated to dryness, and the brown residue was recrystallized from CH₂Cl₂/hexane to afford a red solid; yield 91% (0.11 g). Elemental analysis (%) calcd for C₂₉H₂₀IMnO₄P₂S: C 49.18, H 2.85; found: C 48.87, H 2.82; IR (CH₂Cl₂): $\tilde{\nu}$ = 2081 (s), 2011 (sh), 2001 (vs), 1982 (m) cm^{−1} (CO); ³¹P{¹H} NMR (121.5 MHz, CD₂Cl₂): δ = 36.5 (br); FAB-MS (positive-ion): *m/z*: 708 [*M*⁺], 652 [*M*⁺ – 2 CO].

4: IR (CH₂Cl₂): $\tilde{\nu}$ = 2094 (s), 2036 (m), 2011 (vs) cm^{−1} (CO); Raman (KBr): $\tilde{\nu}$ = 451 (s) cm^{−1} (S–S); ³¹P{¹H} NMR (121.5 MHz, CD₂Cl₂): δ = 34.0 (br); ¹H NMR (300 MHz, CD₂Cl₂): δ = 6.98 (t, ²*J*_{PH} = 7 Hz, 2H; P₂CH).

5·BF₄: AgBF₄ (0.35 g, 0.18 mmol) was added to a solution of **1** (0.1 g, 0.086 mmol) in CH₂Cl₂. The resulting suspension, protected from light, was stirred for 1 h. Then the solution was filtered off and evaporated to dryness. The residue was recrystallized twice in CH₂Cl₂/hexane at −20 °C to afford white crystals; yield 40% (0.054 g). Elemental analysis (%) calcd for C₂₉H₂₀BF₄MnO₄P₂S: C 52.13, H 3.02; found: C 52.03, H 2.96; IR (CH₂Cl₂): $\tilde{\nu}$ = 2093 (s), 2033 (m), 2011 (vs) cm^{−1} (CO); ³¹P{¹H} NMR (121.5 MHz, CD₂Cl₂): δ = 44.0 (br); FAB-MS (positive-ion): *m/z*: 581 [*M*⁺ – BF₄].

6·BF₄: PCy₃ (0.025 g, 0.09 mmol) was added to a solution of **5**·BF₄ (0.06 g, 0.09 mmol) in CH₂Cl₂. After the mixture had been stirred for 20 min at room temperature, the solvent was evaporated to dryness. The residue was washed with Et₂O (20 mL) and recrystallized from CH₂Cl₂/Et₂O to obtain white crystals; yield 70% (0.06 g). Elemental analysis (%) calcd for C₄₇H₅₃BF₄MnO₄P₃S: C 59.51, H 5.63; found: C 59.10, H 5.88; IR (CH₂Cl₂): $\tilde{\nu}$ = 2079 (s), 2014 (s), 1988 (vs) cm^{−1} (CO); ³¹P{¹H} NMR (121.5 MHz, CD₂Cl₂): δ = 32.4 (br), 53.5 (t, ³*J*_{PP} = 7 Hz).

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- [12] Crystal data for **6**·BF₄ (C₄₇H₃₃BF₄MnO₄P₃S): *M*_r = 948.61, triclinic, space group *P*1, *a* = 11.771(2), *b* = 13.909(2), *c* = 16.416(4) Å, *α* = 67.69(1), *β* = 82.86(2), *γ* = 81.43(1)°, *V* = 2452.8(8) Å³, *Z* = 2, *ρ*_{calc} = 1.285 g cm^{−3}, *F*(000) = 988, MoK_α radiation (*λ* = 0.71073 Å), *μ*(MoK_α) = 0.191 mm^{−1}; crystal dimensions 0.10 × 0.28 × 0.40. Diffraction data were collected on an Enraf-Nonius diffractometer at 293 K. The structure was solved by direct methods and refined using full-matrix least-squares on *F*² with all non-hydrogen atoms anisotropically defined. The hydrogen atoms were placed in calculated positions, isotropically refined with common thermal parameters and allowed to ride on their parent carbon atoms. For 4866 observed reflections with *I* > 2σ(*I*) and 551 parameters, the conventional *R* is 0.081 and *wR*₂ = 0.252. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-145733. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Efficient Catalytic Alkane Nitration with NO₂ under Air Assisted by *N*-Hydroxyphthalimide**

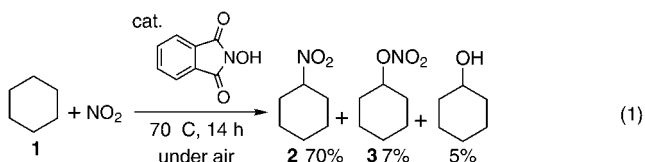
Satoshi Sakaguchi, Yoshiki Nishiwaki, Takaaki Kitamura, and Yasutaka Ishii*

In contrast to the nitration of aromatic hydrocarbons, which is easily performed using nitric acid in the presence of sulfuric acid, the selective nitration of aliphatic hydrocarbons is very difficult because of the exceedingly low reactivity of the latter. Currently, nitrations of aliphatic hydrocarbons are carried out at fairly high temperatures (250–400 °C) using nitrogen dioxide or nitric acid, and they proceed by free radical chain

reactions involving C–H bond homolysis.^[1, 2] Under such high temperatures, higher alkanes undergo not only homolysis of C–H bonds but also cleavage of the C–C skeleton. Therefore, large-scale nitration of alkanes has been limited to lower alkanes such as methane and ethane.^[2] For instance, the nitration of propane produces all of the possible nitroparaffins, namely, nitromethane, nitroethane, 1-nitropropane, and 2-nitropropane.^[1, 3] The development of selective nitration of cyclohexane is very attractive, since nitrocyclohexane is easily converted into cyclohexanone oxime, the raw material of ϵ -caprolactam, which in turn leads to nylon-6.^[4–6]

Recently we developed a catalytic method for the generation of alkyl radicals from saturated hydrocarbons using *N*-hydroxyphthalimide (NHPI), which serves as the radical catalyst.^[7] The phthalimide *N*-oxyl (PINO) radical generated in situ from NHPI and O₂, which lies in a triplet state, abstracts the hydrogen atom from the saturated hydrocarbons, forming the corresponding alkyl radicals. These radicals are readily trapped by O₂ under aerobic conditions to give oxygen-containing compounds such as alcohols, ketones, and carboxylic acids. These results led us to become interested in the nitration of alkanes with NO₂ by the use of NHPI as a catalyst.

In the first trial, NHPI was added at room temperature to a stirred benzene solution containing dissolved NO₂. The ESR measurement of the solution indicated a triplet signal, which is assigned to the PINO radical.^[8] This is believed to be due to the fact that NO₂ is a stronger oxidant than O₂. Thus, the nitration of cyclohexane (**1**) was examined using NO₂ in the presence of a catalytic amount of NHPI under several reaction conditions ([Eq. (1)], Table 1).



The nitration of **1** with NO₂ by NHPI proceeded smoothly at 70 °C to give nitrocyclohexane (**2**, 70% based on NO₂ used; Table 1, run 1) and cyclohexyl nitrite (**3**, 7%) along with a small amount of an oxygenated product, cyclohexanol (5%).

Table 1. NHPI-catalyzed nitration of **1** with NO₂ under selected conditions.^[a]

Run	NHPI [mmol]	<i>T</i> [°C]	Yield of 2 [%] ^[b]
1	0.6	70	70
2 ^[c]	0.6	70	43
3	–	70	< 2
4	0.6	60	58
5	0.6	50	39
6	0.3	70	56
7 ^[d]	0.6	70	63
8 ^[e]	9	70	53

[a] Reactions were run as described in the Experimental Section. [b] Yields are average values obtained from several runs and are based on NO₂ used. [c] Under argon. [d] Recovered catalyst from run 1 was used. [e] The reaction was carried out using **1** (50 mL) and NO₂ (33 mmol). The yield of **2** is based on isolated product.

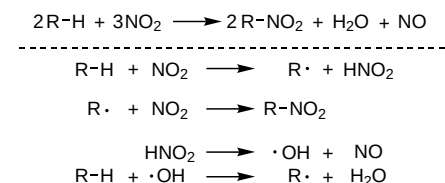
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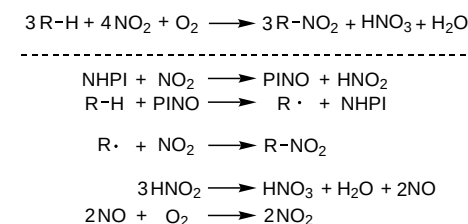
As discussed below, it is important that the NHPI-catalyzed nitration is conducted under air, since NO generated in the course of the reaction can be reoxidized to NO₂ by O₂. For the analogous nitration of **1** in the absence of air, the yield of **2** decreased to 43 % (run 2). Needless to say, the nitration of **1** was difficult to carry out without NHPI under these conditions (run 3). The nitration took place even at 50 °C to give **2** in 39 % yield (run 5). When the amount of NHPI was halved (0.3 mmol), **2** was formed in slightly lower yield (56 %, run 6). The nitration of **1** using recovered NHPI produced **2** in 63 % yield (run 7). The large-scale nitration allowed the isolation of **2** in 53 % yield (run 8).

Scheme 1 shows the reaction pathway for the vapor-phase nitration of alkanes by NO₂.^[2] According to this mechanism, one-third of the NO₂ employed is converted into NO via



Scheme 1. The reaction pathway for the conventional alkane nitration with NO₂.

HNO₂. Hence, the maximum yield of nitroalkanes by this method cannot, in theory, be higher than 66.7%. In fact, the nitration of **1** by NO₂ under argon led to **2** in 43 % yield (Table 1, run 2). It is noteworthy that the present nitration of **1** by NO₂ (under air, catalyzed by NHPI) afforded **2** in 70 % yield, that is, greater than the theoretical yield of 66.7% for the conventional nitration by NO₂ alone. Owing to the complexities of the present nitration, the reaction pathway is uncertain at this stage. A plausible pathway is proposed in Scheme 2.



Scheme 2. A possible reaction pathway for the NHPI-catalyzed alkane nitration with NO₂ under air.

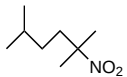
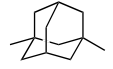
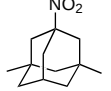
The nitration may be initiated by hydrogen-atom abstraction from the hydroxyimide group of NHPI by NO₂ to generate a PINO radical as described previously. The PINO radical readily abstracts the hydrogen atom from an alkane to form an alkyl radical, which undergoes nitration with NO₂ to give a nitroalkane. It has been reported that HNO₂ is converted into HNO₃, H₂O, and NO.^[9] Under our conditions, the NO formed is expected to be oxidized by O₂ to NO₂, and the generated NO₂ is reused in the nitration. Therefore, the yield of nitrocyclohexane is over 66.7%. In fact, when the reaction mixture was extracted with water after the reaction,

the aqueous phase was acidic, probably because of the formation of HNO₃.

The most promising feature of the NHPI-catalyzed nitration of alkanes by NO₂ is that the nitration is conducted in the presence of air (O₂) under mild conditions. Owing to the higher concentration of NO₂ than air, the alkyl radicals formed can react selectively with NO₂ rather than O₂ to give nitroalkanes in preference to oxygenated products. In contrast, the conventional nitration is difficult to carry out in the presence of air, since under the high temperatures used (250–400 °C) the resulting alkyl radicals react not only with NO₂ but also with O₂ to provide a complex mixture of products.^[2b]

The results of the nitration of other alkanes by the present method are shown in Table 2. The reaction of cyclooctane (**4**) afforded nitrocyclooctane (**5**, 50%; run 1) and cyclooctyl nitrate (2 %) along with oxygenated products, such as cyclo-

Table 2. NHPI-catalyzed nitration of alkanes with NO₂ under selected conditions.^[a]

Run	Substrate	Product	Method	Yield [%]
1	cyclooctane (4)	nitrocyclooctane (5)	A	50
2 ^[b]	cyclooctane (4)	nitrocyclooctane (5)	A	44
3	<i>n</i> -hexane	nitrohexane	A	54 ^[c]
4	isobutane	2-methyl-2-nitropropane	B	46
5			C	46
6			C	66
7			C	70

[a] Reactions were carried out under air (1 atm) at 70 °C for 14 h. Method A: Alkane (5 mL), NO₂ (115 mg, 2.5 mmol), and NHPI (0.6 mmol) were used. Method B: Isobutane (2 mL) was treated with NO₂ (2.5 mmol) in the presence of NHPI (0.6 mmol) in PhCF₃ (3 mL) in a glass autoclave. Method C: The alkanes (3 mmol) were allowed to react with NO₂ (3.3 mmol) in the presence of NHPI (0.6 mmol) in PhCF₃ (5 mL). Yields are based on alkanes used. [b] Under argon. [c] 1-Nitrohexane:2-nitrohexane:3-nitrohexane = 3:53:44.

octanone (**6**, 17 %) and cyclooctanol (**7**, 7 %). Owing to the potent oxidizing ability of NO₂ and the susceptibility of **4** to oxidation, the nitration of **4** with NO₂ led to oxygenated products **6** (8 %) and **7** (5 %), even in the absence of air.^[10] Hexane afforded a 3:53:44 regioisomeric mixture of 1-nitrohexane, 2-nitrohexane, and 3-nitrohexane in 54 % yield (run 3) and the corresponding hexylnitrites (10 %). Only the tertiary position was attacked in the nitration of substituted alkanes such as isobutane, 2,5-dimethylhexane, and adamantanes to form the corresponding nitroalkanes (runs 4–7).

In conclusion, we have achieved the first catalytic nitration of higher alkanes with nitrogen dioxide under air using NHPI as a catalyst. This is the first procedure for catalytic nitration under mild conditions, and by further improvement of the methodology it may become possible to change the industrial process for alkane nitration.

Experimental Section

Representative procedure: NO₂ was used as a liquid at 0 °C. To a pear-shaped flask (100 mL) were added NHPI (98 mg, 0.6 mmol) and cyclohexane (5 mL). The flask was closed with a glass stopper and weighed. Then NO₂ (0.75 mL) was quickly added using a Hamilton gas-tight syringe, and the flask was reclosed with the glass stopper. The flask was weighed again in order to measure the NO₂ added (115 mg, 2.5 mmol). The flask was cooled in an ice bath and then quickly attached to a condenser, and the mixture was stirred at 70 °C for 14 h. After the reaction, GC and GC-MS analyses were performed. The yields of the products were estimated from the peak areas based on the internal standard technique using GC. The products were isolated by column chromatography on silica gel with hexane/ethyl acetate (10/1 – 3/1, v/v), and were identified by comparison of their analytical data with those of authentic samples.

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Immobilization of Redox-Active Ligands on an Electrode: The Dendrimer Route**

Franck Le Derf, Eric Levillain, Gaëlle Trippé, Alain Gorgues, Marc Sallé,* Rosa-María Sebastián, Anne-Marie Caminade, and Jean-Pierre Majoral*

Macrocyclic systems that respond electrochemically when interacting with a guest ion have been extensively studied,^[1] notably in connection with their potential applications as chemosensors. In such host molecules, the complexing ability of the ligand can be tuned by the electrochemical potential applied. Most of these compounds are built by covalent grafting of a receptor subunit onto a redox-active component. Thus, in the case of metal-cation recognition, various ligating fragments, for example, crown ethers, have been attached to an electroactive moiety such as a metallocene or a quinone derivative.^[1] Alternatively, the ability of the tetrathiafulvalene (TTF) core to act as the redox-active subunit is now well established.^[2] Indeed, TTF derivatives are able to exist in three different stable redox stages (neutral, radical cation, and dication) and therefore allow the electrochemical release of metallic cations to be controlled.

A further exciting challenge, less explored, lies in the preparation of sensing devices that can transfer the above-mentioned recognition properties, observed in solution, at the interface of a solid electrode and a liquid.^[3] Results in this direction have been obtained thanks to a) electropolymerization of suitably substituted redox-responsive ligands (e.g., a pyrrole- or a thiophene-based monomer),^[3, 4] and b) preparation of self-assembled monolayers.^[5] Modified electrodes were also recently obtained by Casado et al. by electrodeposition of organometallic-containing silicon dendrimers.^[6] On the other hand, TTF dendrimers, possessing 21 TTF moieties in the highest generation, were described by Bryce et al.,^[7] but no mention was made of their immobilization on an electrode surface.

We describe here the synthesis of a series of dendrimers with up to 96 redox-active TTF moieties on the periphery, which allow the generation of polycationic species bearing up to 192 positive charges on the surface. Modified electrodes incorporating these electroactive TTF dendrimers were

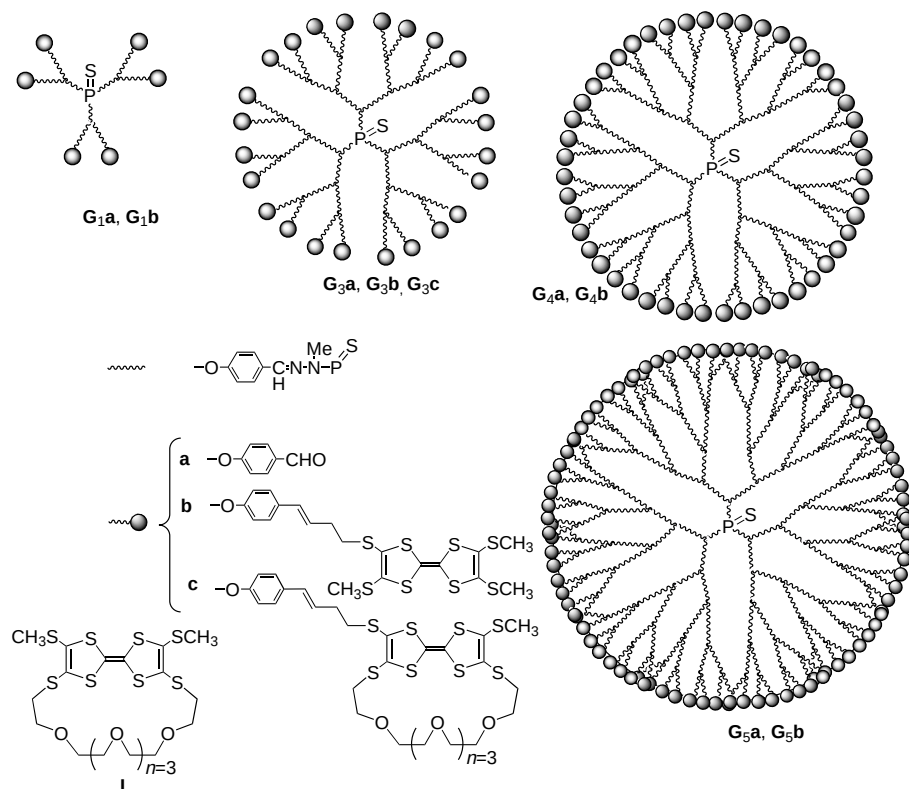
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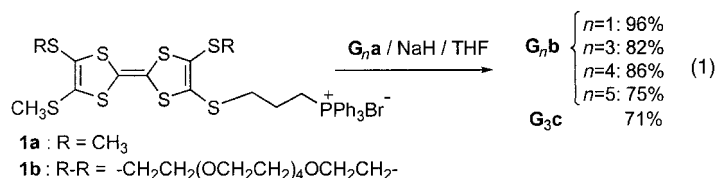
 Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

obtained by electrodeposition. Applicability of these systems was illustrated by the preparation of the first dendrimer-modified electrode able to reproduce the electrochemical sensing of a metal cation (i.e., Ba^{2+}) thanks to the grafting of crown ether/TTF units on the periphery of the dendrimer.

Dendrimers **G₁b**, **G₃b**, **G₄b**, and **G₅b** (generations 1, 3, 4, and 5), bearing respectively 6, 24, 48, and 96 TTF moieties on their periphery, were obtained in good yields (76–96 % after



workup) by a poly-Wittig olefination between the corresponding polyformyl dendrimers (**G₁a** to **G₅a**)^[8] and the phosphonium salt **1a** [Eq. (1)], which was synthesized by a classical three-step sequence from the corresponding cyanoethylsulfanyl precursor.^[9] Analogously, the crown ether/TTF-substituted dendrimer **G₃c** was prepared from **1b** and **G₃a** in a 71 % yield.



The solution electrochemistry of **G_nb** ($n = 1, 3, 4$, and 5) was first studied [Pt working electrode (diameter = 1 mm) in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ (9/1) (Bu_4NPF_6 , 0.1 M)]. All **G_nb** exhibit the classical well-defined two-step reversible oxidation encountered in parent TTF systems. From the cyclic voltammograms (CVs) we observed a clear tendency of the dendrimers to deposit onto the electrode surface, as shown by the narrow shape of the redox waves.^[10]

To obtain insight into the nature of the interactions between the π -donating TTF moieties, electrooxidation of **G_nb** was analyzed by time-resolved and near-IR spectroelectrochemistry under thin-layer conditions (Figure 1 shows the result for **G₃b**). No significant difference was observed between the four generations of dendrimers. Electrochemical oxidation of **G_nb** in the first redox process leads to the development of three absorption bands with maxima at 500 (narrow), 800 (very broad and intense) and 2200 nm (weak). These values, by comparison with those of the parent tetramethylthiotetrathiafulvalene (TMT-TTF) studied under similar conditions,^[11] are respectively assigned to the radical cation $\text{D}^{+\cdot}$ (where D denotes the tetrathio-TTF fragment), to the π dimer $\text{D}_2^{2+\cdot}$, and to the mixed-valence dimer $\text{D}_2^{+\cdot}$. In this potential range, the broadness of the absorption band corresponding to the π dimer compared to the other bands suggests that the cation radical species are, as expected, in strong interaction.^[7a] Interestingly, when a potential of 1.0 V is reached, a single absorption band is observed (700 nm), which is unequivocally assigned to $\text{D}_2^{2+\cdot}$.^[11] Such behavior differs from observations made with other TTF dendrimer derivatives, for which interacting TTF cation radicals are still observed at this potential.^[7a] Therefore, spectroelectrochemical data give indirect evidence for oxidation of each TTF moiety to $\text{TTF}^{2+\cdot}$.

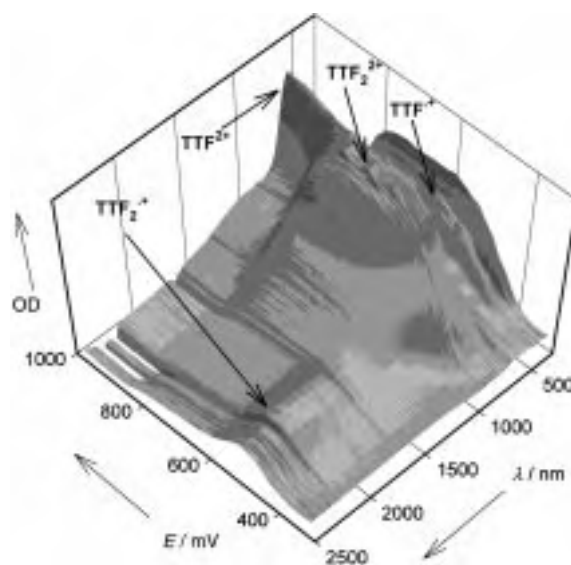


Figure 1. Spectroelectrochemistry under thin-layer ($d \approx 50 \mu\text{m}$) conditions (Pt electrode, $\varnothing = 2 \text{ mm}$) for **G₃b**; $c_{\text{dend}} = 1/24 \text{ mM}$ in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ (9/1), Bu_4NPF_6 (0.2 M), scan rate 0.001 V s^{-1} ; reference electrode Ag/AgCl . OD = optical density.

To favor immobilization of **G_nb** on the electrode surface, we changed the solvent to THF (0.1M Bu₄NPF₆), which allowed a more efficient film growth as the dendrimers were oxidized. Electrodeposition was performed under potentiostatic conditions ($E_p = 0.60$ V) or by recurrent potential scans (0.2–1.0 V). In the latter case, film growth was manifested by a regular increase in both current peaks upon subsequent repeated cycling^[12] (Figure 2). Noticeably, electrodeposition appeared more pronounced for the higher homologues **G₃b**, **G₄b**, and **G₅b**, and was not dependent on the nature of the electrode, since similar results were also obtained with gold or glassy-carbon electrodes.

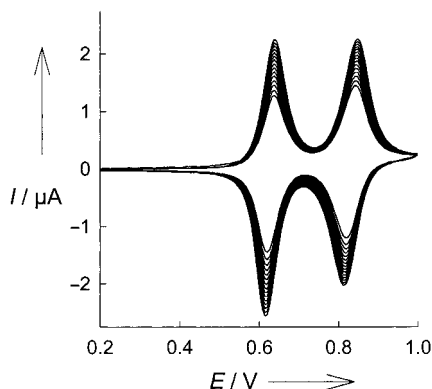


Figure 2. Electrodeposition of **G₃b**; $c_{\text{dend}} = 0.5/24$ mM in THF; Bu₄NPF₆ (0.1M), Pt electrode ($\varnothing = 1$ mm); scan rate 0.1 V s⁻¹; reference electrode Ag/AgCl.

The electrochemical response of the films was studied by cyclic voltammetry in fresh dichloromethane, acetonitrile, or a mixture thereof containing Bu₄NPF₆ (Figure 3). Two well-defined reversible oxidation peaks were observed, which are

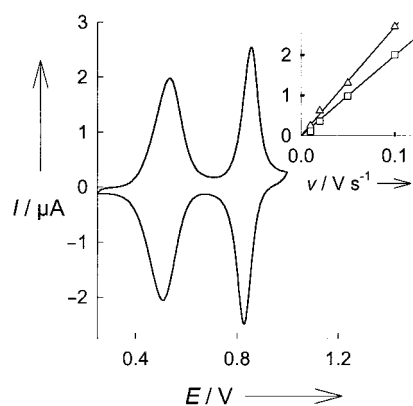


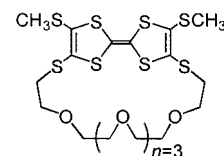
Figure 3. Cyclic voltammogram of a Pt electrode ($\varnothing = 1$ mm) modified with **G₃b** ($\Gamma_{\text{TTF}} = 1.2 \times 10^{-8}$ mol cm⁻²), measured in CH₂Cl₂/CH₃CN (9/1), Bu₄NPF₆ (0.1M). Inset: plot of I_{pa1} ($\square$) and I_{pa2} ($\triangle$) versus scan rate (ν); reference electrode Ag/AgCl.

characteristic of surface-confined redox couples, with the expected linear relationship of both peak currents (I_{pa1} and I_{pa2}) with the potential sweep rate ν (Figure 3, inset). In accordance with the above-mentioned spectroelectrochemical study and as a consequence of the strong interactions

occurring between TTF units in these multi-TTF species, the first redox wave is much broader than the second one.^[13] The surface coverage Γ of electroactive TTF moieties in the film was determined by integration of redox waves in the cyclic voltammogram ($\Gamma_{\text{TTF}} = 1.2 \times 10^{-8}$ mol cm⁻² for the film of Figure 3). It is noteworthy that no change in the electrochemical responses was observed upon repeated potential cycling, even after the sample standing in air for days, and this confirms the high stability of the modified electrodes.

These deposition properties were exploited for the immobilization of dendrimer **G₃c** on a platinum electrode. This sterically hindered dendrimer bearing 24 TTF/crown ether assemblies on its periphery was efficiently transferred onto the surface electrode under potentiostatic (0.6 V) or repeated cycling conditions in THF (Bu₄NPF₆). Electrochemical and spectroelectrochemical properties of the films obtained were essentially the same as for the corresponding nonligating **G₃b**, with two well-resolved redox waves and a linear relationship of the current to the scan rate. Scanning electron micrographs show that deposition of dendrimer **G₃c** on a Pt electrode gives rise to homogeneous coverage over the whole surface.^[14]

The most remarkable feature of these dendrimer films incorporating redox-responsive units is their unique capability to replicate the complexation/expulsion properties detected in homogeneous solution.^[6e,15] Indeed, we previously demonstrated the efficiency and the selectivity of the parent crown ether/TTF ligand **I** in controlling the reversible complexation/expulsion sequence of Ba²⁺.^[2b,e] This property of ligand **I** was illustrated by cyclic voltammetry experiments, in which the progressive addition of Ba²⁺ led to a positive shift of the first oxidation potential (Ba²⁺ complexation).



We observed that a **G₃c**-modified electrode behaves similarly. When exposed to a solution containing increasing concentrations of Ba²⁺ cations, the electrochemical response shows two distinctive regions (Figure 4): a progressive positive shift of E_{pa1} is observed for $[\text{Ba}^{2+}] = 1 \times 10^{-4}$ to 8×10^{-4} M, and then a constant E_{pa1} value at higher concentrations.^[16] This behavior is very similar to that observed in homogeneous solutions for Ba²⁺ titration by **I**, with a first area corresponding to the progressive coordination of Ba²⁺ by the peripheral crown ether/TTF ligands of **G₃c**, and then a plateau indicative of the saturation point. Though lower than in homogeneous solution with compound **I**, for which $\Delta(E_{\text{pa1}}) = 100$ mV,^[2b,e] the shift of E_{pa1} on immobilized **G₃c** reaches a value of $\Delta(E_{\text{pa1}}) = 85$ mV, without affecting the reversibility of the redox system. Contrary to observations made with **I** in solution, for which E_{pa2} remains unchanged upon addition of Ba²⁺, a slight positive shift is observed for E_{pa2} in the film ($\Delta(E_{\text{pa2}}) = 30$ mV for $[\text{Ba}^{2+}] = 0$ to 8×10^{-4} M). Similar observations were made recently by Echegoyen et al. for self-assembled monolayers of ligating TTFs, and were attributed to cooperativity effects between neighboring crown rings.^[5a]

We have prepared modified electrodes by electrodeposition of dendrimer structures incorporating up to 96 TTF moieties. The applicability of this strategy is exemplified by the immobilization of an electroactive receptor on an electrode

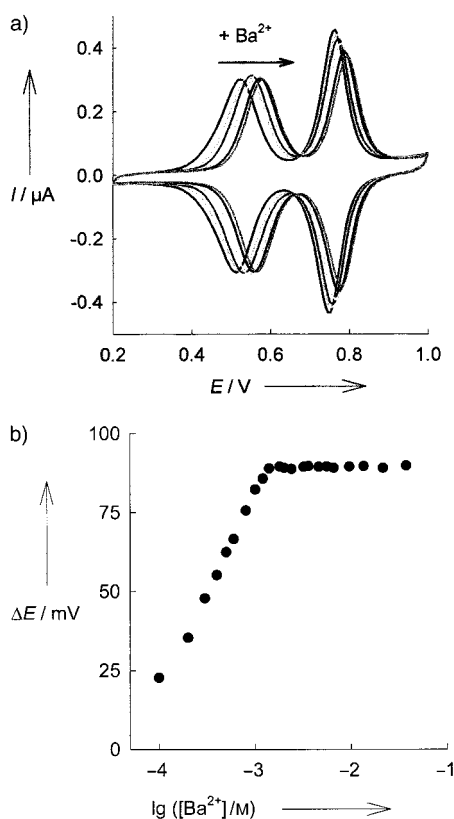


Figure 4. Electrochemical studies with a Pt electrode ($\varnothing = 1$ mm) modified with **G₃c** ($\Gamma_{\text{TTF}} = 5.3 \times 10^{-10}$ mol cm $^{-2}$, CH₂Cl₂/CH₃CN (1/1), Bu₄NPF₆ (0.1 M), scan rate 0.1 V s $^{-1}$). a) Electrochemical response in the presence of increasing concentrations of Ba(ClO₄)₂ ([Ba²⁺] = 0, 1×10^{-4} , 2×10^{-4} , 4×10^{-4} , 6×10^{-4} , 8×10^{-4} M; reference electrode Ag/AgCl), b) plot of $\Delta E (= E_{\text{pa}}([\text{Ba}^{2+}] = 0) - E_{\text{pa}}([\text{Ba}^{2+}] \neq 0))$ versus $\lg([\text{Ba}^{2+}])$.

surface to give a modified electrode that responds to the presence of barium cations.

Experimental Section

Experimental procedure for the synthesis of dendrimers **G_nb** ($n = 1, 3, 4, 5$) and **G₃c**:^[14] To a suspension of NaH (3×2^n equiv + 5 %) in THF (5 mL) were added **G_na** (1 equiv) and the phosphonium salt **1a** or **1b** (3×2^n equiv + 5 %). The resulting mixture was stirred at room temperature for 14 h (**1a**), or at 40 °C overnight (**1b**), then water was added (1 mL). The solution was evaporated to dryness, the residue was extracted with CH₂Cl₂/H₂O (1/1) saturated with NaCl, and the organic phase was recovered. The aqueous phase was washed twice more with CH₂Cl₂. All the organic phases were combined, dried with anhydrous Na₂SO₄, and evaporated to dryness to afford an orange oil. This oil was washed three times with CH₂Cl₂/pentane (1/10) to give an orange solid.

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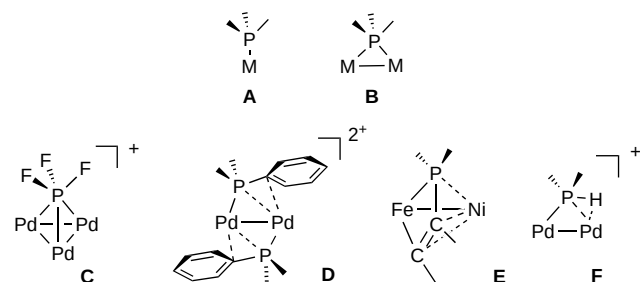
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- [16] We initially noted an unexpected negative shift of E_{pa} for high barium perchlorate concentrations ($> 10^{-3}$ M). This anomaly could be suppressed by using a reference electrode equipped with a double junction (recommendation of Prof. L. Echegoyen, who previously observed similar behavior with other electroactive species). A joint project is in progress on this aspect.

A Rare Phosphane Coordination Mode: A Symmetrically μ_2 -Bridging Phosphole in a Dinuclear Palladium(II) Complex**

Mathieu Sauthier, Boris Le Guennic, Valérie Deborde,
Loïc Toupet, Jean-François Halet,* and Régis Réau*

Tertiary phosphanes are the most common ancillary ligands associated with late transition metals in coordination chemistry and homogeneous catalysis. Among the immense variety of known transition metal complexes featuring $\sigma^3\lambda^3$ -phosphane ligands, very few exceptions to the terminal coordination mode **A** emerge (Scheme 1).^[1] Trifluorophosphane can



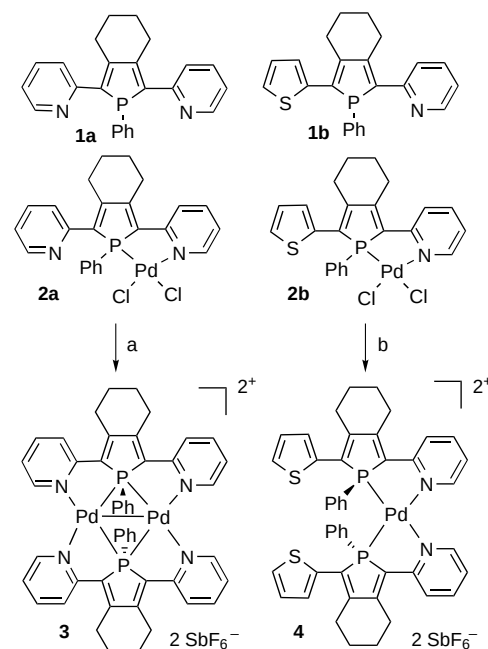
Scheme 1. Coordination modes of phosphanes.

behave as a μ_3 donor towards a triangular palladium core (**C**^[2a,b]), and extremely rare cases of unsymmetrically semi-bridging μ_2 -P ligands—enforced by an agostic-like interaction of a $P-C_{sp^2}$ (**D**^[2c,d] and **E**^[2e]) or a $P-H$ bond (**F**^[2f-h]) with a coordinatively unsaturated Group 10 metal atom—have been described.^[3] The symmetrically bridging μ_2 -coordination mode **B**, which is typical for the other well-established transition metal ligands (e.g. CO, carbenes, hydride, alkyl groups), has little precedent for tertiary ligands based on Group 15 atoms. A symmetrically bridging μ_2 -stilbine has been reported,^[4a] but this coordination geometry has only

been predicted by theoretical calculations for phosphanes.^[4b-d] Herein, we describe the synthesis of a Pd^I dimer featuring a strongly bonded symmetrically bridging μ_2 -phosphole unit, which is the first example of coordination mode **B** for a tertiary phosphane. After submission of this communication, Werner et al. reported dinuclear rhodium complexes with semibridging and bridging phosphane ligands.^[18]

Phospholes behave as classical two-electron donor tertiary phosphanes towards late transition metals.^[5, 6] We thus became interested in 2-(2-pyridyl)phospholes^[7] **1a** and **1b** (see Scheme 2) as new 1,4-chelates combining soft sp^3 phosphorus and hard sp^2 nitrogen centers.

2-(2-Pyridyl)phospholes **1a** and **1b** react with $[(CH_3CN)_2PdCl_2]$ to give rise to complexes **2a** (95 % yield) and **2b** (94 % yield), respectively, as air-stable solids (Scheme 2).^[8] Under classical reducing conditions,^[2c] in the presence of two equivalents of NaSbF₆, **2a** cleanly afforded the new complex **3** (82 % yield), whereas complex **2b** decomposed to give “black palladium” and unidentified P-containing species.



Scheme 2. Synthesis of palladium complexes **3** and **4**. a) H₂ (20 bar), HC(OCH₃)₃, MeOH/CH₂Cl₂, 2 NaSbF₆, 25 °C; b) **1b**, 2 AgSbF₆, CH₂Cl₂.

Between room temperature and -80°C , the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of **3** in CD₂Cl₂ consists of one sharp line at low field ($\delta = +69.9$), and the simplicity of the $^{13}\text{C}\{^1\text{H}, ^{31}\text{P}\}$ NMR spectrum^[8] is in favor of a symmetric structure. An X-ray diffraction study^[9] revealed that **3** is a $[Pd_2(\mathbf{1a})_2]^{2+} \cdot 2\text{SbF}_6^-$ complex (Figure 1), with normal van der Waals distances between the dication and the anions. The pseudo-centrosymmetrical dication consists of two planar 16-electron Pd^I atoms (maximum deviation from the mean plane 0.086 Å) joined by a rather long metal–metal single bond (**3**: 2.7870(19); **D**: 2.5833(7),^[2c] 2.701(3);^[2d] **F**: 2.611(1) Å^[2g,h]) and capped by two

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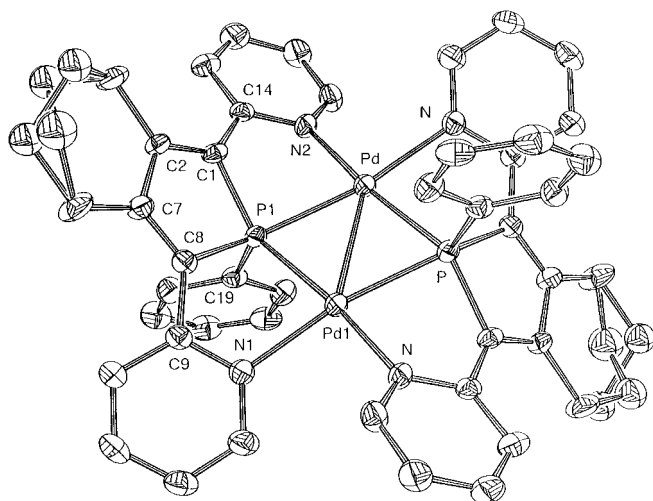


Figure 1. Molecular structure of the cation of complex **3** in the solid state (hydrogen atoms and solvent molecules have been omitted for clarity). Selected bond lengths [Å] and bond angles [°]: P1–C1 1.830(8), P1–C8 1.833(7), P1–C19 1.816(8), Pd1–N 2.162(6), Pd1–N1 2.177(6); P1–Pd1–N1 81.55(16), N1–Pd1–N 91.0(2), N–Pd1–P 80.50(10), P–Pd1–P1 107.40(6).

2,5-bis(2-pyridyl)phospholes **1a** acting as six-electron μ -1 π N:1,2 π P:2 π N donors.

Dinuclear Pd^I complexes involving six two-electron donors arranged about the Pd–Pd bond are well-known,^[10] but complex **3** exhibits two striking features: 1) In contrast to most Pd^I dimers,^[10, 11] the Pd₂²⁺ core of **3** has an edge-bridged planar structure imposed by the topology of ligand **1a**; 2) the phosphorus atoms of both coordinated phospholes **1a** bridge almost symmetrically the Pd–Pd vector (Pd–P: 2.349(2) and 2.358(2) Å). The Pd atoms are coordinatively saturated, with the shortest Pd–C distance (2.949 Å) being considerably longer than the P–C_{ipso} distances reported in complexes **D** (2.385(16),^[2c] 2.336(4) Å^[2d]), indicating the lack of any Pd–C interaction.

The NMR data of **3** are in accordance with this solid-state structure. It is quite likely that the rigidity of the tridentate ligand **1a** enforces the symmetric μ_2 coordination mode and prevents any fluxional behavior. Complex **3** appears to be stable in coordinating solvents (CH₃CN, DMF), under a CO atmosphere, and even in the presence of a large excess of PPh₃. To evaluate whether this unusual coordination severely alters the structure of the ligand and/or the metal–heteroatom bonds, the synthesis of a classical monometallic Pd complex featuring two 2-(2-pyridyl)phosphole ligands was undertaken. All attempts to prepare a [Pd(**1a**)₂]²⁺ complex by abstraction of the Cl[–] ligands of **2a** by a silver salt in presence of one equivalent of **1a** failed. In marked contrast, this strategy was successful when complex **2b** and phosphole **1b** were employed (Scheme 2). According to multinuclear NMR spectroscopy,^[8] complex **4** (75% yield) was obtained as a single diastereoisomer, and an X-ray diffraction study^[9] revealed that, as expected, the P and N atoms are in a mutually *trans* configuration.

For both complexes the phosphole rings are almost planar (maximum deviation from the mean plane: **3**: 0.031; **4**: 0.02 Å) and the dihedral angles between the coordinated pyridine and phosphole moieties are comparable (**3**: 23.5° and

26.8°; **4**: 25.6°). The five-membered metallacycles of complexes **3** and **4** adopt a slightly distorted envelope conformation: The Pd, N, and the two C atoms lie almost in the same plane (maximum deviation: **3**: 0.068; **4**: 0.02 Å) with the P atoms being out of this plane (dihedral angles: **3**: 25.6–25.2°; **4**: 23.5–26.8°). The angles around the Pd atoms and the Pd–N bond lengths are similar for the two complexes ($\pm 5^\circ$ and ± 0.05 Å, respectively) and consistent with known literature values.^[4c] The molecular geometry about the tetracoordinated P atoms in complex **4** can be regarded as a distorted tetrahedron with small endocyclic C–P–C angles (92.3(3), 91.7(4)°) and large C_{ipso}–P–Pd angles (114.6(3), 116.9(3)°). The bridging P atoms of **3** possess a very similar geometry when the midpoint of the Pd–Pd bond is considered as the coordination center (C–P–C 88.8(4)°, C_{ipso}–P–(Pd–Pd) 116.0°). This comparative study reveals that the symmetric μ_2 bridging mode of the P atoms does not dramatically perturb the structure of the ligand. Furthermore, the coordination spheres of the Pd centers in complexes **3** and **4**, although possessing different oxidation states, appear to be very similar. As expected, the only noticeable discrepancy between the two structures lies in the Pd–P bond distances: Those observed in complex **3** (2.349(2), 2.358(2) Å) are considerably longer than those in complex **4** (2.2494(18), 2.260(2) Å), but shorter than those reported for semibridging phosphanes (**D**: 2.690(4),^[2c] 2.753(1),^[2d] **F**: 2.393(3) Å^[2g,h]).

To elucidate the bonding situation in **3**, extended Hückel (EH) calculations^[12] were carried out on the model system [Pd₂(NH₂)₄(μ_2 -PH₃)₂]^{2–} (**3'**), which is isoelectronic to the dication of complex **3**.^[13] The resulting molecular orbital (MO) diagram built up from the interaction of the frontier orbitals (FO) of the dimetallic [Pd₂(NH₂)₄]^{2–} and phosphane moieties is shown in Figure 2. An analysis reveals that the

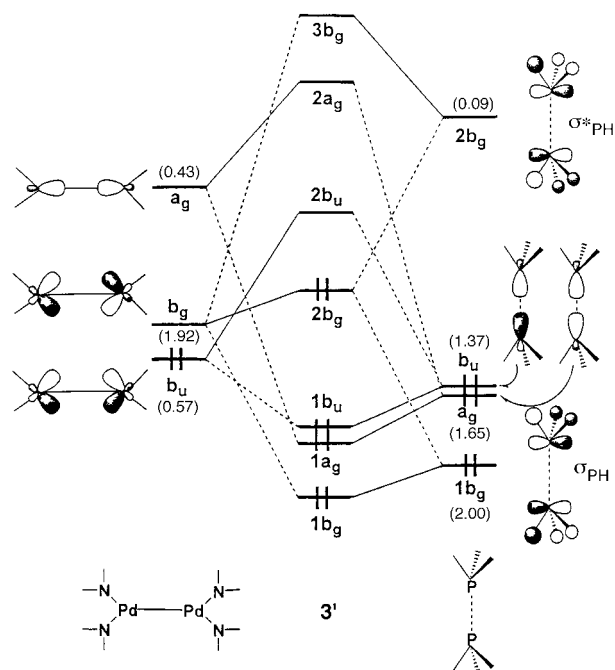


Figure 2. Qualitative MO interaction diagram of **3'**. Symmetry labels are given in C_{2h}. The FO electron occupations after interaction are given in parenthesis.

Pd–Pd and Pd–P bonding is highly delocalized and consists primarily of strong σ -type interactions between phosphane “lone pair” orbitals (a_g and b_u) and metallic orbitals of the same symmetry (σ donation). This bonding is somewhat supplemented by a π -type interaction between one component of the vacant σ_{PH}^* antibonding orbitals of the phosphanes ($2b_g$) and one metallic FO (b_g ; back donation, negative hyperconjugation).^[14] The latter stabilizing interaction is weakened by a destabilizing interaction between the same metallic FO and a low-lying component of the occupied σ_{PH} bonding phosphane orbitals ($1b_g$). Consequently, this metallic FO is weakly perturbed in energy after interaction and becomes the HOMO of **3**. The Pd–Pd antibonding character partly explains the rather long Pd–Pd distance measured in complex **3**.^[15] This bonding description is fully supported by density functional theory (DFT) calculations^[16] carried out on $[Pd(1a)]_2^{2+}$, which indicate that the HOMO is Pd–Pd and Pd–N π -antibonding (Figure 3).

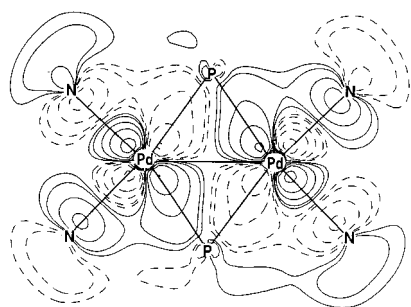


Figure 3. Contour plot of the HOMO (in the Pd_2P_2 plane) of the cation of complex **3**. Contour values are ± 0.01 , ± 0.02 , ± 0.05 , ± 0.1 , ± 0.2 , $\pm 0.5 e^{1/2} \text{ bohr}^{-3/2}$.

The possibility for a tertiary phosphane to act as a symmetrically bridging ligand opens new perspectives in coordination chemistry for the construction of new architectures and the understanding of important mechanisms such as the intramolecular exchange of phosphane between two metal atoms.^[17]

Experimental Section

A solution of **2a** (0.50 g, 0.92 mmol), $NaSbF_6$ (0.49 g, 1.90 mmol), and trimethylorthoformate (1.00 mL, 9.14 mmol) in CH_2Cl_2 (20 mL) and methanol (10 mL) was introduced under argon in a stainless-steel autoclave equipped with a magnetic stirrer. The autoclave was pressurized with H_2 (20 bar), and the solution was stirred for 12 h at room temperature. The autoclave was vented, and the volatile components were removed under vacuum. The brown residue was extracted with CH_2Cl_2 (50 mL), and the solution was concentrated to about 10 mL. After addition of $CHCl_3$ (40 mL), complex **3** precipitated at room temperature as an orange solid (0.53 g, 82% yield). Single crystals suitable for X-ray diffraction were grown from a solution in CH_2Cl_2 /CH₃CN/heptane at $-20^\circ C$.

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- [9] X-ray structural analysis: **3** · 2 CH_3CN · 2 C_6H_{12} ($C_{48}H_{42}N_4P_2SbF_{12}Pd_2$ · 2 CH_3CN · 2 C_6H_{12}): $0.38 \times 0.21 \times 0.18$ mm, triclinic, space group $P\bar{1}$, $a = 9.389(2)$, $b = 11.793(9)$, $c = 14.079(5)$ Å, $\alpha = 70.33(3)$, $\beta = 88.03(2)$, $\gamma = 79.50(3)^\circ$, $\rho_{calcd} = 1.827 \text{ Mg m}^{-3}$, $2\theta_{max} = 54^\circ$, $\lambda(MoK\alpha) = 0.71073$ Å, ω scans, 293 K, 4710 measured reflections, 3468 independent reflections, with $I > 2\sigma(I)$, Lp correction ($\mu = 16.79 \text{ cm}^{-1}$), 328 refined parameters with $R1 = 0.0588$ and $wR2 = 0.161$, max./min. residual electron density $1.090/-1.503 e \text{ Å}^{-3}$. Although the carbon atoms of the butyl bridges appear to be disordered, further studies in space group $P1$ show unambiguously that there is no disorder but a difference in the conformation of the six-membered ring. However, in this space group, the pseudo-symmetry of all the other atoms of **3** leads to important correlations, giving unsatisfactory geometry and estimated standard deviations. **4** · 0.5 $C_2H_4Cl_2$ ($C_{46}H_{40}N_2P_2SbF_6PdS_2$ · 0.5 $C_2H_4Cl_2$): $0.40 \times 0.33 \times 0.33$ mm, triclinic, space group $P\bar{1}$, $a = 13.655(10)$, $b = 14.991(2)$, $c = 16.835(2)$ Å, $\alpha = 108.89(2)$, $\beta = 108.48(3)$, $\gamma = 90.10(3)^\circ$, $\rho_{calcd} = 1.584 \text{ Mg m}^{-3}$, $2\theta_{max} = 54^\circ$, $\lambda(MoK\alpha) = 0.71073$ Å, ω scans, 293 K, 12920 measured reflections, 7587 independent reflections with $I > 2\sigma(I)$, Lp correction ($\mu = 15.28 \text{ cm}^{-1}$), 645 refined parameters with $R1 = 0.0735$ and $wR2 = 0.2112$, max./min. residual electron density $1.570/-0.971 e \text{ Å}^{-3}$. After Lorentz and polarization corrections, the structures were solved with SIR-97, and refined with SHELX97 by full-matrix least squares on F^2 . Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data

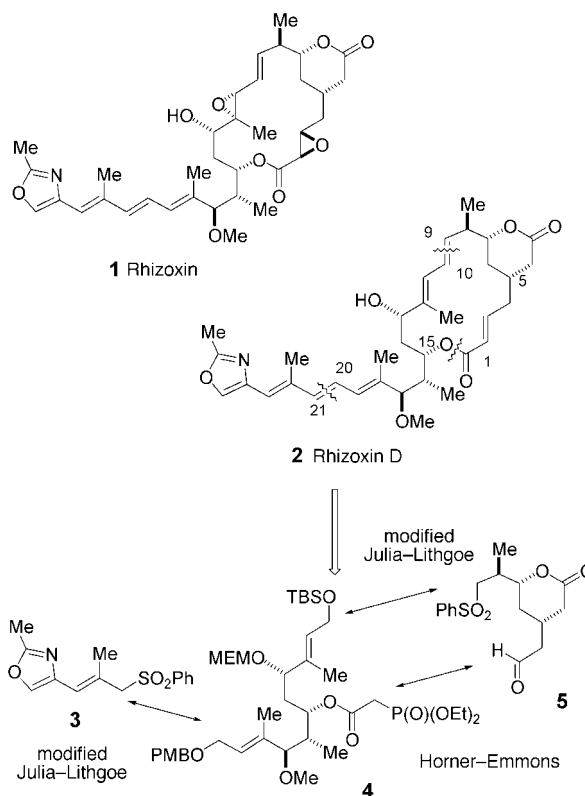
Centre as supplementary publication nos. CCDC-149074 (**3**) and -149075 (**4**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Asymmetric Total Synthesis of Rhizoxin D**

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Rhizoxin (**1**, Scheme 1) and five closely related compounds have been isolated from *Rhizopus chinensis* by Iwasaki and co-workers.^[1] In addition to antibiotic and antifungal activity, these materials have been shown to possess potent antitumor activity,^[2] including activity against vincristine- and adriamycin-



Scheme 1. Structures of rhizoxin and rhizoxin D and retrosynthesis of the latter (see ref. [6] for abbreviations).

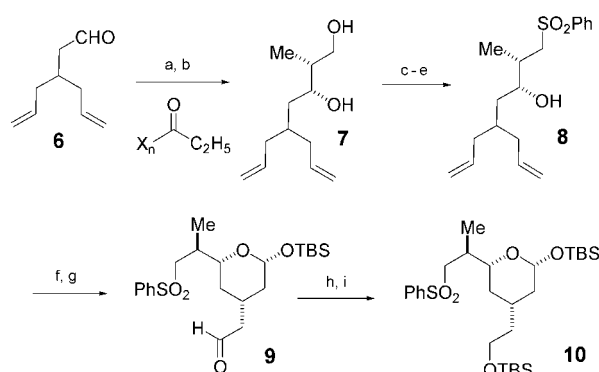
cin-resistant cells.^[3] These compounds have attracted considerable interest with respect to synthesis, and one total synthesis of rhizoxin has been reported,^[4] as well as three syntheses of rhizoxin D (**2**).^[5] We describe herein the synthesis of rhizoxin D by an approach utilizing catalytic asymmetric allylation as a key strategic element.

The overall approach to this synthesis is illustrated in Scheme 1 and relied upon disconnections at the C9–C10 and C20–C21 disubstituted alkenes to yield the three major subunits indicated. In the route described herein, both of these alkene linkages are established by a modified Julia–Lithgoe protocol developed previously in our laboratories,^[7] and the macrocycle is closed by an intramolecular Horner–Emmons reaction. This strategy provides inherent flexibility in the timing of the necessary operations and also allows for other ring closure options to be investigated using the same basic subunits.

In principle the “lactone” subunit could be utilized as either the sulfone component or the aldehyde subunit in the proposed Julia coupling; the choice shown was made based upon model studies. The synthesis of this subunit used a thermodynamic approach for control of stereochemistry at C5 as we have previously described.^[8] Thus, condensation of the aldehyde **6** with the boron enolate of (*S*)-3-(1-oxopropyl)-4-(phenylmethyl)-2-oxazolidinone afforded the aldol product^[9] as a single diastereomer, which was reduced with LiBH_4 to afford the diol **7** (Scheme 2). Elaboration to the sulfone **8** followed by oxidative olefin cleavage provided, upon silylation with TBSCl , the all-equatorial protected lactol **9**. The stereochemistry at C5 is thus set in this sequence by the preference

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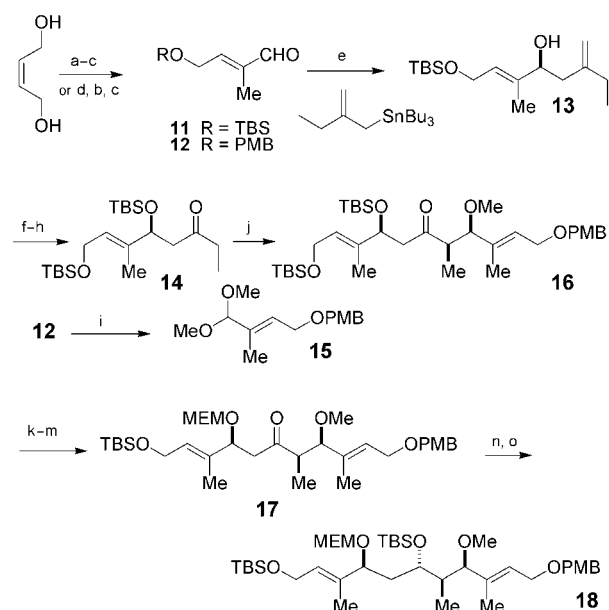
[**] Financial support has been provided by the National Institutes of Health (through grant GM-28961) and by Pfizer, Inc.



Scheme 2. Synthesis of the C1–C9 subunit. a) Bu₂BOTf, Et₃N, CH₂Cl₂, –78 °C; pH 7 phosphate buffer, 30 % H₂O₂, MeOH, 86 %; b) LiBH₄, THF, MeOH, 0 °C, 90 %; c) TsCl, pyr, CH₂Cl₂, –10 °C, 87 %; d) PhSH, KO^tBu, DMF, RT, 87 %; e) Oxone, MeOH/H₂O, 0 °C, 100 %; f) OsO₄, NaIO₄, THF/H₂O, RT; g) TBSCl, imid, CH₂Cl₂, 0 °C → RT; h) NaBH₄, MeOH, 0 °C; i) TBSCl, imid, CH₂Cl₂, 0 °C → RT, 55 % (4 steps).

for an equatorial disposition of the side chain at C5 in the hemiacetal form of the hydroxy dialdehyde, which thus differentiates the two prochiral formyl groups generated by oxidative cleavage.

The synthesis of the C10–C20 subunit was accomplished by an approach which formally corresponds to sequential asymmetric aldol condensations of methyl ethyl ketone with an enal; for purposes of further elaboration the termini of these enals were differently protected. The synthesis began by protection of butene 1,4-diol as either the bis-TBS or the bis-PMB derivative (Scheme 3). Oxidative cleavage of the

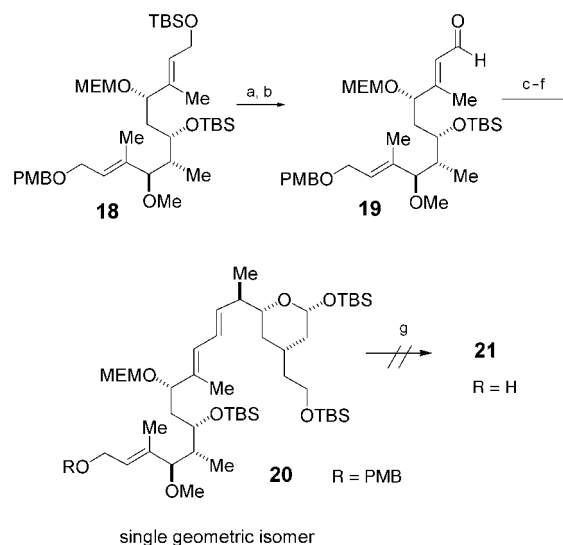


Scheme 3. Preparation of the C10–C20 subunit. a) TBSCl, imid, CH₂Cl₂, 0 °C, 99 %; b) O₃, CH₂Cl₂, –78 °C, then Ph₃P, RT; c) 2-(triphenylphosphoranyliden)propionaldehyde, toluene, 80 °C; d) PMB-Br, NaH, DMF, 72 %; e) (S)-BINOL, Ti(OⁱPr)₄, TFA, 4 Å MS, CH₂Cl₂, –78 → –20 °C, 65 h, 78 %, 99 % ee; f) TBSOTf, *i*Pr₂NEt, THF, 0 °C, 97 %; g) OsO₄, NMO, *i*BuOH, THF, H₂O, RT; h) NaIO₄, THF, H₂O, RT, 74 % (2 steps); i) (MeO)₃CH, MeOH, NH₄Cl; j) TiCl₄, *i*Pr₂NEt, CH₂Cl₂, –90 °C, 52 %; k) 1 % HCl, MeOH, RT, 95 %; l) TBSCl, imid, CH₂Cl₂, RT; m) MEMCl, *i*Pr₂NEt, CH₂Cl₂, 0 °C → RT, 93 % (2 steps); n) SmI₂, MeOH, THF, 0 °C → RT; o) *i*Pr₂NEt, TBSOTf, CH₂Cl₂, RT, 60 % (2 steps).

bis-TBS alkene by ozonolysis yielded the TBS-protected glyceraldehyde which was homologated by Wittig reaction with Ph₃P=C(CH₃)CHO directly to the *E*-enal **11** in 73 % overall yield. This material was then used in a catalytic asymmetric allylation reaction^[10] with tributyl-(2-ethylallyl)-stannane and BITIP-catalysis to afford the alcohol **13** in 78 % yield and 99 % ee. It is noteworthy that this reaction proved very amenable to scale since it could be conducted in very concentrated solution; thus, to process 65 mmol of **11** requires only 130 mL of solvent. After protection of the free alcohol as the TBS ether, the terminal methylene group was oxidatively cleaved to give the ketone **14** in 74 % yield.

In preparation for the next event, the bis-PMB protected diol was processed by Wittig homologation as described above to yield the enal **12**. This enal was then converted to the dimethyl acetal **15** and used in an aldol reaction employing the Evans TiCl₄/NEt₃ conditions.^[11] This afforded what proved to be the desired aldol adduct **16** as a single stereoisomer.^[12, 13] Reduction of the C15 oxo group proved problematic, as no hydride reducing agent could be found which would give the desired stereochemical outcome. Ultimately, application of a protocol developed for this specific problem proved successful.^[14] Removal of the TBS ether and protection of the hydroxy group as the MEM ether gave **17** in 88 % yield. Reduction of the ketone by using SmI₂ in THF containing 20 equiv of methanol cleanly gave the desired alcohol with good stereoselectivity (91:9 on small scale, 88:12 on scale up) and chemical yield. Protection of this alcohol as the TBS ether provided the C10–C20 subunit **18**.

The fragment-assembly sequence deemed most promising commenced by application of our modified Julia protocol to the coupling of the sulfone **10** with the enal **19**, which was prepared by removal of the TBS group in **18** followed by MnO₂ oxidation (Scheme 4). Condensation of the lithiated sulfone **10** (metalation with *n*BuLi in THF) with **19** led to a mixture of all four possible diastereomeric β-hydroxy sul-



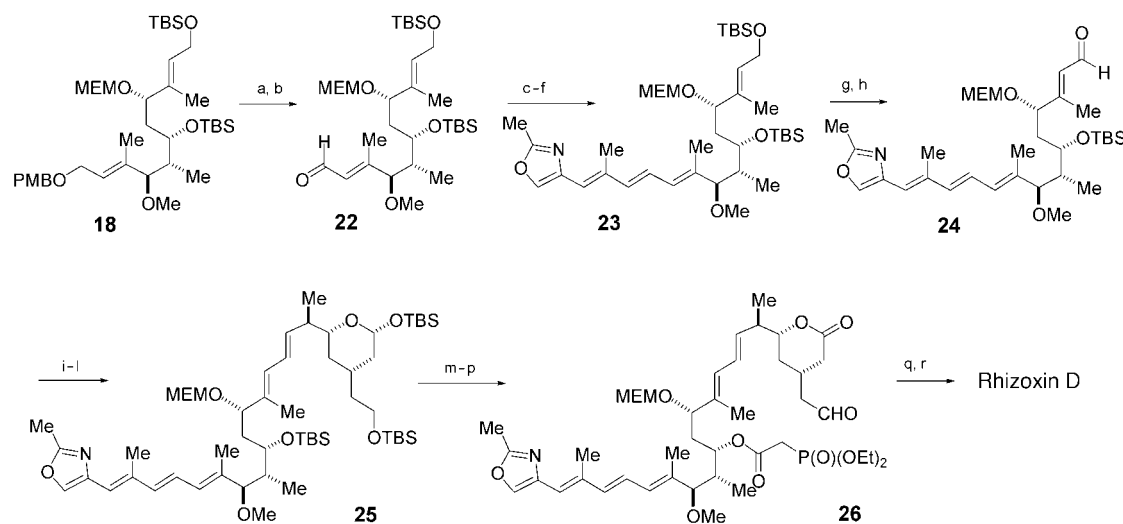
Scheme 4. The initial approach to rhizoxin D. a) HF·pyr, THF, 0 °C; b) MnO₂, CHCl₃/hexanes, RT, 89 %, (2 steps); c) *n*BuLi, C1–C9 subunit **10**, THF, –78 °C; d) Ac₂O, DMAP, pyr, RT; e) DBU, CH₂Cl₂, RT; f) SmI₂, DMPU, MeOH, THF, RT, 70 % (4 steps); g) DDQ, NaHCO₃.

ones, which were processed without purification through a sequence of acetylation, elimination with DBU, and finally reduction with $\text{SmI}_2/\text{DMPU}/\text{MeOH}$ in THF to give the desired *E* alkene as a single geometric isomer in 70 % overall yield. However, we were unable to remove the PMB protecting group in this intermediate and thus were forced to reverse the order of coupling, thus the oxazole–triene segment was incorporated first.

The PMB group in **18**, in contrast, was easily removed by reaction with DDQ and bicarbonate buffer in 98 % yield. After MnO_2 oxidation, condensation with the sulfone **3**^[15] (metalation with Li-HMDS), and processing as described above afforded the desired triene **23** as a single geometric isomer and in 73 % overall yield (Scheme 5).

Selective removal of the primary TBS group followed by oxidation using MnO_2 afforded the enal **24**, which was utilized in a second such Julia sequence with the sulfone **10** as described above (anion formation with *n*BuLi) to give **25** in 84 % overall yield, again as a single *E* isomer. Selective removal of two of the three TBS groups was easily accomplished using HF-pyridine, and oxidation with TPAP-NMO in acetonitrile afforded the desired lactone aldehyde in 51 % yield from **25**. Removal of the final TBS group in the presence of the aldehyde proved difficult but could be accomplished in 50 % yield using HF-pyridine. Phosphorylation of the obtained alcohol with $\text{ClC}(\text{O})\text{CH}_2\text{P}(\text{O})(\text{OEt})_2$ provided the phosphonate **26** necessary for intramolecular Emmons reaction, which was accomplished in 87 % isolated yield using the general procedure of Roush and Masamune et al. (LiCl , Hünig's base, CH_3CN).^[16] Finally, removal of the MEM ether using bromodimethyl borane in 1:1 THF/ CH_2Cl_2 afforded rhizoxin D, with spectral data in excellent agreement with those previously reported.^[2,17]

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Scheme 5. Fragment coupling and completion of the synthesis of rhizoxin D. a) DDQ, NaHCO_3 ; in portions, CH_2Cl_2 , RT, 98 %; b) MnO_2 , $\text{CHCl}_3/\text{hexanes}$, RT, 95 %; c) LiHMDS, oxazole subunit **3**, THF, -78°C ; d) Ac_2O , DMAP, pyr, RT; e) DBU, THF, RT; f) SmI_2 , DMPU, MeOH, THF, RT, 73 % (4 steps); g) HF·pyr, THF, 0°C ; h) MnO_2 , $\text{CHCl}_3/\text{hexanes}$, RT, 80 % (2 steps); i) *n*BuLi, C1–C9 subunit **10**, THF, -78°C ; j) Ac_2O , DMAP, pyr, RT; k) DBU, THF, RT; l) SmI_2 , DMPU, MeOH, THF, RT, 84 % (4 steps); m) HF·pyr, THF, 0°C , 78 %; n) TPAP, NMO, CH_3CN , RT, 65 %; o) HF·pyr, THF, 0°C , 49 %; p) diethylphosphonoacetyl chloride, pyr, THF, $-20^\circ\text{C} \rightarrow \text{RT}$, 82 %; q) LiCl, *i*Pr₂NEt, CH_3CN , RT, 87 %; r) Me_2BBBr , THF/ CH_2Cl_2 , $-78 \rightarrow 0^\circ\text{C}$, 78 %.

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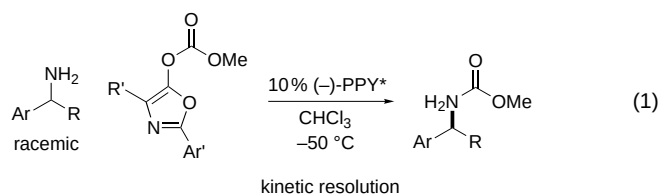
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Kinetic Resolution of Amines by a Nonenzymatic Acylation Catalyst**

Shigeru Arai, Stéphane Bellemin-Lapponnaz, and Gregory C. Fu*

Dedicated to Professor David A. Evans on the occasion of his 60th birthday

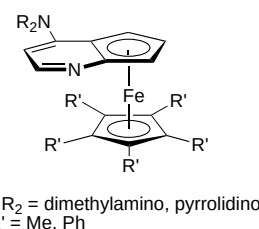
During the past four years, several groups have reported a diverse array of interesting approaches to the development of nonenzymatic acylation catalysts for the kinetic resolution of alcohols, and certain classes of alcohols can now be resolved with useful levels of stereoselection (selectivity factor $s \geq 10$).^[1–3] Amines comprise a second important family of substrates,^[4] but, unfortunately, there has been no significant progress in the development of nonenzymatic acylation catalysts for their kinetic resolution, although some advances have recently been made in the discovery of enantioselective stoichiometric acylating reagents.^[5] Here we describe the first effective nonenzymatic acylation catalyst for the kinetic resolution of amines [Eq. (1)],^[6, 7] and we present preliminary mechanistic data.



In earlier studies, we established that planar-chiral DMAP derivatives such as PPY* can serve as useful catalysts for several different enantioselective acylation processes, including the kinetic resolution of secondary alcohols (DMAP = 4-dimethylaminopyridine).^[8] Our initial efforts to extend this

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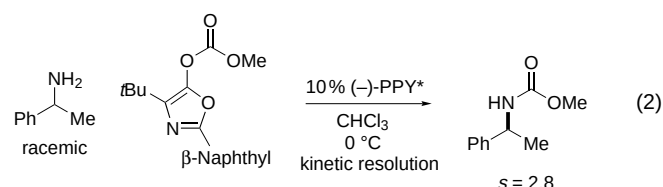
NR₂ = pyrrolidino, R' = Me: (–)-PPY* (1)

work to the acylation of amines were stymied by the nucleophilicity of the amine—it appears that, rather than awaiting the intervention of the enantiopure catalyst, the amine instead reacts directly with the acylating agent. As illustrated in Table 1, a variety of common reagents acylate (±)-1-phenylethylamine with essentially no stereoselection in the presence of (–)-PPY*.^[9]

Table 1. Reaction of (±)-1-phenylethylamine with common acylating agents in the presence of (–)-PPY*.

Acylating agent	<i>s</i>
	1.0
	1.0
	(no reaction)
	1.2

As a fortunate consequence of our studies of enantioselective rearrangement processes,^[8c] we discovered an acylating agent, an O-acylated azlactone, that reacts much more rapidly with PPY* than with a primary amine. With this acylating agent, we observed a significant level of stereoselection in the kinetic resolution of (±)-1-phenylethylamine catalyzed by enantiopure PPY* [Eq. (2)].^[10]



Optimization studies produced an enhancement in stereoselection, primarily as a result of the temperature dependence of the selectivity. Thus, by conducting the reaction at –50 °C and adding the acylating agent in two batches, we can resolve

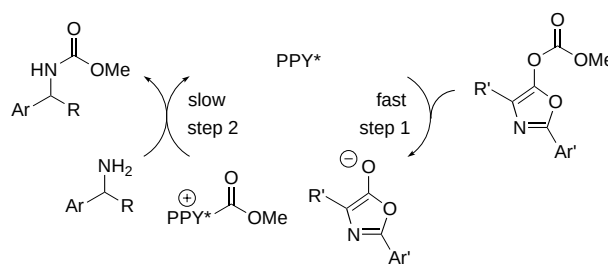
($\pm$)-1-phenylethylamine with a selectivity factor of 12 (Table 2, entry 1).^[11] Other primary amines can also be kinetically resolved with good stereocontrol by PPY*. Higher selectivity factors are obtained for amines in which the aromatic group bears an *ortho* substituent (entries 2 and 3 vs. entry 1).

Table 2. Kinetic resolutions catalyzed by (–)-PPY*.

Entry	Amine	<i>s</i>
1		12
2		27
3		16
4		11
5		13
6		22
7		16
8		11

Electronic effects due to *para* substitution do not appear to impact significantly on stereoselection (entries 4 and 5 vs. entry 1), although enhanced selectivity is observed for a *meta*-methoxy-substituted amine (entry 6). An increase in the size of the alkyl group also leads to a modest increase in stereoselection (entry 7 vs. entry 1). Entry 8 provides an example of a kinetic resolution of a more highly functionalized amine that has been employed in studies of peptide-based Src SH2 inhibitors.^[12]

We believe that these kinetic resolutions proceed through the pathway outlined in Scheme 1. Catalyst PPY* reacts rapidly with the acylating agent, producing an ion pair (step 1), which is the resting state of the catalytic cycle. In the subsequent, stereochemistry-determining step, the methoxycarbonyl group is transferred to the amine, thus furnishing the carbamate and regenerating PPY* (step 2). Consistent



Scheme 1. Proposed mechanism for acylations catalyzed by PPY*.

with this kinetic scheme is our observation that the rate of the reaction is zero order in acylating agent and first order in PPY* and in amine.^[13]

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- A wide array of enantiopure α -arylamines display biological activity, including Exelon, a Novartis compound approved in the US in 2000 for the treatment of Alzheimer's disease. For reviews about Exelon, see: a) M. W. Jann, *Pharmacotherapy* **2000**, *20*, 1–12; b) M. D. Gottwald, R. I. Roaznski, *Expert Opin. Invest. Drugs* **1999**, *8*, 1673–1682.
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- We obtain similar results with our other planar-chiral DMAP-derived catalysts.
- We have examined the use of a number of O-acylated azlactones. These results will be reported in a future full paper.
- Sample experimental: Catalyst (–)-PPY* (5.2 mg, 0.014 mmol), 1-phenylethylamine (17.0 mg, 0.140 mmol), and CHCl₃ (2.5 mL) were added to a Schlenk flask under argon. The resulting purple solution was cooled in a –50 °C bath, and a solution of O-acylated azlactone

(13.5 mg, 0.0420 mmol) in CHCl_3 (0.15 mL) was added by syringe. After 4 hours, additional O-acylated azlactone (13.5 mg, 0.0420 mmol) in CHCl_3 (0.15 mL) was added. After 24 hours (total), the carbamate was isolated by flash chromatography (25% EtOAc/hexanes) (7.3 mg; HPLC analysis: 79% ee). For ee analysis, the unreacted amine was acylated (NEt_3 , Ac_2O , CH_2Cl_2 , RT) and then purified by flash chromatography (EtOAc) to furnish the amide (11.4 mg; GC analysis: 42% ee). These ee values correspond to a selectivity factor s of 13 at 35% conversion.

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[13] A study of stereoselectivity as a function of catalyst ee is consistent with the presence of one catalyst molecule in the stereochemistry-determining step of the process.

High-Nuclearity Chromium–Nickel–Cyanide Clusters: An Open $\text{Cr}_8\text{Ni}_5(\text{CN})_{24}$ Cage and a C_3 -Symmetric $\text{Cr}_{10}\text{Ni}_9(\text{CN})_{42}$ Cluster Incorporating Three Forms of Cyanonickelate**

Jennifer J. Sokol, Matthew P. Shores, and Jeffrey R. Long*

High-nuclearity metal–cyanide clusters may ultimately provide a vehicle for the design of new single-molecule magnet molecules possessing an energy barrier for magnetic moment reversal.^[1] This contention is partly supported by recent work in which an understanding of the factors influencing superexchange interactions across a bridging cyanide ligand has led to the synthesis of Prussian blue type solids^[2] with magnetic ordering temperatures as high as 373 K.^[3] Typically, such solids are obtained from aqueous assembly reactions between octahedral $[\text{M}(\text{H}_2\text{O})_6]^{3+}$ and $[\text{M}'(\text{CN})_6]^{3-}$ complexes. The synthesis of molecular clusters with similarly adjustable magnetic properties is expected to require inhibition of some reactive sites on the precursor complexes through substitution of inert blocking ligands. For example, the use of 1,4,7-triazacyclononane (tacn) as a face-capping tridentate ligand on each metal complex can direct the formation of $[(\text{tacn})_8\text{M}_4\text{M}'_4(\text{CN})_{12}]^{2+}$ clusters with core structures consisting of a single cubic unit excised from the Prussian blue type framework.^[4, 5]

However, to produce the exceptionally large spin states desired—along with magnetic anisotropy—for increasing the spin reversal barrier in single-molecule magnets, it is necessary to develop methods for constructing larger cluster

geometries in which more metal centers can be magnetically coupled.^[6] A simple strategy for achieving higher nuclearities involves the use of a blocking ligand on just one of the reaction components, thereby permitting cluster growth to propagate further before a closed structure forms. Accordingly, the reaction between $[\text{Ni}(\text{H}_2\text{O})_6]^{2+}$ and $[(\text{Me}_3\text{tacn})\text{Cr}(\text{CN})_3]$ ($\text{Me}_3\text{tacn} = N,N',N''$ -trimethyl-1,4,7-triazacyclononane) in aqueous solution generates $[(\text{Me}_3\text{tacn})_8\text{Cr}_8\text{Ni}_6(\text{CN})_{24}]^{12+}$, a 14-metal cluster featuring a cube of eight Cr^{3+} ions with each square face spanned by a $[\text{Ni}(\text{CN})_4]^{2-}$ unit.^[7] In further pursuing reactions of this type, we have discovered two new cluster geometries, including a 19-metal species that represents the largest metal–cyanide cluster reported to date.

Reaction of NiI_2 with $[(\text{Me}_3\text{tacn})\text{Cr}(\text{CN})_3]$ in aqueous solution does not lead to the face-centered cubic $[(\text{Me}_3\text{tacn})_8\text{Cr}_8\text{Ni}_6(\text{CN})_{24}]^{12+}$ cluster obtained with chloride, bromide, nitrate, or perchlorate as counteranions.^[7] Instead, crystallographic analysis^[8] of a red-brown crystal isolated from the reaction mixture revealed a product of composition **1**,



featuring the open-cage cluster depicted in Figure 1. The core structure of this $[(\text{Me}_3\text{tacn})_8\text{Cr}_8\text{Ni}_5(\text{CN})_{24}]^{10+}$ cluster most notably differs from the complete face-centered cubic geometry by having a Ni^{2+} ion missing from one of the cube faces.

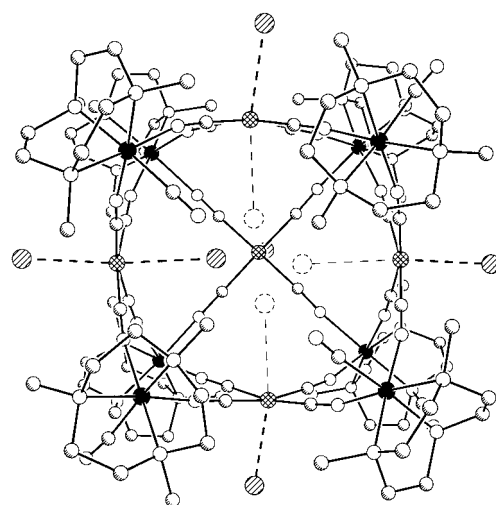


Figure 1. Structure of the $[(\text{Me}_3\text{tacn})_8\text{Cr}_8\text{Ni}_5(\text{CN})_{24}]^{10+}$ cluster and associated I^- anions, as observed in **1**. Black, cross-hatched, shaded, white, and hatched spheres represent Cr, Ni, C, N and I atoms, respectively; H atoms are omitted for clarity. The cluster has maximal point group symmetry C_{2v} . Selected mean interatomic distances [Å] and angles [°]: Cr–N_{CN} 2.05(6), Cr–C 2.04(5), Ni–C 1.86(2), C–N_{CN} 1.14(3), Ni...I_{outer} 2.91(3), Ni...I_{inner} 3.09(3); N_{CN}–Cr–N_{CN} 87(2), N_{CN}–Cr–C 93(3), Cr–N–C_{CN} 170(4), Cr–C–N 172(4), C–Ni–C 89(1), Ni–C–N 177(1).

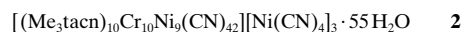
As with $[(\text{Me}_3\text{tacn})_8\text{Cr}_8\text{Ni}_6(\text{CN})_{24}]^{12+}$,^[7] the thermal energy delivered in the course of forming the cluster is apparently sufficient to reorient the cyanide ligands from the $\text{Cr}^{\text{III}}\text{--C--N}$ connectivity of the reactant complex to the more stable $\text{Cr}^{\text{III}}\text{--N--C--Ni}^{\text{II}}$ bridging arrangement. This, rather than the reverse bridging cyanide orientation, was clearly favored in the crystal

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structure refinement, and is consistent with the Ni-C-N angles ($175.8(9) - 179.5(9)^\circ$) being closer to linearity than the Cr-N-C angles ($161(2) - 176.0(8)^\circ$), as well as with the short Ni-C distances ($1.84(1) - 1.893(9) \text{ \AA}$). Note, however, that the absence of a nickel atom from one face of the cluster leaves four terminal cyanide ligands retaining the $\text{Cr}^{\text{III}}\text{-C-N}$ connectivity, two of which are directed away from the center of the open cube face. Thus, while the opening appears sizable, the methyl groups on the nitrogen atoms coordinated *trans* to these two cyanide ligands somewhat inhibit access to the cluster interior, constricting the entryway to a minimum width of approximately $0.6 \text{ \AA}$ (based on van der Waals radii). In contrast to the empty $[(\text{Me}_3\text{tacn})_8\text{Cr}_8\text{Ni}_6(\text{CN})_{24}]^{12+}$ cluster reported previously,^[7] a single iodide anion resides within the metal-cyanide cage of the $[(\text{Me}_3\text{tacn})_8\text{Cr}_8\text{Ni}_5(\text{CN})_{24}]^{10+}$ cluster. As depicted in Figure 1, the encapsulated ion is disordered over four positions in the crystal structure, each approaching an axial ligand site on a nickel center with a mean $\text{Ni}\cdots\text{I}$ distance of $3.09(3) \text{ \AA}$; interestingly, no disposition toward the fifth nickel center is evident in the residual electron density. Stronger axial interactions are formed between all five nickel centers and iodide ions located outside the cluster at a mean $\text{Ni}\cdots\text{I}$ separation of $2.91(3) \text{ \AA}$. Attempts to extract the central iodide ion by metathesis reactions are underway, with the intention of probing the potential host-guest chemistry of this voluminous open-cage cluster.

The square-planar $[\text{Ni}(\text{CN})_4]^{2-}$ complex has long been known to react with excess cyanide ions in aqueous solution to generate $[\text{Ni}(\text{CN})_5]^{3-}$.^[9] Although the latter species favors a square-pyramidal coordination geometry,^[10] a slightly distorted trigonal-bipyramidal structure lies close in energy, as highlighted by the presence of both forms in the crystal structure of $[\text{Cr}(\text{en})_3][\text{Ni}(\text{CN})_5] \cdot 1.5\text{H}_2\text{O}$ (en = ethylenediamine).^[11] In a surprising parallel, $[\text{Ni}(\text{CN})_4]^{2-}$ reacts with the cyanide-rich $[(\text{Me}_3\text{tacn})_8\text{Cr}_8\text{Ni}_5(\text{CN})_{24}]^{10+}$ cluster in aqueous solution to yield **2**, a compound that incorporates square-



pyramidal and trigonal-bipyramidal $[\text{Ni}(\text{CN})_5]^{3-}$ and square-planar $[\text{Ni}(\text{CN})_4]^{2-}$ units in a single cluster. The structure^[8] of this C_3 -symmetric $[(\text{Me}_3\text{tacn})_{10}\text{Cr}_{10}\text{Ni}_9(\text{CN})_{42}]^{6+}$ cluster bears no obvious relationship to its Cr_8Ni_5 predecessor, and consists of a barrel-shaped cage enclosing a bound central $[(\text{Me}_3\text{tacn})\text{Cr}(\text{NC-})_3]$ moiety (Figure 2). The surrounding cage framework is made up of three tiers, each with six metal centers. The top and bottom tiers exhibit pseudo-hexagonal $\text{Cr}_3\text{Ni}_3(\text{CN})_6$ rings, which are joined through cyanide bridges to the three linear $\text{CrNi}(\text{CN})_2$ units of the middle tier. Once again, a $\text{Cr}^{\text{III}}\text{-N-C-Ni}^{\text{II}}$ connectivity is adopted by all bridging cyanide ligands. The square-planar nickel centers in the middle tier are each capped by a square-planar $[\text{Ni}(\text{CN})_4]^{2-}$ counteranion (not shown in Figure 2) through a weak $\text{Ni}\cdots\text{Ni}$ bonding contact of $3.12 \text{ \AA}$. This type of interaction also occurs in the structure of **3**, and is attributed to admixing of empty p_z orbitals with the filled d_{z^2} orbitals in the $\text{Ni}^{\text{II}}\cdots\text{Ni}^{\text{II}}$ pairs.^[7]

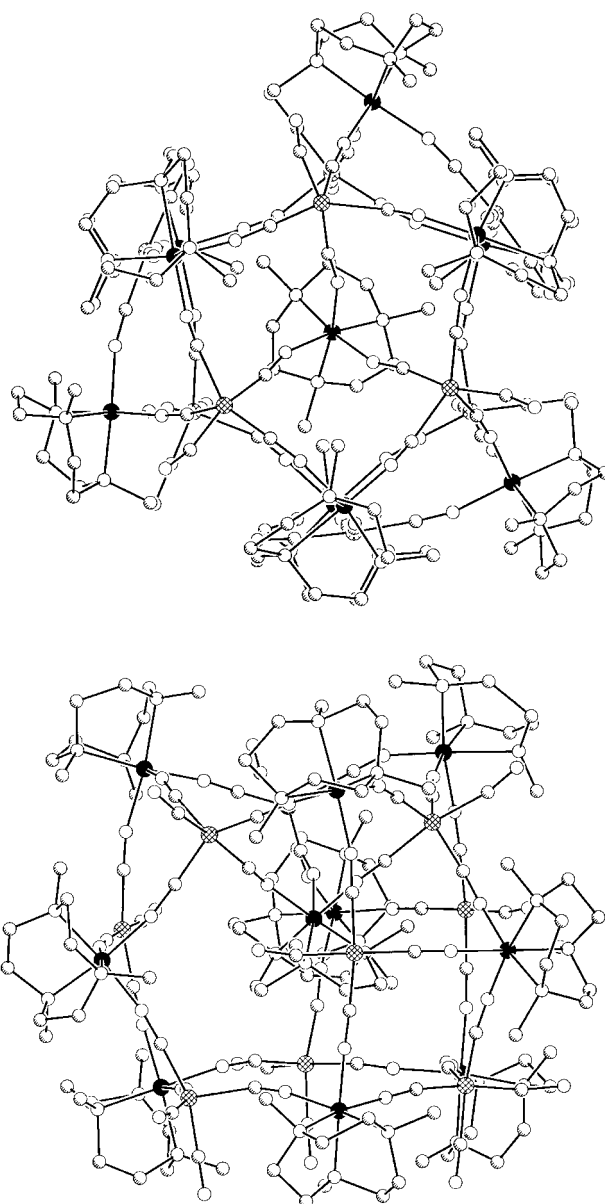
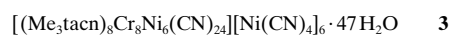


Figure 2. Structure of the $[(\text{Me}_3\text{tacn})_{10}\text{Cr}_{10}\text{Ni}_9(\text{CN})_{42}]^{6+}$ cluster in **2**, viewed parallel (top) and perpendicular (bottom) to the crystallographic 6_3 screw axis. Black, cross-hatched, shaded, and white spheres represent Cr, Ni, C, and N atoms, respectively; H atoms are omitted for clarity. The nickel centers adopting square-planar (Ni(1)), square-pyramidal (Ni(2)), and trigonal-bipyramidal (Ni(3)) coordination geometries are located in the middle, lower, and upper tiers of the cluster, respectively. Selected mean interatomic distances [$\text{\AA}$] and angles [$^\circ$]: $\text{Cr-N}_{\text{CN}} 2.01(5)$, $\text{Ni(1)-C} 1.84(3)$, $\text{C-N}_{\text{CN}} 1.16(3)$, $\text{N}_{\text{CN}}\text{-Cr-N}_{\text{CN}} 90(1)$, $\text{Cr-N-C}_{\text{CN}} 169(4)$, $\text{C-Ni(1)-C} 90(3)$, $\text{Ni-C-N} 173(5)$. Additional distances and angles are listed in the legend of Figure 3.

Compound **2** gradually dissolves in DMSO to give an orange solution exhibiting an IR spectrum consistent with the presence of intact $[(\text{Me}_3\text{tacn})_{10}\text{Cr}_{10}\text{Ni}_9(\text{CN})_{42}]^{6+}$ clusters and dissociated $[\text{Ni}(\text{CN})_4]^{2-}$ counterions.

The two distinct $[\text{Ni}(\text{CN})_5]^{3-}$ units in the structure of **2** are displayed in Figure 3. Analysis of a subset of angles between the normals to adjacent faces of the coordination polyhedra provides a means of distinguishing square-pyramidal and trigonal-bipyramidal coordination geometries.^[12] The perti-

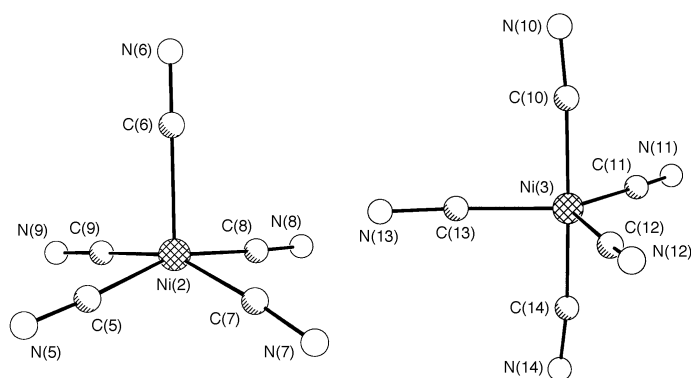


Figure 3. Structures of the two distinct nickel pentacyanide units in the $[(\text{Me}_3\text{tacn})_{10}\text{Cr}_{10}\text{Ni}_9(\text{CN})_{42}]^{6+}$ cluster. Selected interatomic distances [Å] and angles [°]: Ni(2)–C(6) 2.03(2), mean Ni(2)–C_{basal} 1.84(4), mean Ni(3)–C_{ax} 1.84(4), Ni(3)–C(11) 1.82(2), Ni(3)–C(12) 1.98(4), Ni(3)–C(13) 1.83(3); mean C(6)–Ni(2)–C_{basal} 100(8), mean C_{basal}–Ni(2)–C_{basal} 88(3), C(10)–Ni(3)–C(14) 175(2), mean C_{ax}–Ni(3)–C_{eq} 90(4), C(11)–Ni(3)–C(12) 121(1), C(12)–Ni(3)–C(13) 108(1), C(11)–Ni(3)–C(13) 130(1).

nent torsion angles characteristic of the coordination geometry are given in Equations (1)–(6). For comparison, the

$$\text{Ni(2):} \\ e_1 = 180^\circ - [\text{C}(5)\text{--}\text{C}(6)\text{--}\text{C}(7)\text{--}\text{C}(8)] = 68.0^\circ \quad (1)$$

$$e_2 = 180^\circ - [\text{C}(5)\text{--}\text{C}(9)\text{--}\text{C}(6)\text{--}\text{C}(8)] = 80.4^\circ \quad (2)$$

$$e_3 = 180^\circ - [\text{C}(8)\text{--}\text{C}(9)\text{--}\text{C}(7)\text{--}\text{C}(5)] = 4.4^\circ \quad (3)$$

$$\text{Ni(3):} \\ e_1 = 180^\circ - [\text{C}(14)\text{--}\text{C}(11)\text{--}\text{C}(13)\text{--}\text{C}(10)] = 41.4^\circ \quad (4)$$

$$e_2 = 180^\circ - [\text{C}(14)\text{--}\text{C}(12)\text{--}\text{C}(11)\text{--}\text{C}(10)] = 55.6^\circ \quad (5)$$

$$e_3 = 180^\circ - [\text{C}(10)\text{--}\text{C}(12)\text{--}\text{C}(13)\text{--}\text{C}(14)] = 64.6^\circ \quad (6)$$

corresponding angles are $e_1 = e_2 = 75.7^\circ$ and $e_3 = 0.0^\circ$ for an ideal square pyramid, and $e_1 = e_2 = e_3 = 53.1^\circ$ for an ideal trigonal bipyramid. Thus, primarily by virtue of having four surrounding carbon atoms that are approximately coplanar, the coordination geometry of Ni(2) is best described as square-pyramidal, while that of Ni(3), which has no such common plane, is closer to trigonal-bipyramidal. To our knowledge, this represents only the second incidence of nickel pentacyanide in a trigonal-bipyramidal geometry. And indeed, the bond distances and angles for both geometries are remarkably consistent with those observed in $[\text{Cr}(\text{en})_3][\text{Ni}(\text{CN})_5] \cdot 1.5\text{H}_2\text{O}$.^[11] The similarity extends even to the nature of the distortion in the coordination of Ni(3) away from D_{3h} symmetry, which mainly involves a lengthening of one equatorial Ni–C bond (Ni(3)–C(12) 1.98(4) Å) and a widening of the opposite C–Ni–C angle (C(11)–Ni(3)–C(13) 130(1)°). Compound **2** therefore lends support to the claim that this particular distortion from an ideal trigonal bipyramid is not simply a consequence of packing forces, but represents a local energy minimum for the free $[\text{Ni}(\text{CN})_5]^{3-}$ ion.^[11] Regardless, the deviation from square-pyramidal geometry is most likely due to stabilization of the trigonal-bipyramidal form through external forces imposed by the surrounding Cr^{3+} ions or hydrogen bonds^[11, 13] in the two respective instances.

As reflected in the magnetic properties of compounds **1** and **2** (Figure 4), ligation by the strong-field carbon end of cyanide results in exclusively diamagnetic nickel(II) centers, eliminating the possibility of exchange coupling directly between

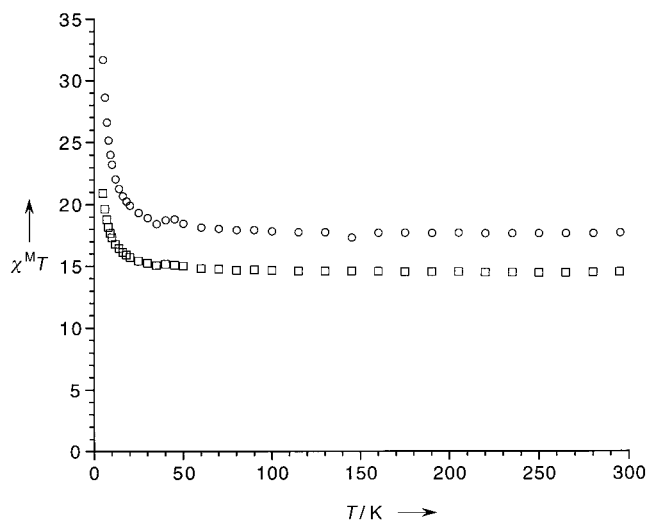


Figure 4. Magnetic behavior of **1** (□) and **2** (○) in an applied field of 1 kG. The data collected at 10 kG for each sample are essentially superimposable. $\chi^M T$ in $\text{cm}^3 \text{K mol}^{-1}$.

cyanide-bridged metal sites. For both compounds, the measured values of $\chi^M T$ at temperatures above 30 K closely approximate the predicted spin-only values of 15 and $18.75 \text{ cm}^3 \text{K mol}^{-1}$, corresponding to eight and ten isolated $S = 3/2$ Cr^{3+} ions per formula unit. In each case, a steady rise in $\chi^M T$ below 30 K suggests the onset of weak ferromagnetic coupling between paramagnetic chromium centers. The minimum intercluster $\text{Cr} \cdots \text{Cr}$ separations of 8.98 and 9.27 Å in the crystal structures of **1** and **2**, respectively, are significantly longer than the minimum intracluster $\text{Cr} \cdots \text{Cr}$ separations of 6.64 and 6.92 Å, implying that the coupling more likely originates from superexchange within the clusters. In contrast, a weak antiferromagnetic coupling has been postulated to occur between chromium(III) centers in the face-centered cubic $[(\text{Me}_3\text{tacn})_8\text{Cr}_8\text{Ni}_6(\text{CN})_{24}]^{12+}$ cluster.^[7] Although well-established for $[\text{Ni}(\text{CN})_4]^{2-}$ and square-pyramidal $[\text{Ni}(\text{CN})_5]^{3-}$,^[9] the low-spin character of the trigonal-bipyramidal form of the latter complex appears not to have been documented previously.

Two high-nuclearity chromium–nickel–cyanide clusters with unprecedented geometries have been prepared. The synthesis of related species utilizing paramagnetic cobalt(II) centers in place of nickel(II) is now being explored as a possible means of generating new single-molecule magnets.

Experimental Section

Absorption spectra were measured with a Hewlett-Packard 8453 spectrophotometer. The IR spectra were recorded on a Nicolet Avatar 360 FTIR spectrometer equipped with an attenuated total reflectance accessory. Mass spectrometric measurements were performed in the positive-ion mode on a Bruker Apex II 7 T actively shielded FTICR mass spectrometer equipped with an analytical electrospray ion source instrument. The water content of each compound was verified by thermogravimetric analysis using a TA

instrument TGA 2950. Magnetic data were collected using a Quantum Design MPMS2 SQUID Magnetometer, and were corrected for diamagnetic contributions.

1: Solid NiI_2 (54 mg, 0.17 mmol) was added to a solution of $[(\text{Me}_3\text{tacn})\text{Cr}(\text{CN})_3]^{7-}$ (72 mg, 0.24 mmol) in 20 mL of water. The deep red-brown mixture was stirred and heated at reflux for 8 h, and the solution volume was reduced to 4 mL with further heating. Upon cooling to room temperature, a small amount of yellow solid was separated from the reaction mixture by filtration. The filtrate was allowed to stand for 2 d, leading to formation of large red-brown rhombic plate-shaped crystals, which were collected by filtration, washed with Et_2O (4×2 mL), and dried in air to yield 85 mg (64 %) of product. Absorption spectrum (H_2O): λ_{max} (ϵ_{M}): 365 (13340), 500 nm (6295, sh); IR: $\tilde{\nu}$ = 2143, 2171 (sh) (ν_{CN}); ES⁺ MS: m/z : 1197.331 ($[\text{I} - 3\text{I} - 27\text{H}_2\text{O}]^{3+}$), 886.272 ($[\text{I} - 4\text{I} - 27\text{H}_2\text{O}]^{4+}$), 667.636 ($[\text{I} - 5\text{I} - 27\text{H}_2\text{O}]^{5+}$), 535.046 ($[\text{I} - 6\text{I} - 27\text{H}_2\text{O}]^{6+}$); elemental analysis calcd for $\text{C}_{96}\text{H}_{222}\text{Cr}_8\text{I}_{10}\text{N}_{48}\text{Ni}_5\text{O}_{27}$: C 25.86, H 5.02, N 15.08; found: C 26.14, H 4.96, N 14.75.

2: A solution (20 mL) of compound **1** was prepared by treating $[(\text{Me}_3\text{tacn})\text{Cr}(\text{CN})_3]^{7-}$ (130 mg, 0.44 mmol) with NiI_2 (100 mg, 0.32 mmol) as described above. Instead of allowing this solution to stand for 2 d, a solution of $\text{Na}_2[\text{Ni}(\text{CN})_4]$ (410 mg, 2.0 mmol) in 12 mL of water was added, producing a fine yellow precipitate. The mixture was centrifuged, and the supernatant solution was decanted and allowed to stand for 3 d. The resulting orange hexagonal plate-shaped crystals were collected by filtration, washed with THF (2×1 mL), and dried in air to yield 42 mg (18 %) of product. IR: $\tilde{\nu}$ = 2123, 2145, 2160 cm^{-1} (ν_{CN}); elemental analysis calcd for $\text{C}_{144}\text{H}_{320}\text{Cr}_{10}\text{N}_{84}\text{Ni}_{12}\text{O}_{55}$: C 32.43, H 6.05, N 22.07; found: C 32.48, H 5.77, N 21.94.

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independent), 576 parameters, and 173 restraints. Single crystals were obtained directly from the reaction products; a slightly low water content was observed in each crystal structure. Data were collected on a Siemens SMART diffractometer using graphite monochromated $\text{MoK}\alpha$ ($\lambda = 0.71073$ Å) radiation, and were corrected for Lorentz, polarization, and absorption effects. Structures were solved by direct methods and refined against all data using SHELXTL 5.0. In the structure of **1**, the cluster is disordered over a crystallographic inversion center, superimposing the open face with the opposite closed face of the cage. Also in this structure, 7 iodide anions and 13 solvate water molecules are disordered over multiple sites and were refined accordingly. The crystal of **2** was found to be a racemic twin, and eight of the solvate water molecules were modeled as disordered over multiple positions in the structure. The final agreement factors for both structures are high due to the extensive disorder present in the crystals and the accompanying poor data quality. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-146872 (**1**) and CCDC-146873 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Chelate Formation around a Hexarhenium Cluster Core by the Diphosphane Ligand $\text{Ph}_2\text{P}(\text{CH}_2)_6\text{PPh}_2^{**}$

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The octahedral hexametal cluster core $\text{M}_6(\mu_3\text{-E})_8$ (E = chalcogenide or halide ions) is one of the most common structural units in metal cluster complexes.^[1–7] Each metal ion possesses an axial (terminal) coordination site, and a pair of the axial ligands at two adjacent M sites are oriented perpendicular to each other. Thus, the unit can be regarded as a giant octahedral center. Mimicking mononuclear octahe-

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dral complexes of the substitution-inert type (such as Co^{III}) would introduce new aspects to octahedral hexametal cluster chemistry. However, this approach requires designed and controlled ligand substitution at the hexametal units.^[1–6] Some features of normal octahedral complexes, including “chelate” formation and geometrical and optical isomerism, have not yet been established systematically for the hexametal clusters because of the synthetic difficulties in controlling the number and the geometry of ligands introduced into the octahedral $\text{M}_6(\mu\text{-E})_8$ cores.

The use of hexarhenium clusters as giant octahedral centers is of special interest not only because of the substitution-inert nature of the Re^{III} center, which allows controlled substitution of a terminal ligand in a stepwise way, but also because of the redox-active and photoluminescent characters.^[2, 3, 6, 8] Recently, Holm et al. reported the stepwise substitution of triethylphosphane for halide ions in $[\text{Re}_6\text{Se}_8\text{I}_6]^{3-}$ and $[\text{Re}_6\text{S}_8\text{Br}_6]^{3-}$.^[1b, 3, 4] Our studies on hexarhenium clusters with pyridine derivatives yielded a new series of $[\text{Re}_6\text{S}_8]^{2+}$ clusters with well-defined structural and physicochemical properties.^[2b–d, 6]

The aim of the present study was to achieve “bridge–chelate” formation on the hexarhenium cluster by using the diphosphane ligands $\text{PPh}_2(\text{CH}_2)_5\text{PPh}_2$ (dpppen) and $\text{PPh}_2(\text{CH}_2)_6\text{PPh}_2$ (dpsh), as shown in Figure 1. For dpppen, the bridge–chelate coordination mode seems to be possible based on the bond lengths and angles in models, but our experiments only gave evidence of monodentate coordination for this ligand.

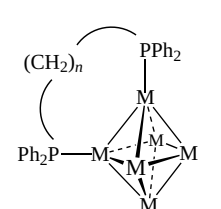


Figure 1. The bridge–chelate mode for the linear diphosphane ligands $\text{Ph}_2\text{P}(\text{CH}_2)_n\text{PPh}_2$.

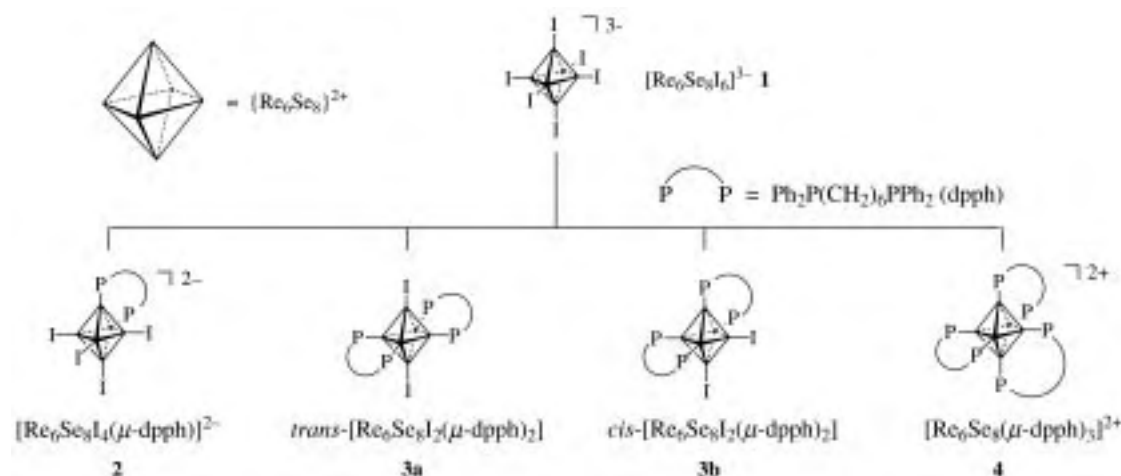
However, the ligand dpsh indeed gave the hexarhenium clusters with bridge–chelate dpsh. In addition to the stepwise replacement of dpsh, the influence of stepwise processes on the physical and chemical properties associated with the $\text{Re}_6\text{Se}_8^{2+}$ ion is also described herein.

Clusters with one, two, and three dpsh ligands are summarized in Scheme 1: $(\text{Bu}_4\text{N})_2[\text{Re}_6\text{Se}_8\text{I}_4(\mu\text{-dpsh})]$

$((\text{Bu}_4\text{N})_2\text{-2})$, $\text{trans-}[\text{Re}_6\text{Se}_8\text{I}_2(\mu\text{-dpsh})_2]$ (**3a**), $\text{cis-}[\text{Re}_6\text{Se}_8\text{I}_2(\mu\text{-dpsh})_2]$ (**3b**), and $[\text{Re}_6\text{Se}_8(\mu\text{-dpsh})_3](\text{SbF}_6)_2$ (**4**– $(\text{SbF}_6)_2$). Reactions between dpsh and the precursor cluster anion $[\text{Re}_6\text{Se}_8\text{I}_6]^{3-}$ (**1**) were carried out in DMF with controlled temperature, reaction time, and reactant ratios (see Experimental Section). As observed for triethylphosphane and pyridine,^[3, 4, 6] the ligand displacements can be controlled to afford stepwise diphosphane-substituted species, including geometric isomers. Two, four, and six iodo ligands of **1** are displaced by dpsh to afford species of general formula $[\text{Re}_6\text{Se}_8\text{I}_{6-2m}(\mu\text{-dpsh})_m]^{2m-4}$ ($m = 1–3$, Scheme 1). In the case of dpppen, only a monodentate diphosphane ligand was found, and the phosphorus center in the dangling arm was oxidized.^[9] No sign of chelate formation was observed for dpppen. Thus, a small modification of the length of the methylene chain of the diphosphane ligands $\text{PPh}_2(\text{CH}_2)_n\text{PPh}_2$ ($n = 5, 6$) has led to a dramatic difference in the structure of the resulting hexarhenium(III) clusters. For the dpsh ligand, bridge–chelate formation occurred even when the reaction was performed under aerobic conditions. Hence, it is the number n of methylene spacer groups in the diphosphane ligand $\text{PPh}_2(\text{CH}_2)_n\text{PPh}_2$ that is the main decisive factor in determining the substitution mode. Of the geometric isomers, the *cis* isomer **3b** was isolated in much higher yield (38 %) than the *trans* isomer **3a** (6 %).

The new dpsh-substituted hexarhenium(III) clusters **2**, **3a**, **3b**, and **4** were characterized by elemental analysis, fast-atom bombardment mass spectrometry (FAB-MS), several spectroscopic methods, and, in the case of **3b**, X-ray crystallography. The expected composition for all of the complexes was unambiguously confirmed by FAB-MS. The X-ray structure of **3b** is shown in Figure 2.^[10]

Two rhenium(III) centers (Re5 and Re6) are coordinated by iodo ligands and the remaining four rhenium(III) centers (Re1, Re2, Re3, and Re4) are occupied by phosphorus atoms of the dpsh ligands, whereby one dpsh is coordinated to Re1 and Re2, and the other to Re3 and Re4, in a bridge–chelate manner. To emphasize the view of the giant octahedron, the ring can geometrically be regarded as consisting of ten atomic members, the two Re atoms of which come from the giant



Scheme 1. Structural formulas of dpsh-substituted octahedral hexarhenium(III) clusters **2–4** showing the substitution mode and geometry of the dpsh ligands around the cluster core.

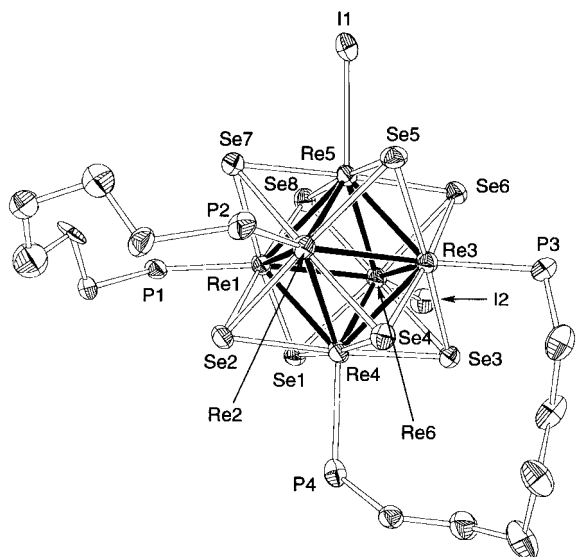


Figure 2. An ORTEP plot of **3b** at 50% probability level. Phenyl substituents on the phosphorus atoms are omitted for clarity. Selected interatomic distances [Å] and bond angles [°]: Re1–Re2 2.6439(9), Re1–Re4 2.657(1), Re1–Re5 2.6388(5), Re1–Re6 2.6520(8), Re1–Se1 2.510(2), Re1–Se2 2.517(2), Re1–Se7 2.517(2), Re1–Se8 2.518(2), Re1–P1 2.488(4), Re2–Re3 2.6573(8), Re2–Re4 2.6756(9), Re2–Re5 2.6404(9), Re2–Se2 2.516(2), Re2–Se4 2.507(2), Re2–P2 2.503(4), Re2–Se5 2.520(2), Re2–Se7 2.517(2), Re3–P3 2.510(5), Re4–P4 2.490(4), Re5–I1 2.779(1), Re6–I2 2.786(1); Re2–Re1–Re4 60.63(3), Re4–Re1–Re5 89.80(3), Se1–Re1–Se2 89.56(5), Se1–Re1–Se7 176.08(6), Se1–Re1–P1 92.7(1), Se2–Re1–P1 89.0(1), Re1–Se1–Re4 63.68(4).

center. Thus, the consecutive member “P–Re–Re–P” embodies the rigid framework, while the remaining six methylene carbon atoms form the more flexible backbone of the chelate ring.^[11] The bond lengths in **3b**, including Re–Re (2.6301(9) to 2.6756(9) Å), Re–Se (2.498(2) to 2.538(2) Å), Re–I (2.779(1) and 2.786(1) Å), and Re–P (2.488(4) to 2.510(5) Å), are similar to those of **1**^[1b] and other octahedral hexarhenium clusters.^[3, 4, 6]

In ³¹P{¹H} NMR spectra recorded on CDCl₃ or CD₂Cl₂ solutions, only one signal is observed for the mono-dpph cluster **2** ($\delta = -29.9$), for the bis-dpph *trans* isomer **3a** ($\delta = -30.5$), and for the tris-dpph cluster **4** ($\delta = -29.7$), while two separate peaks are detected for bis-dpph *cis* isomer **3b** ($\delta = -31.0$ and -31.3). In all cases the results are as expected from the coordination symmetry. Similarly, in the ¹³C{¹H} NMR spectra, six signals for the methylene groups of coordinated dpph ligands are observed for **3b**, but only three for the other clusters. Here, the observation of the structural rigidity with regard to the Re–P bonds for **2–4** is noteworthy; some organometallic clusters with bridged diphosphane ligands display isomerization process that change the coordination mode of the ligands on the NMR timescale.^[12]

Electrochemical and photophysical properties of **2–4** are compared in Table 1. The corresponding data of **1** are also included for comparison. In 0.1 mol dm^{−3} (Bu₄N)PF₆/CH₂Cl₂, the dpph-substituted clusters **2–4** exhibit reversible one-electron transfer processes ascribed to {Re^{III}}/[{Re^{III}Re^{IV}}], the redox potentials of which are significantly dependent on the number of dpph ligands on the clusters. Relative to the $E_{1/2}$ value of **1** (-0.02 V vs. Ag/AgCl), the corresponding values of

Table 1. Electrochemical and photophysical data of clusters **1–4**.

Compound	$E_{1/2}$ [V] ^[a]	λ_{em} [nm] ^[b]	ϕ_{em} ^[c]	τ_{em} [μs]
(Bu ₄ N) ₃ - 1	-0.02			
(Bu ₄ N) ₂ - 2	$+0.35$	787	0.007	2.4
3a	$+0.76$	777	0.008	2.1
3b	$+0.79$	790	0.012	3.2
4 -(SbF ₆) ₂	$+1.06$	779	0.031	6.5

[a] A reversible process. Cyclic voltammograms were recorded at 20 °C for 0.1 mol dm^{−3} (Bu₄N)PF₆/CH₂Cl₂ solutions at a scan rate of 100 mV s^{−1} with a glassy carbon working electrode, a platinum-coil counter electrode, and a Ag/AgCl reference electrode. The sample concentration was 1×10^{-3} mol dm^{−3}. [b] Excitation wavelength was 355 nm. The corrected emission spectra were measured in deoxygenated CHCl₃ at 298 K. [c] Integrated emission quantum yields ϕ_{em} were estimated relative to (Bu₄N)₂[Mo₆Cl₁₄] ($\phi_{em} = 0.19$) as reference.^[13]

the dpph-substituted clusters become more positive with increasing number of dpph ligands on the clusters (**1** → **2** → **3a**, **3b** → **4**), and this indicates that the mixed-valent form {Re^{III}Re^{IV}} becomes highly destabilized upon stepwise introduction of dpph ligands.

Clusters **2–4** containing 24-electron Re₆ cores are highly photoluminescent with lifetimes on the microsecond scale^[2, 6] (Table 1). No appreciable difference in luminescence was observed for the stepwise-substituted clusters or for the isomeric species. However, tris-dpph cluster **4** has the longest lifetime τ_{em} and the highest quantum efficiency ϕ_{em} .^[2d]

In summary, we have developed a new synthetic route to hexarhenium(III) clusters with variable numbers, geometries, and coordination types of the bidentate ligands dpph and dpppen. Structurally characterized ten-membered metalla-cycles were obtained with the former. The synthetic methodology described here will open significant possibilities for introducing various types of ligands into the hexametal cluster frameworks M₆(μ-E)₈, and this may allow the chemical and physical properties associated with the cluster chromophores to be controlled.

Experimental Section

All experiments were carried out under argon by using standard Schlenk-vessel and vacuum-line techniques. Infrared spectra were recorded on a Hitachi 270-50 infrared spectrophotometer on KBr disks. ¹H, ¹³C{¹H}, and ³¹P{¹H} NMR spectra were recorded at 20 °C on a JEOL JNM-EX 270 NMR spectrometer. FAB mass spectra (3-nitrobenzyl alcohol as a matrix) were recorded on a JEOL JMS-HX110 mass spectrometer at the Center for Instrumental Analysis, Hokkaido University.

(Bu₄N)₂-**2**: A DMF solution (20 mL) containing (Bu₄N)₃-**1**^[1b] (100 mg, 0.031 mmol) and dpph (57 mg, 0.124 mmol) was stirred at 100 °C for 1 h. The solution was concentrated to about 2 mL in vacuo. Addition of water (30 mL) resulted in the precipitation of the products, which were collected by filtration. The products were purified by column chromatography (silica gel, CH₂Cl₂/CH₃CN (5/1) as eluent). Yield: 78 mg (79 %).

3a and **3b**: (Bu₄N)₃-**1** (200 mg, 0.062 mmol) and dpph (114 mg, 0.248 mmol) were dissolved in DMF (20 mL), and the solution was heated to reflux with stirring for 3 h. After the volume of solvent was reduced in vacuo to about 1 mL, water (30 mL) was added to precipitate the product. It was collected by filtration and purified by column chromatography on silica gel. The *trans* isomer **3a** was eluted with CH₂Cl₂ as the first band. Yield: 10 mg (6 %). The *cis* isomer **3b** was eluted with CH₂Cl₂/CH₃CN (50/1) as the second band. Yield: 68 mg (38 %).

4-(SbF₆)₂: A solution of chlorobenzene/DMF (2/1, 30 mL) containing [Re₆Se₈(CH₃CN)₆](SbF₆)₂^[3b] (150 mg, 0.061 mmol) and dpph (100 mg,

0.22 mmol) was heated to reflux with stirring for 1 d. After cooling, the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (CH₂Cl₂/ethanol (30/1) as eluent). Yield: 128 mg (59 %).

(Bu₄N)₂-2: Positive-ion FAB-MS: *m/z*: 3198 [*M*⁺]; ¹³C NMR (67.9 MHz, CD₂Cl₂, 20 °C, TMS): δ = 133.8 (m, *ipso*-Ph), 131.8, 130.8 (m, *o*-Ph), 130.1 (m, *p*-Ph), 127.9 (m, *m*-Ph), 59.0 (s, Bu), 37.4 (d, ¹J(P,C) = 30.8 Hz, (PCH₂CH₂CH₂)₂), 17.5 (d, ²J(P,C) = 20.0 Hz, (PCH₂CH₂CH₂)₂), 24.7 (s, Bu), 21.6 (d, ³J(P,C) = 3.8 Hz, (PCH₂CH₂CH₂)₂), 20.4 (s, Bu), 14.1 (s, Bu); ³¹P NMR (109.3 MHz, CDCl₃, 20 °C): δ = -29.9 (s). **3a**: Positive-ion FAB-MS: *m/z*: 2914 [*M*⁺]; ³¹P NMR (CDCl₃, 20 °C): δ = -30.5 (s).

3b: Elemental analysis calcd for C₆₀H₆₄I₂P₄Se₈Re₆·CH₂Cl₂·1.5 H₂O: C 24.23, H 2.30, I 8.39; found: C 24.45, H 2.35, I 8.94; positive-ion FAB-MS: *m/z*: 2914 [*M*⁺]; ¹³C NMR (CD₂Cl₂, 20 °C): δ = 134.8 (m, *ipso*-Ph), 132.1 (m, *o*-Ph), 130.9 (m, *p*-Ph), 128.3 (m, *m*-Ph), 37.5 (d, ¹J(P,C) = 33.0 Hz, (PCH₂CH₂CH₂)₂), 37.3 (d, ¹J(P,C) = 29.6 Hz, (PCH₂CH₂CH₂)₂), 27.1 (d, ²J(P,C) = 14.0 Hz, (PCH₂CH₂CH₂)₂), 27.0 (d, ²J(P,C) = 14.0 Hz, (PCH₂CH₂CH₂)₂), 21.4 (s, (PCH₂CH₂CH₂)₂), 21.3 (s, (PCH₂CH₂CH₂)₂); ³¹P NMR (CDCl₃, 20 °C): δ = -31.0 (s), -31.3 (s).

4-(SbF₆)₂: Elemental analysis calcd for C₉₀H₉₆F₁₂P₆Sb₆Se₆Re₆: C 30.16, H 2.70; found: C 30.18, H 2.85; positive-ion FAB-MS: *m/z*: 3586 [*M*⁺]; ¹³C NMR (CD₂Cl₂, 20 °C): δ = 133.6 (m, *ipso*-Ph), 133.0 (m, *o*-Ph), 131.8, 131.4 (m, *p*-Ph), 128.7 (m, *m*-Ph), 37.9 (d, ¹J(P,C) = 33.5 Hz, (PCH₂CH₂CH₂)₂), 26.6 (d, ²J(P,C) = 15.1 Hz, (PCH₂CH₂CH₂)₂), 21.7 (d, ³J(P,C) = 3.9 Hz, (PCH₂CH₂CH₂)₂); ³¹P NMR (CD₂Cl₂, 20 °C): δ = -29.7 (s).

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- [9] Experimental details for hexarhenium(III) clusters with the ligand dpppen will be described elsewhere.
- [10] Red crystals of **3b** were obtained by slow diffusion of diethyl ether into a solution of **3b** in CH₂Cl₂. Crystal data for **3b**·CH₂Cl₂·1.5 H₂O (C₆₁H₆₉Cl₂I₂O₁₅P₄Re₆Se₈): *M_r* = 3023.75, monoclinic, space group *P2₁/c* (no. 14), *a* = 19.712(1), *b* = 16.587(1), *c* = 22.437(1) Å, β = 100.321(3)°, *V* = 7217.6(7) Å³, *Z* = 4; ρ_{calcd} = 2.782 g cm⁻³; crystal dimensions 0.30 × 0.20 × 0.20 mm³; μ(MoKα) = 151.20 cm⁻¹; *T* = 173 K. Data were collected on a Rigaku R-Axis RAPID diffractometer equipped with an image plate detector with graphite-monochromated MoKα radiation (λ = 0.71069 Å). Total reflections collected 16258. Full-matrix least-squares refinement, final *R* = 0.049, *R_w* = 0.064, GOF = 1.30 for 8526 observed reflections (*I* > 3σ(*I*)) and 735 variable parameters. The maximum and minimum peaks around the rhenium atoms on the final difference Fourier map were +3.66 and -2.95 e Å⁻³. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-145486. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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Coordinatively Unsaturated Metal Centers as Building Blocks for High Coordination Number Metallomesogens**

Koen Binnemans* and Katleen Lodewyckx

Most literature on metal-containing liquid crystals (metallomesogens) is devoted to compounds with Rh^I, Ir^I, Ni^{II}, Pd^{II}, Pt^{II}, Cu^{II}, and Ag^I as the central metal ion, because these complexes have a linear or planar geometry and mimic therefore conventional organic calamitic (rodlike) liquid crystals.^[1] Obtaining high coordination number calamitic metallomesogens is a challenge.^[2] One approach is to make the ligand as anisometric as possible by increasing the number of aromatic rings.^[3, 4]

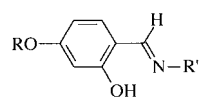
The design of lanthanide-containing liquid crystals is difficult^[5] because the trivalent lanthanide ions have even

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higher coordination numbers (CNs) than d-group transition metal ions. In general, lanthanide complexes have coordination numbers 8 or 9. Octahedral lanthanide complexes (CN = 6) do exist and the best known examples are tris(β -diketonato)lanthanide(III) complexes.^[6] Lanthanide complexes with coordination number 6 are coordinatively unsaturated and can expand their coordination sphere by adduct formation with neutral molecules. Because the trivalent lanthanide ions are hard Lewis acids, hard Lewis bases are preferred for adduct formation. Most of the molecules which add to lanthanide ions are oxygen donors and, to a lesser extent, nitrogen donors. Water is a very common ligand for adduct formation. When tris(β -diketonato)lanthanide(III) complexes are prepared in an aqueous solution, they are most often obtained as dihydrates. This leads to a coordination number of eight, not six for the lanthanide ion.

We serendipitously discovered that adducts of tris(β -diketonato)lanthanide(III) complexes with a salicylaldehyde Schiff base as Lewis base have mesomorphic properties.

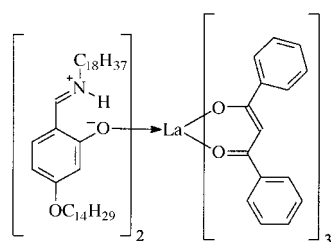


Scheme 1. *N*-Alkyl-4-alkoxy-2-hydroxybenzaldehyde Schiff base ligands. For ligand L discussed in the text, R = C₁₄H₂₉, R' = C₁₈H₃₇.

We used 1,3-diphenyl-1,3-propanedione (dibenzoylmethane, Hdbm) as the β -diketone ligand and 2-hydroxy-*N*-octadecyl-4-tetradecyloxybenzaldehyde (L, Scheme 1) as the Schiff base. This result was totally unexpected, because work by Giroud-Godquin and Rassat has shown that six alkyl chains are insufficient for octahedral tris(β -diketonato)iron(III) complexes to form a real mesophase.^[7] Swager and Zheng

found that tris(β -diketonato) complexes of Fe^{III}, Mn^{III}, and Cr^{III} complexes should have 12 or more alkyl chains (attached to the β -diketone ligand) in order to exhibit stable mesomorphism.^[8, 9] In our complexes, only four long alkyl chains are present.

Complex [La(dbm)₃L₂] (Scheme 2) was obtained from anhydrous [La(dbm)₃] and L. It can be assumed that the coordination number of La^{III} in [La(dbm)₃L₂] is eight, with the two Schiff base ligands binding in a monodentate fashion. It was found for complexes of the type [LnL₃(NO₃)₃] that the Schiff base is in a zwitterionic form and binds to the lanthanide ion through the phenolic oxygen only.^[5d,e]



Scheme 2. Schematic structure of [La(dbm)₃L₂] complex.

It should be noted that neither L nor [La(dbm)₃] are mesomorphic: the melting point of L is 73 °C, and [La(dbm)₃] decomposes when heated in air. [La(dbm)₃L₂] melts at 95 °C to an isotropic liquid, without forming a mesophase. On cooling, a monotropic mesophase was formed at 80 °C. This phase was according to the texture observed under the

polarizing microscope a smectic A phase (SmA). When cooling the isotropic liquid, bâtonnets formed at the clearing point and they coalesced to the typical focal-conic texture (fan texture). It was also possible to observe regions with homeotropic alignment. When the SmA phase was heated, clearing occurred at 81 °C. The rather low viscosity of the mesophase indicates that a real mesophase and not a plastic crystal phase is present. The mesophase ordering could be frozen into a glassy state. By cooling the mesophase, the viscosity gradually increased and finally a solid was obtained. The glassy mesophase had the same optical texture as the (liquid) mesophase. With high cooling rates (we used cooling rates up to 100 K min⁻¹) it was possible to obtain a glass that did not contain any crystallites. Upon heating the glass, the mesophase was reobtained above 75 °C and the compound cleared at 81 °C. However, when the compound was kept in the mesophase at a constant temperature or when the compound was slowly cooled, the clearing process was not complete at 81 °C. Some birefringent regions appeared which only cleared at 95 °C (i.e. at the melting point of the crystalline compound). These birefringent regions were thus crystallites. The melting enthalpy of [La(dbm)₃L₂] is 104 kJ mol⁻¹ (DSC, first heating run), and the clearing enthalpy is -13.8 kJ mol⁻¹ (DSC, first cooling run). The clearing enthalpy is comparable to those found for lanthanide-containing Schiff base complexes exhibiting enantiotropic mesomorphism.^[5b,e]

Liquid crystallinity was also observed for other [Ln(dbm)₃L₂] compounds (Table 1). To obtain mesomorphic adducts, it is possible to follow a route which is used for the synthesis of hydrogen-bonded liquid crystals: dissolving accurately weighed amounts of [Ln(dbm)₃] and L in a 1:2 molar ratio in dichloromethane and subsequently evaporating the solvent.^[10] This method is fast, yields are quantitative, and the transition temperatures are the same as those of the separately synthesized [Ln(dbm)₃L₂] compounds.

Table 1. Mesomorphic behavior of [Ln(dbm)₃L₂] complexes.

Ln	R ^[a]	R' ^[a]	Transition temperatures [°C] ^[b, c]
La	C ₁₄ H ₂₉	C ₁₈ H ₃₇	Cr 95 (SmA 81) I
	C ₁₆ H ₃₃	C ₁₈ H ₃₇	Cr 93 (SmA 77) I
	C ₁₂ H ₂₅	C ₁₆ H ₃₃	Cr 100 (SmA 81) I
Nd	C ₁₆ H ₃₃	C ₁₈ H ₃₇	Cr 89 (SmA 63) I
Eu	C ₁₄ H ₂₉	C ₁₈ H ₃₇	Cr 90 (SmA 60) I

[a] R = 4-alkoxy chain; R' = *N*-alkyl chain (see Scheme 1). [b] Cr = crystalline solid; SmA = smectic A phase; I = isotropic liquid. [c] Clearing points were determined by heating the monotropic mesophase. In general, clearing points determined by cooling the isotropic liquid are 1 K lower than the values reported here.

Because [Ln(dbm)₃] has molecular dimensions similar to those of [60]fullerene, it is interesting to compare [60]fullerene-containing liquid crystals with our mesomorphic complexes. Chuard and Deschenaux functionalized the C₆₀ core with a twin cholesterol malonate derivative and observed a monotropic smectic A phase.^[11] Although the cholesteryl group is known to be strongly mesophase-promoting, two cholesteryl groups were necessary to induce monotropic mesomorphism in the [60]fullerene derivative. By another

approach, Deschenaux et al. were able to obtain an enantio-tropic smectic A mesophase by functionalizing [60]fullerene with 12 alkyl chains each terminated by a cyanobiphenyl group.^[12] It is therefore amazing to observe liquid crystallinity in [Ln(dbm)₃] complexes functionalized by only four alkyl chains.

In conclusion, we obtained lanthanide-containing liquid crystals by forming a bisadduct between tris(β -diketonato)-lanthanide(III) complexes and a salicylaldehyde Schiff base. Our method is a new approach to the design of lanthanide-containing metallomesogens. This approach is versatile, because the β -diketone ligand, the addend ligand, and the lanthanide ion can be varied.

Experimental Section

¹H NMR spectra were obtained on a Bruker WM-250 spectrometer (250 MHz) using CDCl₃ as solvent. IR spectra were recorded on a Bruker FTIR spectrometer IFS66 (KBr pellet technique). Elemental analyses (CHN) were obtained on a CE-Instrument EA-1110 elemental analyzer. Optical textures of the mesophases were observed with an Olympus BX60 polarizing microscope equipped with a LINKAM THMS600 hot stage and a LINKAM TMS93 programmable temperature controller. DSC traces were recorded with a Mettler–Toledo DSC821e module.

Synthesis of [Ln(dbm)₃L₂]: [La(dbm)₃] was obtained by careful dehydration of the corresponding mono- and dihydrates in vacuo (10^{−3} mbar).^[13] A solution of [La(dbm)₃] (3 mmol, 2.42 g) in absolute ethanol was added dropwise to a solution of 2-hydroxy-*N*-octadecyl-4-tetradecyloxybenzaldehyde (L) (3 mmol, 1.76 g) in absolute ethanol at 50 °C. The adduct precipitated immediately. After the mixture had been stirred overnight at room temperature, the precipitate was filtered off, washed with ethanol and dried in vacuo. The compound is obtained as a pale yellow powder. Yield: 2.72 g (91 %). IR (KBr): $\tilde{\nu}$ = 1654 (C=N, s), 1552 (C=O, s) cm^{−1}. Elemental analysis calcd (%) for C₁₂₃H₁₇₅LaN₂O₁₀ (1980.6): C 74.57, H 8.91, N 1.42; found: C 74.74, H 8.97, N 1.30.

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Singly and Doubly Oxidized Phthalocyanine (pc) Rings: [Cu(pc)(ReO₄)] and [Cu(pc)(ReO₄)₂]*

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Numerous molecular conductors and semiconductors are known that are based on partially oxidized macrocycles,^[1–4] and several singly oxidized metal phthalocyanine complexes have been isolated.^[5, 6] Doubly oxidized complexes are more intriguing, with the most widely known example being “Compound I”, which results from the double oxidation of ferrihemes.^[7] This oxidation occurs by the loss of one electron from the metal ion (giving formally iron(IV)) and one from the ring. There are examples of crystalline doubly oxidized metal phthalocyanine complexes^[8–11] where both oxidations are metal centered, but there are only a few reports of doubly ring-oxidized metallophthalocyanine complexes, and these only for solutions.^[12–14] As far as we know there have been no reports of isolated compounds in which the phthalocyanine (pc) ring is doubly oxidized.

We describe here the syntheses of the singly and doubly oxidized compounds [Cu(pc)(ReO₄)] (**1**) and [Cu(pc)(ReO₄)₂] (**2**), together with their characterization by means of single-crystal X-ray diffraction (Figure 1) and electron paramagnetic resonance (EPR) methods. The structures of these compounds differ from those of porphyrinic conductors^[15] and other singly oxidized derivatives^[16] in that they contain isolated, rather than stacked, macrocycles. We show that these both are compounds of Cu^{II}, essentially unperturbed by the oxidation. In **1** the pc ring is singly oxidized to pc^{•+};

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in **2** the pc ring is doubly oxidized to pc^0 . Compound **2** is the first compound containing a pc^0 ring to be isolated.

The galvanostatic oxidation of $[Cu(pc)]$ in a 1-chloronaphthalene solution of $[N(C_4H_9)_4][ReO_4]$ yielded crystals of **1** and **2**. The structure of **1** is shown in Figure 1A. There are two independent molecules in the asymmetric unit. They closely

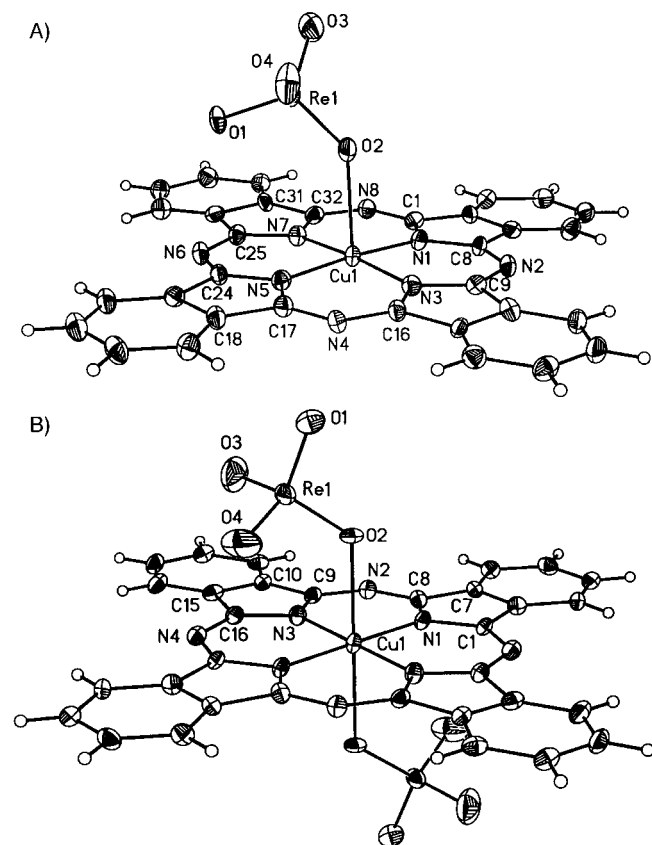


Figure 1. Molecular structures of **1** (A) and **2** (B). The average Cu–O bond length is 2.446(5) Å in **1** and is 2.526(5) Å in **2**. Displacement ellipsoids are set at the 50% probability level.

resemble one another, each consisting of a $Cu(pc)$ unit with a $Cu-OReO_3$ linkage. The angle between the two independent units is $68.56(4)^\circ$. The 24-atom cores of both of the symmetry-independent macrocycles are essentially planar, the mean deviations being 0.02(1) Å and 0.03(3) Å. The Cu atoms lie 0.096(1) Å and 0.092(1) Å out of the planes of the 24-atom cores, displaced toward the O atoms. In each macrocycle, one of the fused benzene rings is slightly puckered. The maximum out-of-plane distances are 0.163(7) Å and 0.307(7) Å. The average Cu–N bond length is 1.957(8) Å; the Cu–O distances are normal at 2.440(4) Å and 2.451(5) Å. The van der Waals contacts between neighbors are 3.35–3.37 Å.

The structure of **2** is shown in Figure 1B. The molecule, which has a crystallographically imposed center of symmetry, consists of a $Cu(pc)$ unit with two $Cu-OReO_3$ linkages. The mean deviation from the 24-atom core is 0.025(16) Å; the maximum deviation is 0.082(8) Å. The average Cu–N distance is 1.97(1) Å; the Cu–O distance is 2.526(5) Å, longer by 0.08 Å than the average value for **1** but still normal. The packing displays a herringbone pattern.

To obtain information about the nature of the oxidation the electronic structure of each compound was investigated by EPR spectroscopy. Crystals of **1** were ground in KBr to produce an isotropic sample for powder EPR analysis. A spectrum taken at 35 GHz (Q-band) and 77 K showed a broad peak, centered at $g = 3.7$. We assign this resonance to the “half-field” transition (or $\Delta m_s = \pm 2$) of an $S = 1$ spin system with zero-field splitting (ZFS) that is large compared with the X-band microwave quantum. This implies that the $[Cu(pc)]^+$ moieties in the crystal exhibit a triplet state formed by the exchange coupling of a d^9 Cu^{II} center and a pc π radical formed by the oxidation of the pc^{2-} ring to pc^- . Such an $S = 1$ state has been observed in frozen solutions of Cu^{II} porphyrin radical species by means of EPR spectroscopy,^[17] and also by means of magnetic-susceptibility measurements.^[16, 18] By analogy,^[19] we take the $S = 1$ state of **1** to be the ground state.

The absence of clear fundamental transitions ($\Delta m_s = \pm 1$) in the present spectrum does not permit a precise determination of the triplet-state zero-field splitting parameter (D) but through the use of second-order perturbation theory^[20] we estimate $D \approx 0.5$ cm^{−1} (14 GHz), substantially larger than the D parameter seen in the corresponding copper–porphyrin systems (0.116 cm^{−1}).^[21, 22]

In the two extreme ($S = 1/2$) valence-bond formulations of **2**, the compound would contain either $Cu^{III}pc^-$ with a diamagnetic (d^8) Cu^{III} center and an anion radical $pc^{\cdot-}$, or it would contain $Cu^{II}pc^0$ with a paramagnetic d^9 Cu^{II} center and a diamagnetic neutral pc^0 . To determine the correct description, EPR studies of a single crystal were carried out.

A face-indexed crystal of **2** was fixed to a simple dual-axis goniometer where the primary axis was a Kel-F rod perpendicular to the applied field and the secondary axis was a Kel-F screw. The crystal was aligned with its [101] direction along the secondary axis of rotation so that one set of pc planes was approximately perpendicular to the primary rotation axis. EPR spectra were recorded at 10° intervals of rotation about the primary axis. Figure 2 shows a spectrum for an orientation in which B_0 is perpendicular to the plane of one of the sites, along $g_{\parallel}$. The values of $g_{\parallel} = 2.16$ and $A_{\parallel} = 575$ MHz derived

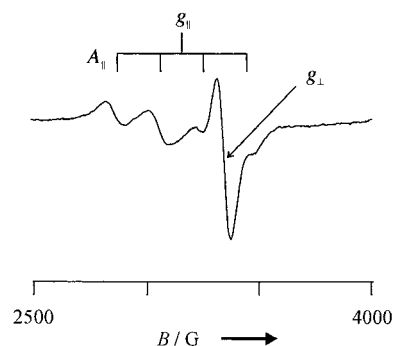


Figure 2. Single-crystal EPR spectrum of compound **2** taken at an orientation that maximizes the observed Cu hyperfine splitting. The measured $A_{\parallel}$ splitting is 190 G (575 MHz) at $g_{\parallel} = 2.16$. The observed line widths of the individual hyperfine transitions in the $g_{\parallel}$ region and $g_{\perp}$ peak are both ≈ 200 MHz, suggesting that the $A_{\perp}(Cu)$ is close to zero. The crystal was mounted and manipulated as described in the text. Experimental conditions: Temperature 295 K; microwave frequency, 9.527 GHz; microwave power, 200 mW; modulation amplitude, 10 G; scan time, 4 min.; time constant, 64 ms.

for this site are in good agreement with the values of 2.179 and 605.5 MHz, respectively, for [Cu(pc)].^[23]

The spectrum also contains a narrow (40 G peak–peak) feature that occurs at $g = 2.04$ and shows no resolved Cu (or N) hyperfine splittings. Given the structure, this must correspond to the perpendicular resonance for the magnetically inequivalent molecule of **2**. The observed value of $g_{\perp} = 2.04$ is in agreement with that of 2.05 for [Cu(pc)].^[23] This line is substantially narrower than that of a Cu(pc) $g_{\perp}$ feature. We attribute the decrease in line width in **2** to inter-ion exchange effects in this magnetically concentrated crystal.^[24]

These measurements show that both the g tensor and the $^{63,65}\text{Cu}$ hyperfine interactions are negligibly perturbed when the Cu(pc) unit is doubly oxidized to [Cu(pc)]²⁺. Thus, the Cu^{II} ion remains in its d^9 electronic configuration. The similarities in the $g_{\parallel}$ values of [Cu(pc)]²⁺ and Cu(pc) further show that the energy separation between the ground state $d_{x^2-y^2}$ and the d_{xy} orbitals are essentially the same in these two compounds.

In summary, structural and EPR studies show that [Cu(pc)(ReO₄)] (**1**) contains Cu(pc) units singly oxidized at the ring to produce the spin triplet formed by ferromagnetic coupling between the d^9 Cu^{II} ion and a π radical delocalized on the ring. Compound **2**, [Cu(pc)(ReO₄)₂] which contains [Cu(pc)]²⁺ moieties, also retains the paramagnetic Cu^{II} center, and thus contains a diamagnetic, doubly oxidized pc⁰ ring.

Experimental Section

Single crystals of both **1** and **2** grew at the anode of an electrolytic cell that consisted of two compartments separated by a glass frit. The [Cu(pc)] starting material was synthesized by metallation of very pure H₂(pc)^[2] with CuCl₂· x H₂O (99.9999%, dehydrated), followed by repeated sublimation. The electrolytic cell was protected from light, kept purged with dry N₂, and maintained at 120(5) °C. Each half-cell contained a solution of 1-chloronaphthalene (20 mL) that was 0.013 M in [N(*n*-Bu)₄][ReO₄]; the solution in the anode compartment was saturated with [Cu(pc)] ([Cu(pc)] < 10^{−3} M; $E_{\text{ox}} = 0.98$ V versus SCE^[23]). A 2.0 μA current was passed through the cell by platinum electrodes for three weeks, during which time the initially blue solution turned green. A few dark-purple crystals of **1** and several dark-red crystals of **2** grew on the anode in about a 1:10 ratio. These crystals were separated manually. The Cu:Re ratio of each crystal was determined by energy dispersive spectroscopy to provide a confirmation of the visual identification. Both compounds are air and light stable.

General crystallographic details: Bruker Smart 1000 CCD diffractometer,^[26] MoK α radiation ($\lambda = 0.71073$ Å), ω -scans, $T = 153$ K. For **1**, two hemispheres were collected, one at $2\theta = -28^\circ$, the other at $2\theta = -75^\circ$. The structures were solved by direct methods^[27] and refined with the program SHELXTL.^[28] Face-indexed absorption corrections were performed in the program XPREF.^[28] All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on their respective carbon atoms. Crystal structure analysis of **1**: C₃₂H₁₆CuN₈O₄Re, dark purple prism, $0.42 \times 0.25 \times 0.24$ mm, monoclinic, $P2_1/c$, $a = 20.455(4)$ Å, $b = 11.947(2)$ Å, $c = 27.327(6)$ Å, $\beta = 126.86(3)^\circ$, $V = 5343.4(19)$ Å³, $T = 153$ K, $Z = 8$, $\rho_{\text{calc}} = 2.054$ g cm^{−3}, $2\theta_{\text{max}} = 56.6^\circ$, 32531 reflections measured, 12544 unique, 10343 observed with $I > 2\sigma(I)$. $\mu = 53.8$ cm^{−1}, min/max transmission = 0.19/0.35. $R_1 = 0.064$, $wR_2 = 0.127$ (all data). Crystal structure analysis of **2**: C₃₂H₁₆CuN₈O₈Re₂, Deep red polyhedron, $0.24 \times 0.37 \times 0.49$ mm, monoclinic, $P2_1/c$, $a = 8.9825(18)$ Å, $b = 9.3147(19)$ Å, $c = 17.712(4)$ Å, $\beta = 95.96(3)^\circ$, $V = 1474.0(5)$ Å³, $T = 153$ K, $Z = 2$, $\rho_{\text{calc}} = 2.425$ g cm^{−3}, $2\theta_{\text{max}} = 56.54^\circ$, 9208 reflections measured, 3541 unique, 3223 observed with $I > 2\sigma(I)$. $\mu = 89.8$ cm^{−1}, min/max transmission = 0.063/0.18. $R_1 = 0.0550$, $wR_2 = 0.128$ (all data). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-

149171 (**1**) and CCDC-149172 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Highly Active Metathesis Catalysts Generated In Situ from Inexpensive and Air-Stable Precursors**

Janis Louie and Robert H. Grubbs*

The preparation of well-defined ruthenium alkylidene complexes bearing *N*-heterocyclic carbene ligands such as 1,3-dimesitylimidazol-2-ylidene (**1**) and 4,5-dihydroimidazol-2-ylidene (**2**) have led to catalysts (such as **3** and **4**; see Figure 1) which are highly active in ring-closing metathesis (RCM), cross metathesis (CM), and ring-opening metathesis polymerization (ROMP).^[1] These catalysts show increased thermal stability and similar tolerance to oxygen and moisture when compared to their parent bisphosphane complexes, [(PCy₃)₂Cl₂Ru=CHPh] (**5**, Figure 1).^[2] Since all synthetic routes to catalysts **3** and **4** proceed through the transformation of a ruthenium bisphosphane carbene,^[3] a direct route through readily available starting materials is still desirable.

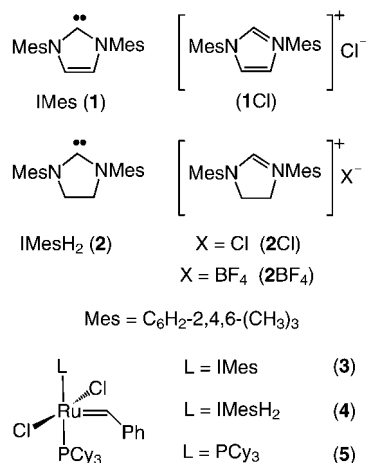


Figure 1. Well-defined ruthenium benzylidene complexes **3–5** possessing phosphane or imidazolylidene ligands **1** and **2**.

Ruthenium vinylidene complexes can be easily prepared from commercially available terminal alkynes and ruthenium sources.^[4] Unfortunately, such complexes have displayed only limited metathesis activity, such as the ROMP of highly strained norbornenes and the RCM of unsubstituted α,ω -dienes.^[4,5] As observed in other systems,^[1] ruthenium vinylidene compounds coordinated with an imidazolylidene ligand should exhibit increased activity and thus facilitate a broader range of metathesis reactions.

Our initial efforts were directed towards preparing and measuring the metathesis activity of various imidazolylidene ruthenium vinylidene complexes. The reaction of 1,3-diiso-

propyl-4,5-dimethylimidazol-2-ylidene (*i*PrIm)^[6] and [(PCy₃)₂Cl₂Ru=C=CHPh] (**6a**; Figure 2)^[4] quantitatively afforded [(*i*PrIm)₂Cl₂Ru=C=CHPh] (**7**) as a bright blue solid. Disappointingly, RCM of diethyl diallylmalonate using this complex was not observed, even under forcing conditions.^[7] This is somewhat surprising since the analogous bisimidazolylidene benzylidene complex is a known RCM catalyst.^[8]

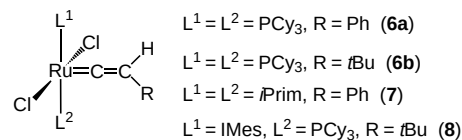


Figure 2. Ruthenium vinylidene complexes.

The mechanism of olefin metathesis appears to involve ligand (phosphane or imidazolylidene) dissociation and it is known that imidazolylidene ligands have relatively high binding energies.^[9] However, carbenes bearing a mixed ligand set, that is, one imidazolylidene and one phosphane, have more pronounced activities than their [L₂Cl₂Ru=CHR] (L = phosphane or imidazolylidene) counterparts. Thus, a ruthenium vinylidene complexes possessing a mixed ligand system was prepared and investigated for RCM activity. Simple phosphane displacement of the known complex [(PCy₃)₂Cl₂Ru=C=C(H)*t*Bu] (**6b**, Figure 2)^[4] by bulky 1,3-dimesitylimidazol-2-ylidene (**1**) afforded vinylidene complex **8** in 85 % yield as a brown solid. Complex **8** catalyzed the RCM of diethyl diallylmalonate in 86 % yield (Table 1, entry 1 a), although the reaction rate was much slower than with the ruthenium carbene complexes **3–5**. The slow rate of reaction may result from slow initiation since the propagating species, presumably methylidene, should be the same as that produced by carbene complex **3**. Noteworthy is that the replacement of a phosphane with an imidazolylidene in neutral allenylidene complexes does not provide a metathesis-active catalyst.^[10]

These results indicated that increased ligand dissociation (i.e., of phosphane) was necessary to accelerate initiation and thereby enhance catalytic activity. Previously, addition of phosphane sponges, such as copper salts or acids, has been used to facilitate RCM catalyzed by ruthenium carbenes. An alternative approach would involve the direct generation of the phosphane-free active species in situ, thus circumventing the need to add additional reagents to remove phosphane. Ruthenium vinylidene complexes can be conveniently prepared by adding two equivalents of phosphane and a terminal alkyne to [(*p*-cymene)RuCl₂]₂ (**9**).^[4] As shown in Table 1 (entry 1 b), the combination of 2.5 mol % dimer **9**, 5 mol % ligand **1**, and 5 mol % of *tert*-butyl acetylene catalyzed the RCM of diethyl diallylmalonate affording the ring-closed product in 95 % yield (80 °C, 12 h). The complex formed in situ displayed higher catalytic activity than vinylidene complex **8** (86 %, 65 °C, 24 h), which suggests that a vinylidene complex with a low coordination number, such as phosphane-free **8'** (Scheme 1), may be formed as a catalyst precursor (see below).

The scope of the reagents needed to generate vinylidene catalysts in situ was investigated further. As expected, the

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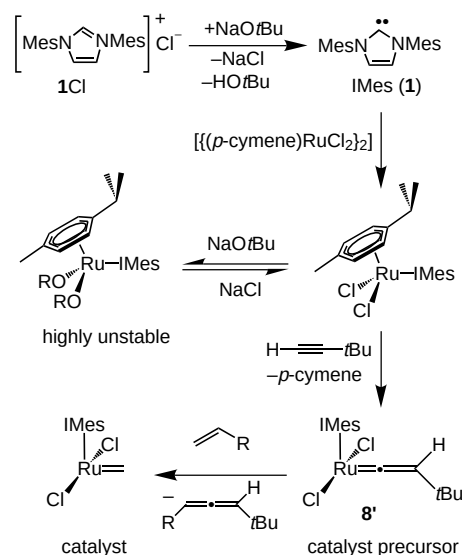
[**] J.L. acknowledges the National Institute of Health for a postdoctoral fellowship. We thank Christopher W. Bielawski for helpful discussions.

Table 1. Metathesis reactions using $[(p\text{-cymene})\text{RuCl}_2]_2$ (**9**), **1Cl**, NaOtBu, and *tert*-butyl acetylene.^[a] E = CO₂Et.

Entry	Substrate	Product	<i>t</i> [h]	Yield [%] ^[b]
1a			24 ^[d]	86 ^[c]
b			12 ^[e,f]	95 ^[c]
c			2 ^[e,f,h]	51 ^[c,i]
d			2 ^[e,f]	86 ^[c,i]
e			2 ^[e,g,h]	44 ^[c,i]
f			2 ^[e,g]	73 ^[c,i]
g			10	96
h			10 ^[h]	0
2			10	98
3			24	96
4			24	79
5			10	76
6			10	80
7			8	93
8			1 ^[j]	95

[a] Performed at 80 °C with 2.5 mol % of **9** in hexanes unless otherwise indicated. [b] Yield of isolated product. [c] Determined by ¹H NMR spectroscopy or GC using 1,3,5-mesitylene as an internal standard. [d] 5 mol % **8** as catalyst at 65 °C. [e] Performed with ligand **1Cl** instead of **1** and NaOtBu. [f] Toluene as solvent. [g] THF as solvent. [h] No *tert*-butyl acetylene was added. [i] Percent conversion. [j] No solvent.

absence of a ruthenium source **9** or ligand **1** failed to provide any ring-closed product. Unfortunately, other ruthenium sources such as [RuCl₂(PPh₃)₃] and [(RuCl₂(cod))_n] (cod = 1,5-cyclooctadiene), afforded no metathesis active species. While the absence of alkyne (*tert*-butyl acetylene) did provide ring-closed product, the reaction rates were slower (Table 1, compare entries 1c and d). Presumably, [(*p*-cymene)(IMes)-RuCl₂], a known RCM catalyst precursor, was generated in situ.^[11] However, when the RCM reaction was performed in THF the inclusion of alkyne resulted in substantially higher yields (compare entries 1e and f). It was also apparent from these control reactions that solvent plays an important role in the generation of a metathesis catalyst in situ (see below).



Scheme 1. Proposed pathways for catalyst generation and decomposition.

Although a number of imidazolylidene compounds are stable as their free carbene, an easier method would involve the generation of the free imidazolylidene carbene in situ from the appropriate salt and base. Such a method has been used to generate complexes **3** and **4** as well as PdL (L = imidazolylidene), a highly efficient aryl-amination catalyst.^[12] In hope of extending this methodology, we examined the RCM of diethyl diallylmalonate using $[(p\text{-cymene})\text{RuCl}_2]_2$, NaOtBu, and 2BF₄, **2Cl**, or **1Cl** under various conditions. Unfortunately, all the RCM reactions with the ligand 2X (X = BF₄, Cl) failed to give a cyclized product and may be related to the instability of the saturated imidazolylidene-free carbene.^[13] Alternatively, the formation of the vinylidene precursor may be blocked because of deprotonation of the alkyne by base, although addition of alkyne as the final reagent afforded only starting material. Similar results were obtained with **1Cl** when the reactions were performed in either toluene or THF. However, dramatically different results were obtained in hexanes. For example, diethyl diallylmalonate was converted into the corresponding ring-closed product in 96 % yield (Table 1, entry 1g). In the absence of alkyne, it is possible that a

highly unstable and unsaturated alkoxide ruthenium complex is generated by the presence of NaOtBu since no product was formed under these conditions (entry 1h).^[14] A proposed mechanism for the generation of the active species and the decomposition product is shown in Scheme 1. The combination of a low concentration of metal complex that is soluble in hexanes as well as the generation of a vinylidene complex from the addition of alkyne may produce a stable ruthenium vinylidene species resistant to decomposition.

A variety of metathetical reactions were performed using this system (Table 1). Interestingly, in addition to RCM, the catalyst generated in situ was also effective in CM, ene-yne metathesis, and ROMP. While reaction times were longer,

sterically hindered olefins were cyclized in comparable yields to those obtained by using complexes **3** and **4**.

Since all of the starting materials are air stable, we tried setting up the RCM reaction on the benchtop, thus eliminating the use of a drybox or vacuum line. The solid components (commercially available) were weighed in air into a reaction flask. The atmosphere was purged with argon followed by the addition of reagent grade hexanes, *tert*-butyl acetylene, and diethyl diallylmalonate. After 10 h at 80 °C, ring-closed product was obtained in 88 % yield. The reaction rate and yield were comparable to those when degassed solvents and drybox procedures were employed (96 %, Table 1, entry 1 g).

In conclusion, when coordinated to a bulky imidazolylidene ligand, ruthenium vinylidene complexes are effective catalysts for a variety of metathetical reactions. Although reaction rates were slower, their general reactivity profile towards a variety of substrates was similar to the analogous highly active ruthenium alkylidenes (**3** and **4**). In addition, the catalysts can be generated in situ from inexpensive, air stable, and commercially available starting materials, which circumvents the need for a drybox or special Schlenk equipment.

Experimental Section

Representative procedure: In a drybox, [(*p*-cymene)RuCl₂]₂ (0.02 mmol), ligand **1**Cl (0.045 mmol), and NaOtBu (0.045 mmol) were weighed directly into a screw cap vial. A stir bar was added followed by hexanes (2 mL). Substrate (0.85 mmol) and *tert*-butyl acetylene (0.045 mmol) were added and the vial was sealed with a PTFE lined cap. The vial was removed from the drybox and the contents stirred at 80 °C. The reaction was monitored by GC and after complete consumption of substrate, the products were purified by chromatography on silica gel. All products listed in Table 1 have been previously characterized.

Selected NMR data for **8**: ¹H NMR (300 MHz, C₆D₆): δ = 6.76 (s, 2H; NCHCHN), 5.99 (s, 1H; C(*t*Bu)H), 2.78–2.67 (m, 3H, 3CH of PCy₃), 2.44 (s, 9H; 3CH₃), 2.14 (s, 9H; 3CH₃), 2.14–2.09 (m, 8H; CH₂ of PCy₃), 1.69–1.58 (m, 14H; CH₂ of PCy₃), 1.28–1.17 (m, 8H; CH₂ of PCy₃), 1.12 (s, 9H; C(CH₃)₃); ³¹P NMR (121.4 MHz, C₆D₆): δ = 17.4 (s).

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Highly Enantioselective Palladium-Catalyzed Ene-Type Cyclization of a 1,6-Enyne**

Manabu Hatano, Masahiro Terada, and Koichi Mikami*

Dedicated to Professor Barry M. Trost on the occasion of his 60th birthday

Transition metal catalyzed ene-type carbocyclizations of 1,6-enynes such as cycloisomerization^[1] and the ene reaction^[2] are powerful synthetic methods leading to five-membered rings.^[3–5] However, examples for the corresponding enantioselective catalysis are limited,^[6] hence it is a challenge to establish high levels of asymmetric induction as well as high yields. Herein we report a highly efficient catalysis by chiral palladium(II) complexes for enantioselective ene-type carbocyclizations of the 1,6-enyne **1** leading to highly enantioenriched five-membered rings [Eq. (1)].

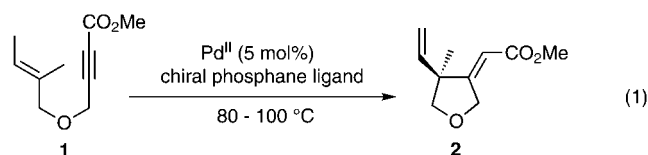
The palladium(II)-catalyzed carbocyclization reactions of 1,6-enynes have generally been performed with Pd(OAc)₂ or by the combined use of Pd⁰ species (e.g. [Pd₂(dba)₃ · CHCl₃] (dba = *trans,trans*-dibenzylidene acetone) and a weak acid such as acetic acid or trifluoroacetic acid.^[3] However, in the presence of a chiral bidentate phosphane ligand, such as BINAP (BINAP = 2,2'-bis(diphenylphosphanyl)-

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1,1'-binaphthyl), these typical palladium catalysts were ineffective with the 1,6-enyne **1** exhibiting insufficient catalytic activity and low levels of asymmetric induction (Table 1: entries 1–3). The Pd^{II}-catalyzed asymmetric cyclization of **1** to 1,4-diene (*S*)-**2** was successfully achieved in quantitative yield and with high enantioselectivity (93% *ee*) (entry 4) by using 5 mol % of Pd(OCOCF₃)₂ and 10 mol % of (*R*)-BINAP in thoroughly degassed C₆D₆ at 100 °C. The absolute configuration of **2** was determined, by X-ray crystallographic analysis, as a chiral amine salt of the corresponding carboxylic acid with (*S*)-1-phenylethylamine.^[7] Furthermore, decreasing the ratio of BINAP to Pd^{II} from 2:1 to 1.1:1 and lowering the temperature (entry 5) did not compromise enantioselectivity.^[8]

Table 1. Enantioselective ene-type carbocyclization of the 1,6-enyne **1** catalyzed by BINAP–Pd complexes^[a].

Entry	Pd species (mol %)	Solvent	Reaction time [h]	Yield [%]	<i>ee</i> [%] ^[b] (Config.)
1	Pd(OAc) ₂ (5)	C ₆ D ₆	72	68	11 (<i>S</i>)
2 ^[c]	[Pd ₂ (dba) ₃]·CHCl ₃ (2.5)/AcOH (12)	C ₆ D ₆	96	18	77 (<i>S</i>)
3 ^[c]	[Pd ₂ (dba) ₃]·CHCl ₃ (2.5)/TFA (12)	C ₆ D ₆	96	25	84 (<i>S</i>)
4	Pd(OCOCF ₃) ₂ (5)	C ₆ D ₆	24	> 99	93 (<i>S</i>)
5 ^[c,d]	Pd(OCOCF ₃) ₂ (5)	C ₆ D ₆	80	> 99	94 (<i>S</i>)
6 ^[c]	Pd(OCOCF ₃) ₂ (5)	DMSO	16	> 99	72 (<i>S</i>)
7 ^[c]	[(MeCN) ₄ Pd](BF ₄) ₂ (5)	DMSO	6	> 99	73 (<i>S</i>)

[a] Reactions were carried out in thoroughly degassed solvents at 100 °C with 5 mol % of Pd catalyst and 10 mol % of (*R*)-BINAP as a chiral ligand unless otherwise noted. [b] The *ee* value was based on chiral GC analysis of **2**. [c] Reactions were carried out at 80 °C. [d] 5.5 mol % of (*R*)-BINAP was used.

A remarkable solvent effect was also observed in this catalytic reaction. In a “polar solvent” such as DMSO, the reaction was completed within a shorter period of time at lower reaction temperature (entry 6), but the enantiomeric excess decreased to 72% *ee* as compared with that in the “less-polar solvent” (entry 4).^[9] The dicationic Pd^{II} species, [(MeCN)₄Pd](BF₄)₂, was found to dramatically accelerate the reaction in DMSO (entry 7). Nevertheless these reactions suffered from lower enantioselectivity with (*R*)-BINAP (entries 6 and 7).

Further exploration of modified BINAP ligands^[10] with either the Pd(OCOCF₃)₂/C₆D₆ or the [(MeCN)₄Pd](BF₄)₂/DMSO system led to a remarkable improvement in the enantioselectivity (Table 2). In the less-polar solvent (Pd(OCOCF₃)₂/C₆D₆ system), we eventually obtained the enantiopure product (**2**) by using (*R*)-SEGPHOS (SEGPHOS = seagull phosphane)^[11] as a bidentate phosphane ligand. (*R*)-tol-BINAP and

(*S*)-H₈-BINAP ligands were effective (entries 1 and 2), but did not afford enantioselectivities significantly higher than that with the parent BINAP ligand. The use of the sterically more demanding (*S*)-xylyl-H₈-BINAP ligand resulted in a significant lowering in enantioselectivity (entry 3). Presumably because of its bulkiness, (*S*)-xylyl-H₈-BINAP is forced to dissociate from the Pd^{II} complex during the catalysis generating an achiral Pd^{II} species. We finally achieved the virtually complete enantioselectivity with (*R*)-SEGPHOS to give the cyclized product **2** in quantitative yield and in an enantiopure form (> 99% *ee*) (entry 4). The (*R*)-SEGPHOS ligand is also effective in the polar solvent. Thus, the [(MeCN)₄Pd](BF₄)₂/DMSO system (entry 5) exhibited a higher enantioselectivity than that with BINAP. Noteworthy is that a further improvement in the enantioselectivity was achieved by using the sterically demanding (*S*)-xylyl-H₈-BINAP ligand (entry 6) in sharp contrast to the low enantioselectivity observed in the less-polar solvent using Pd(OCOCF₃)₂/C₆D₆ system (entry 3). By the combination of a SEGPHOS skeleton and a bulky xylyl substituent in the (*S*)-xylyl-SEGPHOS ligand, highly enantioselective catalysis (96% *ee*) could be envisioned in the [(MeCN)₄Pd](BF₄)₂/DMSO system (entry 7).

We next turned our attention to the mechanism of this highly efficient enantioselective catalysis. The key to clarifying the catalytic cycle is to determine whether or not hydride–palladium (H–Pd) is the active species. Taking advantage of hydride exchange between D₂O and H–Pd to generate D–Pd species,^[12] we examined the reactions under excess D₂O (600 mol %) conditions (Figure 1 and Table 3). Consequently, the deuterated product at the vinylic position was obtained without diminution of catalytic activity under either polar or less-polar conditions. These results indicate that the hydride(deuteride)–palladium is the active species. The possible catalytic cycle would be completed as shown in

Table 2. Ene-type carbocyclization of **1** catalyzed by Pd(OCOCF₃)₂/C₆D₆ or [(MeCN)₄Pd](BF₄)₂/DMSO with modified BINAP ligands.

(<i>R</i>)-BINAP (Ar = Ph)		(<i>S</i>)-H ₈ -BINAP (Ar = Ph)		(<i>R</i>)-SEGPHOS (Ar = Ph)	
(<i>R</i>)-tol-BINAP (Ar = <i>p</i> -MeC ₆ H ₄)		(<i>S</i>)-xylyl-H ₈ -BINAP (Ar = 3,5-Me ₂ C ₆ H ₃)		(<i>S</i>)-xylyl-SEGPHOS (Ar = 3,5-Me ₂ C ₆ H ₃)	
Entry	System ^[a]	Ligand	Reaction time [h]	Yield [%]	<i>ee</i> [%] (Config.)
1	Pd(OCOCF ₃) ₂ /C ₆ D ₆	(<i>R</i>)-tol-BINAP	43	> 99	94 (<i>S</i>)
2	Pd(OCOCF ₃) ₂ /C ₆ D ₆	(<i>S</i>)-H ₈ -BINAP	48	> 99	95 (<i>R</i>)
3	Pd(OCOCF ₃) ₂ /C ₆ D ₆	(<i>S</i>)-xylyl-H ₈ -BINAP	20	> 99	12 (<i>R</i>)
4	Pd(OCOCF ₃) ₂ /C ₆ D ₆	(<i>R</i>)-SEGPHOS	37	> 99	> 99 (<i>S</i>)
5	[(MeCN) ₄ Pd](BF ₄) ₂ /DMSO	(<i>R</i>)-SEGPHOS	6	> 99	90 (<i>S</i>)
6	[(MeCN) ₄ Pd](BF ₄) ₂ /DMSO	(<i>S</i>)-xylyl-H ₈ -BINAP	12	> 99	94 (<i>R</i>)
7	[(MeCN) ₄ Pd](BF ₄) ₂ /DMSO	(<i>S</i>)-xylyl-SEGPHOS	14	> 99	96 (<i>R</i>)

[a] Reactions were carried out with 5 mol % of Pd catalyst and 10 mol % of chiral ligand in thoroughly degassed solvents at 100 °C in the Pd(OCOCF₃)₂/C₆D₆ system or at 80 °C in the [(MeCN)₄Pd](BF₄)₂/DMSO system.

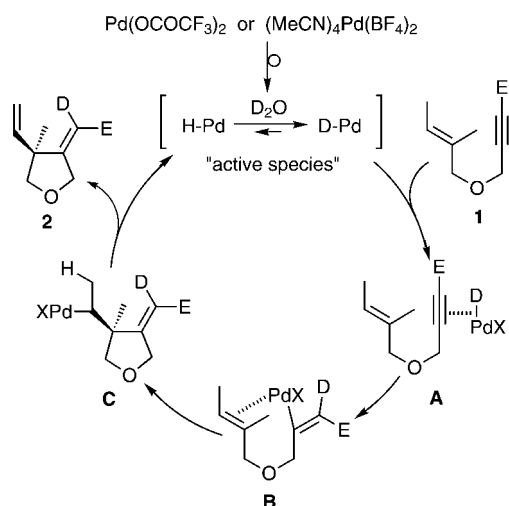


Figure 1. Catalytic cycle involving H(D)–Pd as the active species.

Table 3. Ene-type carbocyclization of **1** in the presence of D₂O^[a].

Entry	Pd ^{II} catalyst	Solvent	Reaction time [h]	Yield [%]	D-Content [%]	ee [%]
1	Pd(OCOCF ₃) ₂	C ₆ D ₆	30	> 99	56	93
2	Pd(OCOCF ₃) ₂	DMSO	24	> 99	74	68
3	[(MeCN) ₄ Pd](BF ₄) ₂	DMSO	24	> 99	77	65

[a] Reactions were carried out at 100 °C with 5 mol % of Pd^{II} catalyst and 10 mol % of (*R*)-BINAP in the presence of 600 mol % of D₂O.

Figure 1:^[13] the initially formed H–Pd coordinates to acetylene (**A**), followed by insertion (**B**), cyclization (**C**), and β-H elimination to give the product **2** and regenerate the H–Pd species.

It should be pointed out that this Pd-catalyzed carbocyclization reveals a) the dependence of both the enantioselectivity and the catalytic activity on the solvent polarity (Table 1: entries 4 and 6 and Table 3: entries 1 and 2) and b) the independence of the enantioselectivity on the Pd^{II} source, Pd(OCOCF₃)₂ or [(MeCN)₄Pd](BF₄)₂, under the polar conditions (Table 3, entries 2 and 3). These observations are fully rationalized on the basis of coordination modes (**B-4C** and **B-5C**;^[14] Figure 2) in the intermediates (**B**). In the

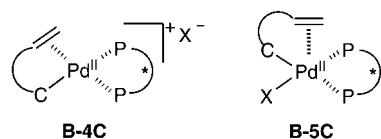


Figure 2. Four- and five-coordinate intermediates (**B-4C**, **B-5C**).

polar solvent, the [(MeCN)₄Pd](BF₄)₂/DMSO system facilitates the generation of a cationic four-coordinate intermediate (**B-4C**) as result of the solvent polarity and the weakly coordinating nature of the BF₄[−] ion. The same levels of enantioselectivity are obtained under the polar conditions regardless of the Pd^{II} sources and imply that the reaction proceeds via the identical intermediate (**B-4C**) in the Pd(OCOCF₃)₂/DMSO system. In the polar solvent, Pd(OCOCF₃)₂ associatively releases the counter anion, even

a CF₃COO[−] ion, to offer one coordination site on the square-planar cationic complex. The olefin moiety is able to occupy this site to give the four-coordinate intermediate (**B-4C**) identical to that obtained in the [(MeCN)₄Pd](BF₄)₂/DMSO system (Figure 2). The catalytic activity of the [(MeCN)₄Pd](BF₄)₂/DMSO system is higher than in the Pd(OCOCF₃)₂/DMSO system (Table 1: entries 7 vs. 6), consistent with the stabilization of the cationic intermediates by the counter ion, that is BF₄[−] versus CF₃COO[−]. In contrast, in the less-polar solvent (Pd(OCOCF₃)₂/C₆D₆ system), the counter anion remains coordinated to the Pd^{II} species. The olefin moiety is forced to coordinate to the fully occupied square-planar Pd^{II}, generating a relatively unfavorable five-coordinate intermediate (**B-5C**) as a neutral complex (Figure 2).^[15] The higher catalytic activity under the polar conditions is rationalized by the preferred four-coordinate intermediate (**B-4C**). The high enantioselectivity obtained by sterically demanding xylyl-BINAP under the polar conditions (Table 2: entries 6 and 7) contrasts sharply to the low enantioselectivity under the less polar conditions (Table 2: entry 3). Under the less polar conditions the bulky xylyl-H₈-BINAP ligand is forced to dissociate from the sterically congested five-coordinate intermediate (**B-5C**) to generate an achiral Pd^{II} species. The dependence of the enantioselectivity on the solvent polarity reveals strong evidence that the reaction takes place via different coordination modes.

The high enantioselectivities are rationalized on the basis of these intermediates (Figure 3). Under the polar conditions, the reaction took place via the four-coordinate transition states (**4C-1** and **4C-2**) to afford the cyclized product (*S*)-**2** and (*R*)-**2**, respectively. The transition state (**4C-2**) is relatively less favorable because of steric repulsion between the terminal Me group of the substrate **1** and the equatorial Ph group of (*R*)-BINAP or its analogue. On the other hand, the transition state (**4C-1**) avoids this repulsion, eventually affording (*S*)-**2** through β-H elimination. Under the less-polar conditions, the olefin is forced to coordinate to the Pd^{II} center on one side of the Z-axis to reach the five-coordinate transition states (**5C-1** and **5C-2**). The repulsive interaction between the terminal Me group of the substrate **1** and the equatorial Ph group of the (*R*)-BINAP ligand or its analogue is significant in the transition state (**5C-2**), giving (*R*)-**2** in higher %ee. The reaction takes place entirely via the transition state (**5C-1**) to afford (*S*)-**2**.

In summary, we have developed a highly efficient palladium(II)-catalyzed ene-type carbocyclization of a 1,6-enyne leading to enantiopure five-membered rings. This highly enantioselective catalysis is applicable for the construction of an enantioenriched quaternary chiral center.^[16] Possible mechanisms including neutral and cationic intermediates have been proposed.

Experimental Section

Thoroughly degassed C₆D₆ (2.0 mL) was injected under argon into a pyrex Schlenk tube containing Pd(OCOCF₃)₂ (8.3 mg, 0.025 mmol) and (*R*)-BINAP (31.1 mg, 0.050 mmol), and this suspension was stirred at room temperature for 5–10 min at which time the solution become clear. Then **1** (91.1 mg, 0.500 mmol) was added, the tube was sealed with a screw cap. The mixture was stirred at 100 °C for 24 h. The crude mixture was checked by

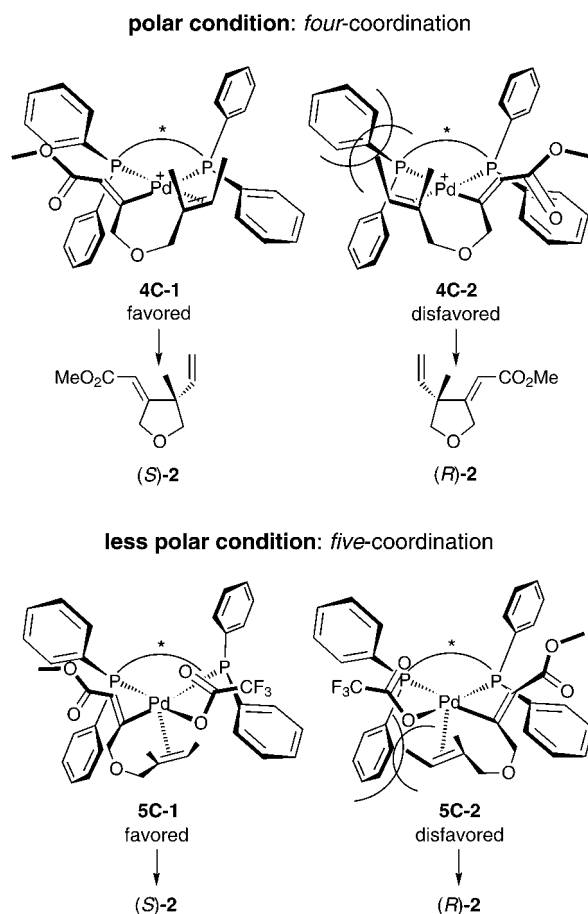


Figure 3. Transition states for enantioselective carbocyclization catalyzed by chiral Pd^{II} complexes under polar or less-polar conditions.

¹H NMR spectroscopy (C₆D₆), before purification by column chromatography (on a short, neutral silica-gel column, pentane/ether = 100/3) to afford (S)-**2**, 93% ee ($[\alpha]_D^{25} = +37.6$ ($c = 0.586$ in CHCl₃); chiral GC column; CP-Cyclodextrin- β -2,3,6-M-19 (0.25 mm $\times$ 25 m, CHROMPACK, GL Sciences Inc.; $t_R = 31.8$ min (R) and 33.7 min (S)) in quantitative yield. ¹H NMR (300 MHz, CDCl₃): $\delta = 1.26$ (s, 3H), 3.62 (d, $J = 8.7$ Hz, 1H), 3.69 (s, 3H), 3.72 (d, $J = 9.0$ Hz, 1H), 4.77 (dd, $J = 17.7, 2.4$ Hz, 1H), 4.91 (dd, $J = 17.7, 2.4$ Hz, 1H), 5.16 (d, $J = 11.1$ Hz, 1H), 5.17 (d, $J = 17.7$ Hz, 1H), 5.63 (t, $J = 2.4$ Hz, 1H), 5.79 (dd, $J = 17.7, 10.5$ Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): $\delta = 22.2, 50.7, 51.4, 72.2, 78.3, 111.0, 114.9, 140.7, 166.8, 169.4$.

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- [7] Compound **2** was converted into the corresponding carboxylic acid through hydrolysis, and then crystallized as a diastereomeric salt of (S)-1-phenylethylamine in an Et₂O/CH₂Cl₂ mixture at room temperature Figure 4. X-ray data for this salt: formula (C₉H₁₂O₃)₂ · C₈H₁₁N,

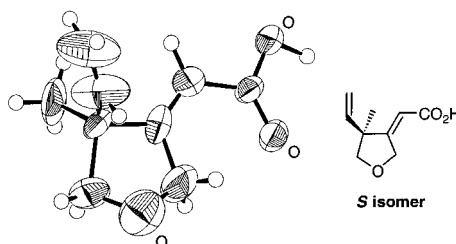


Figure 4. ORTEP representation and the structural formula of the chiral amine salt. The chiral amine was omitted for clarity.

monoclinic, space group $P2_1$, $a = 12.0888(7)$, $b = 6.1803(4)$, $c = 16.859(1)$ Å, $\beta = 91.042(3)^\circ$, $V = 1259.3(2)$ Å³, $Z = 2$, and $\rho = 1.207$ g cm⁻³. X-Ray diffraction data were collected on a Rigaku RAXIS-RAPID Imaging Plate diffractometer with graphite-monochromated MoK α ($\lambda = 0.71069$ Å) at -160°C and the structure was solved by direct methods (SIR97). The final cycle of full-matrix least-squares refinement was based on 2100 observed reflections ($I > 3\sigma(I)$) and 297 variable parameters and converged to $R = 0.067$ and $R_w = 0.094$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-149520. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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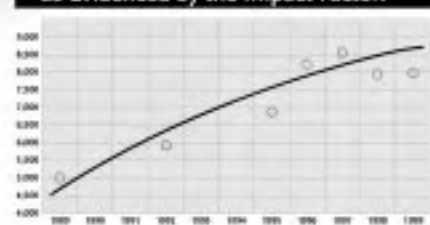


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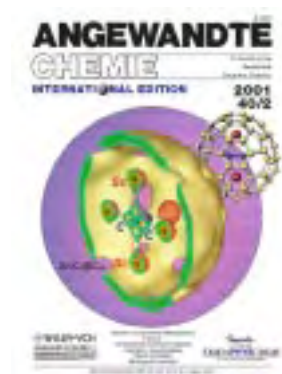
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Cover Picture

Chun-Ru Wang, Tsutomu Kai, Testuo Tomiyama, Takuya Yoshida, Yuji Kobayashi, Eiji Nishibori, Masaki Takata, Makoto Sakata, and Hisanori Shinohara*

The cover picture shows a section of the electron charge density of the first metal carbide endohedral metallofullerene (Sc_2C_2)@ C_{84} obtained from a synchrotron X-ray powder diffraction study by the maximum entropy method (MEM). The several density maxima, which correspond to scandium and carbon atoms, are clearly seen inside the C_{84} carbon cage. The MEM charge density distribution also reveals that the C_{84} cage has D_{2d} symmetry (no. 23) and that the C_2 axis is parallel to the $\langle 100 \rangle$ face-centered cubic (fcc) direction of the unit cell. As a consequence of the site symmetry being $4mm$, the C_2 axis of (Sc_2C_2)@ C_{84} is oriented to six equivalent $\langle 100 \rangle$ directions and shows a merohedral disorder. The resultant $\text{Sc} \cdots \text{Sc}$ distances and $\text{C}-\text{C}$ bond lengths of the Sc_2C_2 cluster are 0.429(2) and 0.142(6) nm, respectively. The observed $\text{C}-\text{C}$ bond length is between that of a typical single and a double bond, and is very close to that of the $\text{C}-\text{C}$ bond (0.143 nm) combining two pentagons in a C_{60} molecule. More about this fascinating structure can be found in the contribution by Shinohara and co-workers on p. 397 ff.



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Buried Dielectric Mirrors for the Lateral Overgrowth of GaN-Based Microcavities

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The use of lateral overgrowth techniques to develop III-nitride microcavities with both mirrors fabricated from very highly reflecting dielectric multilayers (e.g. SiO₂/ZrO₂) will be discussed. Multilayer mirror stacks with broad high reflectivity stop-bands and peak reflectivities in excess of 99% at wavelengths near the emission energies of typical InGaN/GaN quantum well structures, have been patterned in order to be compatible with subsequent lateral epitaxial overgrowth or pendeoepitaxy. Improvements in material quality resulting from lateral overgrowth above single layer masks are demonstrated using spatially resolved photoluminescence and cathodoluminescence imaging.

1. Introduction The impressive development of violet and blue edge-emitting laser diodes with InGaN/GaN active regions has been well documented [1] and promises great technological impact. Microcavity devices, such as resonant cavity LEDs and vertical cavity surface emitting lasers (VCSELs), constructed from III-nitride materials should possess a number of additional advantages over these edge-emitters, including lower thresholds, improved mode quality and possibilities for planar arrays of large numbers of devices. Recent reports of optically-pumped surface emitted lasing [2–4] have indicated good progress towards short wavelength GaN-based VCSELs. However, viable devices still require improvements in the quality of the active material and in the performance of the distributed Bragg reflectors (DBRs) forming the microcavity.

We have proposed the use of lateral overgrowth techniques, including lateral epitaxial overgrowth (LEO) [5] and pendeoepitaxy [6], to achieve concurrent improvements in both these areas [7]. High quality laser material is known to result from these overgrowth techniques, which conventionally employ single layer dielectric masks or etched seed structures. In this paper we will describe improvements in the quality of GaN grown at Strathclyde using conventional LEO. We will then discuss how both lateral growth techniques can be used to “bury” dielectric DBRs in order to form the lower

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reflector in a microcavity. Such DBRs have significant advantages, including higher peak reflectivities and wider reflectivity stop-bands, compared to conventional AlGaIn-based DBRs [8].

2. Dielectric Mirrors Fabricated from $\text{SiO}_2/\text{ZrO}_2$ The measured reflectivity of an electron-beam-deposited $10^{1/2}$ -period dielectric DBR, composed of $\text{SiO}_2/\text{ZrO}_2$ and centred near 420 nm, is shown in Fig. 1 and the high-reflectivity bandwidth is seen to be in excess of 80 nm. The lower part of the figure shows the effect of a similar DBR on the low temperature photoluminescence (PL) from an InGaIn/GaN single quantum well structure.²⁾ The high reflectivity of the upper mirror is indicated by the appearance of cavity modes in the luminescence following DBR deposition. The fringe spacing indicates that the lower reflector is formed by the weakly reflecting GaN–sapphire interface region. The incorporation of a second highly reflecting dielectric DBR beneath the quantum well region will significantly enhance the finesse of the cavity. Methods to achieve this will now be considered.

3. Lateral Epitaxial Overgrowth Replacement of the single SiO_2 layers conventionally used as masks for LEO with SiO_2 -terminated, multilayer dielectric DBRs, of the type discussed above, makes it possible to “bury” these mirrors beneath laterally grown III-N material. As shown in Fig. 2 we have prepared arrays of striped dielectric mirror elements suitable for LEO over the surface of 2-inch GaN-on-sapphire wafers using lift-off techniques [8]. The widths of the mirror stripes and “window” regions between stripes have been varied in the range 4–10 μm .

In advance of utilising these patterned mirror layers as masks for overgrowth we have investigated the properties of GaN LEO above a single dielectric layer in the

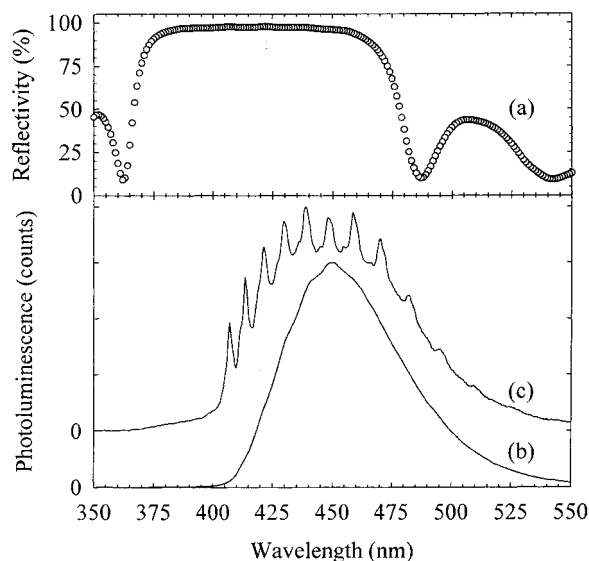


Fig. 1. Upper panel: Reflectance spectrum (a) measured from a $10^{1/2}$ -period $\text{SiO}_2/\text{ZrO}_2$ DBR on GaN. Lower panel: PL data from an InGaIn/GaN single quantum well before (b) and after (c) deposition of such a DBR above the quantum well

²⁾ The authors are grateful to Dr. S. Nakamura for supply of this InGaIn/GaN material, which emits over an unusually large spectral range.

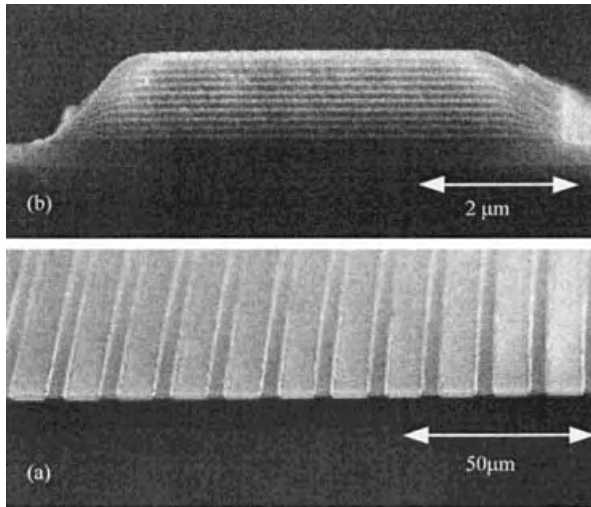


Fig. 2. a) Scanning electron micrograph of a $10^{1/2}$ -period $\text{SiO}_2/\text{ZrO}_2$ DBR on GaN patterned into 4 μm stripes using a single layer lift-off technique. b) Cross-sectional view of a 6 μm wide stripe

Aixtron MOCVD reactor at Strathclyde. Good coalescence is observed above 200 nm thick $[1\bar{1}00]$ -oriented SiO_2 stripes, with a range of widths and spacings. Room temperature cathodoluminescence (CL) imaging clearly shows the improved quality of the laterally grown material. The inset to Fig. 3 shows a CL image of the GaN band-edge luminescence (365 ± 10 nm) from an LEO region with 9 μm wide stripes and 7 μm wide window regions. The bright bands correspond to the higher quality laterally grown GaN lying above the SiO_2 stripes. Photoluminescence is collected from regions containing

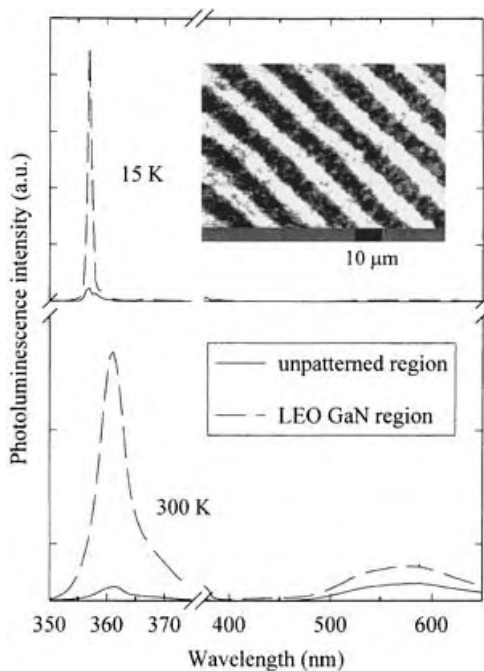


Fig. 3. PL data from LEO GaN at room temperature and low temperature, showing the improvement in moving from an unpatterned region to an area above silica stripes of width 4.1 μm, with 4.5 μm wide windows. The inset shows a room temperature CL image at (365 ± 10) nm from an LEO region, with 9 μm wide stripes and 7 μm wide window regions

Table 1

The ratio of the GaN band-edge PL peak intensities for striped and unpatterned regions of LEO wafers

stripe width (μm)	window width (μm)	ratio of PL peak intensities	
		$T = 300\text{ K}$	$T = 15\text{ K}$
4.1	4.5	15	18
4.1	6.8	17	
9.1	4.5	14	14
9.1	6.8	16	

several stripes and windows, using HeCd laser light focussed to a spot of approximately $20\text{ }\mu\text{m}$ diameter, and compared with PL data from unpatterned regions of the same wafer. As shown in Fig. 3 the striped regions show considerably better luminescence than the unpatterned regions. The ratio of the GaN band-edge PL peak intensities in the striped and unpatterned regions is approximately 15 for several stripe/window combinations and at both high and low temperature, as shown in Table 1.

4. Dielectric Mirrors for Pendeoepitaxial Overgrowth During pendeoepitaxy [6] lateral growth of III–N is seeded from ridge structures. If the dielectric mirrors are prepared in the regions between ridges this overgrowth technique may be used to bury them under a III–N active region. We have demonstrated [9] fast and controllable inductively coupled plasma etching of III-nitrides, using a STS multiplex system and $\text{Cl}_2/\text{BCl}_3/\text{Ar}$ gas chemistries, and have used this to produce ridges suitable for GaN pendeoepitaxy. Micrographs showing the results of an initial attempt to prepare $\text{SiO}_2/\text{ZrO}_2$ multilayer DBRs between the ridges are shown in Fig. 4. Some deposition of dielectric material is observed on the ridge side-walls and further work is in progress to produce clean GaN side-walls suitable for seeding lateral growth across the mirror surface.

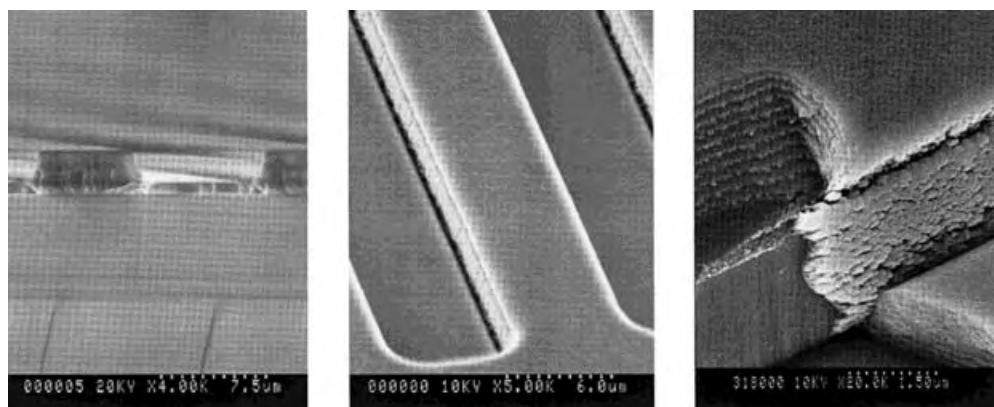


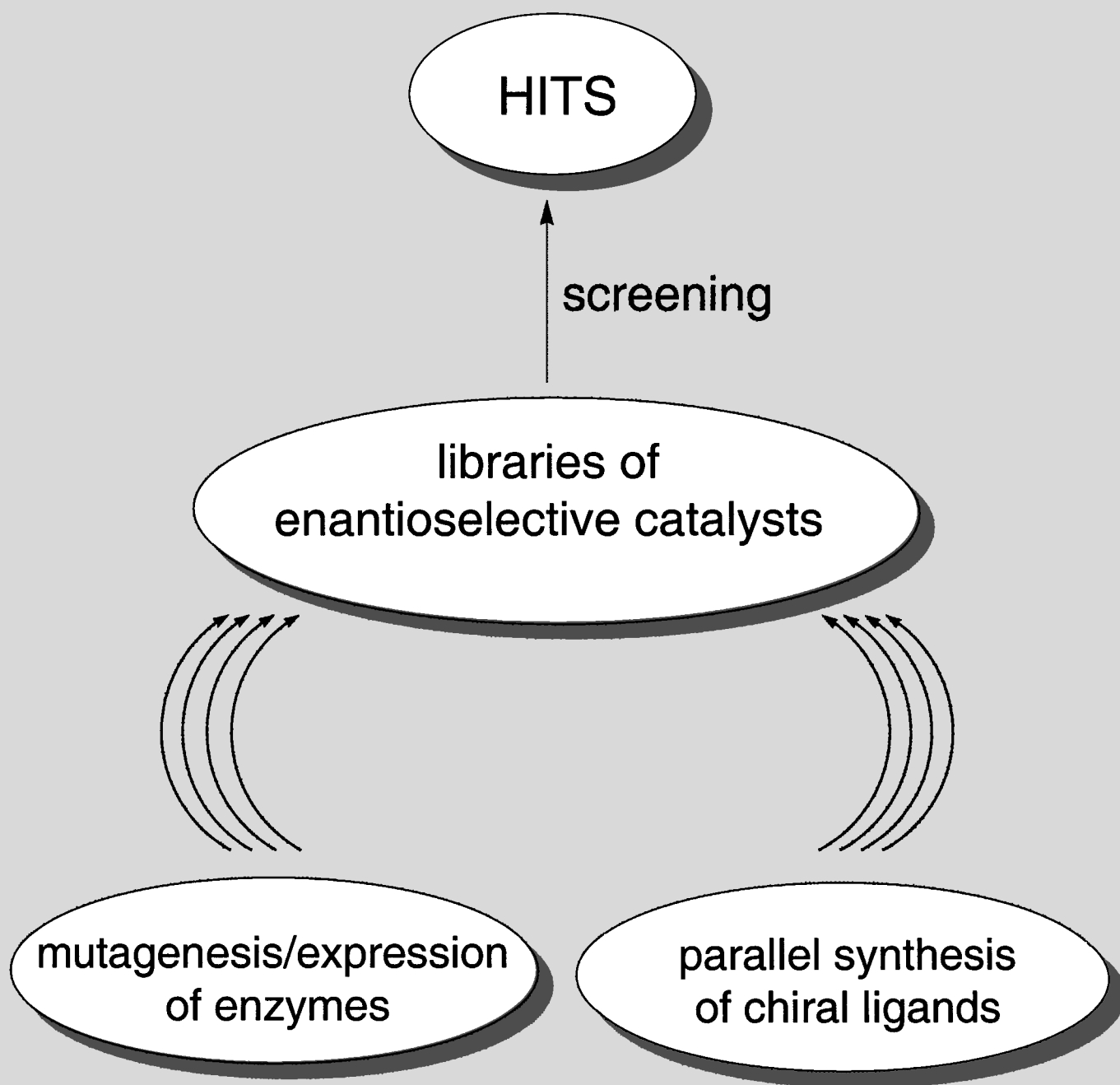
Fig. 4. Scanning electron micrographs showing a $\text{SiO}_2/\text{ZrO}_2$ dielectric DBR deposited above and between ICP etched ridges in GaN. The first and second images show cross-sectional and plan views of the ridges, whilst the third image illustrates the DBR structure along with the side-wall deposition discussed in the text

5. Conclusions The use of lateral overgrowth techniques for the production of high quality GaN-based microcavities has been discussed. These are predicted to enhance the performance of III–N microcavities, due to simultaneous improvement in the quality of the active material and in the performance of the reflector beneath the cavity. Improvements in GaN luminescence resulting from lateral overgrowth and progress towards the use of dielectric multilayers in overgrowth have been described.

Acknowledgement The authors are grateful for funding from the U.K. EPSRC and HSK is grateful for a research fellowship from the Korea Research Foundation.

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Combinatorial and Evolution-Based Methods in the Creation of Enantioselective Catalysts

Manfred T. Reetz*

Dedicated to Professor K. Barry Sharpless on the occasion of his 60th birthday

Combinatorial methods in the development of enantioselective homogeneous catalysts constitute a new branch of catalysis research. The goal is to prepare libraries of potential asymmetric catalysts, rather than choosing the traditional one-catalyst-at-a-time approach. Several conceptional advancements have been reported in the parallel preparation of chiral ligands. Currently the most meaningful systems constitute modularly constructed ligands on solid supports, which allow high degrees of structural diversity and thus the maximum probability of finding enantioselective catalysts or even new types of ligands for asymmetric catalysis. Search strategies have been developed which amongst other things, lead to catalysts not likely to have been discovered by traditional methods. Genuine application of such strategies involve thousands of catalysts and

require high-throughput screening systems capable of assaying enantioselectivity. The first high-throughput *ee*-screening systems were in fact developed for use in the directed evolution of enantioselective enzymes, a process based on "evolution in the test tube" in which the appropriate methods of random mutagenesis, gene expression, and *ee* assays are combined. Since no screening system is likely to be universal, different approaches are necessary. Thus far these include assays based on UV/Vis, fluorescence, circular dichroism, mass spectrometry, and even modified gas chromatography as well as special forms of capillary electrophoresis. One of the most efficient systems involves the concept of the mass-spectrometric detection of deuterium-labeled pseudo-enantiomers and pseudo-prochiral compounds with which about 1000 exact *ee* determina-

tions can be achieved per day, although the assay is restricted to kinetic resolution and/or reactions of prochiral compounds bearing enantiotopic groups. Super-high-throughput screening for enantioselectivity is possible in many cases by making use of chirally modified capillary array electrophoresis in a parallel step. Accordingly, 7000 to 30000 *ee* determinations can be carried out per day. These and other analytical developments are expected to stimulate further research in the combinatorial search for asymmetric homogeneous catalysts and in the directed evolution of enantioselective enzymes for use in organic chemistry.

Keywords: analytical methods • asymmetric catalysis • combinatorial chemistry • directed evolution • enzyme catalysis • high-throughput screening

1. Introduction

The importance of enantiomerically pure or enriched organic compounds in pharmaceutical, agricultural, synthetic organic, and natural products chemistry is steadily growing.^[1] This is also reflected by the so-called "chiral market" of industrial pharmaceutical products which in 1999 amounted to more than \$80 billion and which is expected to continue to grow.^[1d,e] Although many of these products are not prepared synthetically in the laboratories of organic chemists, nor are

they ever likely to be so, many chiral target compounds or intermediates are in fact amenable to synthesis by organic chemists. Although classical separation of enantiomers coupled with racemization of the undesired stereoisomer is still the preferred industrial process,^[1d] in the future the economically and ecologically most attractive strategy is likely to be enantioselective catalysis. Indeed, a good part of basic research in organic chemistry during the last three decades has been devoted to the development of methods in the area of asymmetric synthesis,^[2] but more efforts are necessary. The two options are man-made catalysts, such as transition metal complexes,^[3] on the one hand and biocatalysts on the other.^[4] In the former case one considers a known transition metal catalyzed reaction and modifies the catalyst by introducing chiral ligands. Although application of such a catalyst in a given reaction necessarily leads to diastereomorphic transition states with formation of the two possible enantiomeric

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products, the respective energy difference $|\Delta G_R^* - \Delta G_S^*|$ may be so small that no appreciable enantioselectivity is observed. Indeed, more than 2000 chiral phosphorus-containing ligands have been prepared, yet only a handful are truly enantioselective ($ee \geq 95\%$), and application is generally restricted to certain classes of substrates or even specific substitution patterns.^[3] As a result of ligand tuning, second and n th generation catalysts continue to be developed in a process that requires experience, intuition, knowledge of the reaction mechanism, the ability to apply molecular modeling and other theoretical techniques, as well as a great deal of trial and error (Figure 1 a). In almost all cases not only do steric and

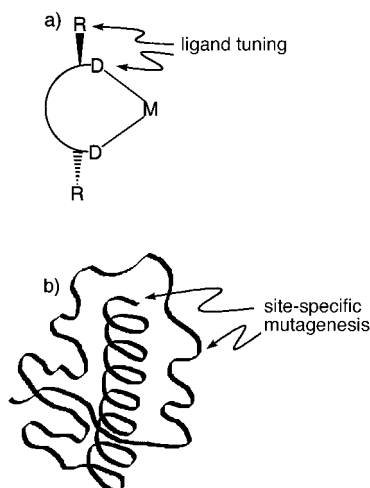


Figure 1. a) Schematic representation of ligand tuning in the design of a chiral transition metal (M) catalyst (the C_2 symmetry is arbitrarily shown); the arrows symbolize points of potential structural variation and D denotes donor atom. b) Schematic representation of a de novo design of an enantioselective enzyme; the arrows symbolize the exchange of amino acids on the basis of site-specific mutagenesis.

electronic properties of the chiral ligand need to be considered, but also the nature of the metal, temperature, solvent, and chiral or achiral additives. Since each catalyst is optimized one by one, an enormous amount of costs and labor is involved. Stereoselectivity is routinely ascertained by measuring the enantiomeric excess (ee) of a given product using conventional techniques such as gas chromatography (GC),^[5] high-performance liquid chromatography (HPLC),^[6] or (less often) capillary electrophoresis (CE),^[7] all with chiral sta-

tionary phases. A few dozen samples can be assayed per day, which is certainly not the slow step in the overall process of developing an enantioselective catalyst in a traditional way. If biocatalysis is the option, as many commercially available enzymes as possible are tested until success emerges.^[4] If enantioselectivity remains unacceptable for a given reaction of interest, then a process analogous to ligand tuning in transition metal catalysis can be attempted, namely the exchange of the amino acid present at a given position against one of the remaining 19 naturally occurring amino acids using site-directed mutagenesis^[8] (Figure 1 b). Unfortunately, as a consequence of the structural complexity of the enzyme and the lack of appropriate theoretical techniques, very few successful cases have been reported so far.

In addition to enantioselectivity, catalyst performance includes such parameters as activity, stability, and ability to be recycled. The challenges in preparing active and enantioselective transition metal catalysts or engineering enzymes for real use in asymmetric transformations are thus reminiscent of (but not identical to) the problems that chemists encountered in traditional therapeutic drug development prior to the advent of combinatorial chemistry, namely, when compounds were synthesized and tested sequentially one by one in a labor-intensive manner. Combinatorial methods in the discovery of pharmaceuticals and other biologically active compounds constitute tools with which large libraries of compounds can be synthesized and screened within a short period of time.^[9] Two different strategies can be used, namely, the iterative split-and-mix (also called split-and-pool) or parallel synthesis. The advantage of the split-and-mix synthesis, which is performed on polymer resin beads, relates to the enormously high number of compounds that are theoretically possible within a short period of time as a result of the permutational possibilities provided by the number of synthetic steps and reaction components. However, the identification of the members of the library requires time and effort as a consequence of deconvolution or encoding.^[9g] In parallel synthesis all reactions are performed in separate vessels using robotic equipment, with the products being lower in number, but available in defined arrays. Such spatially addressable libraries of compounds are readily amenable to high-throughput screening for biological properties, with many methods being based on fluorescent-active or radiolabeled receptors. Although a consensus concerning terminology has not been



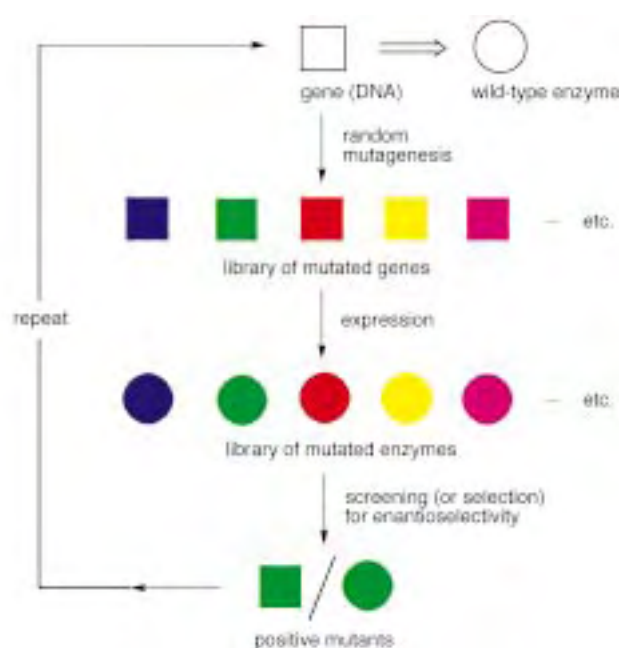
Manfred T. Reetz was born in 1943 in Germany and obtained a B.S. degree from Washington University (St. Louis) in 1965 and a M.S. degree in chemistry from the University of Michigan in 1967. In 1969 he received his PhD. degree from the University of Göttingen (Germany) under the direction of U. Schöllkopf. Following postdoctoral training under R. W. Hoffmann at the University of Marburg, he obtained his Habilitation there in 1974, spent two years as Associate Professor at the University of Bonn before becoming Full Professor in Marburg in 1980. In 1991 he moved to Mülheim/Ruhr and two years later became director of the Max-Planck-Institut für Kohlenforschung. His current interests include organometallic reagents and catalysts in organic synthesis, nanostructured transition metal clusters, and directed evolution as a means to create enantioselective biocatalysts.

reached,^[10] in a strict sense “combinatorial” was originally reserved for designating split-and-mix methods.^[9] Indeed, parallel methods in solution or on a solid phase are not basically new, except that automation and robotics allow for high throughput on a small scale by using miniaturized equipment such as microtiter plates. Perhaps the simple definition of combinatorial chemistry by Combs reflects the opinion of the majority of researchers in the area:^[11] “the applied use of technologies and automation for the rapid chemical syntheses of relative large numbers of compounds”. It has been noted that in drug discovery there is increasing emphasis on parallel synthesis, although future trends are difficult to predict.^[9]

The enormous success of combinatorial methods in pharmaceutical^[9] and subsequently in material science^[12] research has stimulated chemists to apply the techniques to catalysis.^[12] Rather than synthesizing and testing catalysts individually in a time-consuming process as, for example, in the famous Haber–Bosch production of ammonia, in which thousands of catalysts or catalyst formulations had to be prepared and tested one by one, the idea is to create and evaluate large numbers of catalysts all at once (or nearly so).^[12, 13] Efforts concerning this fascinating prospect were hampered by two factors, one real—because the appropriate techniques were lacking—the other psychological: critics maintained that any strategy lacking structural and/or mechanistic aspects is not only ill-suited for intellectual reasons (lack of creativity!), but also doomed to fail. However, it has become abundantly clear that the use of combinatorial and traditional methods in catalysis research are in fact complementary. Therefore one method will never displace the other.

Research in the combinatorial development of enantioselective transition metal catalysts involves two distinct problems: 1) devising strategies and methods for the preparation of large libraries of chiral ligands and/or catalysts displaying high degrees of structural diversity; and 2) developing methods for the high-throughput screening of such catalysts. Screening for catalyst activity and selectivity involves the study of kinetic properties. It may thus be more difficult than developing assays for biological properties based on binding phenomena. The problem of identifying chiral selectors in large libraries of potential candidates for use in chromatographic enantiomer separation^[14] is also different from the challenge of devising high-speed assays for asymmetric catalysts. Although significant progress in developing high-speed detection systems for achiral homogeneous and heterogeneous catalysts has been made since the mid 1990s,^[12, 13] analogous research in the area of enantioselective catalysts was slow to start.

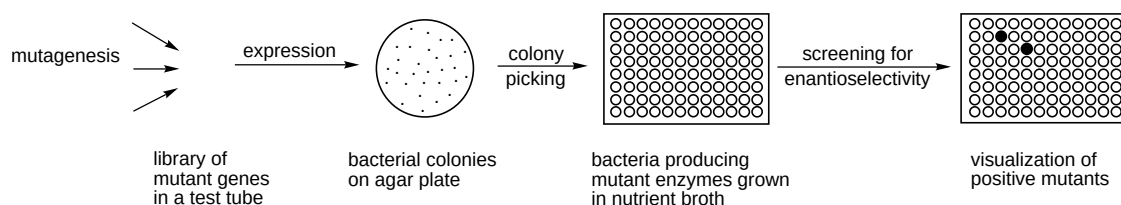
In 1995 my research group encountered the need to develop high-throughput screening systems for assaying the enantioselectivity of thousands of biocatalysts.^[15] We had just initiated a project with the aim of exploiting the tools of directed evolution^[16] in the creation of enantioselective enzymes for use in organic synthesis.^[17] Accordingly, the proper combination of molecular biological methods for random mutagenesis^[16, 18] and gene expression with appropriate high-throughput screening systems formed the basis of our strategy (Scheme 1).^[17, 19]



Scheme 1. Directed evolution of an enantioselective enzyme.^[19]

The starting point for evolving an enantioselective catalyst for a given reaction ($A \rightarrow B$) is a wild-type enzyme (that is, occurring in nature) which catalyzes the chemical transformation, but not with an acceptable level of enantioselectivity. The gene that encodes the enzyme is subjected to random mutagenesis using the error-prone polymerase chain reaction (epPCR)^[16a,b] or recombinant methods such as DNA shuffling.^[16c] Following expression in a suitable bacterial host, thousands of mutant enzymes are produced which then have to be screened for enantioselectivity in the reaction of interest ($A \rightarrow B$).^[17] Since conventional techniques for determining the *ee* value of a reaction (for example, GC or HPLC)^[5, 6] are not suitable for handling such huge numbers of samples within a reasonable span of time, new methods had to be developed.^[15] Although no such screening systems were available in 1995, we at least did not have any problems regarding deconvolution or encoding. The reason for this is simple. Upon plating the biological material out on agar plates, each bacterial colony produces a single mutant enzyme because it originates from a single cell. Thus, upon harvesting the bacterial colonies individually using a robotic colony picker and placing them in the wells of microtiter plates containing nutrient broth, arrays of thousands of potentially enantioselective catalysts become spatially accessible for testing (Scheme 2).^[15, 17, 19]

At this point the method has the character of combinatorial catalysis. However, the overall process goes far beyond combinatorial chemistry because the evolutionary nature now comes into play. Following the identification of the most enantioselective enzyme, the corresponding mutant gene is subjected once more to mutagenesis and screening, and the process is repeated as often as is needed until enantioselectivity has reached the desired level.^[17, 19] Since the inferior enzymes/genes are discarded and only the most enantioselective one is considered, a type of “evolution in the test tube” is at work. This approach to enantioselectivity is radically different from all other strategies such as ligand tuning in



Scheme 2. Individual steps in the directed evolution of an enantioselective enzyme.^[19]

homogeneous metal catalysis,^[3] de novo design of enzymes,^[8] or formation of catalytic antibodies^[20] because it is independent of any structural or mechanistic considerations. In a certain sense such an evolution-based strategy is strictly rational. Indeed, proof of principle was first presented in 1997 (Section 3.1.),^[17] and further advancements have been achieved.^[19, 21]

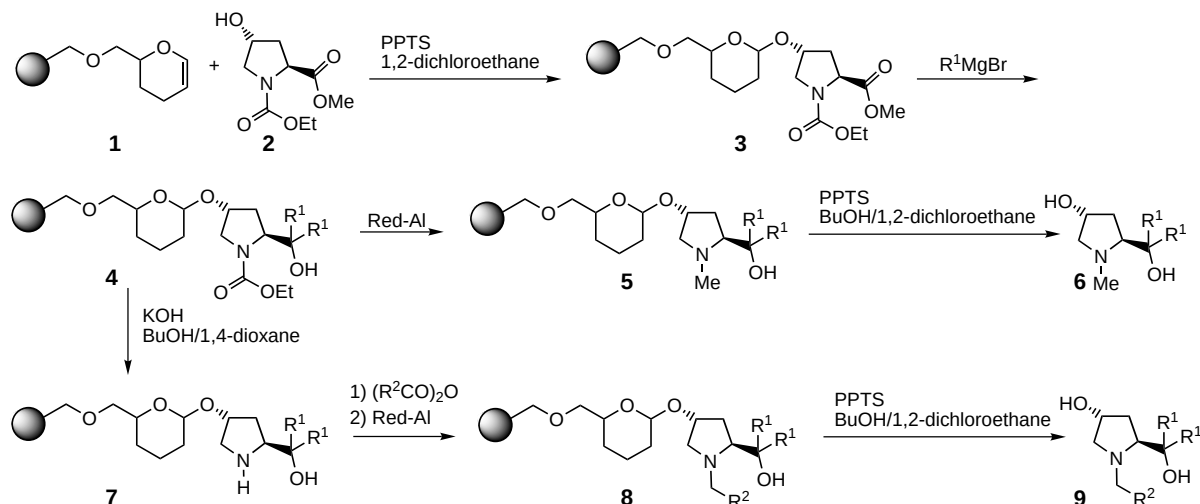
Most high-throughput *ee*-screening systems designed for assaying enzyme-catalyzed reactions are expected to work for asymmetric transition metal catalyzed processes as well. For this reason many recent efforts in developing such assays have attracted a great deal of attention, and in fact this research is ongoing. Before presenting and evaluating the screening systems that we and others have described in the literature thus far (Section 3), a short summary of the key developments in the combinatorial preparation of enantioselective transition metal catalysts is appropriate (Section 2). It will become apparent that these seminal contributions constitute the beginnings of a fascinating new research area, but that the actual goal of preparing and evaluating truly large numbers of potentially enantioselective catalysts has not been reached, primarily because of a lack of screening systems.

2. Strategies in the Combinatorial Design and Preparation of Enantioselective Transition Metal Catalysts

Early studies concerning combinatorial methods in enantioselective transition metal catalysis resulted in the emer-

gence of two basic approaches: 1) the preparation of analogues of known types of ligands, preferably using a modular building block strategy to incorporate diversity with respect to steric and electronic effects at the metal binding site, and 2) optimization of reaction conditions in a given catalytic asymmetric transformation, including solvent and temperature, in conjunction with known ligands. Since solid-phase chemistry has been shown to be ideal for the preparation of libraries of potential therapeutic drugs,^[9] the advantages involved are also likely to pertain in the preparation of chiral ligands for asymmetric catalysis. Specifically, parallel synthesis, as opposed to the split-and-pool methodology, allows spatial access to each ligand, which means that catalysts can be screened individually. Of course, theoretically this limits diversity and therefore the size of the libraries, which raises the question whether the method is only applicable to the optimization of known ligands, or whether new types of chiral ligand systems can also be discovered combinatorially by parallel synthesis. We tend to favor the latter prediction, provided that search systems are set up creatively.

Based on previous reports involving the use of chiral β -amino alcohols as catalytically active ligands in the enantioselective addition of Et_2Zn to aldehydes, Ellman and co-workers reported in 1995 the parallel solid-phase synthesis of a small library of substituted 2-pyrrolidine methanol derivatives **6** and **9** (Scheme 3).^[22] *trans*-4-Hydroxy-L-proline methyl ester (**2**) was first anchored onto a polystyrene (Merrifield) resin **1** through a cleavable tetrahydropyranol linker. Addition of various Grignard reagents followed by protective-group manipulation at the nitrogen atom afforded ten differ-

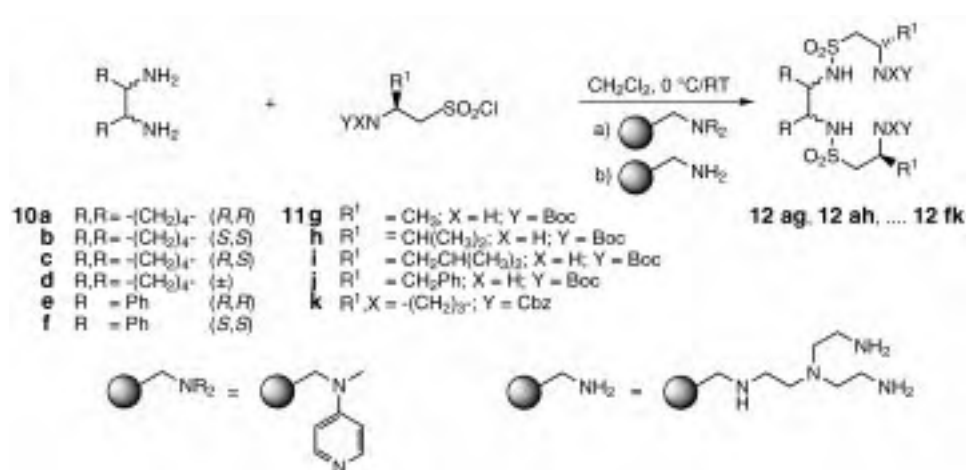


Scheme 3. Solid-phase synthesis of chiral 2-pyrrolidinemethanol ligands.^[22] PPTS = pyridinium-*p*-toluene sulfonate.

ent immobilized ligands **5** and **8**, which on an optional basis could be released from the resin by an acid-induced hydrolytic cleavage to form **6** and **9**, respectively. They were then tested one by one in the addition of Et_2Zn to various aldehydes using classical methods, including *ee* determination by conventional GC on a chiral stationary phase. On-bead performance in the best cases (for aromatic and aliphatic aldehydes up to 94 and 85% *ee*, respectively) was also studied and turned out to be slightly inferior relative to the enantioselectivity of the corresponding free ligand in solution. This early contribution demonstrates the feasibility of the solid-phase parallel synthesis of new members of a specific ligand class, but it did not include any hint as to how high-throughput screening might be achieved in real applications. Indeed the authors did not claim that the concept of high-throughput preparation and screening of new enantioselective catalysts had been put into practice. It is conceivable that the diversity of the library and therefore the probability of finding even better catalysts could be increased by using hundreds of different Grignard reagents and *N*-protective groups. Automation would make larger ligand libraries available within a short period of time.

In another effort Gilbertson and Wang applied the Geysen polyethylene pin technique to synthesize a 63-member library of phosphane-modified peptides as ligands in the enantioselective Rh-catalyzed hydrogenation of methyl-2-acetamidoacrylate.^[23] Individual on-bead screening in a parallel 24-vial reactor was performed conventionally using GC. Although the *ee* values did not exceed 18%, correlations between peptide sequence and enantioselectivity were observed. The actual chemistry is novel, but it does not go deeply into combinatorial catalysis because truly large libraries of ligands as well as the appropriate high-throughput screening systems were not considered. Nevertheless, this research is a noteworthy first step because phosphanes constitute a very important class of ligands. Indeed, it remains a challenge to devise an efficient combinatorial approach to the preparation and use of chiral phosphanes. Gilbertson and Wang also described a similar strategy for optimizing Pd catalysts for use in asymmetric allylic substitution (up to 85% *ee*).^[24]

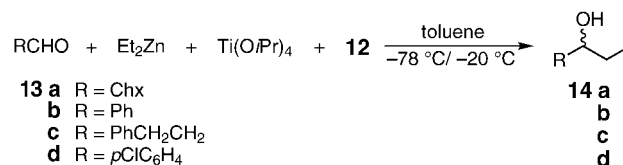
Gennari et al. went one step further in developing new enantioselective catalysts by parallel synthesis, although again genuine high-throughput screening was not part of the effort.^[25] New members of a known family of chiral ligands based on sulfonamides were constructed in a modular manner using solid-phase extraction (SPE) techniques. Vicinal diamines **10** were treated with an excess of sulfonyl chlorides **11** to ensure complete conversion (Scheme 4). To avoid laborious purification of the sulfonamide products **12** the reactions were run in dichloromethane in the presence of polymer-



Scheme 4. Solid-phase synthesis of chiral sulfonamide ligands.^[25] Boc = *tert*-butoxycarbonyl; Cbz = benzyloxycarbonyl.

bound dimethylaminopyridine, which not only catalyzes the coupling reaction but also scavenges the liberated HCl. The excess sulfonyl chloride was then removed by reaction with solid-phase-bound tris(2-aminoethyl)amine. Thus, modular preparation and smooth separation of the “side products” from the “pure” ligands were possible in a simple protocol.

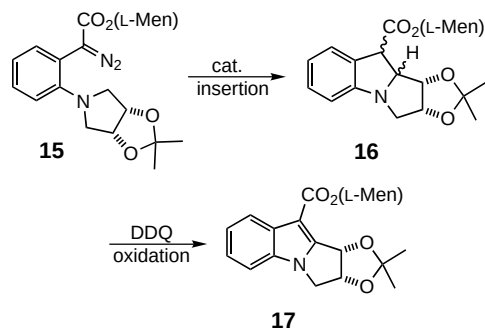
The disulfonamide library was tested in the $\text{Ti}(\text{O}i\text{Pr})_4$ -mediated addition of Et_2Zn to aldehydes **13** (Scheme 5),^[25] a reaction first described by Yoshioka, Ohno, and co-workers using the bis-trifluoromethylsulfonamide of 1,2-diaminocyclohexane.^[26] The tests were run in 30 different reaction



Scheme 5. Ti-promoted enantioselective addition of Et_2Zn to aldehydes in the presence of catalytic amounts of chiral sulfonamide ligands.^[25] Chx = cyclohexyl.

vessels in a parallel format. In order to increase throughput each vessel was charged with four different aldehydes, and the enantioselectivities of the four reaction products were determined by conventional GC analysis of the crude mixtures. The idea of using a given catalyst to screen the reactions of different substrates combinatorially had previously been proposed by Kagan in a different context.^[27] In the present case each mixture required about one hour to be screened, which means that about 96 *ee* determinations of products **14** could be performed per day. A total of 120 results were collected and the best enantioselectivities were greater than 90% *ee*. More recently, a similar approach was taken by Liskamp and co-workers, who used solid-phase synthesis to prepare a small library of peptidosulfonamides as chiral ligands for the same reaction (up to 66% *ee*).^[28] Again, about 96 *ee* determinations per day were supposedly possible by GC, but only a few dozen were actually carried out.

Based on earlier work by Lim and Sulikowski concerning enantioselective Cu-catalyzed intramolecular C-H insertions of metal carbenoids,^[29] Burgess et al. devised an interesting system for optimizing the proper combination of ligand, transition metal, and solvent for the reaction of the diazo compound **15** (Scheme 6).^[30] The reaction parameters were



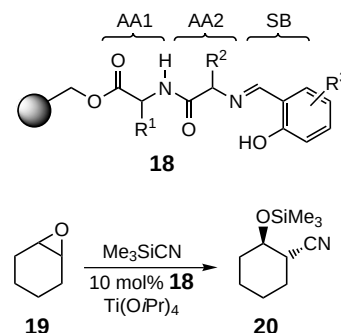
Scheme 6. Catalytic stereoselective intramolecular carbene insertion.^[30] L-Men = L-menthyl; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

varied systematically on a standard 96-well microtiter/filtration plate. In total five different ligands, seven metal precursors, and four solvents were tested in an iterative optimization mode. Standard HPLC was used to monitor the stereoselectivity following a DDQ-induced oxidation. This type of catalyst search led to the discovery that Ag^I ions catalyze the process, a finding that had no precedence in the literature. Moreover, by using a Pfaltz-type ligand^[31] the diastereoselectivity in the formation of the final product **17** increased from the original 2.3:1 (at 64% yield) to 3.9:1 (at 75% conversion) and to 5.9:1 (at 23% conversion).^[30] Here again it would be of interest to see if truly high-throughput screening of a much greater number of reactions would lead to even better results. Such proof of principle would really illustrate the power of combinatorial techniques relative to the traditional approach based on the sequential study of individual catalysts under different conditions.

Burgess and Porte also studied the Pd-catalyzed asymmetric allylic substitution using seven different phosphanyloxazoline ligands at various ligand-to-metal ratios.^[32] An aluminum block containing 27 wells was placed in a dry-box in which the reactions were carried out in parallel. Analyses were performed by conventional GC on a column with a chiral stationary phase and equipped with an autosampler. Such a setup would allow about 33 catalyst evaluations per day. Apparently, only a few dozen were carried out in the study, and resulted in the identification of a catalyst showing an *ee* value of 74% in the reaction of 4-acyloxy-2-pentene with malonate. It is not clear whether further ligand diversification would lead to a ligand more selective than the record set in this case by the Trost catalyst (92% *ee*).^[33]

An important development concerning the optimization of asymmetric catalysts was described by Snapper, Hoveyda, and co-workers in 1996.^[34] They pioneered, amongst other things, diversity-based procedures in the Ti-mediated enantioselective ring-opening reaction of *meso* epoxides such as **19** with

cyanotrimethylsilane (TMSCN) to nitrile **20** (Scheme 7). Peptides composed of three independently variable subunits, namely Schiff base (SB), amino acid 1 (AA1), and amino



Scheme 7. Ti-catalyzed ring-opening of **19** in the presence of modular ligands **18**.^[34]

acid 2 (AA2) were chosen as the catalysts. The modular nature of this system allows for a high degree of diversity and is therefore ideally suited for combinatorial catalyst research. For example, a simple calculation shows that the use of 20 different aldehydes for the Schiff bases and 20 natural amino acids would give rise to 8000 different chiral ligands. However, the lack of high-throughput screening systems at the time of this seminal study contributed to the decision *not* to generate such large libraries. Rather, only a small library of ligands was prepared. All of them were detached from the respective beads and screened in the Ti-catalyzed reaction of cyclohexene oxide (**19**) with TMSCN in solution by conventional GC. Later a similar study was performed on the catalytically active beads themselves.^[35a]

Snapper, Hoveyda, and co-workers utilized a search strategy which in their opinion makes possible the “identification of effective ligands without examination of all possibilities”.^[34, 35a-c] Accordingly, each of the three modular subunits was successively optimized while the other two subunits were kept constant (Figure 2). The best catalyst from a total of only 60 was identified as inducing an enantioselectivity of 89% *ee* for the model reaction. As the authors emphasize, positional scanning of this type is based on the assumption that additivity but not cooperativity between the three subunits pertains. Although this evaluation cannot be

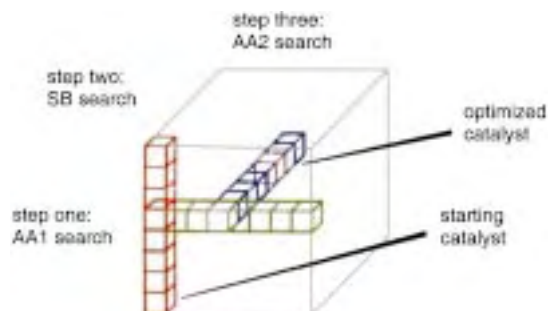
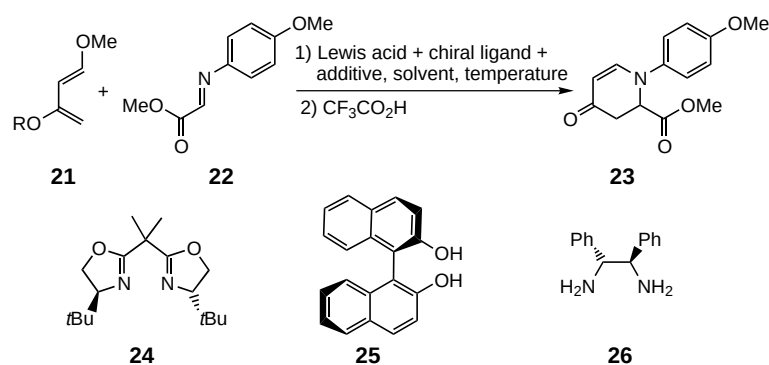


Figure 2. Search strategy for screening enantioselective modularly constructed catalysts.^[34, 35] AA = amino acid; SB = Schiff base.

proven or disproven without scrutinizing larger libraries, it appears reasonable. A similar search strategy has been applied by the authors in the Ti-catalyzed enantioselective addition of cyanide to imines.^[35d,e] Nevertheless, finding and optimizing modular catalyst systems which *do* show synergistic effects between subunits may be an intriguing goal for the future.

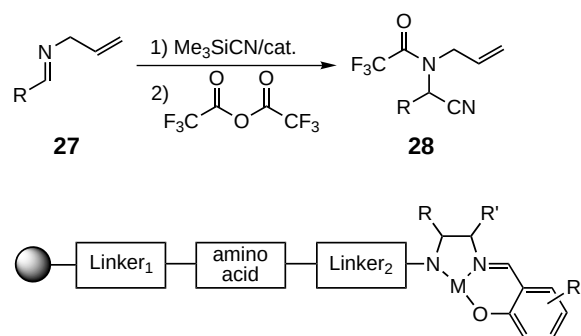
In the quest to find optimal conditions for an enantioselective Lewis acid catalyzed aza-Diels–Alder reaction (**21** + **22** → **23**; Scheme 8), Whiting and co-workers varied several parameters in parallel.^[36] Good literature precedent for a potential catalyst was not so clear, although it was known that many different Lewis acids, including Yb(OTf)₃ (Tf = tri-



Scheme 8. Hetero-Diels–Alder reaction catalyzed by Lewis acids in the presence of ligands **24**, **25**, or **26**.^[36] R = trimethylsilyl.

fluoromethanesulfonyl) catalyze Diels–Alder reactions. Three different chiral ligands (**24**–**26**) known in the literature were tested in conjunction with Yb(OTf)₃, Cu(OTf)₂, MgI₂, and FeCl₃ as Lewis acids, with a limited number of additives and solvents also being evaluated. By using an autosampler and a conventional HPLC instrument equipped with a column having a chiral phase, 144 approximate yields and *ee* values were obtained in about one week, which means that in this system approximately 20 evaluations of catalyst systems for a given reaction are possible per day. Four of the best hits were then applied in scaled-up reactions. The optimal catalyst Yb(OTf)₃/**26**, resulted in cycloadduct **23** with 97% *ee* and in 64% yield (Scheme 8). Although quite successful in this particular case, it is not clear how effective this type of search really is, since ligand diversity was hardly considered. In principle, it can be expected that libraries composed of modular chiral ligands or of simple chiral ligands in conjunction with a high diversity of achiral additives are more meaningful in the combinatorial search for enantioselective catalysts.

In 1998 Sigman and Jacobsen published a seminal paper in which they demonstrated that a combinatorial diversity-based method leads to the discovery of highly enantioselective catalysts that are not readily available by the traditional one-at-a-time approach to catalyst optimization.^[37] A strategy for the parallel synthesis of a certain class of modularly constructed ligands, specifically for use in the catalytic asymmetric Strecker reaction of imines **27** (Scheme 9) was described. As in the Snapper, Hoveyda, and co-workers case,^[34, 35] the

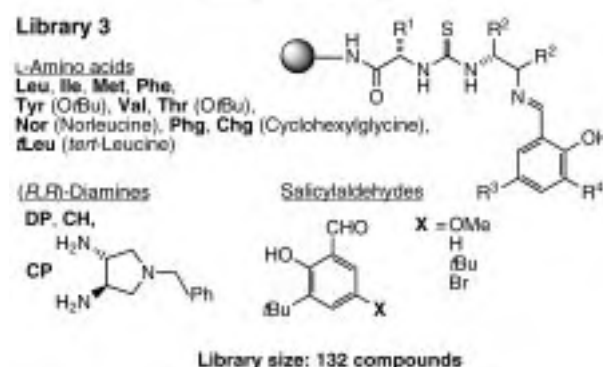
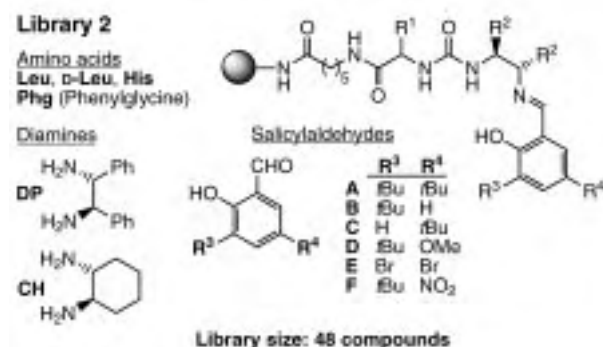
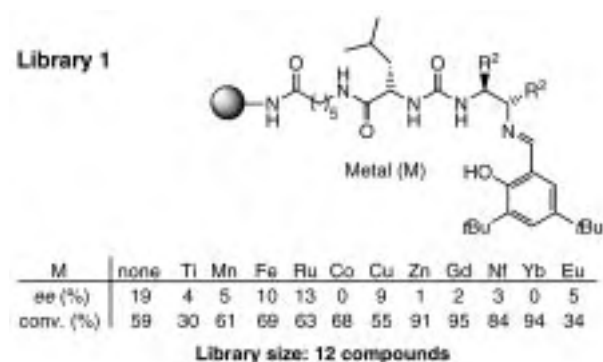


Scheme 9. Asymmetric Strecker reaction of aldimines **27** catalyzed by modular metal complexes.^[37]

first step in the parallel preparation of a catalyst library is the selection of a ligand system amenable to solid-phase synthesis and systematic structural variation.^[37] In addition to the requirement of high-yield reactions in the modular construction of the ligands, an unobtrusive site for the attachment to the solid support is necessary. A number of traditional C₂-symmetric ligands would require several tedious synthetic steps. In contrast, tridentate Schiff base compounds, which are known to be ligands for a variety of catalytic reactions, are in fact suitable for solid-phase synthesis.^[37] These systems are normally comprised of three units: a chiral amino alcohol, a salicylaldehyde derivative, and a metal

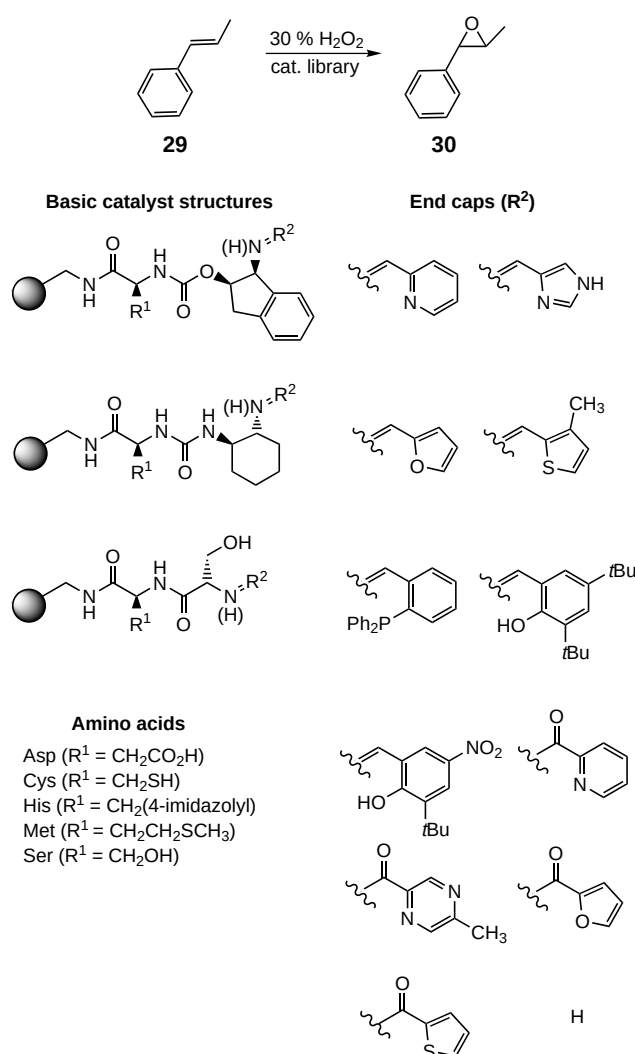
ion. In the above study the amino alcohol unit was replaced by chiral diamines, with the two linkers also contributing to structural diversity (Scheme 9).

Initially, a given ligand system was prepared on the solid support and a small collection of catalysts (library 1) generated by adding 11 different metals and in one case no metal (Scheme 10). The best *ee* value (19%) was in fact obtained in the metal-free system. Based on this observation a parallel ligand library of 48 members (library 2) was prepared using two different chiral 1,2-diamines and a variety of amino acids and Schiff bases. The combination of L-leucine and an (*R,R*)-diamine was shown to be optimal, the substitution pattern in the salicylaldehyde also playing a crucial role. Thereafter, the linker elements were optimized by a traditional one-catalyst-at-a-time approach, which resulted in the emergence of the more-selective catalysts having thiourea linkers. Finally, these results were used to prepare library 3 containing 132 thiourea derivatives (Scheme 10). The enantioselectivity in the addition of HCN to a variety of imines turned out to be greater than 80%, with the best case being 91% *ee* at –78 °C in a lab-scale experiment.^[37] The *ee* determinations were performed using conventional HPLC with a chiral stationary phase. The actual throughput, however, was not defined. Nevertheless, the importance of this contribution concerns the fact that it touches on the question of the complexity arising from interrelated variables in catalytic processes. Indeed, the diversity-based method led to synergistic effects between catalyst components which were unexpected and which do not correspond to “normal” intuition.



Scheme 10. Catalyst libraries for the asymmetric Strecker reaction.^[37]
DP = 1,2-diphenyl-1,2-ethanediamine; CH = 1,2-cyclohexanediamine;
CP = *N*-benzyl-3,4-diaminopyrrolidine.

The next important conceptional advancement, reported by Francis and Jacobsen, addresses the question whether combinatorial methods can be used to discover new types of chiral ligands.^[38] In this case efforts concentrated on the combinatorial search for a chiral ligand/metal system which catalyzes the H₂O₂-mediated enantioselective epoxidation of *trans*- β -methylstyrene (**29**) (Scheme 11). First, the solid-phase synthesis of modularly constructed ligands composed of 1) amino acids, 2) 1-amino-2-indanol, *trans*-1,2-diaminocyclohexane, or serine, and 3) end groups was performed on a Wang resin. End-capped salicylamine was also attached to the Wang resin so as to include types of ligands known to be active in metal-catalyzed epoxidations. The combined library of 192 ligands was then treated with 30 different metal salts, which theoretically would result in 5760 possible metal–ligand complexes. On the basis of earlier experience concerning the application of metal-binding combinatorial libraries for the identification of coordination complexes^[39] it was possible to show by visual



Scheme 11. Ligand libraries for the asymmetric metal-catalyzed epoxidation of olefin **29**.^[38]

color assays and by qualitative inorganic color tests that about 80 % of the 5760 possible metal–ligand complexes had been generated.^[38]

A type of deconvolution strategy had to be developed to identify the most active and stereoselective bead. For this purpose a mixture of all 192 ligands was treated individually with a single metal source, and each group of catalysts was tested in the model epoxidation reaction. Conventional GC analysis of these 30 experiments showed that the two groups derived from VOSO₄ and FeCl₂ were the most active. Since it was observed that VOSO₄ alone is also catalytically quite active, the rest of the efforts focused on FeCl₂. Accordingly, 12 ligand libraries, each containing the 16 basic structures and one of the various end groups, were prepared and treated with FeCl₂. The usual screening procedure showed that the most active catalysts were those which contained a pyridine-type end group. It was then logical to test the 16 ligands with the most active end groups. However, since an active catalyst might theoretically be overlooked by such a restrictive procedure, further encoding was not carried out.^[38] Rather, all FeCl₂ complexes of the original 192 ligands were screened

for activity. Pyridine-capped ligands turned out to be most active. This small group was then assayed with respect to enantioselectivity, and culminated in the identification of three FeCl_2 /ligand complexes which led to *ee* values of 15–20% for product **30** in the model reaction. Although the enantioselectivities are modest, this study shows for the first time that it is possible to discover new lead ligand structures for use in asymmetric catalysis. Nevertheless, a combinatorial search system based on a strict analogy to the split-and-mix strategy used in therapeutic drug discovery has yet to be devised. One of the challenges would be the question of high-throughput screening.

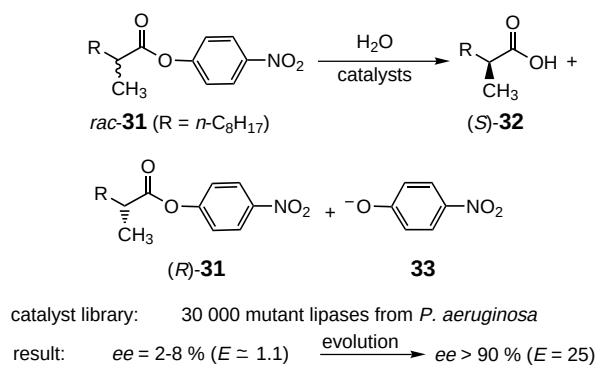
In summary, the overview presented in this section clearly shows that a number of important conceptual advancements have been made with regard to the synthesis of libraries of chiral ligands and catalysts. Several systems were designed to make possible a relatively high diversity of ligands, although in practice the actual number of ligands prepared was not pushed anywhere near the theoretical limits. Further examples have appeared.^[40] The problems associated with the second part of putting asymmetric combinatorial catalysis into genuine practice, namely high-throughput screening systems for assaying enantioselectivity of truly high numbers of catalysts, were hardly addressed in these studies.

3. High-Throughput Screening Systems for Assaying Enantioselective Catalysts and Enzymes

In the 1990s several systems were developed for the high-throughput screening of the activity of enzymes^[16] and of transition metal catalysts^[12, 13] in reactions that do not involve enantioselectivity. Color tests or mass spectrometric (MS) assays were usually used. Moreover, many of the assays were rather crude, but sufficiently effective to identify particularly active catalysts out of large libraries. Once identified, these “hits” were subjected to conventional kinetic studies to ascertain precise data concerning their activity. Unfortunately, the extension of these systems to enantioselective processes was not straightforward which meant that new concepts had to be developed. Indeed, prior to 1997 not a single high-throughput *ee*-screening system existed.

3.1. UV/Vis-Based Systems

As delineated in Section 1 we were first confronted with the problem of developing a high-throughput *ee*-screening system in our studies relating to the directed evolution of enantioselective enzymes (Scheme 1).^[17] Specifically, the goal was to create a highly enantioselective enzyme for the hydrolytic kinetic resolution of racemic 2-methyl decanoate (**31**, Scheme 12). The starting point was the lipase from *Pseudomonas aeruginosa*, which catalyzes the hydrolysis of the substrate, but only with a marginal degree of enantioselectivity (selectivity factor $E \approx 1.1$, reflecting the relative reaction rates of (*S*)- and (*R*)-**31** and corresponding to *ee* values of 2–8% *ee* at 40–50% conversion) with a slight preference for the (*S*)-acid **32**.



Scheme 12. Kinetic resolution of ester **31** catalyzed by mutant lipases produced in the process of directed evolution.^[17, 19, 21]

The *p*-nitrophenol rather than the methyl ester was used in the study because the appearance of the yellow-colored *p*-nitrophenolate (**33**) in buffered medium provides a simple means to monitor the reaction by measuring the absorbance at 410 nm as a function of time. Since the racemate would only afford kinetic information concerning total activity, the (*R*)- and (*S*)-esters **31** were synthesized and tested *separately* pairwise for each mutant lipase. Thus, using a standard 96-well microtiter plate, 48 mutants could be screened within a few minutes. Two typical experimental plots are displayed in Figure 3. The top one shows a lipase with almost no stereo-selectivity (in this case the wild-type) and the bottom one indicates the improved enantioselectivity of the best mutant identified in the first library of approximately 1500 members.^[17]

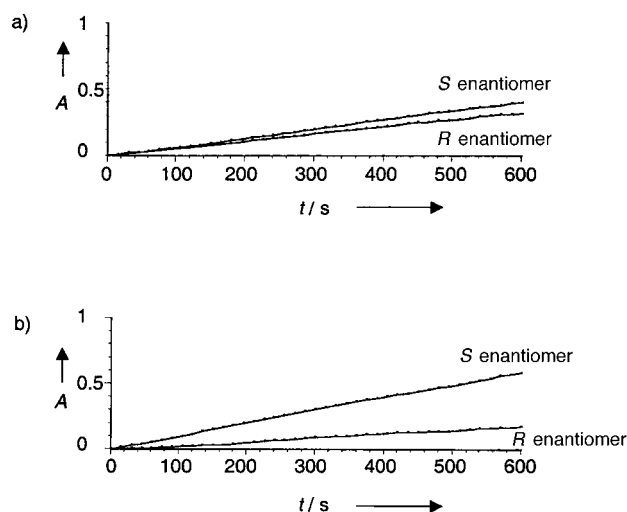


Figure 3. Course of the lipase-catalyzed hydrolysis of the (*R*)- and (*S*)-**31** as a function of time.^[17] a) Wild-type lipase from *P. aeruginosa*, b) improved mutant in the first generation.

In the next three rounds of random mutagenesis, about 2000–2400 mutants were screened in each generation. The most selective mutant (“hit”) was subsequently studied by performing the kinetic resolution of the racemate, with the assay being conventional GC. On average about 6–7 improved variants were observed per library of 2000–2400 mutant enzymes. In each case the gene of the best

variant was used in subsequent mutagenesis. After four rounds of mutagenesis a mutant lipase displaying a selectivity factor of $E = 11.3$, which corresponds to an ee value of 81 % at 30 % conversion, in favor of (*S*)-**32** was identified.^[17] Improved methods based on the combination of error-prone PCR and saturation mutagenesis for exploring protein sequence space with respect to enantioselectivity led to the creation of a small family of mutant lipases, all showing E values of 20–25 ($ee > 90–93\%$).^[19, 21] The total effort for this achievement involved about 30 000 mutants which were all screened by the above assay. Moreover, by inverting the direction of the evolutionary pressure, that is, by screening for *R*-selective mutants, it was possible to reverse the sense of the enantioselectivity.^[19]

In the early phase of this study many of the steps were performed manually, for example, colony picking and pipetting, which limited the number of mutants which could be screened.^[15, 17, 41] Nevertheless, about 500 catalysts were assayed per day. This was later increased to about 1000 mutants per day, primarily by introducing a pipette robot. The use of complete automation including a colony picker and a robotic workstation increased throughput to about 1500 mutants per day.^[42] Moreover, since the process of random mutagenesis is expected to create a certain percentage of mutant enzymes showing no lipase activity whatsoever (“dead variants”), we recently introduced a rough pre-screening based on the tributyrin test.^[42] Accordingly, the agar plates containing the bacterial colonies (Scheme 2) were charged with glyceryl tributyrin (tributyrin), which is a well-known substrate for lipases. The plates have a milky appearance because of the insolubility of tributyrin in the medium. A catalytically active mutant lipase causes hydrolysis of tributyrin with formation of water-soluble products, which results in clear spots around the respective colony (Figure 4). Thus, the absence of such clear spots signals an absence of catalytic activity. These bacterial colonies need not be harvested, which leads to a reduced number of mutants that have to be scrutinized by the actual screening system.

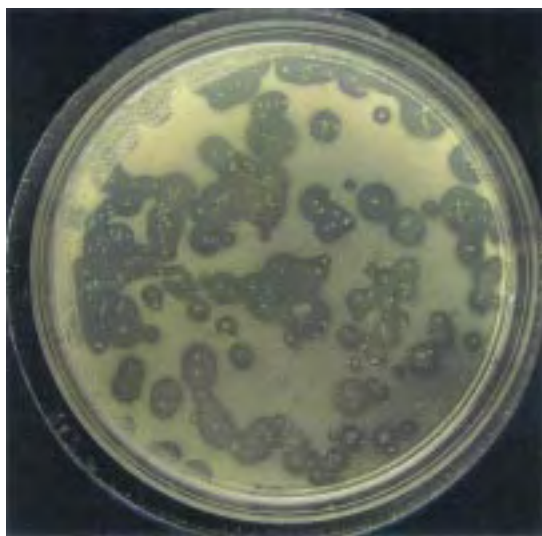
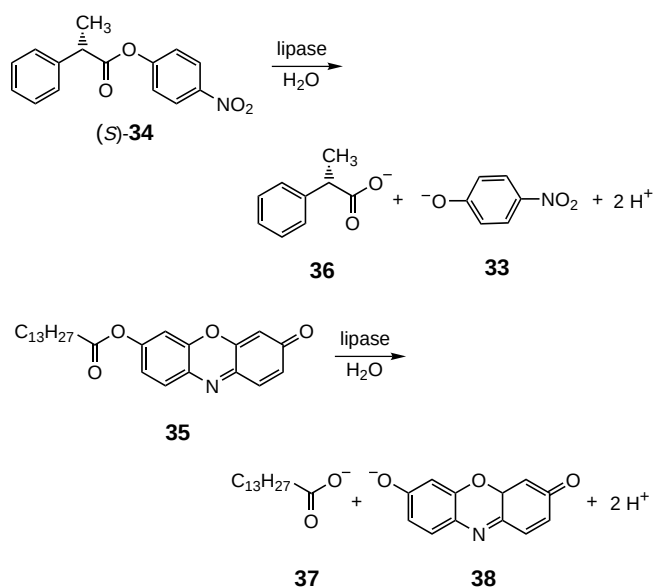


Figure 4. Typical tributyrin test for lipase activity in which the agar plate is placed on a black background for visualization.^[42] White dots represent bacterial colonies; those having no (clear) black background contain inactive mutants.

Although the UV/Vis-based method constitutes the first example of high-throughput screening for enantioselectivity, it suffers from two limitations. Since (*R*)- and (*S*)-**31** need to be screened separately, substrate competition with respect to the enzyme is not ensured. Normal enzymatic conditions do not pertain. Therefore, the kinetic diagrams in Figure 3 cannot be used to derive reliable E or ee values, which means that the assay is simply a convenient way to identify positive “hits”. Problems arise at high ee values. A more serious disadvantage has to do with the fact that evolution-based optimization is performed on the *p*-nitrophenol ester **31** and not on a more practical candidate such as the analogous methyl ester.

James and Kazlauskas have also developed a colorimetric assay for testing the enantioselectivity of lipases or esterases in ester hydrolyses.^[43] The so-called Quick-*E*-Test was developed to simulate the state of competitive conditions of an enzymatic process. In this test a mixture of the *p*-nitrophenol ester of one enantiomeric form of a chiral ester **34** and a resorufin ester **35** is subjected to enzyme-catalyzed hydrolysis, with the latter taking on the “role” of the enantiomer (Scheme 13). The two hydrolyses are monitored by recording



Scheme 13. Quick-*E*-Test for the enantioselectivity of lipases or esterases.^[43]

the UV/Vis absorption of the two products **33** and **38** at two distinctly different wavelengths (410 and 570 nm, respectively). The same is performed with (*R*)-**34/35**. Although this makes a more precise determination of E values possible, the method suffers from the same disadvantage as noted for our system, namely the necessity of employing the *p*-nitrophenol ester of the chiral acid.^[43] Nevertheless, appropriate automation should allow a throughput of several thousand samples per day.

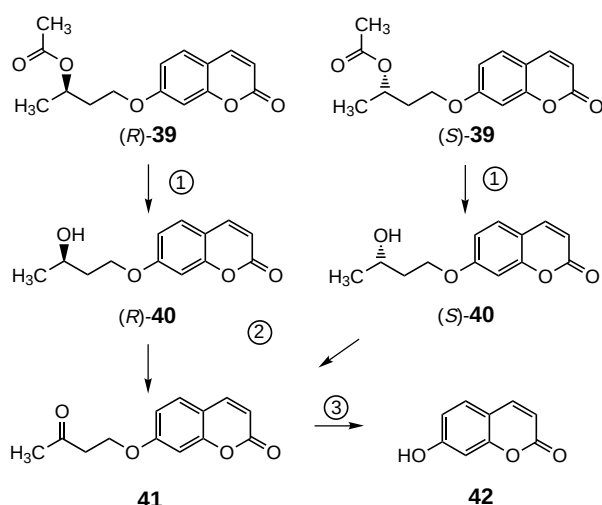
Following this report, Kazlauskas and co-workers devised a second test based on the notion that hydrolysis leads to a change in acidity, which should be measurable by an appropriate pH indicator.^[44] A linear correlation between the amount of acid generated and the degree of protonation of the indicator was established when a buffer (*N,N*-bis(2-

hydroxyethyl)-2-(aminoethanesulfonic acid) and a pH indicator (*p*-nitrophenol) having the same pK_a value were used. In this case the two enantiomeric esters were studied separately pairwise in a similar manner to our assay,^[17] with the color change upon protonation in each case being monitored colorimetrically. Currently it is not quite clear how general and how precise this method actually is, since it was later observed that appreciable discrepancies exist in some cases between the E value obtained and the E value measured conventionally in control experiments.^[45]

Several other related colorimetric high-throughput assays for enantioselective enzymes have been described recently.^[46] These and the systems summarized here are not restricted to the evaluation of enantioselective enzymes, since any enantioselective catalyst should be amenable to such screening. Nevertheless, most of the systems require the incorporation of some kind of a chromophoric moiety, which means that the evolutionary creation of an enzyme or the combinatorial optimization of a transition metal catalyst focuses on reactions of chromophorically modified substrates and not on "normal" compounds of interest in laboratory- or industrial-scale reactions.

3.2. Fluorescence-Based Systems

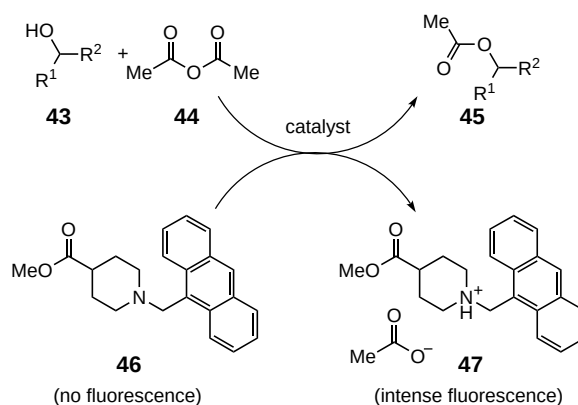
A major advantage of assays based on fluorescence is the high degree of sensitivity, which allows one to use very dilute substrate concentrations and extremely small amounts of catalysts.^[47] This is not always necessary, but in some situations the conditions cannot be modified, for example, when assaying catalytic antibodies in cell cultures. Klein and Reymond have developed a simple and practical fluorogenic assay for the hydrolytic kinetic resolution of chiral acetates, such as **39** (Scheme 14).^[48] It is based on a sequence of two coupled enzymatic steps that converts a pair of enantiomeric alcohols formed by the asymmetric hydrolysis under study (for example, (*R*)- and (*S*)-**40**) into a fluorescent product (for example, **42**). In the first step (*R*)- and (*S*)-**39** are subjected



Scheme 14. Fluorescence assay for the determination of enantioselectivity of catalytic ester hydrolysis.^[48]

separately to hydrolysis in reactions catalyzed by a mutant enzyme (lipase or esterase), a catalytic antibody, or in principle a synthetic catalyst compatible with the system. The goal of the assay is to measure the enantioselectivity of this kinetic resolution. The relative amount of (*R*)- and (*S*)-**40** produced after a given reaction time is a measure of the enantioselectivity and can be ascertained rapidly, but not directly. Two subsequent chemical transformations are necessary. First the enantiomeric alcohols (*R*)- and (*S*)-**40** are oxidized separately by horse-liver alcohol dehydrogenase (HLDH) to the ketone **41**, from which the fluorescent final product umbelliferone (**42**) is then released in each case by the catalytic action of bovine serum albumin (BSA). Thus, by measuring the fluorescence of **42** for the *R* and *S* substrate separately, the relative amounts of (*R*)- and (*S*)-**40** can be determined. The authors tested 30 different esterases and lipases and followed the rate of release of **42** in the wells of standard microtiter plates by fluorescence.^[48] Control experiments ensured that the apparent rate of umbelliferone release is directly proportional to the rate of acetate hydrolysis. The predicted and observed E and ee values (as checked by standard HPLC assay on a chiral phase) were found to lie within $\pm 20\%$. Only in one case was a larger discrepancy observed, a result that was believed to be caused by the occurrence of an unusually low Michaelis constant K_M for one of the enantiomers. Thus, since the test can be carried out on 96-well microtiter plates, high-throughput should be possible. Of course, the inherent disadvantage noted earlier for the colorimetric tests also applies here, namely the fact that the optimization of a potential catalyst is focused on a specific substrate **39** modified by incorporation of a probe, in this case the fluorogenic moiety **42**.

More recently Copeland and Miller described a novel fluorescence-based method for assaying the *activity* of catalysts in acylation reactions.^[49] Since in principle it should be possible to extend it to include the determination of enantioselectivity, we describe it here in detail. The underlying idea is to use a molecular sensor which fluoresces upon formation of a product (Scheme 15). In exploratory experiments isopropanol (**43**; $R^1 = R^2 = \text{CH}_3$) was treated with acetic acid anhydride (**44**) in the presence of the nonfluorescent chemosensor **46**. No fluorescence was observed in the absence of catalysts. In contrast, known nucleophilic acylation



Scheme 15. Fluorescence screening system for assessing the activity of acylation catalysts.^[49]

catalysts such as dimethylaminopyridine (DMAP) or piperidinopyridine (PPY) led to intense fluorescence as a result of the fact that the chemosensor is protonated by the acetic acid to form **47**. The study was then extended to include these and other catalysts such as the modularly constructed tetrapeptides previously reported by the authors in the acylation of a racemic chiral alcohol.^[49] Seven different catalysts were added to solutions of the substrate in toluene in the wells of a 96-format microtiter plate at three different loadings, each reaction being replicated three times for a total of 63 experiments. The reaction progress was monitored within 30–40 minutes by a fluorescence plate reader, and the results were in excellent agreement with control experiments based on standard kinetics. Interestingly, in the case of chiral catalysts based on various tetrapeptides shown previously to be enantioselective, a correlation was observed between the absolute rate and degree of asymmetric induction determined by traditional assays.^[49] In this sense the system can be viewed as an *ee*-detection assay. However, the generalization of this assumption to include new substrates and/or other catalysts is not justified. In contrast, *E* and *ee* determinations should be possible simply by performing the tests on *R*- and *S*-configured substrates separately on the microtiter plates, as in our UV/Vis-based system^[17] (Section 3.1).

In an extension of their work Copeland and Miller showed that their activity assay can be applied to the real-time simultaneous screening of one bead/one compound combinatorial libraries.^[49] In this interesting variant, the aminomethyl-anthracene sensor and modularly prepared tetrapeptide catalyst were attached to a support by solid-phase synthesis. Upon exposing sets of beads to the reaction conditions, the relative fluorescence intensities as measured by fluorescence microscopy were shown to correlate with the relative rates of reaction previously determined in solution using standard techniques. This approach, if modified and extended appropriately, may have considerable potential in the application of high-throughput screening of enantioselective acylation catalysts.

Reymond and co-workers recently continued their studies of fluorogenic assays by developing a catalyst screening system using antibody sensors.^[50] Although not yet adapted to enantioselective processes, this system also seems promising. It is based on an idea first developed by Green and co-workers,^[51] who showed that catalytic activity can be monitored by an immunoassay in the same way as in a regular enzyme-linked immunosorbent assay (ELISA). The catELISA assay, as it is now called, was used by Reymond and co-workers to monitor the hydrolysis of an ester on a solid support,^[50] a procedure that was also used and developed further by MacBeath and Hilvert in their study of Diels–Alder reactions catalyzed by antibodies.^[52] The substrate is first bound to a solid support which is then exposed to a solution containing potential catalysts. After sufficient reaction time the test solution is washed away and the product assayed quantitatively by ELISA using a product-specific polyclonal rabbit antibody. Whereas a chromophoric group was required in the original catELISA, Reymond and co-workers used an antibody sensor consisting of a product-specific antibody tightly bound to a product analogue which is

covalently labeled with a sensitive fluorescent tag (acridone).^[50] The system is compatible with 96- or 384-well plastic microtiter plates and allows for high throughput. It will be interesting to see if the concept can be extended to include the quantitative assay of enantioselective processes.

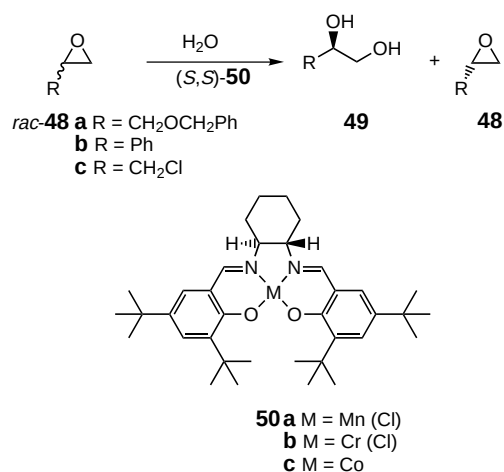
A different approach to fluorescence-based *ee* assays is theoretically possible by developing fluorescent-active sensors capable of distinguishing between enantiomers. The principle has been known for some time, although the effects involved, namely high fluorescence intensity (or quenching) and efficient enantiomeric recognition, turned out to be rather small.^[53] Nevertheless, a relationship between fluorescent properties and enantiomeric purity was established. An example was described by Iwanek and Mattay who used 2,2'-dihydroxy-1,1'-binaphthol (BINOL, **25**; see Scheme 8) as a weakly fluorescent sensor in the chiral discrimination of amines which cause fluorescence quenching upon interaction.^[53a] We have prepared a highly fluorescent chiral sensor capable of unusually efficient enantiomeric recognition, namely the helical compound [2,15]-dihydroxyhexahelicene.^[54] Fluorescent quenching studies show that chiral discrimination between enantiomeric amines and amino alcohols is pronounced. It remains to be seen if a high-throughput *ee*-screening system can be developed. Finally, it needs to be pointed out that fluorescence can be used as a detection system in chromatography (see Section 3.6).

3.3. IR-Thermographic Assays

All objects emit infrared radiation (black body radiation), a process that can be detected by modern photovoltaic IR cameras equipped with focal plane array (FPA) detectors.^[55] The picture obtained thereby provides a two-dimensional thermal image which is nothing but a spatial map of the temperature and emissivity distribution of all objects in the picture. It is customary to use different colors in the pictures to visualize different photon intensities of the detected infrared radiation, for example, red areas indicate “hot spots” and blue areas denote “cold spots”. The technique was first used by Pawlicki and Schmitz^[56] to monitor the dynamics of reactions on solid surfaces and was extended by Sermon and co-workers^[57] to obtain temperature profiles of exothermic gas-phase reactions catalyzed by SiO₂-supported platinum particles. The first case of parallel testing of the activity of the members of a small library of catalysts was reported by Moates et al. in 1996.^[58] Two years later Taylor and Morken demonstrated that the activity of acylation catalysts on beads, prepared by the split-and-pool method, could be detected by IR thermography provided the beads swim on the surface of the solution containing the alcohol and the acylation agent.^[59] Only then is detection possible. At about the same time Maier and co-workers reported another conceptual advancement,^[60] namely emissivity-corrected IR thermography of large libraries of heterogeneous catalysts, a technique that requires only very small amounts of catalysts (<200 µg). The main object of this study was to visualize temperature differences arising solely from the catalytic activity of the catalysts. This was achieved by applying a linear correction to

the detector response and subtracting the IR image of the library just before the start of the reaction, namely, the background (offset), from the images during catalytic experiments. This process means that local emissivity differences are no longer visible, and the heat evolution arising from the catalytic reactions on a microtiter plate can then be reliably detected. This technique was successfully applied to large libraries of heterogeneous catalysts in gas-phase hydrogenation and oxidation.^[60] However, quantification still needs to be achieved here and in the other IR-thermographic studies.

In our own efforts directed towards developing high-throughput screening systems for assaying enantioselectivity, we envisioned the use of IR thermography in the kinetic resolution of chiral substrates.^[61] However, it was not certain that IR thermography could actually be applied to homogeneous solutions since this question had never been posed previously. We set out to test the concept by studying the hydrolytic kinetic resolution of chiral epoxides **48** catalyzed by the Jacobsen catalysts **50**^[62] in homogeneous solutions of moist toluene by using an AIM-256² IR camera equipped with a PtSi-FPA detector and a germanium lens (Scheme 16).^[61]



Scheme 16. Hydrolytic kinetic resolution of epoxides **48** catalyzed by the Jacobsen catalysts **50**. Screening was carried out by IR thermography.^[61]

After some experimentation with regard to the optimal materials,^[63] we developed a special microtiter plate which allows for efficient heat transfer and which could be shaken so as to ensure sufficient mixing. A commercially available Eppendorf-Thermomixer was modified such that the top was replaced by an aluminum plate. Holes were then drilled into the plate and cylindrical glass reaction vessels about 8 mm in diameter and 35 mm in height placed therein (Figure 5). Thus, the whole microtiter plate can be shaken so as to ensure agitation of the reaction contents in each well.

Since the use of a racemate would deliver information regarding only the overall catalyst activity, the *S* and *R* enantiomers were tested pairwise in separate wells of the microtiter plate. This is the same trick that we used in our original UV/Vis-based screening system (Section 3.1).^[17] In the present case we also included the racemate. Following placement of moist toluene solutions of (*S,S*)-**50** in the wells of the microtiter plate, (*R*)- and (*S*)-epichlorohydrin ((*R*)- and



Figure 5. Commercially available Eppendorf shaker with a modified aluminum plate on which the microtiter plate is placed (for better visualization half of the Al plate is uncovered).^[61,63]

(*S*)-**48c**) were added and the temperature calibrated in the range of 24–39 °C. The reaction was then initiated by the addition of water. After a specified amount of time the shaking was interrupted for 10 s, 500 IR-thermographic pictures taken, and the average of these printed out as an image. The time-resolved results (Figure 6) show for the first time that IR thermography can be used to detect heat evolution caused by a reaction occurring in homogeneous solution, and that a highly enantioselective catalyst can indeed be identified.^[61] Thus, the cobalt complex (*S,S*)-**50c** was found to exhibit the highest catalyst activity and selectivity; it reacts enantioselectively with the epoxide (*S*)-**48c**. The chromium catalyst (*S,S*)-**50b** is also selective, although less active, whereas the manganese complex (*S,S*)-**50a** displays no significant activity. This is in line with results obtained by Jacobsen and co-workers using benzoic acid as the nucleophile in lab-scale reactions.^[62] It was also seen that heat generation after seven minutes is so pronounced in the case of the cobalt complex for the reaction of (*S*)-**48c** and *rac*-**48c** that no significant difference in the visualization using the applied temperature window (1 °C) could be detected. Therefore, the temperature scale covered by the window was increased to a total of 10 °C, which resulted in the clear identification of the “hottest” reaction (compare Figure 6e and 6f).^[61]

Moreover, using the cobalt catalyst (*S,S*)-**50c** it was possible to perform substrate screening so that the chiral epoxides **48a–c** could be studied in parallel. It was found that (*S*)-**48a** is the most reactive substrate followed by (*S*)-**48c** and (*R*)-**48b**. The relative reactivity of (*R*)-**48b** and (*S*)-**48c** corresponds to that reported by Jacobsen and co-workers for lab-scale reactions,^[62] whereas the reaction of (*S*)-**48a**, which is most rapid, had not been described in the literature previously. Thus, the IR-thermographic images contain an interesting chemical prediction.

In another series of experiments time-resolved detection of an enantioselective enzyme-catalyzed kinetic resolution was

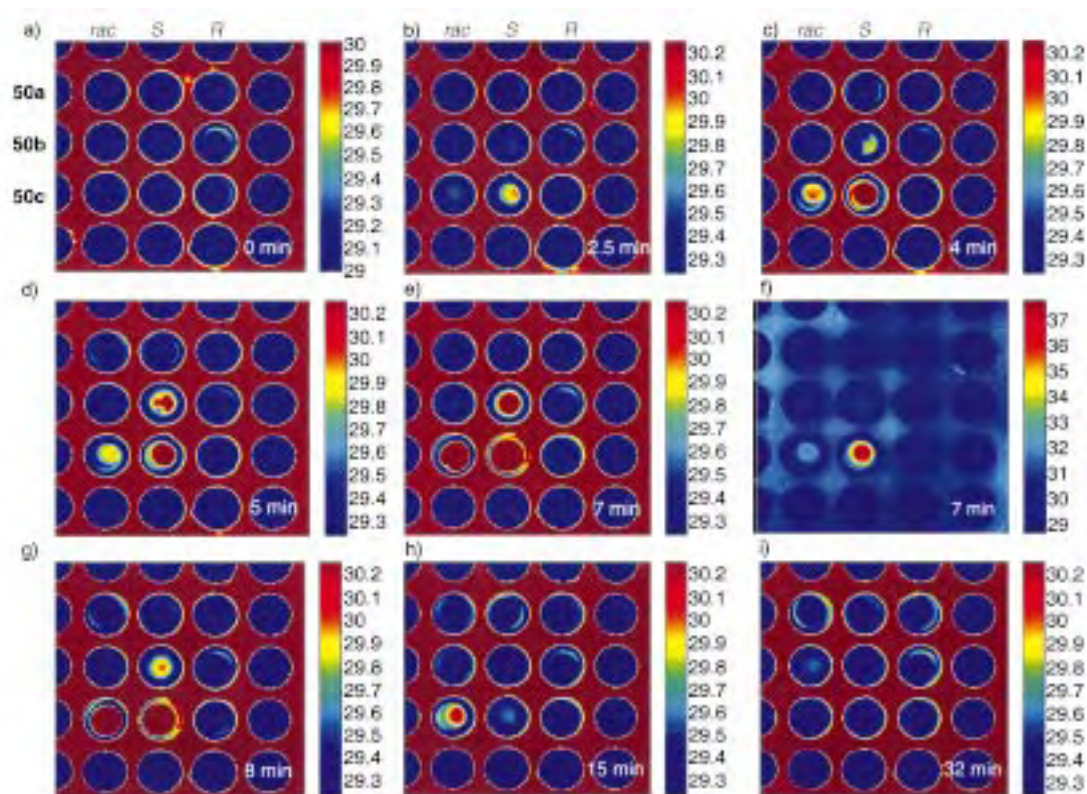
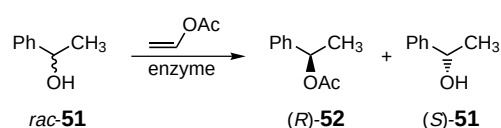


Figure 6. Time-resolved IR-thermographic imaging of the enantioselective hydrolysis of epoxide **48c** catalyzed by (S,S)-**50a–c** after a) 0, b) 2.5, c) 4, d) 5, e) 7, g) 8, h) 15, and i) 32 min.^[61] In f) the same image is shown as in e), except that the temperature window ranges over 10 K. The bars on the far right of each image is the temperature/color key of the temperature window used [°C].

also demonstrated.^[61] In this case the enzyme (lipase from *Candida antarctica*) was added to the wells of the microtiter plate in immobilized form, that is, the reaction was catalyzed by a heterogeneous catalyst. It was demonstrated using (*R*)- and (*S*)-1-phenylethanol ((*R*)- and (*S*)-**51**) as the substrate and vinyl acetate as the acylating agent that the reaction is highly *R*-selective, namely, hot spots appeared above the wells of the microtiter plate containing (*R*)-**51** (Scheme 17). This is



Scheme 17. Enzyme-catalyzed kinetic resolution of alcohol **51**. Screening was carried out by IR thermography.^[61]

in perfect agreement with the literature data, which shows that the *ee* value of the acylated form at 50% conversion is >99% in favor of (*R*)-**52**.^[64] More recently we have studied this particular assay in more detail using an IR camera with even higher resolution and likewise obtained good time-resolved images.^[65]

In conclusion, IR thermography is an excellent tool in the high-throughput identification of highly active and enantioselective catalysts. The method allows one to distinguish such “hits” from other members of a library of catalysts which are much less active or less enantioselective. However, quantifi-

cation has yet to be achieved. This means that small differences in enantioselectivity, as usually observed in sequential rounds of enzyme mutagenesis (Scheme 1), cannot (yet) be picked up by IR-thermographic assays. Another limitation of the method, which by nature is expected to persist, pertains to the fact that in the absence of special effects, such as gas evolution, thermoneutral reactions cannot be assayed. This stands in contrast to endothermic processes which in fact show “cold spots” in the IR images.^[66] Although this intriguing effect has not been demonstrated in an enantioselective process, the method was shown to work quite well in the search for active olefin-metathesis catalysts, the most active catalysts being identified on the microtiter plates as “cold spots”.^[66]

3.4. Circular Dichroism Assays

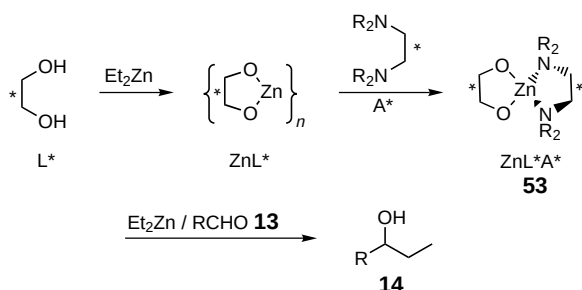
In principle it should be possible to use HPLC^[6] in the high-throughput determination of enantiomeric purity provided that efficient separation of enantiomers by chirally modified columns is possible within a reasonable amount of time. Since rapid separation of this kind is a formidable challenge, an alternative approach is to use normal columns which simply separate the starting materials from the enantiomeric products. The enantiomeric excess (*ee*) of the mixture of enantiomers is then determined by circular dichroism (CD) spectroscopy. Indeed, this principle was first established by

Mason and co-workers^[67] in 1980 and developed on a broad basis by Salvadori et al.^[68] and Mannschreck.^[69] Recently, Mikami and co-workers have shown that the method can be applied in the screening of combinatorially prepared enantioselective catalysts.^[70] The method is based on the use of sensitive detectors for HPLC which determine in a parallel manner both the circular dichroism ($\Delta\epsilon$) and the UV absorption (ϵ) of a sample at a fixed wavelength in a flow-through system.^[67–70] The CD signal depends only on the enantiomeric composition of the chiral products, whereas the absorption relates to their concentration. Thus, only short HPLC columns are necessary.^[67–69] Upon normalizing the CD value with respect to absorption, the so-called anisotropy factor g [Eq. (1)] is obtained.^[67]

$$g = \frac{\Delta\epsilon}{\epsilon} \quad (1)$$

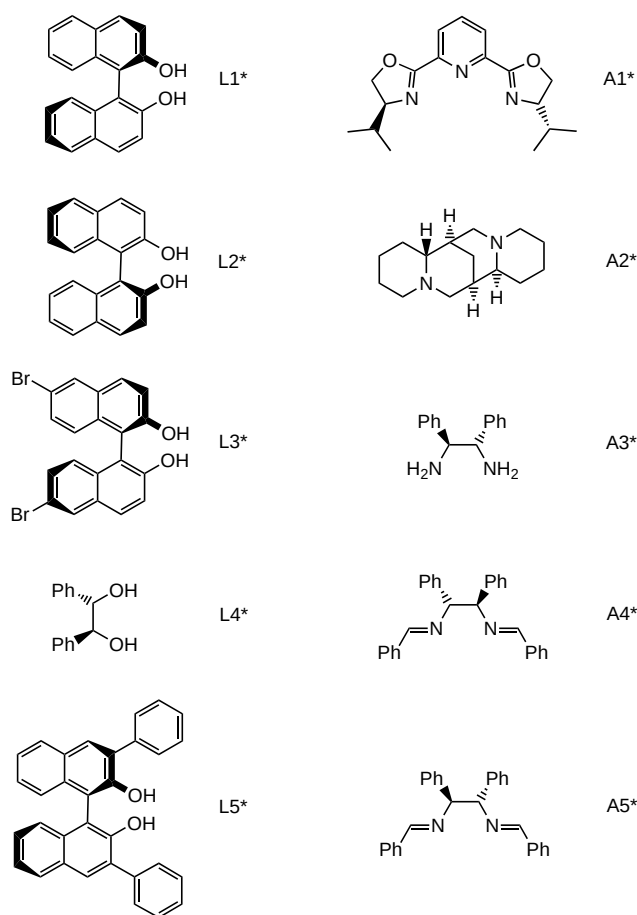
For a mixture of enantiomers it is thus possible to determine the ee value without recourse to complicated calibration. The fact that the method is theoretically valid only if the g factor is independent of concentration and if it is linear with respect to the ee value has been emphasized repeatedly.^[67–70] However, it needs to be pointed out that these conditions may not hold if the chiral compounds form dimers or aggregates, because such enantiomeric or diastereomeric species would give rise to their own particular CD effects. Although such cases have yet to be reported, it is mandatory that this possibility be checked in each new system under study.

Mikami and co-workers studied various libraries of chiral ligands and activators in the addition of Et_2Zn to aldehydes (Scheme 18).^[70] First the primary combinatorial library of

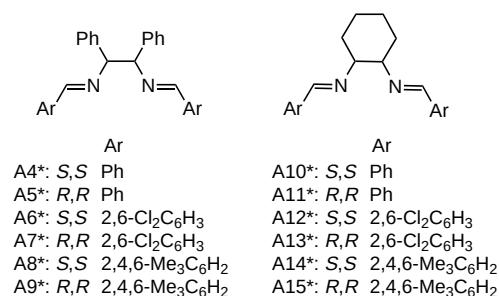


Scheme 18. Addition of Et_2Zn to aldehydes **13** catalyzed by chiral Zn-diols in the presence of chiral diamine additives^[70] and screened by CD.

chiral ligands **L1***–**L5*** and chiral activators **A1***–**A5*** (Scheme 19) were studied in order to optimize the lead structure of the next generation of chiral ligands and activators. The best combinations were found to be **L5*/A4*** and **L5*/A5***, with ee values of up to 65% being observed in the Et_2Zn addition to benzaldehyde. Based on these results a new library composed of chiral diimines as activators was scrutinized (Scheme 20).^[70] The best combination turned out to be **L5*/A9*** ($ee = 90\%$ at room temperature and 99% at -78°C with benzaldehyde and $ee = 92–99\%$ with other aldehydes). Although only a few dozen reactions were monitored by a JASCO-CD-995 instrument, the CD-based



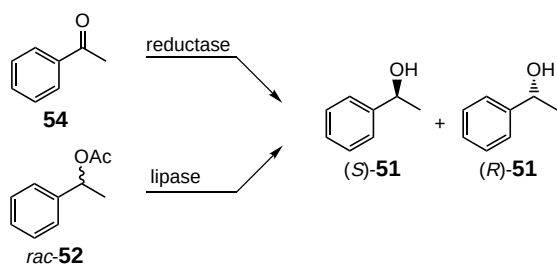
Scheme 19. Chiral diols as ligands and diamino compounds as additives in the addition of Et_2Zn to aldehydes **13**.^[70]



Scheme 20. Chiral dialdimines as additives in the addition of Et_2Zn to aldehydes **13**.^[70]

assay is theoretically amenable to high-throughput screening of enantioselective catalysts.

Following the publication of Mikami and co-workers^[70] we reported our independent results in the assay of related chiral alcohols.^[71,72] In our work concerning the directed evolution of enantioselective enzymes we needed to develop fast and efficient ways to determine the enantiomeric purity of these compounds, which can be produced enzymatically either by reduction of the prochiral ketone (for example, **54**) using reductases or by kinetic resolution of *rac*-acetates (for example, *rac*-**52**) by lipases (Scheme 21). In both systems the CD assay is theoretically possible. In the former case liquid chromatography would have to be used to separate the



Scheme 21. Reductase-catalyzed reduction of ketone **54** and lipase-catalyzed kinetic resolution of acetate **52**. Screening was carried out by CD.^[71]

starting material **54** from the product (*S*)/(*R*)-**51**, whereas in the latter case (*S*)/(*R*)-**51** would have to be separated from (*S*)/(*R*)-**52**.

Since acetophenone (**54**) has a considerably higher extinction coefficient than 1-phenylethanol (**51**) at about 260 nm, the separation of starting material from product was absolutely necessary and was accomplished on a relatively short reversed-phase HPLC column. The maximum value of the CD signal was determined in preliminary experiments using enantiomerically pure product **51**.^[71] Mixtures of **51** having different enantiomer ratios (and therefore *ee* values) were prepared and analyzed precisely by GC on a chiral stationary phase. The same samples were studied by CD and resulted in the compilation of *g* values. A linear dependency with a correlation factor of $r = 0.99995$ was in fact observed upon plotting the *g* against the *ee* values, which translates into a simple equation for enantioselectivity [Eq. (2)].

$$ee = 3176.4g - 8.0 \quad (2)$$

We then studied the possible dependency of the *g* factors on concentration.^[71] A mixture of (*S*)- and (*R*)-**51** with *ee* = 20 % was prepared at a concentration of 10 $\mu\text{L mL}^{-1}$ in acetonitrile, which was then successively diluted. Figure 7 clearly shows

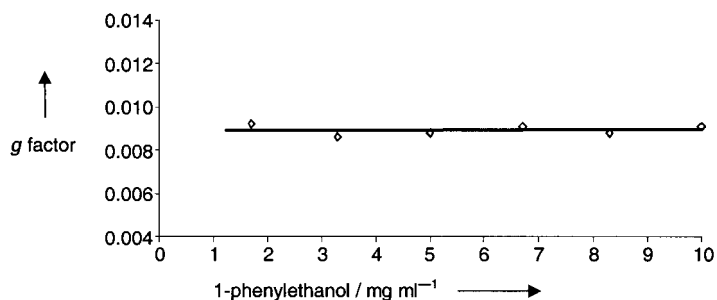


Figure 7. Dependency of the *g* factors on concentration in a mixture of (*S*)- and (*R*)-**51** (*ee* = 20 %).^[71]

there is no dependency of *g* on concentration (standard deviation = 2.6 %). Thus, possible aggregation as a consequence of hydrogen bonding between two or more molecules of the product (*S*)- and (*R*)-**51** in this medium which could lead to artifacts is not involved, thus making the system amenable to CD analysis.

The question whether high-throughput screening of the above reaction system can in fact be put into practice was now

reduced to the problem of the efficient and fast separation of **54** from (*S*)/(*R*)-**51**. Although complete optimization was not carried out, separation was in fact accomplished using reversed-phase silica as the column material and methanol/water (47/53) as the eluant. In view of the results concerning the dependency of the *g* factor on concentration (see above), aggregation can be excluded in this protic medium. Figure 8 shows the corresponding HPLC chromatogram in which the mixture is fully separated within less than 1.5 minutes. Thus, it is possible to perform about 700–900 exact *ee* determinations per day by using the JASCO-CD-1595 instrument in conjunction with a robotic autosampler.^[71, 72]

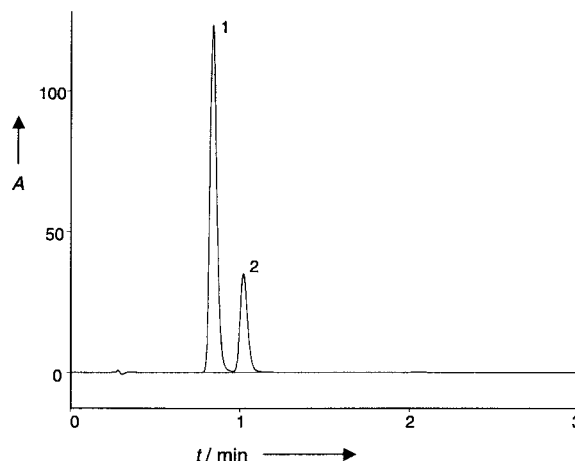
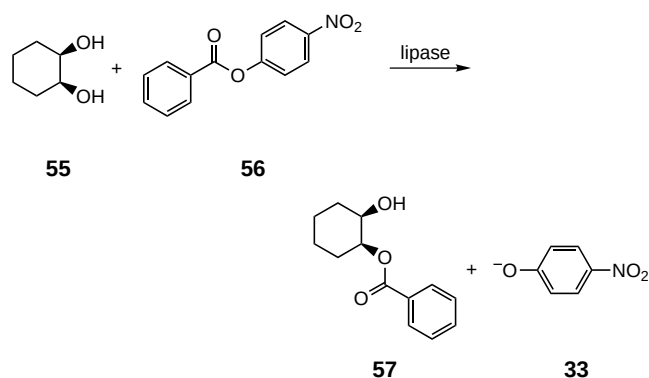


Figure 8. HPLC chromatogram of a mixture of **54** (peak 1) and (*S*)/(*R*)-**51** (peak 2).^[71]

Finally, we wish to point out the possibility that reliable *ee* determinations using CD-based assays are theoretically possible in certain systems even though no liquid chromatographic separation is performed whatsoever.^[71–73] Prerequisite is a prochiral substrate (for example, a *meso* compound) as well as a UV-active product (chromophore) which is formed as the enantioselective reaction proceeds. The absorption maximum of the chromophore formed has to differ considerably from that of the desired chiral product. This new principle is illustrated by the lipase-catalyzed enantioselective acylation of the *meso*-diol **55** by benzoic acid *p*-nitrophenyl ester (**56**) with formation of the chiral product **57** and the yellow-colored *p*-nitrophenolate (**33**) which has a characteristic UV/Vis-absorption at 410 nm (Scheme 22). Upon measuring the *g* value of the absorption maximum of **57** and the additional UV absorption of **33**, all information necessary to determine the conversion and enantiopurity is available without the need to perform any liquid chromatographic separation. The advantage of this novel approach has to do with ease of performance and the clear prospect of higher throughput.^[71–73]

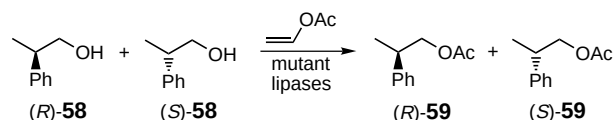
In conclusion, on the basis of these and previous studies HPLC-UV-CD or UV-CD alone may well constitute a viable high-throughput screening system for enantioselective (bio)-catalysts in a given situation. Success will depend upon the particular substrate under study. Moreover, the precautions as delineated above need to be considered.



Scheme 22. Lipase-catalyzed asymmetric acylation of *meso*-diol **55**. Screening was carried out by GC.^[71–73]

3.5. Chromatographic Assays

Conventional GC or HPLC based on the use of chiral stationary phases can only handle a few dozen *ee* determinations per day.^[5, 6] However, we have recently demonstrated that GC can be modified so that in certain cases about 700 exact *ee* and *E* determinations are possible per day.^[74] The case study concerns the lipase-catalyzed kinetic resolution of the chiral alcohol (*R*)- and (*S*)-**58** with formation of the acylated forms (*R*)-**59** and (*S*)-**59** (Scheme 23). Thousands of mutants of the lipase from *Pseudomonas aeruginosa* were created by error-prone PCR^[17] for use as catalysts in the model reaction.^[72]



Scheme 23. Lipase-catalyzed kinetic resolution of alcohol **58**. Screening was carried out by GC.^[72, 74]

The idea for accomplishing a reasonably high throughput was to somehow combine two GC columns in one configuration. The initial approach concerned the use of two columns in a single GC oven.^[72, 74] However, this turned out to have a number of disadvantages. The successful construction consists of two GC instruments,^[75] one prep-and-load sample manager (PAL),^[76] and a PC (Figure 9). The instruments are connected to the PC through a standardized data bus (HP-IB)^[75] which controls pressure, temperature, etc. and handles other data such as that from the detector. A wash station as well as a drawer system with a maximum of eight microtiter plates were included. Using a special construction developed in-house, the sample manager was attached to the unit in such a way as to reach both injection ports. Since the sample manager can inject samples from 96- or 384-well microtiter plates, over 3000 samples can be handled without manual intervention. The software (Chemstation)^[77] enables additional programs (macros) to be applied before and after each analytical run. Such a macro controls the sample manager, with each position on the microtiter plate being

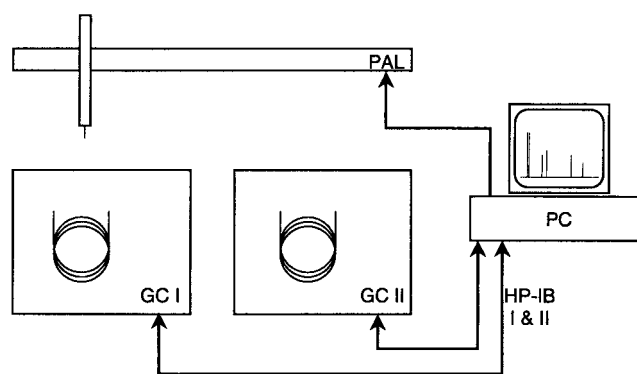


Figure 9. Schematic representation of a GC screening system comprising two GC instruments.^[74]

labeled by the sequence table. Another macro ensures that the analysis following each sample is carried out in a specified manner, namely, the peaks of the chiral compounds **58** and **59** are analyzed quantitatively. The analytical data are transferred to an Excel spreadsheet by DDE (Dynamic Data Exchange)^[78] in a table format or in microtiter-format, which allows for a rapid overview. Finally, since the carrier gas is hydrogen the setup includes H_2 guards which monitor the H_2 concentration in the ovens; at concentrations exceeding 1% (potentially explosive at > 4% H_2) the systems responds and automatically switches to nitrogen as the carrier gas.^[72, 74]

Using a stationary phase based on a β -cyclodextrin derivative (2,3-di-*O*-ethyl-6-*O*-*tert*-butyldimethylsilyl- β -CD) complete separation of (*R*)- and (*S*)-**58** (but not of (*R*)/(*S*)-**59**) was achieved within 3.9 minutes.^[72, 74] About 700 exact *ee* determinations of (*R*)/(*S*)-**58** are possible per day with the two simultaneously operating GC units shown in Figure 9. Moreover, the corresponding values for the conversion and the selectivity factor *E* are likewise automatically provided in microtiter format. A typical example is shown in Figure 10 in which the data corresponding to the most selective mutant enzymes are shown in gray boxes ($E \geq 2.4$).^[74] Mutants displaying 0% conversion imply complete lack of enzyme activity. Negative *ee* values indicate reversal of enantioselectivity.

MTP 1	1	2	3	4	5	6	7	8	9	10	11	12																
A	15	4	15	3	30	15	0	-	0	-	27	11	28	12	26	11	8	-2	30	12	0	-	0	-	0	C	0	
	1.6	1.4	2.1	-	-	-	2.0	2.1	2.1	0.7	1.9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	E	
B	0	-	15	5	16	4	0	-	0	-	21	8	26	10	0	-	16	4	12	2	21	5	16	0	0	0	C	0
	-	-	1.6	1.5	-	-	-	1.9	1.9	-	1.6	1.3	1.6	1.5	-	-	-	-	-	-	-	-	-	-	-	-	E	
C	12	3	0	-	0	-	20	7	0	-	28	13	20	5	0	-	22	6	0	-	0	-	26	6	0	0	C	0
	1.5	-	-	-	1.6	-	2.2	1.5	-	2.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	E	
D	29	13	27	11	8	-4	19	7	25	16	30	13	16	4	26	12	0	-	29	13	6	-2	26	11	0	0	C	0
	2.2	2.0	0.4	2.0	2.1	2.1	1.5	2.2	-	2.3	0.6	2.1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	E	
E	12	2	29	13	0	-	35	18	22	8	0	-	19	5	27	13	0	-	6	-2	24	10	17	5	0	0	C	0
	1.6	2.2	-	-	2.4	1.9	-	1.6	2.4	-	0.5	2.2	1.8	-	-	-	-	-	-	-	-	-	-	-	-	-	E	
F	0	-	29	9	27	12	12	1	22	9	23	9	16	4	13	2	23	9	16	6	23	8	12	2	0	0	C	0
	-	-	2.1	2.2	1.1	2.1	2.0	1.7	1.4	2.0	1.9	1.9	1.4	-	-	-	-	-	-	-	-	-	-	-	-	-	E	
G	27	10	0	-	26	11	0	0	-	0	-	29	13	12	1	22	7	0	-	0	-	5	-2	0	0	0	C	0
	2.0	-	2.2	1.1	-	-	-	-	2.2	1.2	1.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	E	
H	37	21	0	-	17	5	18	6	31	15	22	8	0	-	10	0	0	-	0	-	13	3	19	6	0	0	C	0
	2.5	-	1.7	1.9	2.3	1.9	-	1.1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	E	

Figure 10. Excel spreadsheet of GC data in microtiter plate (MTP) format showing values for conversion *c* [%], *ee* value [%], and selectivity factor *E* for mutant lipases catalyzing the hydrolytic kinetic resolution of alcohol **58**.^[74]

Thus, contrary to common belief, it is possible to utilize GC in the high-throughput screening of enantioselectivity in appropriate cases. This type of GC setup should also be useful in the screening of achiral transformations. Moreover, it is sometimes possible to increase throughput even further by injecting samples at proper times which are shorter than the total time span of the actual chromatogram, thus enabling the maximum use of time between runs (interlocking chromatograms).^[72, 74] Major advantages relative to the employment of two totally separate GC units include optimal use of laboratory space and the utilization of a single sampler and computer system, which results in high instrumental and economical efficiency. Although optimization needs to be performed for each new chiral compound to be tested, it can be anticipated that in appropriate cases 600–800 samples can easily be handled per day. It remains to be seen if a similar adaptation of HPLC can be developed to suit the requirements of a given analytical problem. However, it is unlikely that truly high-throughput *ee* determinations, that is, many thousands of samples per day, can be achieved in a general way on the basis of GC or HPLC. Of course, depending upon the particular problem at hand, a throughput of 600–800 *ee* determinations per day may suffice.

A related question concerns the high-throughput screening of enantioselectivity based on thin-layer chromatography (TLC).^[72] It is known that enantiomer separation is possible using chirally modified stationary phases and that the relative size of the “spots” for the *R* and *S* isomers correlate with enantiomeric purity (*ee*).^[79] Günther has applied this technique in the determination of the *ee* values of chiral amino acids and hydroxycarboxylic acids,^[79b] although the authors did not strive for high throughput. This can principally be achieved by

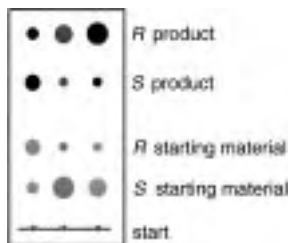


Figure 11. Schematic representation of a TLC plate showing the result of kinetic resolution of a *rac*-starting material.^[72]

applying appropriate computer image processing. One possibility that we suggest is the routine MORFO of the commercially available IMAGIC-5 software package which recognizes and “integrates” spots on a given surface.^[80, 81] In the case of kinetic resolution, the relevant TLC plate would have the schematic form shown in Figure 11.^[72] It is easy to imagine that hundreds

of these TLC plates can be scanned rapidly. The real challenge is to find efficient chiral selectors which result in sufficient enantiomer separation.

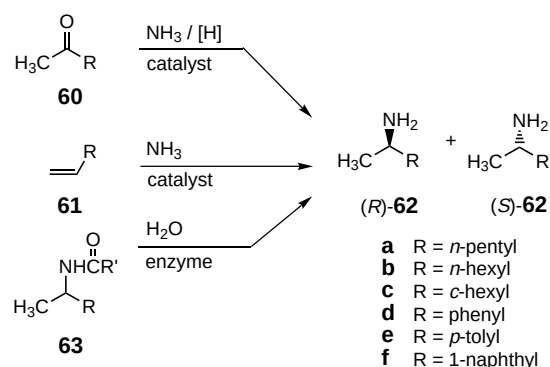
3.6. Parallel Chirally Modified Capillary Electrophoresis

As mentioned in Section 1 the determination of enantiomeric purity is sometimes carried out by capillary electrophoresis (CE) in which the electrolyte contains chiral selectors such as cyclodextrin (CD) derivatives.^[7] Unfortunately the conventional forms of this analytical technique allows for only a few dozen *ee* determinations per day. However, as a consequence of the analytical demands arising

from the Human Genome Project CE has been revolutionized in recent years so that efficient techniques for instrumental miniaturization are now available, which make the super-high-throughput analysis of biomolecules possible for the first time.^[82, 83] Two different approaches have emerged, namely capillary array electrophoresis (CAE)^[82] and CE on microchips (also called CAE on chips).^[83] Both techniques can be used to carry out DNA sequence analyses and/or to analyze oligonucleotides, DNA-restriction fragments, amino acids, or PCR products. Many hundreds of thousands of analytical data points can be accumulated per day.^[82, 83] We therefore thought that chiral modification of such techniques would allow for the first time the super-high-throughput analyses of enantiomeric purity (*ee*).^[84]

In the case of CAE, commercially available instruments have been developed which contain a high number of capillaries in parallel, for example, the 96-capillary unit MegaBACE which consists of 6 bundles of 16 capillaries.^[85] The system can therefore address a 96-well microtiter plate. Each capillary is about 50 cm long.

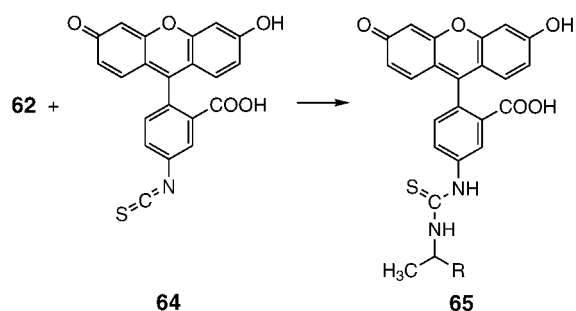
We therefore set out to adapt this system as a super-high-throughput analytical tool for *ee* determination.^[86] In this initial study chiral amines of type **62**, which are of importance in the synthesis of pharmaceutical and agrochemical products,^[87] were used as the model substrates. They are potentially accessible by catalytic reductive amination of ketones **60**, Markovnikov addition of ammonia to olefins **61**, or enzymatic hydrolysis of acetamides **63** (the reverse reaction also being possible; Scheme 24).



Scheme 24. Catalytic formation of chiral amines **62**. Screened was carried out by CAE.^[86]

In exploratory experiments the conditions for a conventional CE assay of the amines **62** were first optimized using various α - and β -CD derivatives as chiral selectors.^[86] The amines were first derivatized by conventional reaction with fluoresceine isothiocyanate (**64**) to give the fluorescence-active compounds **65** (Scheme 25) that would enable a sensitive detection system, specifically laser-induced fluorescence detection (LIF), to be used. Although extensive optimization was not carried out (only six CD derivatives were tested), satisfactory baseline separation was accomplished in all cases (Table 1).

The next step involved the use of compounds **62c/65c** as the model substrates for CAE analysis using a MegaBACE type



Scheme 25. Derivatization of chiral amines **62** for LIF detection in CAE screening.^[86]

of instrument. Known enantiomeric mixtures of the amine **62c** were transformed into the fluorescence-active derivative **65c**. The latter samples were then analyzed by CAE. Unfortunately, the results of the conventional single capillary system could not be reproduced in the CAE experiments because of unstable electrophoretic runs. The problem was solved by developing a special electrolyte having a higher viscosity. It is composed of 40 mM 2-(*N*-cyclohexylamino)-ethanesulfonic acid (CHES; pH 9.1) and 6.25 mM γ -CD (5/1) diluted with a buffer containing linear polyacrylamide. The MegaBACE instrument was operated at a voltage of -10 kV (at $8 \mu\text{A}$) per capillary and a sampling voltage of -2 kV (9 s). Under these conditions baseline separation was excellent (Figure 12). The agreement between the *ee* values of mixtures of (*R*)- and (*S*)-**65c** determined by CAE and those of the corresponding mixtures of (*R*)- and (*S*)-**62c** as measured by GC turned out to be excellent.^[86]

The enantiomer separation of (*R*)/(*S*)-**65c** on the MegaBACE instrument required about 19 minutes. This means that even though the conditions are far from optimized the automated 96-array system can provide more than 7000

Table 1. Results of CE-based enantiomeric separation of amine derivatives **65** as a function of the electrolyte.^{[a][86]}

Buffer, cyclodextrin used ^[b]	65a	65b	65c	65d	65e	65f
40 mmol CHES, 40 mmol γ -CD + 15 % CH_3CN	B	B	–	n.m.	–	–
20 mmol borate, 20 mmol DM- β -CD	–	–	–	–	–	–
40 mmol CHES, 20 mmol DM- β -CD	–	–	–	–	–	–
40 mmol CHES, 5 mmol DM- β -CD	–	–	–	P	–	–
40 mmol CHES, 40 mmol HE- β -CD	–	–	–	–	–	–
40 mmol CHES, 20 mmol HE- β -CD	P	–	–	P	P	–
40 mmol CHES, 10 mmol HE- β -CD	P	–	–	P	P	–
40 mmol CHES, 5 mmol HE- β -CD	aB	P	P	aB	aB	–
40 mmol CHES, 2.5 mmol HE- β -CD	aB	P	P	P	aB	–
40 mmol CHES, 5 mmol HP- α -CD	–	–	–	–	–	–
40 mmol CHES, 20 mmol HP- β -CD	–	–	–	P	–	–
40 mmol CHES, 5 mmol HP- β -CD	P	–	P	aB	P	–
40 mmol CHES, 20 mmol HP- β -CD + 15 % CH_3CN	P	–	–	P	–	P
40 mmol CHES, 25 mmol HP- γ -CD	–	–	P	–	–	–
40 mmol CHES, 6.25 mmol HP- γ -CD	–	–	B	–	P	aB
40 mmol CHES, 25 mmol HP- γ -CD + 15 % CH_3CN	–	–	B	–	–	–
40 mmol CHES, 10 mmol NH_2 - β -CD	–	–	–	–	–	–
40 mmol CHES, 10 mmol β -CD	–	–	–	–	–	–

[a] P: Partial separation; B: baseline separation; aB: almost baseline separation; –: no separation; n.m.: not measured. [b] DM: heptakis(2,6-di-*O*-methyl); HE: hydroxyethyl; HP: hydroxypropyl; NH_2 : 6'-amino-6'-deoxy; CHES: 2-(*N*-cyclohexylamino)ethanesulfonic acid.

ee determinations in a single day.^[86] In related cases optimization resulted in shorter analysis times for the separation of the enantiomers, so that a daily throughput of 15000 to 30000 *ee* determinations is realistic. Such super-high-throughput screening for enantioselectivity is not possible by any other currently available technology. In view of the possibility of chiral selector optimization and the fact that CAE has many advantages such as the use of extremely small amounts of samples, essentially no solvent consumption, the absence of high pressure pumps and valves, as well as high durability of columns, we believe that our CAE assay is ideally suited for high-speed *ee* determination.

In 1997 we described a variation of the above method, namely the possibility of high-throughput *ee* screening of chiral organic compounds, by utilizing capillary electrophoresis on microchips.^[84] The general procedure for CE (or more specifically CAE) on microchips (typically 10×10 cm) had previously been developed by Manz and co-workers^[83a] and others^[83c–h] for the analysis of biomolecules. Traditional photolithographic techniques were used to produce capillary arrays on plastic or glass microchips.^[83] In our work we discovered that the enantiomer separation of organic molecules on plastic microchips is not generally feasible as a result of the chemical instability of such systems. The situation is quite different in the case of glass chips.^[86] In such a modification the separation of enantiomers, for example, of compound **65c**, is possible with a detection system based on laser induced fluorescence (LIF). Automation using robotics is currently being optimized, which means that a second CAE-based assay for super-high-throughput *ee* determination will soon emerge. In view of the recent reports by Mathies and co-workers^[83c] and Li and co-workers^[83h] concerning enantiomer separation of aqueous solutions of amino acids on CAE microchips, we expect that this type of assay will play a significant role in the future.^[88] Of course, for a given analytical problem, derivatization and antipode separation

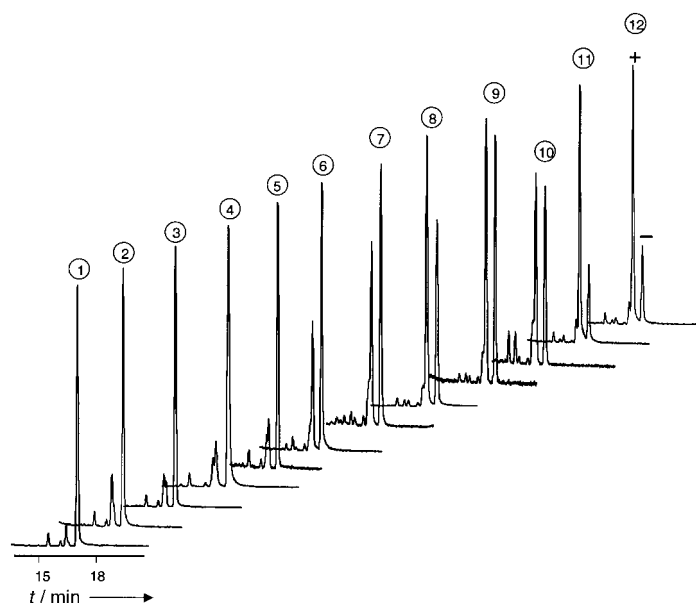


Figure 12. CAE antipode separation of the enantiomers of **65c** in a representative sample.^[86]

need to be efficient, which means that universal generality cannot be claimed.

In summary, the two forms of capillary array electrophoresis constitute powerful methods for the determination of the enantiomeric purity of chiral compounds in a truly high-throughput manner. Various modifications are possible, for example, detection systems based on UV/Vis, MS, or electrical conductivity. Moreover, chiral selectors in the CE electrolyte are not even necessary if the mixture of enantiomers is first converted into diastereomers, for example, using chiral fluorescent-active derivatization agents.^[86b]

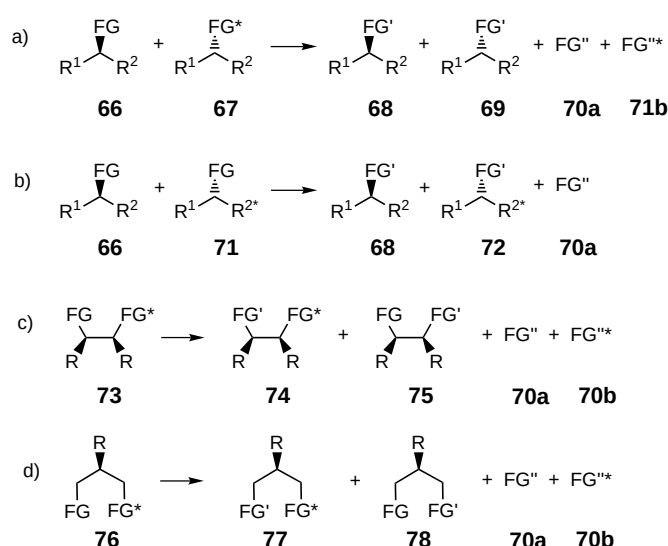
3.7. Mass-Spectrometric Assays

Although several mass-spectrometric (MS) assays have been developed for use in combinatorial catalysis,^[12, 13b, 13d, 13g, 13j] their application to the screening of enantioselective catalysts is not straightforward simply because the *R* and *S* forms of a chiral compound show identical mass spectra. We have nevertheless devised an MS-based system which makes possible the determination of enantioselectivity (*ee* and/or *E* value) without any chromatographic separation or diastereomer formation. Typically about 1000 catalyst evaluations are possible per day.^[89] Ionization can be accomplished by a number of standard methods, including electrospray ionization (ESI) and matrix-assisted laser-desorption ionization (MALDI).^[63] Two basically different stereochemical processes can be monitored by our method: the kinetic resolution of racemates and the asymmetric transformation of prochiral substrates with enantiotopic groups.^[89, 90]

The underlying principle is based on the use of isotopically labeled substrates in the form of pseudo-enantiomers or pseudo-prochiral compounds (Scheme 26). The course of the asymmetric transformation, that is, the relative amounts of reactants and/or products, are detected by ESI-MS.

In the case of kinetic resolution, compounds **66** and **67**, which differ in their absolute configuration and in their labeling at the functional group FG*, need to be prepared in enantiomerically pure forms and then mixed in a 1:1 manner to simulate a racemate (Scheme 26a). Following asymmetric functional group transformation (in an ideal kinetic resolution there is 50% conversion), the true enantiomers **68** and **69** are formed together with the nonlabeled and labeled achiral products **70a** and **70b**, respectively. The ratios of the total intensities of **66/67** and **70a/70b** in the mass spectra (*m/z* intensities of the quasi-molecular ions) allow for the determination of enantiomeric purity and therefore enantioselectivity of a catalyst. In some cases it may be advantageous to use an internal standard to determine the extent of conversion.^[89]

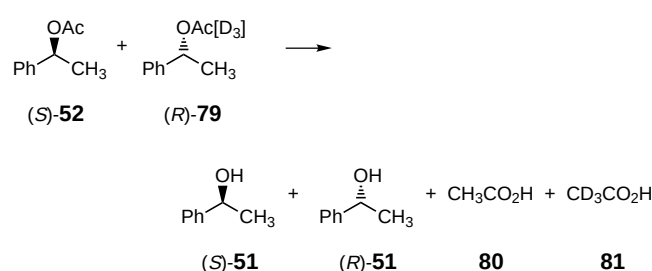
As a variation of this theme, kinetic resolution of the pseudo-enantiomers **66** and **71** which are labeled at residue R² affords a new pair of pseudo-enantiomers **68** and **72** (Scheme 26b). Based on the *m/z* intensities of the quasi-molecular ions of **66/71** and **68/72**, the conversion, enantioselectivity (*ee*), and selectivity factor (*E*) can be obtained. An internal standard is not necessary.^[89]



Scheme 26. a) Asymmetric transformation of a mixture of pseudo-enantiomers involving cleavage of the functional groups FG and labeled functional groups FG*. b) Asymmetric transformation of a mixture of pseudo-enantiomers involving either cleavage or bond formation at the functional group FG; isotopic labeling at R² is indicated by the asterisk. c) Asymmetric transformation of a pseudo-*meso* substrate involving cleavage of the functional groups FG and labeled functional groups FG*. d) Asymmetric transformation of a pseudo-prochiral substrate involving cleavage of the functional groups FG and labeled functional groups FG*.^[89]

In the case of prochiral substrates having enantiotopic groups, for example, *meso* compounds (Scheme 26c), the synthesis of a single pseudo-*meso* compound, such as **73**, suffices, since the stereodifferentiating reaction of interest delivers a mixture of two MS-detectable pseudo-enantiomers **74** and **75**. The same applies to other pseudo-prochiral substrates of type **76** (Scheme 26d).

The first system to be tested concerned the kinetic resolution of racemic 1-phenylethyl acetate (**52**) (Scheme 27).^[89] For this purpose the pseudo-enantiomers (*S*)-**52** and (*R*)-**79** were prepared in enantiomerically pure



Scheme 27. Kinetic resolution of pseudo-enantiomers (*S*)-**52** and (*R*)-**79**. Screening was carried out by ESI-MS.^[89]

form. These two compounds were mixed in various ratios and the resulting mixtures analyzed by GC in order to ascertain the exact pseudo-*ee* values as a control. Thereafter the same samples were analyzed by ESI-MS. A typical ESI-mass spectrum is shown in Figure 13. Since the deuterium labeling results in the sodium adducts of (*S*)-**52** and (*R*)-**79** appearing at different *m/z* values, integration is a simple manner. A total of 17 control samples were studied, and the agreement

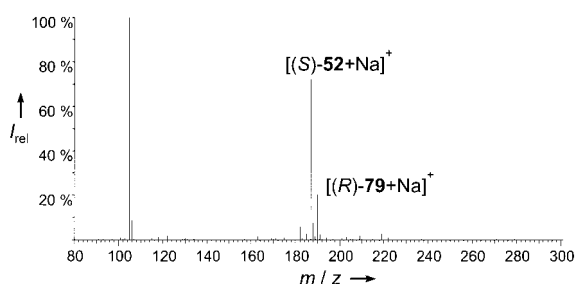
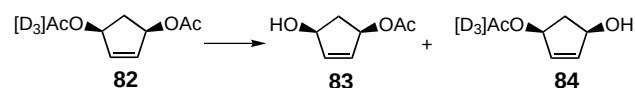


Figure 13. ESI-mass spectrum of a sample containing (S)-52 and (R)-79.^[89]

between the *ee* values determined by GC and ESI-MS was excellent ($\pm 5\%$).^[89] In contrast to a number of other methods which suffer from the fact that *R*- and *S*-configured substrates are tested separately as pairs on microtiter plates, the present system utilizes 1:1 mixtures of pseudo-enantiomers in kinetic resolutions. Moreover, analogous reactions on the solid phase, if necessary, should pose no problems.

An experimental setup capable of high-throughput screening of enantioselective reactions was then devised. This was achieved by combining an automated liquid sampler for microtiter plates (96-format) with an ESI-MS system, both commercially available (Figure 14).^[89, 90] This unit allows about 1000 determinations of the *ee* value and the conversion (and thus *E*) of such transformations as the above model reaction to be made in a single day. As shown in Scheme 26, deuterium labeling can be performed at any position of the substrate. It is advisable to perform a quick kinetic study of labeled and nonlabeled substrates in order to exclude possible secondary isotope effects.

As an example of an asymmetric transformation of a prochiral substrate, we considered the known desymmetrization of *cis*-1,4-diacetoxycyclopentene.^[89] In this case the pseudo-prochiral compound **82** was prepared (Scheme 28). The products of the asymmetric transformation are compounds **83** and **84**, each having two stereogenic centers. Since



Scheme 28. "Desymmetrization" of a pseudo-prochiral substrate **82**. Screening was carried out by ESI-MS.^[89]

they are pseudo-enantiomers they can easily be distinguished by ESI-MS. Indeed, we are currently studying the directed evolution of an enantioselective lipase for this transformation, with the screening being possible by the unit shown in Figure 14.

This approach constitutes a powerful method for high-throughput screening of enantioselective enzymes or synthetic asymmetric catalysts. Instead of deuterium labeling, mass-tagging (for example, methyl groups in place of hydrogen atoms) at remote positions in the molecule is also possible. However, the method has limitations because it is restricted to the analysis of the two classes of compounds having the symmetry properties delineated above (Scheme 26). This means that transformations involving prochiral compounds lacking enantiotopic groups cannot be screened (for example, reduction of acetophenone (**54**) to 1-phenylethanol (**51**); Scheme 21).

A different MS-based approach, specifically in the determination of *ee* values of alcohols, was described by Finn and co-workers^[91] and can be viewed as an extension of Horeau's method.^[92] It is based on derivatization using chiral mass-tagged acylation reagents. The method requires a measurable degree of kinetic resolution in the derivatization step.^[91] The technique makes use of an equimolar mixture of pseudo-enantiomeric mass-tagged chiral acylating agents that differ in a substituent remote to the stereogenic center (for example, methyl versus hydrogen) in a way that the mass of the molecule correlates with its absolute configuration. In principle the reactions of enantiomers with chiral reagents can proceed with unequal rate constants ($k_f > k_s$; f = fast, s = slow). Scheme 29 shows the case of chiral alcohols (*R*)-OH and (*S*)-OH and mass-tagged enantiomerically pure acylating agents.^[91] The enantiomeric alcohols (*R*)-OH and (*S*)-OH are first treated with the chiral mass-tagged acids A-CO₂H and B-CO₂H in the presence of 1,3-dicyclohexylcarbodiimide (DCC). The relative amounts of the product esters as measured by MS can then be used (after two calibration measurements) to determine the enantiomeric composition of the starting mixture (*R*)-OH/(*S*)-OH and therefore the *ee* value.

Finn and co-workers used the proline-derived mass-tagged acylating agents **85** and **86**.^[91] The reagents need to be used in great excess, and for the system to work it is necessary that a small but measurable degree of kinetic resolution occurs. The sensitivity of the method was shown to be $\pm 10\%$ *ee*. The

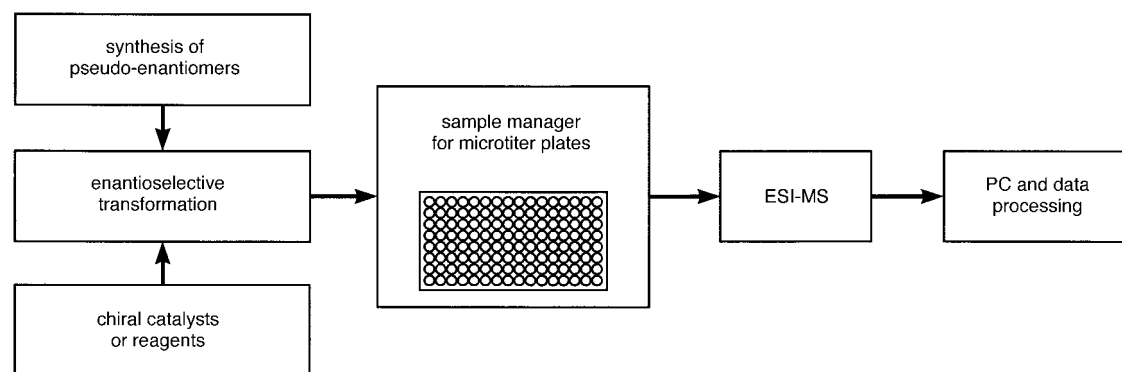
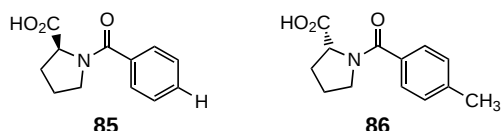
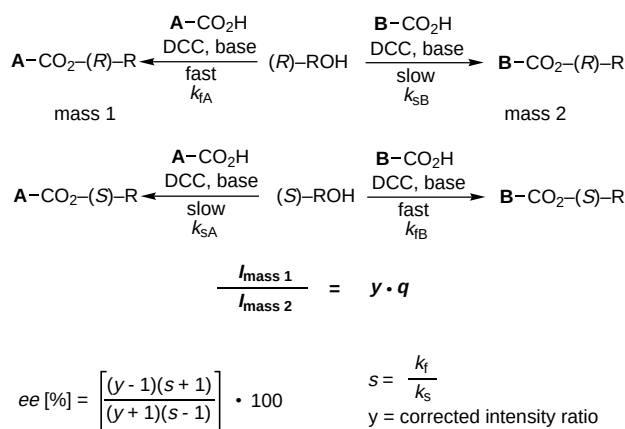


Figure 14. Experimental setup of an ESI-MS *ee*-screening system.^[89]

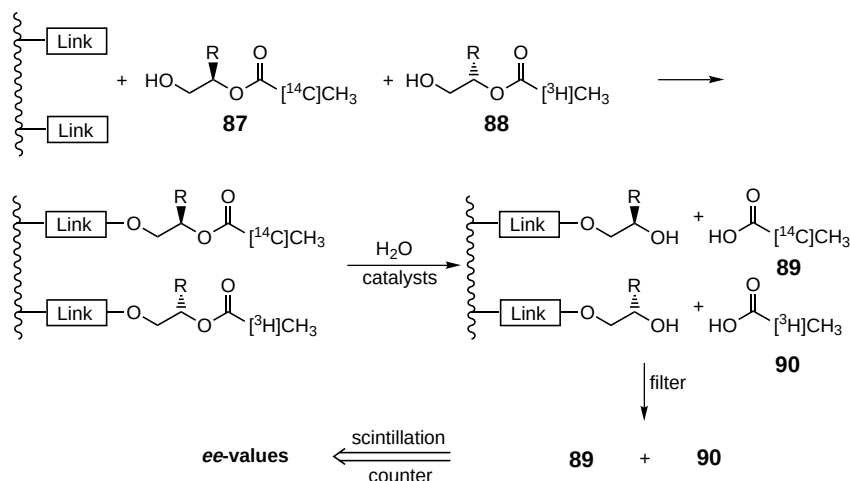


Scheme 29. Mass-spectrometric *ee* determination in the kinetic resolution of alcohols (*R*)-OH/(*S*)-OH.^[91] *I* = peak intensity; *q* = correction factor for ionization; DCC = dicyclohexylcarbodiimide.

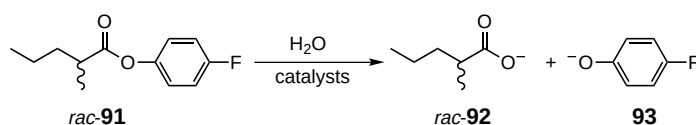
technique can also be reversed using mass-tagged chiral nucleophiles for measuring the *ee* values observed when using acylating agents. As in our own MS-based system,^[89] chromatographic separation is not involved. Moreover, the authors have pointed out the possibility of a robotic high-throughput screening system using microtiter plates,^[91] which should certainly work. Finally, instead of mass-tagging based on the use of methyl groups, it is also possible to carry out the same type of analyses using deuterium-labeling.^[63]

3.8. Radioactivity Assays

In 1997 we pointed out the possibility of a detection system for the determination of *ee* values using radiolabeled substrates on a solid support and measuring the radioactivity of the solution containing the cleaved products.^[84] For example, attachment of appropriate radiolabeled pseudo-enantiomers **87/88** is necessary in the case of the hydrolytic kinetic resolution of esters of the type ROCH₂CH(R)OC(O)CH₃ by the enantioselective formation of the corresponding *O*-protected diols ROCH₂CH(R)OH (Scheme 30). With this system thousands of (bio)catalysts can then be screened. Following catalytic hydrolysis in the wells of microtiter plates, the solution is separated from the solid support and the relative amounts of radiolabeled acetic acids **89** and **90** are determined using a conventional scintillation counter. This provides the *ee* values at different conversions. In special cases this method may be advantageous, although automation using a robotic scintillation counter needs to be developed.



Scheme 30. Schematic representation of an *ee* assay based on radioactivity measurements.^[84]



Scheme 31. Model reaction for an NMR-based screening system.^[72, 94]

3.9. NMR and IR Assays

NMR spectroscopy is a relatively slow analytical procedure and therefore may not appear to be amenable to high-throughput analyses. However, progress has in fact been made in the utilization of NMR methods in combinatorial drug discovery processes both on solid supports and in solution.^[93] Of course, one of the drawbacks is low sensitivity necessitating the use of high concentrations. Developments in the design of NMR flow probes and cryoprobes are expected to stimulate future progress in the use of NMR spectroscopy in combinatorial chemistry.

Since high throughput stands at the heart of combinatorial catalysis and because it is of advantage to carry out the measurements on a large number of samples simultaneously, we have considered the application of magnetic imaging (NMR tomography) for sample screening. This technique is used successfully in medicine to image tissues and organs. In our case the goal was to obtain tomograms of microtiter plates on which enantioselective reactions were occurring.^[72] In exploratory experiments we decided to utilize the ¹⁹F nucleus in order to monitor the hydrolysis of the *R*- and *S*-configured ester **91** (Scheme 31).^[72, 94] In an initial measurement a 3:2

mixture of *rac*-**91** and *p*-fluorophenolate (**93**) in DMF and tris(hydroxymethyl)methylamine (TRIS) buffer (pH 7.5) in D₂O:H₂O (3:7) was studied. Separate ¹⁹F NMR peaks of **91** and **93** were readily observed ($\delta = -117$ and -124 , respectively).

In further exploratory experiments NMR tubes were charged with mixtures of **91** and **93** in ratios of 1:1.4 (sample A) and 1:9 (sample B). The samples were measured with a micro-5 micro-imaging probe head on a Bruker DMX300WB spectrometer.^[94] The 3D chemical shift imaging

(CSI) allows two dimensions to be resolved spatially and the third is chemical shift sensitive (Figure 15).^[94] It is easy to identify the resonance of the ester **91** (left signal) and that of *p*-fluorophenolate (**93**; right signal). In each case the traces along the *x*- and *y*-axes reflect the total absorption of the resonance frequency of *p*-fluorophenolate (in sample A) and that of the ester **91** (in sample B). Ester **91** is present in such a low concentration in the case of sample B that only a weak signal is discernable.

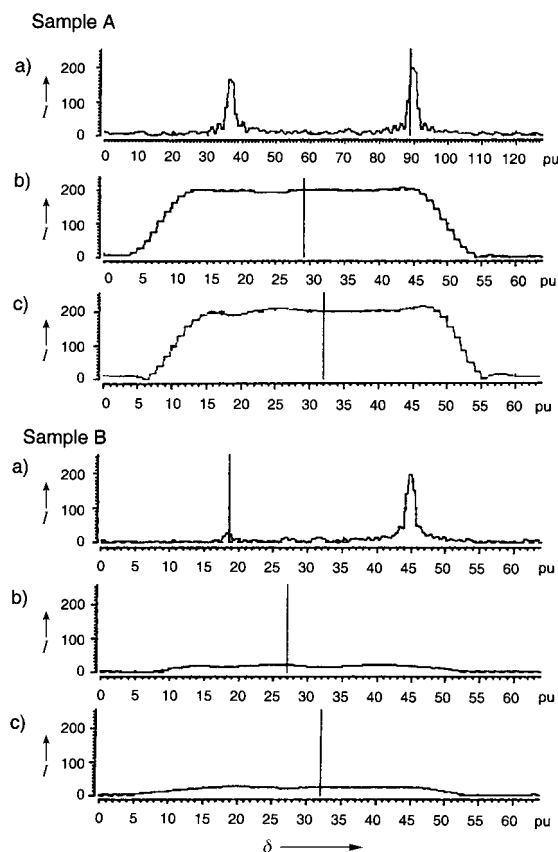


Figure 15. Chemical shift in two dimensions using 3D-CSI.^[72, 94] Sample A: **91**:**93** = 1:1.4; Sample B: **91**:**93** = 1:9. In each case the chemical shift (a) as well as the signals along *x* (b) and *y* axes (c) are given; *I* = intensity; pu = pixel units.

The data of this type of 3D-CSI measurements can be presented visually in different ways. In addition to the traces shown in Figure 15, spatial positioning of the ¹⁹F NMR resonance lines is possible, as shown by the images in Figure 16.^[72, 94] The two discs represent the two-dimensional resolved distribution of the NMR resonance lines of sample A. Just as in an NMR tomogram these can be rotated in space. The intensities of the images correlate with the concentrations of the compounds in the samples (**93**: light disc, **91** dark disc corresponding to a 1.4:1 ratio). In a potential *ee* assay (*R*)- and (*S*)-**91** would be allowed to react separately pairwise with each catalyst on a microtiter plate.

On the basis of these experiments it should indeed be possible to image the enantiomeric purity of products in the wells of a microtiter plate by NMR tomography.^[72] However, the instrumentation currently available is not yet sensitive

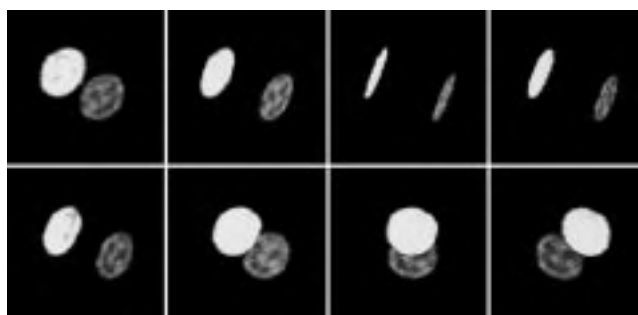


Figure 16. Different ways to present 3D-CSI measurements of sample A (**93**:**91** = 1.4:1).^[72, 94]

enough for practical applications. We conclude that this method nevertheless has some potential in the determination of *ee* values (and other types of screening). Finally, van Leeuwen has shown that in some cases IR spectroscopy is useful in the evaluation of asymmetric reactions.^[95]

4. Conclusion

Considerable advances in the parallel synthesis of chiral ligands for use in catalytic enantioselective reactions have been made during the last five years. At the same time strategies for exploiting the principles of combinatorial chemistry in the search for enantioselective catalysts have been proposed. It currently appears that the greatest prospects for successful applications are to be found in the study of modularly constructed chiral ligands because these offer the maximum degree of structural diversity and therefore maximize the prospect of finding enantioselective catalysts. This approach is also expected to pave one of the ways to the discovery of new types of chiral ligands for use in asymmetric catalysis, provided the experiments are devised intelligently. As one of the referees of this review has rightly pointed out, the perhaps most important message emerging from this research concerns the question: "How much have we missed over the years by *not* using diversity-based approaches to catalyst discovery and optimization?"

The systematic screening of achiral additives in appropriate systems which not only cause rate enhancement^[96] but also influence the degree of enantioselectivity is also worthy of mention. Such additives are almost unlimited in number. Of particular academic and practical interest are those additives which are only formally achiral, for example, most *meso*-compounds, but which are in fact two rapidly interconverting enantiomers. These compounds form diastereomers upon interaction with the actual chiral ligand used in the catalytic transformation.^[97] A variation of this theme is the covalent attachment of such compounds to the chiral ligand,^[98] with combinatorial diversity again being possible.

In spite of considerable conceptual progress, the actual goal of preparing truly large libraries of chiral ligands or catalysts has not been put into practice to date, in part this is a result of the lack of high-throughput screening systems. An exception is the application of directed evolution as a means to create enantioselective enzymes for use in organic chem-

istry.^[17,19] It is this area of endeavor which led to the development of the first high-throughput assays for enantioselectivity. Most of the more recent screening systems can also be used in the combinatorial search for asymmetric transition metal catalysts. This opens up completely new perspectives for the future, simply because now extremely large libraries can actually be screened rapidly. This means that the creative chemist can put more of his/her ideas into practice per unit of time. Hopefully, the application of genetic algorithms^[99] and/or neural networks^[100] can be of help in the combinatorial search for enantioselective catalysts.

Among the various approaches described for high throughput *ee*-screening systems, those based on mass spectrometry^[89–91] and capillary array electrophoresis^[86] currently appear to be most promising. However, no single system is expected to be universal, which means that the use and/or development of alternatives continue to be important. In the case of directed evolution of enantioselective enzymes, one such possibility is the application of phage display^[101] as a selection system. Such systems would allow the evaluation of millions of mutant enzymes with respect to the enantioselectivity of a given reaction.

Whatever screening systems will be used in the future to assay enantioselective catalysts, data management needs to be considered as super-high-throughput emerges.^[86] Thus, research in this general aspect of combinatorial catalysis is expected to gain in importance. Finally, the ideal screening system in any combinatorial catalyst system should include the possibility to detect and identify the unexpected result, which would provide the chemist with a means to harness the all important phenomenon of serendipity.^[102]

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Combinatorial Heterogeneous Catalysis—A New Path in an Old Field

Selim Senkan*

Combinatorial catalysis is the systematic preparation, processing, and testing of large diversities of chemically and physically different materials libraries in a high-throughput fashion. It also embodies microfabrication, robotics, automation, instrumentation, computational chemistry, and large-scale information management (informatics), and as such carries the promise of a renaissance in catalytic reaction engineering. Significant progress has already been made in demonstrating the speed and economic advantage of

combinatorial approaches by the discovery of superior catalytic materials in a matter of hours and days, as opposed to the months and years required using traditional methods. Combinatorial methods can also significantly contribute to our understanding of catalytic function by increasing our chances of discovering totally new and unexpected catalytic materials, and by expediting the recognition of trends and patterns of structure–activity relations, from which new catalytic materials can be

designed more efficiently. Combinatorial catalysis undoubtedly will be the new paradigm of catalysis research as the industry faces increasing global competition and pressure for the development of environmentally friendly processes at a time when resources for research are diminishing.

Keywords: combinatorial chemistry • heterogeneous catalysis • high-throughput screening • catalysts

1. Combinatorial Catalyst Research

1.1. A New Route

Solid catalysts are used in the manufacture of a vast array of chemicals and fuels, and as such significantly contribute to our economy and high living standards.^[1, 2] Catalysts are used in the production of over 7000 compounds worth over \$3 trillion globally. Catalyst-based manufacturing accounts for about 60 % of chemicals production and 90 % of processes.^[1] These figures will likely increase in the future as a result of increasing pressures for the development of environmentally friendly manufacturing processes (see Table 1). The economic benefits of an efficient catalyst are enormous: catalytic processes are less capital intensive, have lower operating costs, produce higher purity products and fewer by-products. In addition, catalysts provide important environmental benefits, such as catalytic converters for automobiles. However, in spite of their significance and broad utility, the discovery of new catalysts continues to be an arduous and rather unpredictable trial-and-error process.^[3]

Table 1. Role of catalysis in the economy.^[a]

Catalysts are used globally in the manufacture of over 7,000 products worth over \$3 trillion per year	
Catalysts are used in 60 % of chemicals production and 90 % of processes	
Globally catalyst manufacturing is about an \$8.5 billion per year industry	
Globally there are about 100 catalyst manufacturing companies	
Catalyst usage	Annual turnover
Petroleum Refining	\$2.2 billion
Polymerization	\$2.2 billion
Chemicals Production	\$2.1 billion
Environmental Protection	\$2.1 billion

[a] Sources: "Catalysts", *Chem. Week*, September 1999 and *Chem. Eng. News* September 20, 1999; CMA, U.S. Chemical Industry Statistical Handbook, 1996.

Catalysts traditionally are developed using a variety of tedious and time consuming recipes, characterized and tested for performance repeatedly until no further improvements are justified. In addition, the time scales for success often are measured in months and years. This level of productivity can no longer be justified by the industry because of increasing pressures to remain profitable in an environmentally responsible manner while facing increasing global competition. The industry needs innovative ideas, shorter lead and development times for lower-cost products all at a time when significantly less resources are available for research and development. Such pressure was previously encountered by the pharmaceutical industry about a decade ago which

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subsequently led to the explosive growth of combinatorial chemistry as the new paradigm of doing business.^[4, 5] The field of catalysis is poised for a similar transformation as evidenced by the increase in the number of conferences and workshops held on combinatorial catalysis since 1999, whereas there were none a few years ago. Notable examples of such meetings, where issues pertaining to combinatorial catalysis were discussed, are presented in Table 2. In addition, the subject of combinatorial catalysis is also receiving attention from both academic and industrial research communities as evidenced by the increased number of papers presented and sessions organized in scientific and technical meetings around the world (see for example the recent National Meetings of the American Chemical Society (ACS) and the American Institute of Chemical Engineers (AIChE)).

Table 2. Recent meetings where combinatorial catalysis was covered.

<i>Combinatorial Approaches for Materials Discovery 1999 (San Jose, USA) and 2000 (San Diego, USA) and CombiEurope (Frankfurt, Germany)</i> organized by the Knowledge Foundation, Brookline, MA
<i>Combinatorial Catalysis and Catalyst Optimization 1999 (Philadelphia, USA)</i> , organized by the Catalyst Group, Springhouse, PA
<i>Combinatorial Chemistry: Beyond Pharmaceuticals 1998 and Microscale Characterization for Materials Discovery 1999 (Newark, USA)</i> , organized by the University of Delaware, Newark, DE
<i>Engineered Catalysis 1999 (New Orleans)</i> , organized by the Cambridge Healthtech Institute, Newton Upper Falls, MA
<i>Analytical Techniques in Combinatorial Chemistry 1999 (New Orleans, USA)</i> , organized by the American Chemical Society
<i>Combinatorial Methods for High Throughput Catalyst Design and Testing 1999 (Vilamoura, Portugal)</i> , organized by the University of Liverpool as a NATO Advanced Study Institute
<i>Advanced Technology Program 1999 (San Jose, USA)</i> , organized by the National Institute for Standards and Technology
<i>Combinatorial Catalysis and High Throughput and Combinatorial Methods in Catalyst Preparation and Testing 2000 (Los Angeles, USA)</i> organized by the American Institute of Chemical Engineers

1.2. Combinatorial Approaches

Combinatorial catalysis is a methodology or a set of tools^[6] where large diversities of solid-state materials libraries are prepared, processed, and tested for activity and selectivity in a high-throughput fashion.^[7] Since the data and information

generated are vast, the development and use of sophisticated high-capacity information-management systems (informatics) is also an essential component of this methodology. In fact, the successful implementation of combinatorial approaches will require that all of the components shown in Figure 1 must be in place and function smoothly, otherwise “bottlenecks” will limit the throughput.

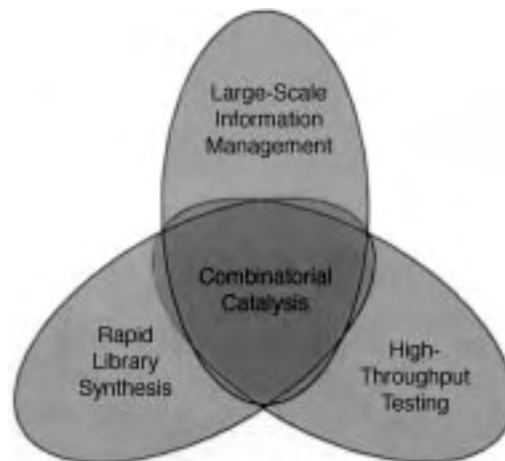


Figure 1. Essential components of combinatorial catalysis.

The integration of all the components of combinatorial catalysis is the ultimate goal of this field, enabling the intelligent planning and execution of highly parallel experiments with minimal human intervention. Initial integration of library synthesis and high-throughput screening is nearly realized as evidenced by numerous publications in these fields, which are summarized below. However, the development of software to organize and analyze the data and then provide an automatic feedback to library design is in its infancy. In this review, the status of each of the components of combinatorial catalysis as shown in Figure 1 will be summarized with examples.

It is important to note that combinatorial approaches can also contribute to our understanding of catalysis in a number of ways. First, by speeding up the pace of research, the chances of discovery of totally new and unexpected catalytic materials are increased. New discoveries should lead to a quantum leap



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in our understanding of catalysis, analogous to the impact that the discovery of high-temperature superconductors had in physics. Second, through the use of systematically acquired data and data-mining technologies, combinatorial catalysis should expedite the discovery of trends and patterns of structure–activity relations from large databases, which will be useful to develop practical catalysts. The issues related to data management are covered in Section 1.5. In addition, since surface characterization techniques can also be miniaturized, automated, and coupled with combinatorial tools, a closer link between traditional and combinatorial catalysis research can be made.

Interestingly, the idea of applying combinatorial approaches to heterogeneous catalysts is not new. In the early part of the 20th century Alwin Mittasch implemented an impressive program preparing and testing a large number of combinations of metals to catalyze the synthesis of NH_3 from H_2 and N_2 . These and related efforts subsequently were summarized in a review article in *Advances in Catalysis*.^[8] Consequently, the genesis of combinatorial inorganic chemistry should rightfully be attributed to heterogeneous catalysis and not to materials research,^[9] as is often done in the literature. However, the Mittasch approach for catalyst discovery and optimization was not pursued much further due, in part, to the high labor costs involved. Instead, the field evolved into its present form, which emphasizes step by step surface science approach fueled by the availability of extensive surface characterization equipment. In fact, according to a recent survey, nearly 50% of all the papers published in heterogeneous catalysis today are devoted to the surface characterization of these materials.^[10] However, recent advances in automation, robotics, microfabrication, and instrumentation should propel combinatorial approaches as the new paradigm in catalytic reaction–engineering research.

The implementation of combinatorial techniques to heterogeneous catalysis is a significantly more challenging problem than in other application areas of materials science.^[11] Additional challenges arise from the complex and dynamic nature of catalysts.^[12] First, real heterogeneous catalysts generally are extended solids with multiple discontinuities in structure and composition allowing very limited systematic variation in these properties with the overall composition. This is illustrated in the scanning tunneling microscope picture of a typical heterogeneous catalyst (Figure 2), where sharp changes in composition and structure are evident. In addition, these structures are strongly dependent on the methods of preparation and change with time under reaction conditions, with better catalysts being more resilient to change. All of these issues render heterogeneous catalysis research a difficult subject. In addition, the absence of markers or descriptors of diversity in solid-state mixtures impede the undertaking of systematic studies.^[13]

Second, heterogeneous catalysts must bind the reactants, induce them to bonding interactions, and allow the products to depart so that the catalytic cycle progresses. These requirements demand that no catalyst intermediate be too stable or the product too strongly adsorbed, otherwise the turnover number can not be high enough to be practically useful. In other words, heterogeneous catalysts must expedite the

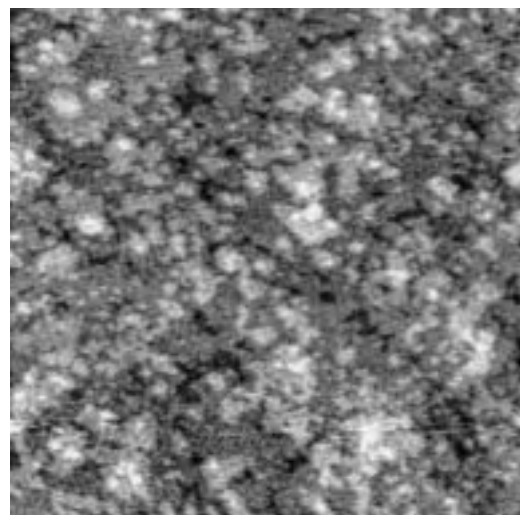


Figure 2. Scanning tunneling microscope picture of a real catalyst showing discontinuities in composition and structure.

formation of a suitable and energetically favorable transition state. Transition states are induced by the three-dimensional active sites on catalyst surfaces, both of which are poorly understood. It is likely that a multitude of active sites exist on solid surfaces and their distribution changes with time. The rates of change or shift of these sites is influenced by the rates of solid-state diffusion and gas–solid interactions both of which are influenced by temperature and local composition. Typically, catalysts deactivate with time as a consequence of events such as, surface reconstruction, sintering, poisoning, coke formation, and volatilization.^[14] Conversely, the activities of some catalysts peak only after a period “on stream”,^[15] again suggesting the involvement of events such as reconstruction. These considerations clearly call for the development of methodologies that will allow the undertaking of a large number of systematic, parallel experiments to unravel the underlying elementary events.

1.3. The Parameter Space

Before recent progress in combinatorial catalysis is summarized, it is useful to establish the magnitude of the parameter space that needs to be dealt with. For this purpose let us assume first that there are 50 useful, stable elements in the periodic table that are suitable candidates for heterogeneous catalysis. Based on this premise and the combinatorial formula [Eq. (1)], it can be shown that there will be 1225 binary, 19600 ternary, 230000 quaternary, and 10^{10} decanary combinations of these elements.

$$N(n_E/n_T) = n_E!/[n_T!(n_E - n_T)!] \quad (1)$$

N is the total number of combinations, n_E and n_T are the number of elements and their specific groups (binary, ternary etc.), respectively. It must be recognized that this parameter space becomes significantly larger if compositional and structural diversities are also considered. For example, if n_C compositional increments are used, the total number of

possible combinations can be shown to be given by the recursion formula [Eq. (2)].

$$N(n_{E+1}, n_C) = N(n_E, n_C) + N(n_{E+1}, n_{C-1}) \quad (2)$$

In Table 3 the number of multielement compositional combinations possible are presented for a variety of n_E and n_C values. For example, for a ternary mixture ($n_E = 3$) the use of 11 discrete concentrations on the binary axes would require the consideration of a total of 66 combinations. Similarly, for a quaternary system, the total number of combinations that must be evaluated would be 286. As evident from Table 3, the number of combinations increase geometrically with the increase in number of elements and the number of different compositions to be considered. For example, the consideration of a library having 10 elements from the periodic table and 25 composition increments in the binary axes require the evaluation of 38 567 100 discrete combinations! It must be recognized that the numbers presented in Table 3 are on the low side as they do not account for the physical or structural diversity induced by the methods of preparation.

Parameters describing the methods of preparation, for example, the temperature, the chemical composition of the atmosphere, and duration of calcination, must also be considered as independent variables that influence the parameter space in catalysis research. These considerations easily increase the number of parameter combinations to billions (Table 3). In view of this large parameter space, combinatorial techniques represent the most rational approach for the discovery and optimization of new catalytic materials. However, even with the development of high-throughput experimentation tools, we will be able to search only a small fraction of this large parameter space. Thus, one of the most important goals of combinatorial catalysis research should be to build representative libraries that ensure the greater probability of obtaining leads for a given reaction, by exploiting the accumulated know-how in traditional catalysis research, as well as chemical intuition and numerical simulation techniques.

Challenges imposed by large parameter space are also compounded because there are no well understood systematic variations of catalytic properties with composition and structure, that is, structure–activity relationships are still primitive and no markers for diversity exist. These issues render the application of conventional design of experiments impractical because of the difficulties associated in constructing response surfaces.^[16] The initial successes in combinatorial catalysis will probably be accomplished by the application of a variety of search strategies that will be investigator specific,

until sufficient experience accumulates. Nevertheless, possible search strategies can be categorized into two major groups:

1. Heuristic or stochastic formulation of initial catalyst libraries followed by steepest-gradient optimization search around the hits found in the library.
2. Totally stochastic methods of library preparation and modification.

The former approach appears most suitable for catalyst optimization problems where improvements of existing formulations are the goal. Indeed, a number of superior catalytic materials have already been discovered as variants of existing ones. Examples include the development of amorphous microporous mixed oxides (AMM) containing metals for the hydrogenation of 1-hexyne^[17] and the oxidation of propylene,^[18] the discovery of a superior quaternary Pt-Ru-Os-Ir catalyst for the reforming of methanol,^[19] the discovery of a superior ternary Rh-Pd-Pt catalyst for the oxidation of CO,^[20] a ternary Pt-Pd-In catalyst for the dehydrogenation of cyclohexane to benzene,^[21] and a ternary Mo-V-Nb catalyst for the oxidative dehydrogenation of ethane.^[22]

1.4. Stochastic Methods

Stochastic methods of library preparation include genetic algorithms (GA), Monte Carlo methods such as simulated annealing and tempering, branch and bound, and tabu search. These techniques are most suitable for the discovery and optimization of new catalytic materials. They rely on the implementation of some ad hoc rules to make progress in the search process and can be applied for the planning of combinatorial catalysis experiments.

1.4.1. Genetic Algorithms

Genetic algorithms are based on the concepts in natural evolution and the survival of the fittest.^[23, 24]

The GA approach involves the iterative preparations of libraries, which are screened for catalytic function, for example, conversion and selectivity, and the experimentally determined responses are then used as input to the GA to find better leads. The GA generally result in a set of very good, but not necessarily the best, solutions in a very large parameter space. The elements used in the creation of first generation catalysts can be selected from a subset of elements in the periodic table either heuristically or randomly, together with their corresponding concentration levels and methods of preparation. First generation catalysts that exhibit an acceptable performance level are then selected as parents for the creation of next-generation catalysts through crossover and

Table 3. Total number of compositional combinations of multielement mixtures.

n_C	$n_E = 2$	$n_E = 3$	$n_E = 4$	$n_E = 5$	$n_E = 6$	$n_E = 7$	$n_E = 8$	$n_E = 9$	$n_E = 10$
6	6	21	56	126	252	462	792	1287	2002
11	11	66	286	1001	3003	8008	19448	43758	92378
15	15	120	680	3060	11628	38760	116280	319770	817190
21	21	231	1771	10626	53130	230230	888030	3108105	10015005
25	25	325	2925	20475	118755	593575	2629575	10518300	38567100
31	31	496	5456	46376	324632	1947792	10295472	48903492	211915132
41	41	861	12341	135751	1221759	9366819	62891499	377348994	2054455634

mutations. In crossover, the elements and preparation methods from a “fit” parent are exchanged to some extent with another material. This operation enables the evolutionary process to move forward toward promising regions of the search space. The mutation processes are intended to prevent premature convergence to a local optimum by randomly introducing new elements or removing existing ones, or by changing the concentration of elements.

Genetic algorithms have been applied to the synthesis of combinatorial chemical libraries,^[25–28] for the design of heterogeneous catalysts,^[29] and the preparation and optimization of combinatorial libraries of heterogeneous catalysts.^[30, 31] Recently GA were also combined with high-throughput synthesis and screening methods for the discovery of new catalytic materials for the low-temperature oxidation of low concentrations of propane.^[32] This work is significant because it demonstrates for the first time how all of the essential components of combinatorial methodologies can be integrated for the discovery of totally new catalysts, see Section 5.

1.4.2. Monte Carlo Methods

Simulated annealing is a Monte Carlo approach in which one of the variables of the catalyst preparation process is subjected to a random change. If the new catalyst formulation performs better than the previous one, for example, provides higher yields (Y), the new catalyst is accepted unconditionally. If the performance of the new catalyst is inferior, then the new configuration is accepted with the Metropolis probability $p_M = \exp(-\alpha(Y_{\text{new}} - Y_{\text{old}}))$, where α is a weighting factor.^[33] Simulated tempering is an adaptation of simulated annealing, in which the weighing factor α is also treated stochastically. Recently simulated annealing has been used to design combinatorial libraries.^[34–36] Modifications of these methods, such as parallel tempering^[37] can also be used in the search for heterogeneous catalysts.

1.4.3. Other Methods

Tabu search is another iterative method to solve discrete combinatorial optimization problems.^[38] The basic idea behind the tabu search is to explore the parameter space by a sequence of moves, where each move represents the best course of action based on both the short-term and long-term history of the earlier moves. The tabu search intends to prohibit moves which take the solution to points previously visited, thereby forcing the exploration of a larger solution space. Tabu search is also finding application in combinatorial chemistry.^[39] Other optimization techniques such as branch and bound have also been applied to combinatorial materials research.^[40, 41] Undoubtedly we will see intensified activities both on the application of these stochastic optimization methods and the development of new techniques for the design of libraries of catalytic materials in the near future.

1.5. Data Mining

As evident from the foregoing discussion, although the number of experiments in combinatorial catalysis is large, the amount of data generated will be even larger. Consequently the development and implementation of large-scale information management tools will be crucial for the success of combinatorial catalysis (Figure 1). While the initial efforts in combinatorial catalysis will be directed towards answering specific short-term questions, the accumulated data will be of significant strategic value to discover patterns relating catalyst formulation (composition and methods of preparation) to catalytic function (activity, selectivity, and lifetime). In other words, the accumulated data, stored in data warehouses, can be a source of significant new knowledge. “Data mining”, also called “knowledge discovery” in data bases, is a rapidly emerging software technology that can be employed to accomplish this goal. Data mining can broadly be defined as the efficient and automatic discovery of previously unknown patterns in large databases, rather than to verify that a pattern exists.^[42, 43]

Data mining already has been used in a host of applications from commercial retail business decision support,^[44] to the estimation of the potential toxicity of chemicals from their molecular structure,^[45] from gene mapping,^[46] to aircraft component replacement.^[47] In addition, data mining can be used to determine the time evolution of patterns, which is important in time-on-stream testing of catalysts. Parallel data-mining algorithms are also being developed to speed up the analysis of very large databases.^[44] In summary, recent developments in data warehousing and data mining, in conjunction with advances made in discrete optimization methods provide a strong impetus for the application of combinatorial methods for the discovery and optimization of new catalytic materials.

2. Library Synthesis

The preparation of solid-state libraries of catalytic materials can be accomplished using techniques that can basically be grouped into two primary categories *thin film deposition based* methods of synthesis, and *solution-based* methods of synthesis of combinatorial libraries. In Table 4 recent studies involving combinatorial heterogeneous-catalyst library synthesis methods are presented. This table clearly illustrates the infancy of the field and shows that abundant research and development opportunities exist for the discovery and optimization of new and improved heterogeneous catalysts through the application of combinatorial approaches.

An important practical issue in library synthesis is scale-up. Since the ultimate goal of catalysis research is to develop industrial catalysts, it is desirable that each step of the combinatorial effort lends itself to large-scale production. This requirement places a lower limit on the number of milligrams for each site in combinatorial libraries to enable characterization and seamless transition to bulk production. Clearly, as the cluster dimensions are reduced, the substrate surface chemistry will play an increasingly important role in

Table 4. Recent research on combinatorial heterogeneous catalysis.

Catalyst library	Site size	Reaction investigated	Preparation method	Screening method	Major conclusion	Reference
0.5 % Ag, Bi, Co, Cr, Cu, Er, Fe, Gd, Ir, Ni, Pd, Pt, Rh, Ti, V, Zn, on γ -Al ₂ O ₃ pellets	100 mg	H ₂ + O ₂	Solution based: Impregnation	Infra-red thermography	Relative activities observed	[65]
37, 1–10 % Co, Cr, Cu, Fe, Ir, Mn, Ni, Pd, Pt, Rh, Ru, V, Zn on Si, Ti oxides	200 μ g	Hydrogenation of 1-Hexyne	Solution based: Sol-gel method	Infra-red thermography	Relative activities observed	[17]
100 Na ₂ O-Al ₂ O ₃ -SiO ₂ Zeolites with Li and Cs	1–10 mg	–	Solution based hydrothermal zeolite synthesis	–	Parallel synthesis of mg zeolites demonstrated	[63]
37 TiO ₂ -Al ₂ O ₃ -SiO ₂ -TiO ₂ -ZrO ₂ zeolites	50–150 μ g	–	Solution based hydrothermal zeolite synthesis	–	Parallel synthesis of μ g zeolites demonstrated	[64]
645 clusters of Pt, Ru, Os, Ir on carbon	50–200 μ g	Methanol reforming	Solution based: Co-precipitation	Fluorescence- acid-base indicator	Superior catalyst discovered	[19]
120 ternary thin film clusters of Pt, Pd, Rh, and Pd, Rh, Cu	2–4 μ g	CO oxidation, CO + NO	Thin film based: Sputtering	Scanning quadrupole mass spectrometry	Reactivity trends observed	[20]
72 commercial 0.5–1 % Pt and Pd pellets	40 mg	Cyclohexane dehydrogenation to benzene	Commercial vendor	Resonance enhanced multiphoton ionization, REMPI	Application of REMPI technique demonstrated	[71]
66 ternary combinations of 1 % Pt, Pd and In on γ -Al ₂ O ₃	30 mg	Cyclohexane dehydrogenation to benzene	Solution based: Impregnation	REMPI	Superior ternary composition discovered	[21]
16 Au/Co ₃ O ₄ and Au/TiO ₂ powders	46 mg	CO oxidation	Solution based: Co-precipitation	Quadrupole mass spectrometry	Parallel synthesis and automatic testing of conventional microreactors demonstrated	[61]
33 1–6 % Ag, Au, Bi, Co, In, Cr, Cu, Fe, Mo, Ni, Re, Rh, Sb, Ta, Te, V, Y on Si, Ti, Zr oxides	2 mg	Propylene oxidation	Solution based: Sol-gel method	Quadrupole mass spectrometry	Spatially resolved analysis of an array of batch microreactors	[18]
50 ternary and quaternary oxides of Co, Cd, Fe, Ga, Ge, In, Mn, Mo, Ni, Nb, V, W, Zn	300 mg	Ethane and propane dehydrogenation	Solution based: Co-precipitation	Gas chromatography	Evolutionary method for catalyst discovery demonstrated	[30]
30 binary combinations of Na ₂ WO ₄ and Mn on SiO ₂ ; Au and In on ZrO ₂ , TiO ₂ , SiO ₂ , MgO, ZnO, Nd ₂ O ₃ , Y ₂ O ₃ , CeO ₂ , Mn ₂ O ₃	300 mg	Oxidative coupling of methane and CO oxidation	Solution based: Impregnation and deposition, precipitation	Quadrupole mass spectrometry	Parallel synthesis and automatic testing of conventional microreactors demonstrated	[76]
66 ternary combinations of oxides of Mo, V and Nb	150 μ g and 50 mg	Ethane oxidative dehydrogenation	Solution based: Sol-gel deposition	Quadrupole mass spectrometry, photothermal deflection, gas chromatography	Superior selectivity ternary composition discovered	[22]
144 ternary combinations of oxides of V-Al-Nb, and Cr-Al-Nb	150 μ g	Ethane oxidative dehydrogenation	Solution based: Sol-gel deposition	Quadrupole mass spectrometry, photothermal deflection	Superior selectivity ternary composition discovered	[62]
66 ternary combinations of 1 % Pt, Pd and In on γ -Al ₂ O ₃	30 mg	Cyclohexane dehydrogenation to benzene	Solution based: Impregnation	Quadrupole mass spectrometry	Higher activity ternary composition discovered	[72]
45 3–5 element combinations of Pt, Pd, Rh, Ru, Au, Cu, Ag, and Mn on TiO ₂ and α -Fe ₂ O ₃	200 mg powder and 23 mg pellets	C ₃ H ₈ total oxidation	Solution based: Impregnation	Quadrupole mass spectrometry	Higher activity compositions discovered after 3 generations using the GA	[32]
56 quaternary combinations of Pt, Pd, In, Na on γ -Al ₂ O ₃	23 mg	NO reduction by C ₃ H ₆	Solution based: Impregnation	Quadrupole mass spectrometry	Higher activity quaternary composition discovered	[73]
V ₂ O ₅ –TiO ₂ mixtures	1 to 60 μ g	Oxidation on naphthalene to naphthoquinone	Solution based: Co-precipitation	Laser induced fluorescence imaging (LIFI)	Feasibility of LIFI demonstrated	[70]

influencing both the chemical and physical structure of the final catalyst product. For example, substrate surfaces can selectively adsorb trace additives from the solution, thereby limiting their incorporation into the crystal structure of the catalyst.

2.1. The Thin Film Deposition Based Method

The so called sputtering with physical masking has recently been used to deposit solid-state libraries for the discovery and optimization of CO oxidation catalysts.^[20] The techniques used by these investigators are based on the pioneering work of Hanak^[9] and more recently by Xiang et al.^[48] where the methodologies for parallel synthesis of spatially addressable solid-state materials libraries were reported. The thin-film library of Cong et al.^[20] contained 120 ternary combinations of Rh-Pd-Pt, and was prepared by sequentially depositing films of the individual elements onto a quartz substrate (7.5 cm diameter and 1.5 mm thick) as 1.5 mm diameter spots using masks. The deposition process was accomplished in 10 sequential steps, with 10 nm of material being deposited in each step. The total library synthesis took about 1 h. Following the deposition of the films, the library was annealed at 773 K under an H₂/Ar atmosphere for 2 h to induce interfilm diffusion and to form alloys. A sketch of the ternary library prepared is shown in Figure 3.

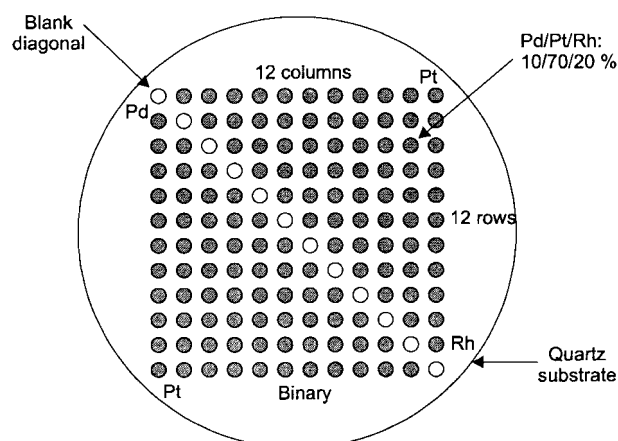


Figure 3. Catalyst library prepared by sequential sputtering.^[20]

Even greater speeds of synthesis of solid-state materials libraries can be accomplished by the simultaneous or co-sputtering of multiple-target materials, an idea originally proposed by Hanak.^[9] In the example shown in Figure 4, four targets are used to simultaneously create a quaternary library where a continuum of compositions can be generated. With the use of a mask, which is also indicated in Figure 4, a discrete and spatially addressable library can be created. Because with sputtering a large number of sites can be prepared simultaneously with very high speed, this technique can be a useful tool for the creation of very large discovery libraries. Thin films, once deposited, can then be processed, for example, calcined and reduced to produce catalytic

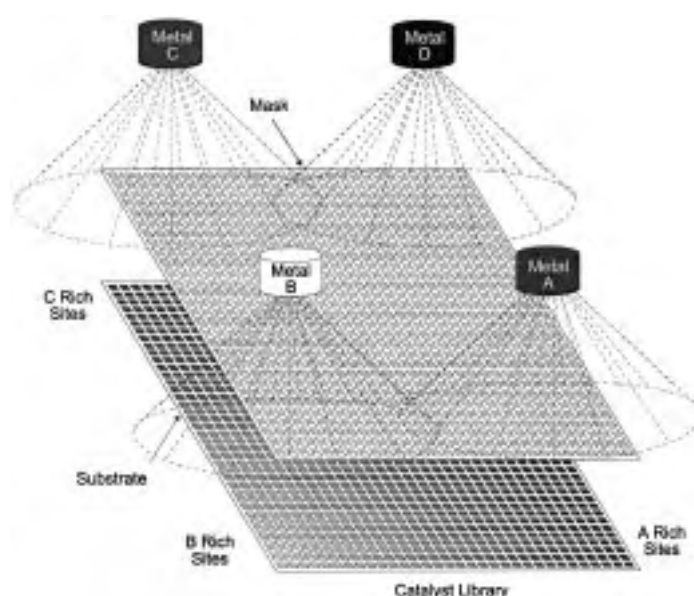


Figure 4. Preparation of libraries of catalytic materials by co-sputtering.

materials. In addition, other thin-film deposition methods, such as thermal^[49, 50] and plasma chemical-vapor deposition,^[51, 52] molecular beam epitaxy,^[53] and pulsed-laser deposition^[54, 55] can be used to create solid-state catalyst libraries.

Thin film deposition based catalyst preparation techniques are particularly promising for use in conjunction with micro-electro-mechanical systems (MEMS) that are created by using semiconductor device manufacturing techniques.^[56] In fact, the recently developed sub-millimeter size reactor systems with flow and temperature sensors would be an ideal platform for testing microgram quantity catalysts.^[57] For example, thin films of catalytic materials can be introduced into these microreactors during the MEMS fabrication process, and can then be tested readily without the need to transfer any solid-state materials. When developed, this should be an efficient mechanism for the creation of libraries of catalytic materials.

There are significant technical challenges that need to be resolved before utilizing MEMS technology in catalysis research. First, these reactor systems must allow for the pre-processing of catalytic materials under realistic conditions, that is, similar to those encountered in high-temperature calcination processes. At present, temperature limitations of MEMS devices restrict their utility in catalysis. The Second, and equally important concern, is the issue of scale-up of the leads obtained in MEMS reactors to produce gram quantities of catalytic materials for bench-top testing. Nevertheless, the MEMS technology promises to be an exciting tool in combinatorial catalysis.

2.2. Solution-Based Synthesis of Libraries

Most commercial catalysts are prepared today using highly refined, solution-based techniques that were developed over decades of trial and error experiments. Solution-based methods can be divided into two primary groups: coprecipi-

tation and impregnation.^[58–60] There are also a number of other techniques that can be considered as variants of these two primary methods; they include complexation, gelation, crystallization, ion exchange, grafting, adsorption, and deposition.^[60]

Coprecipitation involves the mixing of two or more solutions or suspensions, followed by precipitation, filtration, washing, drying, forming, and activation. Consequently, the surface area and mechanical properties of the catalytic materials have to be considered as an integral part of the preparation process. Impregnation involves the contact of a porous carrier with a solution containing the catalytic components, followed by drying and activation. In this case, the carrier primarily determines the surface area and mechanical properties of the final catalyst. Since most commercial catalysts are prepared by techniques that are variations of these two techniques, the miniaturization and automation of coprecipitation and impregnation methods is likely to be the route to exploit combinatorial techniques in the near future.

Efforts in this direction have already met with success as shown in Table 4. For example, solution-based ink-jet print-head technology has successfully been used to prepare a 645 combination Pt-Ru-Os-Ir library for the reforming of methanol.^[19] This study led to the discovery of a superior catalyst with composition 44 % Pt/41 % Ru/10 % Os/5 % Ir. A larger-scale (quantity) automation of the coprecipitation technique was also recently developed and used for the synthesis of a 16 combination library of Au-Co₃O₄ and Au-TiO₂ for the oxidation of CO.^[61]

In related studies, the sol–gel method was applied for the preparation of 37 combinations of 1–10 % Co, Cr, Cu, Fe, Ir, Mn, Ni, Pd, Pt, Rh, Ru, V, Zn on AMM of Si and Ti as catalysts for the hydrogenation of 1-hexyne.^[17] The same group also reported the preparation of 33 combinations of 1–6 % Ag, Au, Bi, Co, In, Cr, Cu, Fe, Mo, Ni, Re, Rh, Sb, Ta, Te, V, Y on Si, Ti, and Zr AMM as catalysts for the oxidation of propylene.^[18] A group at Symyx reported a 66 combination ternary Mo-V-Nb catalyst library for the oxidative dehydrogenation of ethane also prepared using a miniaturized and automated sol–gel method.^[22] Recently, the Symyx group prepared V-Al-Nb and Cr-Al-Nb oxide libraries for the oxidative dehydrogenation of ethane.^[62] In related efforts, solution-based crystallization techniques were miniaturized for the parallel synthesis of libraries of zeolites.^[63, 64]

Impregnation techniques were also successfully miniaturized and used for the preparation of libraries of catalytic materials. Moates et al. reported in 1996 the preparation of a 16 site library by the manual impregnation of commercial γ -Al₂O₃ pellets with up to 0.5 % Ag, Bi, Co, Cr, Cu, Er, Fe, Gd, Ir, Ni, Pd, Pt, Rh, Ti, V, and Zn using aqueous precursor solutions.^[65] Previously, we reported on the development of an automated, multinozzle liquid-dispensing system to rapidly and precisely prepare micro-liter level solution libraries.^[21] This system was used for the impregnation synthesis of a 66 combination catalyst library of Pt-Pd-In on γ -Al₂O₃ which subsequently was used to study the dehydrogenation of cyclohexane to benzene. This library preparation system developed is shown in Figure 5. In the resulting library, the 0.8 % Pt/0.1 % Pd/0.1 % In composition was determined to give best benzene productivity in the range of conditions investigated.

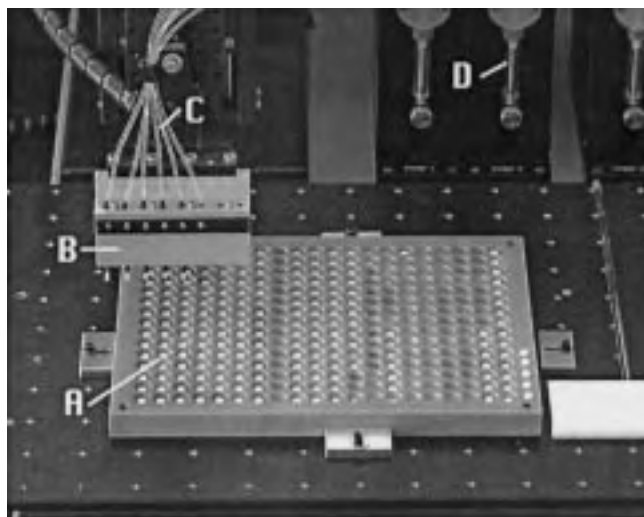


Figure 5. Micro-jet liquid-dispensation system for the preparation of solution libraries. A) Wells to hold solution libraries and catalyst carrier pellets, B) liquid injector nozzles, C) solution delivery lines, D) syringe pumps.

This catalyst preparation system was also used for the preparation of quaternary libraries of Pt-Pd-In-Na and Ag-Cu-Co-Ga for the selective catalytic reduction of NO using propene.^[66]

Recently a similar, single-nozzle liquid-dispensation system was also developed and used to prepare supported multimetal catalysts for the low-temperature oxidation of propane.^[32] In this work TiO₂ and α -Fe₂O₃ powders were impregnated with the aqueous precursor solutions of Pt, Pd, Rh, Ru, Au, Ag, Cu, and Mn in groups of 3–5 elements under incipient wetness conditions. Catalyst libraries containing 45 discrete combinations were prepared using the GA approach, and resulted in the discovery of a number of superior catalytic materials after three iterations; further details will be provided in the case study in Section 5.

In summary, a number of techniques are emerging for the systematic and automatic synthesis of large combinatorial libraries of catalytic materials. These techniques or their variants will probably be the way of the future in catalysis research and development because of their superior accuracy and reliability compared to traditional methods. Fully automated thin-film deposition methods based on sputtering are now available for the synthesis of libraries of multimetal catalysts. Similarly, solution-based impregnation systems are rapidly developing as useful tools for the preparation of supported multimetal catalyst libraries. On the other hand methods to prepare metal oxide catalysts and zeolites by techniques such as coprecipitation and sol–gel synthesis have yet to reach a similar level of miniaturization and automation.

3. Library Screening

The screening of libraries of catalytic materials continues to be a challenging task because of the dynamic, that is, the time-dependent nature of catalytic function. As noted in Section 1.2, the activities of most catalytic materials change with time on stream. Most catalysts deactivate with time, although some catalysts have significant induction periods before they become active. Consequently, to truly assess the practical

value of the new catalytic materials developed, their reaction performance must be tested for extended reaction times. This is likely to remain the primary bottleneck in combinatorial catalysis research and development. However, the development and application of miniaturized and highly parallel reactor systems coupled to suitable high-speed screening systems promises to ease this bottleneck. This is being researched by a number of groups worldwide.^[17, 18, 21, 61]

To date a number of complementary techniques have been developed to screen and/or test libraries of solid-state materials for catalytic activity. Table 4 also summarizes the variety of screening methods developed. Although each specific application must be evaluated to identify the most suitable screening tool, optical methods and mass spectrometry have been the most commonly used methods in catalyst screening because of their broad applicability and relative speed compared to other techniques, such as chromatography. The most significant advantage of optical techniques is that they are *in situ* methods, and as such do not require the withdrawal of samples.

3.1. Optical Methods

Perhaps the simplest optical screening is the color indicator method, which is applicable to liquid-phase reactions. This technique was applied first to determine the relative activity of a series of conventional hydrosilation catalysts.^[67] For this, a dye was chosen in which an electron-donor ferrocenyl group and an acceptor pyridinium functional group were separated by a reactive C=C or C=N group. When the hydrosilation reaction saturated these links, the intensity and hue of the color changed signaling a hit.

A related technique was developed to screen ternary and quaternary alloy catalysts for the electrooxidation of methanol.^[19] In the latter case, the libraries were evaluated for their hydrogen ion generation by monitoring the color change of the fluorescent pH-indicator quinine under UV light. Visual inspection of the library allowed these investigators to pick a superior quaternary alloy of 44 % Pt/41 % Ru/10 % Os/5 % Ir for the oxidation of methanol. An important challenge and limitation of these color-based screening methods is that they provide information only on products for which specific indicator molecules are available or can be developed.

3.1.1. Infrared (IR) Techniques

Among the optical methods, infrared (IR) thermography is most widely used to screen the activities of libraries of catalytic materials because of its ease of applicability. Willson and co-workers were the first to demonstrate the utility of IR thermography as a heterogeneous catalyst screening tool using hydrogen oxidation as the model reaction.^[65] Subsequently, Maier and co-workers refined the IR thermography method by taking into account the different emissivities of catalyst clusters, and made it a more quantitative tool.^[17] In IR thermography, radiation energy is emitted from surfaces according to the modified Stefan–Boltzmann law [Eq. (3)].

$$q = \epsilon \sigma T^4 \quad (3)$$

T is the absolute temperature, ϵ is the temperature- and composition-dependent emissivity of the surface and σ is the

Stefan–Boltzmann constant. As evident from Eq. (3), energy radiation is extremely sensitive to surface temperature, allowing the detection of very small differences in temperature by the IR technique. IR thermography was also applied as a time-resolved screening tool for catalytic reactions^[68] and in the selection of encoded polymer-bead catalysts in solution.^[69] However, although IR thermography is an extremely fast and nonintrusive screening technique, it clearly does not provide information on the chemical identity of the products formed in a reaction. Nevertheless, IR thermography can be a useful preliminary activity screening tool to explore very large discovery libraries.

Fourier transform infrared (FTIR) spectrometry can also be used to screen libraries of solid-state catalytic materials.^[83, 84] The FTIR approach provides a significant improvement over IR thermography as it provides chemically specific information. However, the detection of gas-phase species at low concentrations creates a challenge that must be addressed for the effective use of FTIR to screen large libraries of catalytic materials.

Recently, the use of thermistor arrays were also proposed to screen libraries of catalytic materials,^[85] as an alternate method to IR thermography. In spite of their intrusive nature, thermistors provide a greater sensitivity to temperature, allowing the measurement of temperature changes of the order 100 μ K, as opposed to 10 mK in IR thermography.

3.1.2. Laser Induced Fluorescence Imaging (LIFI)

An improved optical screening technique based on laser induced fluorescence imaging (LIFI) has been reported recently by Su and Yeung.^[70] This technique exploits the alteration of fluorescence properties of molecules as a consequence of the breakage and formation of chemical bonds. However, as evident from its name, LIFI is only for the detection of fluorescent species, and this limits the use of this technique.

3.1.3. Resonance-Enhanced Multiphoton Ionization (REMPI)

A broadly applicable optical screening technique that provides specific product information on gas-phase species has been reported by Senkan.^[71] The approach is based on the *in situ* ionization of reaction products by UV lasers, followed by the detection of the photoions or electrons by spatially addressable microelectrodes placed in the vicinity of the laser beam. When the laser frequency is tuned to a real intermediate electronic state of a molecule, the cross section for ionization is significantly enhanced, resulting in resonance-enhanced multiphoton ionization (REMPI).^[71] On the other hand, when the laser wavelength is not tuned to a real electronic state, the probability for photoionization is much smaller. There are several means by which REMPI can be induced. The most common method is the resonant 2-photon ionization (R2PI or 1+1), in which one photon ($h\nu_1$) energizes the molecule to an excited electronic state (this is the step where selectivity is introduced) and the second photon ionizes the molecule. The two photons used can have the same or different frequencies.

There are several advantages as well as some limitations of the REMPI approach. First, REMPI can be used for the

detection of a wide variety of polyatomic molecules and radicals in situ.^[71] This is in contrast to other optical techniques such as laser induced fluorescence (LIF; which is essentially applicable to monatomic and diatomic species, and LIFI for fluorescent species (see Section 3.1.2). Second, molecules are ionized from a selected vibrational level of an electronically excited state, thereby allowing for the specific photoionization of target molecules. This can be used to distinguish between isomers. Third, the REMPI process can be used repeatedly to detect different products using different laser frequencies, and thus can allow the rapid determination of selectivities. Finally, REMPI is a highly sensitive technique with real-time detection limits at low parts per billion values readily achievable.^[71]

Unfortunately, the REMPI features of many molecules are not known, and thus must be determined first before the technique can be applied for catalyst screening. That is, considerable research still needs to be done to establish appropriate REMPI strategies and libraries. It is also possible that some molecules may simply not exhibit REMPI features or that these features occur at photon energies that are not accessible using commercial lasers. The implementation of REMPI also requires a considerably more investment of capital than other optical techniques, although this is rapidly changing by the availability of less expensive, tunable solid-state lasers.

Recently the REMPI technique was combined with array microreactors as an effective catalyst-screening tool.^[21] Array microreactors consist of isolated channels that are micromachined on a flat nonporous substrate (Figure 6). Each channel possesses a cylindrical well to hold the pellets of catalytic materials. This system was used to screen the activities and selectivities of a ternary Pt-Pd-In library for the dehydrogenation of cyclohexane to benzene.^[21] The screening protocol demands the unambiguous detection of benzene at the exit of each microreactor against a background of cyclohexane, hydrogen, helium, and other reaction byproducts, under the reaction conditions. To accomplish this goal, the REMPI spectra of the reactants and products were explored to identify a suitable UV-laser wavelength that selectively produces benzene REMPI ions. In Figure 7, the atmospheric pressure REMPI spectra of benzene at various temperatures are presented over a wavelength range of 248 to 265 nm. Based on this and related information, a 259.6 nm laser light was chosen to detect benzene in situ in the reactor exhaust gases. This screening process led to the discovery of 0.8% Pt/0.1% Pd/0.1% In on γ -Al₂O₃ as a catalyst superior to other combinations considered (see Figure 5).

3.1.4. Photothermal Deflection (PTD)

Additional optical techniques will probably be developed and applied to screen libraries of catalytic materials on a case-



Figure 6. Array microreactor equipped with REMPI-screening components. A) Laser beam, B) catalyst pellets in wells, C) flow distribution baffles, D) feed-gas line, E) feed-gas preheater, F) metal heating block, G) electrodes, H) laser-power meter.

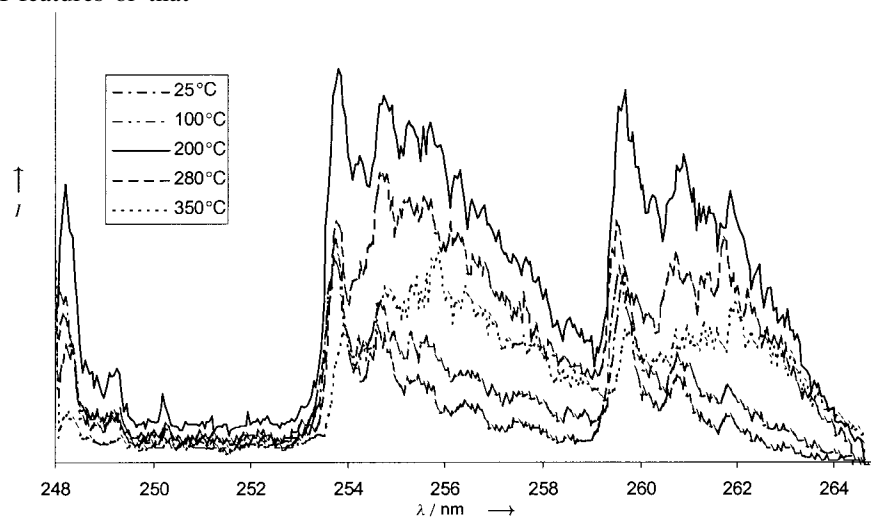


Figure 7. Effect of temperature on the atmospheric-pressure REMPI spectra of benzene.

by-case basis. For example, a photothermal deflection (PTD) method has recently been reported to provide a highly sensitive and selective detection of ethylene in an ethane background.^[22] The PTD method was developed to overcome the problem of ethylene signal contamination caused by the fragmentation of ethane in electron impact ionization mass spectrometry. In PTD, ethylene was excited at 10530 nm by a tunable CO₂ laser, followed by the measurement of the changes in refractive index caused by hot C₂H₄, detected by using an HeNe probe laser beam. The authors report a discrimination factor of about 10⁶ against C₂H₆, thereby providing an effective means to detect trace C₂H₄ in an ethane background. As with other optical techniques, the further utility of PTD will depend on the identification of suitable IR laser wavelengths that will selectively excite specific molecules of interest.

3.2. Mass Spectrometry Methods

Mass spectrometry is a mature and widely used detection technology and can readily be applied to analyze complex

gaseous mixtures. However, it requires sample withdrawal, and application to combinatorial catalysis needs the development and implementation of new strategies.

Recently, Cong et al.^[20] reported a quadrupole mass spectrometer (QMS) based system to screen heterogeneous catalyst libraries in a sequential fashion. The catalyst library consisted of small circular patches of films deposited on a nonporous silicon wafer using sputtering with masks (see Figure 3). Each catalyst site on the library was sequentially heated to the desired reaction temperature by a CO₂ laser beam. The reactant gases were then transported to the catalyst site through the annular section of a double concentric probe in a stagnation-flow manner. The gases deflected from the catalyst site also contain the reaction products, and were then withdrawn through the innermost tubing of the probe and analyzed by on-line quadrupole mass spectrometry (Figure 8). After the completion of the screening of a particular site, the library was physically moved to facilitate the testing of the next site. The total time to heat and screen one catalyst site was reported to be about 1 min. With this technique these investigators were able to evaluate a large number of catalysts for the oxidation of CO (see Table 4).

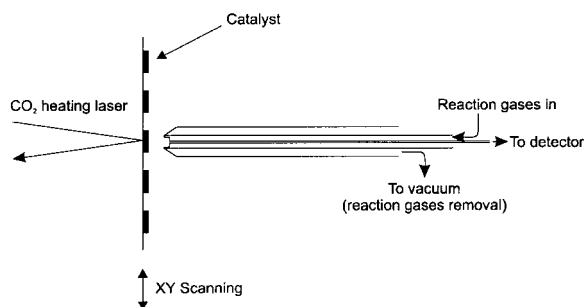


Figure 8. Scanning mass spectrometer system to screen catalysts.^[20]

A similar mass spectrometer based screening technique was also reported by Maier and co-workers.^[18] In this case the library consisted of an open structure where catalyst powders, prepared for example by the sol–gel method, were placed in a spatially addressable configuration on a heated substrate. Library screening was achieved again by sequentially flowing the feed gas onto the surface of a particular site through a capillary feed line and by withdrawing the products through another capillary (Figure 9). The capillary bundle, containing both the feed and sampling lines, was then removed from site to

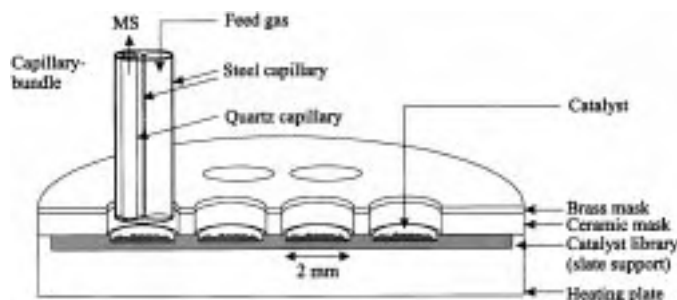


Figure 9. Spatially resolved mass spectrometer system to screen catalysts.^[18]

site by using a robotic movement mechanism. The time to screen each site was reported to be around 1 min. The utility of this system as a viable catalyst-screening tool was then demonstrated by determining the identities of different products in the partial oxidation of propylene as a function of catalyst formulation. It should be noted that the screening systems developed by Cong et al.^[20] and Orschel et al.^[18] cannot efficiently address issues related to the time-dependent behavior of catalytic materials because they were designed to provide reactant–catalyst contact only for a short period of time, about 1 min.

3.3. Array Microreactors

One approach to evaluate the time on-stream performance of catalytic materials is the use of array microreactors,^[72] as shown in Figure 10. In this approach, it is possible to test a large number of catalysts in parallel and for extended periods

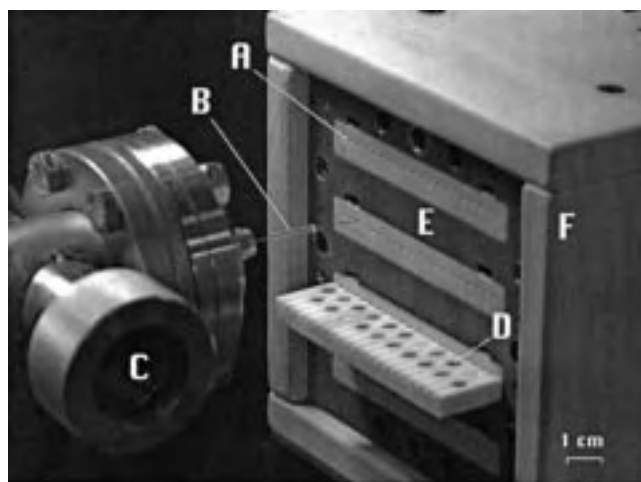


Figure 10. Array microreactor block details: A) ceramic microreactor array, B) capillary sampling line, C) mass spectrometer, D) catalyst pellets in wells, E) aluminum heating block, F) insulation.

of time, thereby identifying leads that have greater chances of becoming practical catalysts. Catalyst screening can be accomplished by analyzing the reaction products by QMS, REMPI, or any other suitable technique. Array microreactors and QMS were recently used to screen the activities and selectivities of an entire 66 combination Pt-Pd-In ternary catalyst library for the dehydrogenation of cyclohexane to benzene in 24 h.^[72] In Figure 11 the benzene levels in the exhausts (indicating conversion) of all the microreactor channels are presented as a function of time-on-stream.

As can be seen from Figure 11, the activities of all the catalysts decreased significantly during the 24 h testing period, demonstrating the need to evaluate the time-on-stream performance of libraries for the discovery and optimization of practical heterogeneous catalysts. Of particular significance is that the activity profiles of some catalysts cross one another over time, suggesting that initial activity measurements are not sufficient for catalyst screening.

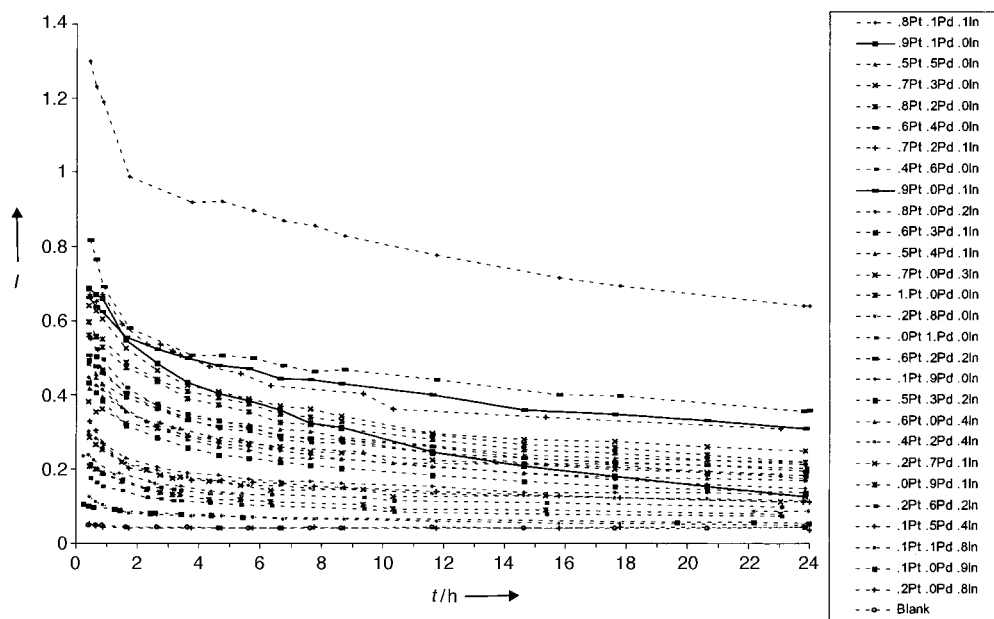


Figure 11. Time-on-stream dependence of the activity (I) of the ternary Pt-Pd-In catalysts in the dehydrogenation of cyclohexane to benzene.

Recently array channel microreactors and mass spectrometry were used for the discovery and the optimization of catalysts for NO reduction,^[73] and low-temperature oxidation of propane.^[32] In the former work, a quaternary library of Pt-Pd-In-Na was prepared by the impregnation of γ - Al_2O_3 pellets. Using a feed-gas composition of about 3500 ppm NO, 3500 ppm C_3H_6 , 1.5% O_2 , and the rest helium, a 56 combination quaternary library was screened for NO reduction activity at a space-time velocity of $50\,000\text{ h}^{-1}$ and over a temperature range of $200\text{--}550^\circ\text{C}$.

In Figure 12 the actual results of one particular screening test are presented at a temperature of 350°C . The mass abundances are presented in terms of arbitrary units as a function of microreactor channel number. Signal peaks correspond to levels present in the reactor effluent and sharp increases and/or decreases represent signals acquired during the transit of the capillary probe from one channel to another.

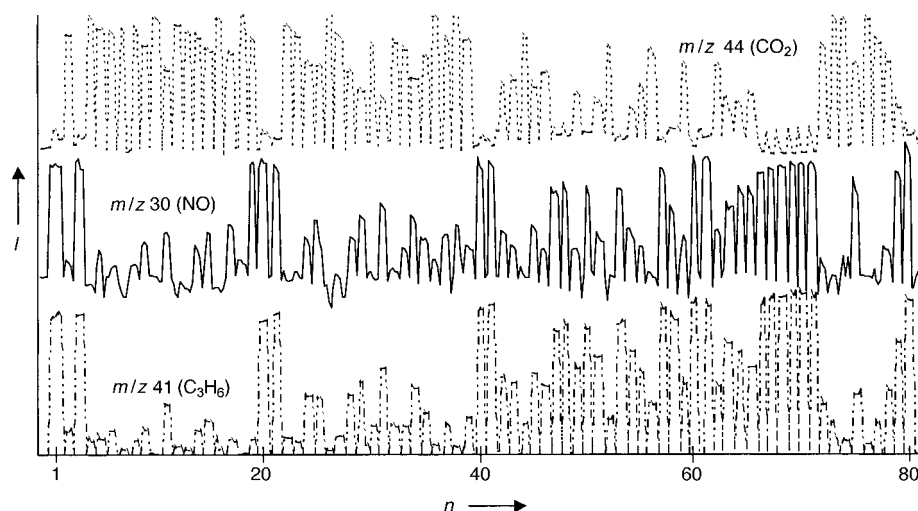


Figure 12. Channel microreactor exit concentrations of NO, C_3H_6 , and CO_2 during an experiment. n = Channel number.

As evident from Figure 12, decreases in NO signals are always associated with decreases in the C_3H_6 signal, clearly suggesting the close coupling of these species in the NO-reduction process. On the other hand, for some catalysts while the C_3H_6 signals were significantly decreased, no reduction in the NO signals was observed. An example of this behavior can be seen in the microchannel reactor 19. Evidently, some catalysts were efficient at oxidizing C_3H_6 , thereby depriving the NO-reduction process of the necessary hydrocarbon species. The CO_2 mass signals (mass 44), that are also presented in Figure 12 clearly support this picture.

In Figure 13, the microreactor exit concentrations of NO are presented for the quaternary Pt-Pd-In-Na catalyst library at different reaction temperatures. The different library compositions are represented as discrete coordinates on the equilateral tetrahedron. Each corner of the tetrahedron corresponds to pure metal on alumina as indicated. Exit NO concentrations are represented as variations in gray scale and size and the conversion by the size of the circles, as indicated in Figure 13. Consequently, catalysts that exhibit increasingly darker and larger circles (Figure 13) are better performers as far as the NO-reduction process is concerned. An examination of Figure 13 indicates several significant features. First, the NO reduction activities of the catalyst formulations, when present, increase first and then decrease with the increase in temperature. This feature is evident in Figure 13 by the appearance and then disappearance of black circles upon increase in temperature. This trend is in complete agreement with the literature and our current understanding of the interplay that exists between the reactions with NO and the combustion of hydrocarbons.^[74]

Second, and most significantly, multicomponent formulations provided superior NO reduction performances compared to single-component Pt and Pd catalysts under these conditions. A closer examination of Figure 13 also reveals that the catalyst formulation of 0.6% Pt, 0.2% Pd, and 2% Na had the best NO conversion performance, resulting in nearly 75% reduction at 350°C . Noteworthy is that while Pt-rich mixtures

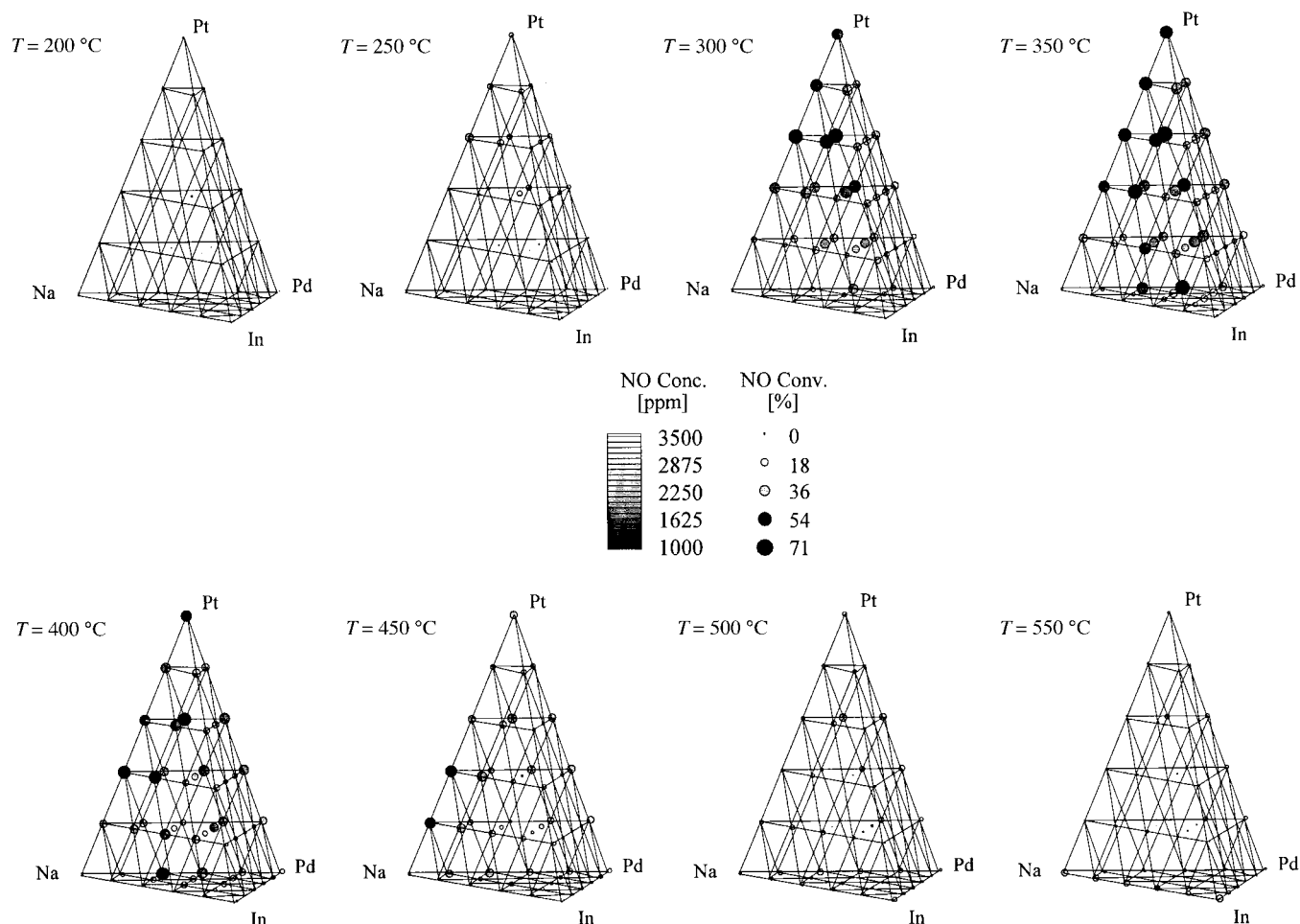


Figure 13. NO-reduction activities (exit concentration and conversion) of the quaternary Pt-Pd-Na-In catalysts as a function of temperature.

generally exhibited superior NO reduction activities over a limited temperature range of 300–450 °C, multielement catalyst formulations were effective over a broader temperature range. The former result is consistent with reported Pt-based, selective, NO-reduction catalysts.^[74, 75]

To better illustrate the speed advantage of combinatorial approaches relative to traditional methods, the time elements associated with each step in our combinatorial approach leading to the results shown in Figure 13 are presented in Table 5. As can be seen from this Table, it was possible to prepare, process, and then screen 56 quaternary catalysts over

the entire 200–500 °C range, in less than 10 h. Clearly, traditional methods would have taken much longer to arrive at the same set of results.

As can be ascertained from the foregoing discussion, the implementation of combinatorial techniques to heterogeneous catalysis is being pursued in two parallel paths. In the first approach, a large number of potential solid-state materials are screened for catalytic properties in short-term tests.^[18, 20] The initial hits identified in the primary screening must then be followed-up by secondary or bench-scale testing studies for the determination of the time-on-stream performance of the catalytic materials. In the second approach the primary and secondary screening methods are essentially combined through the use of array channel microreactors.^[21, 72] Clearly, to successfully implement the former approach, conventional bench-top reactor systems must also be automated. This is indeed being pursued by a number of research groups around the world. For example, the development of an automated high-pressure system containing 16 parallel multitube reactors (each 1 cm diameter) was recently reported by Schüth and co-workers.^[61] A similar block-reactor system containing 15 packed-bed reactors was developed by the Baerns group,^[32, 76] and in a related study, a catalyst screening system consisting of 6 parallel reactors was also reported.^[77]

Table 5. Time associated with the preparation, processing, and screening of 56 catalysts.

Operation	<i>t</i> [h]
<i>Library preparation</i>	
Preparation of precursor solutions	0.5
Preparation of solution library	0.25
Incipient wetness impregnation	0.25
Drying	2.0
Calcining	2.0
Reduction	2.0
<i>Library screening</i>	
One time mass spectrometric screening	0.50
Total time for discovery and optimization	7.5

4. Numerical Simulations

Numerical simulation codes are gaining wide spread use in catalysis research as evidenced by the increasing number of papers published in this area and special issues of journals devoted to this subject.^[78] Computational methods to date have been used primarily to unravel the mechanisms of elementary steps of known catalytic reactions. However, they can also serve as valuable tools for the discovery and optimization of new catalytic materials. That quantum chemistry as well as molecular simulation programs have already proven to be useful tools to complement experiments is most encouraging.^[78, 79] Some areas where computational methods could contribute to combinatorial catalysis include the building of structural models and pre-screening of catalytic materials before undertaking experiments, the determination of structure–activity relationships from which the activities of new catalytic materials can be rapidly ascertained.

The successful application of computational tools to combinatorial catalysis will probably involve the implementation of a two-step approach, as in the case with experiments. In the first stage, approximate but fast simulation methods, such as semi-empirical quantum chemistry, can be employed to establish qualitative trends in reactivity. If these initial efforts prove promising, then the undertaking of more rigorous and time consuming computational methods, such as *ab initio* and/or density functional theory (DFT) calculations, can be justified. For example, the utility of semi-empirical quantum chemistry as a rapid catalyst-screening tool has recently been demonstrated in the oxidative coupling of methane (OCM) reaction.^[80] This investigation showed that lithium doping significantly reduces the activation energy barrier for the dissociative adsorption of methane on MgO from 40 to 15 kcal mol⁻¹, suggesting that Li/MgO should be a better catalyst for the OCM reaction than MgO alone. This conclusion is in complete harmony with earlier experimental results,^[81] demonstrating the potential utility of semi-empirical quantum chemistry as a fast pre-screening tool in combinatorial catalysis.

In another, but more detailed study molecular dynamics and DFT calculations were utilized to evaluate and design more effective (i.e. water resistive) ion-exchanged ZSM-5 catalysts for the selective reduction of NO.^[82] These investigators determined that the differences in calculated enthalpies of adsorption of NO and H₂O correlated well with the available experimental data regarding the water stability of ion-exchanged ZSM-5. Based on this observed correlation, Cr³⁺-, Ir³⁺-, and Ti³⁺-exchanged ZSM-5 zeolites were proposed as new and potentially superior catalysts.

It should be recognized, however, that although computational methods have the promise to make important contributions to combinatorial catalysis, there are several difficulties that need to be recognized. First and foremost is the experimental synthesis of new materials that have been identified by the simulation studies. It is very simple to create new materials with well-defined structures on a computer screen. However, the laboratory syntheses of these materials

are seldom straight forward and in some cases synthesis may be impossible. Second, the simulation of realistic surfaces and catalytic function is likely to remain a demanding computational problem. As noted earlier, catalysts provide three-dimensional active sites that enhance the formation of suitable transition states, and the realistic simulation of such sites requires the use of a very large numbers of atoms, many of which are elements with d- and f-orbital electrons. Consequently, numerical simulations can take as much time as the experiments, diminishing their value to direct experiments. In addition, some catalytic centers can exhibit dynamic behavior during the reactions, rendering molecular simulations significantly more difficult to implement and connect with the experiments. Nevertheless, computational chemistry holds promise as a useful tool to complement and, in the future, to direct experiments in combinatorial catalysis.

5. A Case Study

It is important to end this review with a case study demonstrating how high-throughput synthesis and screening methods can be integrated with discrete optimization methods for the *automatic discovery* of new catalytic materials. Recently the impregnation method of catalyst preparation was coupled with multitube packed-bed reactors^[76] and array microchannel reactors^[71] within the framework of genetic algorithms^[31] to find catalysts for the low-temperature oxidation of propane at low concentrations.^[32] The catalytic materials libraries were prepared by use of an automatic liquid- dispensation system applying the incipient wetness method. A total of 8 active components (Pt, Pd, Rh, Ru, Mn, Cu, Au, Ag) were selected as candidates for incorporation into TiO₂ or α -Fe₂O₃ as carrier materials. The selection of these materials was based, in part, on the accumulated know-how in related studies. The following procedure was used in the discovery process:

1st Step: Initialization of the 1st generation of catalytic materials based on the predefined primary components. For this a library containing of 45 supported catalytic materials consisting of mixtures of active elements at different quantitative and qualitative compositions were prepared in a stochastic manner in such a way that each catalytic material consisted of up to five of eight primary components.

2nd Step: Parallel testing of catalytic materials and evaluation of catalyst quality. The libraries were tested for their catalytic performance (conversion of C₃H₈ to CO₂) in both the multitube packed-bed reactors^[76] and in array channel microreactors.^[71] Catalysts were used as powders (200 mg) in multitube packed-bed reactors and as pellets (23 mg) in the array microreactors. Feed-gas composition was kept at about 0.1 % propane and 20 % O₂ with the rest He. The operating conditions were atmospheric pressure, temperature range 50 to 250 °C, and residence times were of the order of 10 ms in the array microreactor experiments and 100 ms in the multitube reactors.

3rd Step: Creation of the next generation library based on the catalytic results of the previous generation. This was accom-

plished using mutation and cross-over operators of the genetic algorithm approach^[31] as applied to the previous generation catalysts. This led to the creation of another library also containing 45 supported catalytic materials.

Steps 2 and 3 can be repeated until satisfactory results are obtained. In Figure 14, the array microreactor screening results of the 1st and 3rd generation catalyst libraries are compared with one another at 250 °C. As is evident from Figure 14, the application of GA successfully steered the catalyst development process and led to a substantial improvement in activity in only two generations using a modest library size of 45 catalytic materials.

In Table 6 the compositions of all the 3rd generation catalysts prepared and tested are presented. This table also shows the propane conversions obtained using both the multitube packed-bed and array microreactors. As a consequence of the differences in contact times, array microreactors had to be operated at higher temperatures to achieve levels of conversion similar to those of the packed-bed reactors. As can be seen in Table 6 significant propane conversions could be achieved even at 50 °C with few catalytic materials even in the 3rd generation. Catalysts providing propane conversions of the order 90% were also achievable at higher temperatures. The best catalytic materials, indicated in bold characters, were found to be rich in ruthenium; multimetal combinations were significantly superior.^[32] These results clearly show the benefits of exploring large parameter spaces to make progress in the discovery of superior catalysts. Noteworthy is that the ordering of the activities of the catalysts obtained by the multitube and array microreactors were the same, albeit at different temperatures, thus supporting the suitability of array microreactors as a practical discovery tool. This case study is important in demonstrating, for the first time, how all the components of combinatorial catalysis can be integrated and used for the discovery and optimization of totally new catalytic materials. Therefore, it represents an important milestone in establishing combinatorial catalysis as an effective new tool catalyst research.

6. Summary

With recent advances in experimental methods (both library preparation and screening) together with data management and numerical optimization tools, combinatorial catalysis is poised to make a significant impact on the pace of research leading to the discovery and optimization of new generations of superior heterogeneous catalysts. By a suitable combination of methods, it is now feasible to prepare, process, and test thousands of potentially catalytic materials in a day. New catalyst discoveries are routinely occurring now in a number of laboratories in time scales of the order of days and weeks as opposed to the months and years required by traditional methods. In the next few years we should see intensified activities in all aspects of combinatorial catalysis as well as the commercialization of new discoveries. All of this should spur further interest in combinatorial catalysis as the new paradigm in catalyst research and development.

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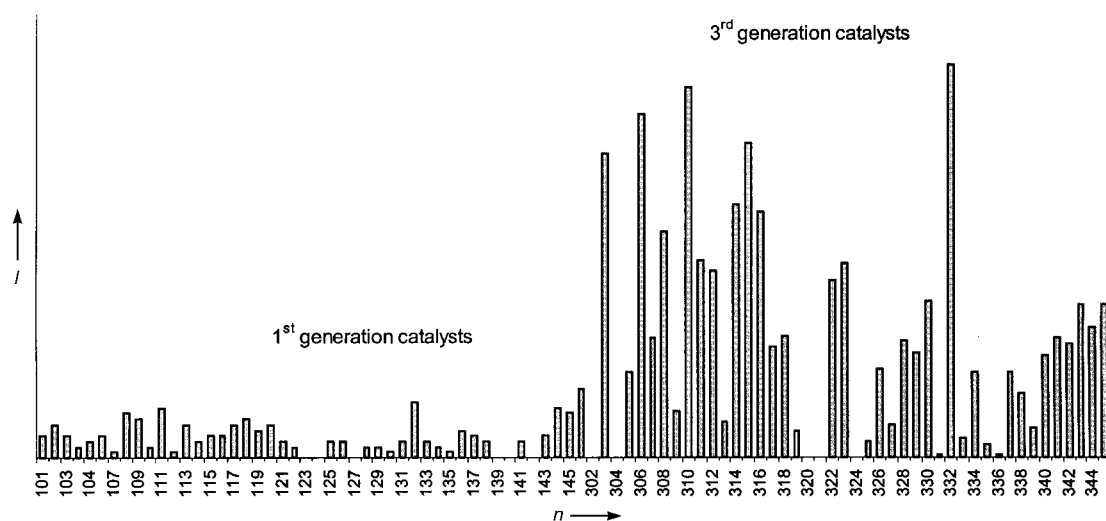


Figure 14. Comparison of the performance of the 1st and 3rd generation catalysts for the oxidation of propane. Feed-gas composition: about 1000 ppm C_3H_8 , 19.6% O_2 , rest He, $T=150\text{ }^\circ\text{C}$. n = Catalyst numbers (1st generation 101–145, 3rd generation 301–345), I = intensity of the signal for $m/z=44$.

Table 6. Metal contents (wt %) and catalytic results (propane conversion percent) of the TiO₂-supported catalysts of the 3rd generation (from ref. [32]).^[a]

Cat. No.	Pt	Pd	Rh	Ru	Au	Cu	Ag	Mn	Multitube reactor			Array microreactor				
									50 °C	100 °C	150 °C	150 °C	175 °C	200 °C	225 °C	250 °C
301	0.55	–	–	0.98	–	1.47	–	–	6	14	50	7	16	10	44	67
302	–	0.59	0.71	0.04	0.65	1.00	–	–	0	2	9	4	8	0	5	9
303	–	–	0.88	2.12	–	–	–	–	12	18	57	24	28	51	76	85
304	–	–	–	–	–	3.00	–	–	0	0	0	5	12	0	1	0
305	0.59	–	–	1.22	–	0.57	0.62	–	2	14	47	11	20	25	57	75
306	–	–	–	3.00	–	–	–	–	12	30	75	19	26	64	85	90
307	0.51	–	0.80	0.91	–	–	0.78	–	2	16	51	9	15	24	55	72
308	–	–	1.57	1.43	–	–	–	0.00	2	25	72	12	23	33	71	83
309	–	0.79	0.68	0.58	0.95	–	–	–	3	22	66	3	7	12	45	64
310	–	0.59	–	2.41	–	–	–	–	4	32	81	17	27	52	73	85
311	–	–	0.43	0.75	1.44	–	–	0.38	1	20	58	7	12	32	57	76
312	0.20	–	1.15	1.17	0.47	–	–	–	4	30	67	6	13	31	74	84
313	–	2.55	–	–	–	–	0.45	–	0	1	5	0	0	0	0	3
314	0.26	–	–	0.91	–	–	0.78	1.06	1	13	49	6	12	34	57	73
315	0.65	–	–	2.35	–	–	–	–	7	34	84	6	16	50	77	89
316	1.07	–	–	1.93	–	–	–	–	9	32	83	12	24	47	71	84
317	0.15	–	0.84	0.86	0.69	0.47	–	–	1	20	55	10	7	22	44	66
318	–	–	1.10	1.00	0.91	–	–	–	12	33	68	7	12	29	60	76
319	–	–	0.77	0.71	0.64	0.47	0.41	–	5	13	38	3	6	10	31	58
320	–	–	1.91	0.13	0.18	–	0.78	–	4	14	26	1	4	0	8	28
321	1.52	–	–	–	–	1.49	–	–	4	2	3	2	2	8	0	10
322	0.24	–	0.76	1.33	–	–	–	0.67	9	30	60	8	11	30	65	82
323	–	–	–	1.66	1.34	–	–	–	10	31	80	14	9	43	74	88
324	–	1.08	0.65	0.07	1.19	–	–	–	3	7	21	0	0	0	0	1
325	0.32	0.68	–	–	–	1.05	–	0.95	0	1	3	0	0	0	1	1
326	0.21	–	1.19	0.61	0.99	–	–	–	12	29	67	4	3	14	46	69
327	–	–	2.14	0.15	0.20	–	–	0.52	5	13	20	0	-3	7	7	24
328	–	0.01	0.72	1.00	–	–	1.27	–	5	18	43	1	8	26	50	70
329	0.70	0.01	–	1.01	–	–	1.29	–	5	11	43	2	3	23	54	74
330	–	–	1.60	1.40	–	–	–	–	12	33	68	0	0	25	58	77
331	1.19	–	–	–	–	–	1.82	–	1	1	1	0	0	0	0	7
332	–	–	–	1.72	–	–	–	1.28	11	37	84	11	30	55	76	85
333	–	0.05	–	–	1.27	0.90	0.78	–	1	2	1	0	1	0	6	8
334	–	1.49	–	1.52	–	–	–	–	9	28	58	1	7	15	48	72
335	1.46	–	–	–	–	–	1.55	–	1	0	0	0	0	3	5	5
336	–	–	–	–	1.22	0.73	0.55	0.49	1	0	1	0	3	0	5	7
337	0.10	–	–	0.56	0.45	–	0.39	1.49	4	15	43	0	9	12	33	55
338	–	1.29	–	0.98	0.72	0.02	–	–	7	22	51	3	10	14	42	61
339	–	–	1.60	–	–	–	–	1.40	4	3	7	0	5	1	13	17
340	0.49	–	–	1.76	–	–	0.75	–	7	14	67	5	9	26	61	78
341	–	0.01	–	0.82	–	–	1.04	1.13	8	13	50	7	13	18	41	60
342	–	–	–	1.52	–	–	1.48	–	8	18	59	8	10	27	63	77
343	0.20	–	1.15	1.17	0.47	–	–	–	16	30	70	1	12	24	57	80
344	0.24	–	1.36	1.39	–	–	–	–	13	28	59	2	8	21	60	82
345	0.65	–	–	2.35	–	–	–	–	15	29	78	7	17	38	75	90

[a] The materials with the best catalytic activity are indicated in bold.

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Wilhelm Schlenk: The Man Behind the Flask**

Thomas T. Tidwell*

In 1943 there appeared in *Berichte der Deutschen Chemischen Gesellschaft*^[1] a brief notice (Figure 1) of the death of Wilhelm Schlenk, the former President of the German Chemical Society (Deutsche Chemische Gesellschaft).^[2a] It was stated that a fuller biography of Schlenk would appear later, but this has not been forthcoming, although there were short articles in specialized Austrian^[2b] and Bavarian^[2c] journals. Underneath the notice about Schlenk there was a list of individuals who had died in 1942, and this list was headed by the traditional German Iron Cross, emblazoned with the swastika, the emblem of the ruling National Socialist Party led by Adolf Hitler. A name that stands out on this list is that of Max Bodenstein, another pioneer in free radical chemistry and one of Schlenk's successors as President of the Deutsche Chemische Gesellschaft (1930–1932), for whom a detailed memorial appeared in 1967.^[2d]

The name Schlenk is familiar to many chemists because of the widespread use of "Schlenk" glassware, as illustrated in many textbooks and reviews on the handling of air-sensitive compounds.^[3] Who was Schlenk, and why has the promised obituary never appeared? A brief study of the life of this extraordinary scientist provides an answer to the first question, and also makes a strong case that he should be better known, not only for his scientific achievements but also for the example he set as a man of principle and political courage.

Wilhelm Johann Schlenk (Figure 2) was born in Munich in 1879, the son of Georg and Emilie Schlenk, and attended the Realgymnasium there. He had a fine singing voice and considered a career in music, but instead followed the example of his brother Johann Oskar Schlenk (1874–1951; Figure 2, right) in the study of chemistry. Another brother Hermann became a Director of the Löwenbräu brewery in

Sitzung am 22. Mai 1943

Vorsitzender: R. Kuhn, Präsident.

Am 28. April 1943 verstarb in Tübingen im Alter von 64 Jahren der frühere Präsident der Gesellschaft Hofrat Professor Dr.

WILHELM SCHLENK.

In einem Nachruf in den „Berichten“ wird seiner besonders gedacht werden.

Die Gesellschaft verlor am 13. Mai 1943 eines ihrer ältesten Mitglieder; in Brunn verstarb der seit 1886 der Deutschen Chemischen Gesellschaft angehörende Professor Dr. h. c.

GUSTAV ULRICH.

Die Anwesenden ehren das Andenken an die Toten durch Erheben von den Sitzen.

Herr Dipl.-Ing. Horst Ademeit (Potsdam) erhielt als Leutnant der Luftwaffe das Ritterkreuz zum Eisernen Kreuz. Die Gesellschaft sprach ihrem Mitglied die besten Glückwünsche zu der hohen Auszeichnung aus.

In der Sitzung wurde folgender Vortrag gehalten:

K. Freudenberg (Heidelberg): Beiträge zur Chemie der Kohlenhydrate.

Der Vorsitzende:

R. Kuhn.

Der Schriftführer:

R. Weidenhagen.

Mitteilungen der Gesellschaft.

Die Toten aus dem Jahre 1942



Für Großdeutschland sind gefallen:

Benecke, Dr. Hans Joachim, Stöckheim/Altmark Krs. Salzwedel,
John, Dr. phil. habil. Walter, Göttingen,
Junge, Dipl.-Ing. Werner, Berlin,
Schlötzer, Dr. Arnulf, Berlin,
Will, Dr.-Ing. Erich, Berlin.

Es sind verstorben:

Antrick, Dir. Dr. Otto, Berlin; Becka, Prof. Dr. Jan, Brunn; Betti, Prof. Dr. Mario, Bologna (Italien); Bodenstein, Prof. Dr. Max, Berlin; Brüggemann, Dir. Dr. R., Singen; Claasz, Prof. Dr. M., München; Darapsky, Prof. Dr. A., Köln a. Rh.; Degen, Dr. Jos., Düren/Rhld.; Ehrlich,

Figure 1. Announcement of the death of Wilhelm Schlenk in *Berichte der Deutschen Chemischen Gesellschaft*, 1943.

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Munich. Oskar was a student of Adolf von Baeyer and Johannes Thiele in Munich and after a brief stay at the University in Heidelberg in 1900 spent his career at the Heyden chemical company in Radebeul near Dresden. He worked on pharmaceuticals, and published papers on the 100th anniversaries of the discoveries of benzene by Faraday and of aniline by Unverdorben, and a historical paper on aspirin. Wilhelm also studied in the Chemistry Department of the Academy of Science in Munich, which was led by the



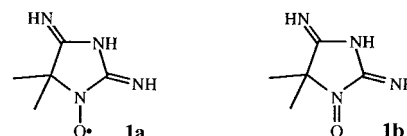
Figure 2. Left: Wilhelm Schlenk (about 1905); right: Schlenk family (1915): sister Augusta, Hermann, Emile, Wilhelm, Georg, Oskar, (courtesy of Edward Schlenk).

legendary Adolf von Baeyer. He received his Ph.D. in 1905 for work under the direction of Oskar Piloty (Figure 3), the son-in-law of von Baeyer, and also in 1905 married Mathilde von Hacke (1881–1973).



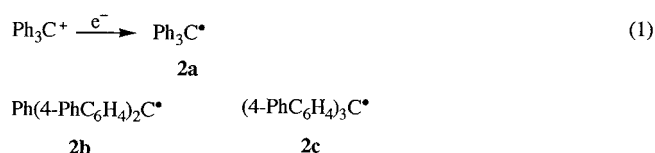
Figure 3. Oskar Piloty (from reference [4c]).

Schlenk's thesis was entitled "Über Metall-Isobutyr-Adine und ihre Salze", and although unpublished gave Schlenk an introduction to organometallic chemistry. The work was a continuation of studies by Piloty and Graf Schwerin^[4a] that had produced the first isolated organic free radical, the nitroxyl radical porphyrexide (**1a**),^[4b] although they did not recognize it as a radical and formulated as **1b**.



Piloty also studied pyrroles related to the chemistry of hemoglobin, and was one of the promising figures in this competitive field. When World War I broke out Piloty, although past the normal age of service, enlisted in a burst of patriotic enthusiasm, and was killed by the Somme in 1915.^[4c]

After Schlenk had worked briefly in the chemical industry, for the firm of Weiler-ter Meer in Uerdingen, and received a patent for the study of quinoid compounds,^[5] he was Unterrichtsassistent in Munich from 1906. He completed his Habilitation in 1909, and was Privatdozent from 1910. His interest in quinoid compounds may have helped to spark his interest in the study of the triphenylmethyl radical **2a**, which had been reported by Moses Gomberg in 1900 [Eq. (1)].^[6a]



This discovery attracted widespread attention and controversy.^[6b,c] One reason that the structure of triphenylmethyl was elusive was that this species is highly associated to the dimer, and so the radical was hard to observe. Schlenk brilliantly solved this problem with the preparation of phenylbis(4-biphenyl)methyl radical (**2b**), and tris(4-biphenyl)methyl radical (**2c**).^[7a] The latter was obtained as a black crystalline

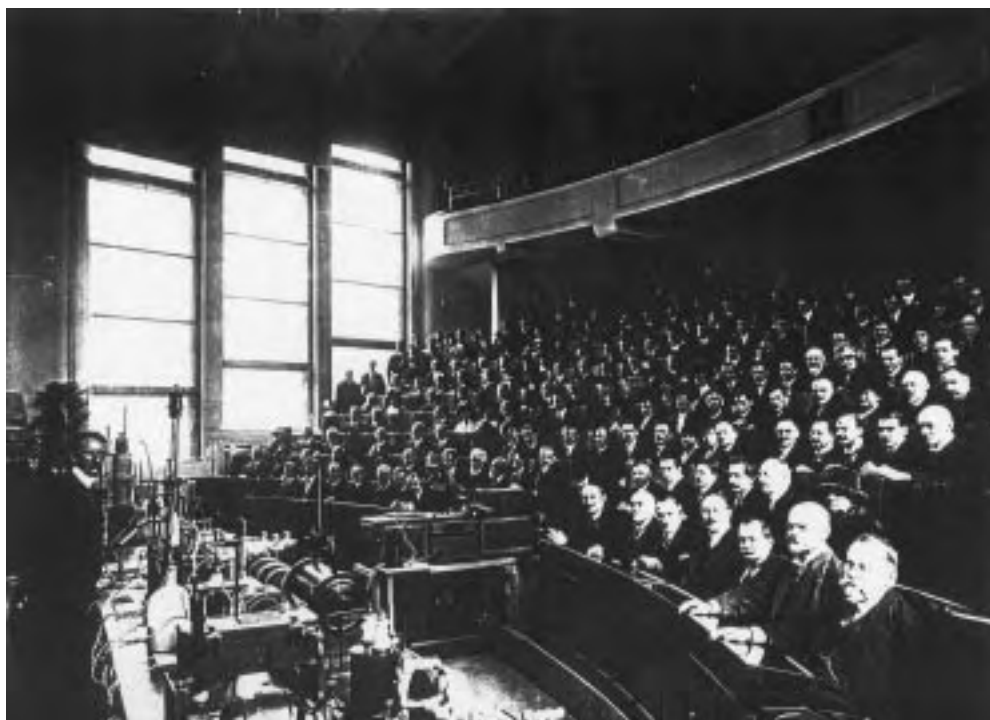


Figure 5. Schlenk at the dedication of the new lecture hall in Vienna, January 15, 1921. Albert Einstein is in the second row, third from right. Schlenk's sons Wilhelm and Fritz are in the balcony. This hall was renovated and rededicated, May, 2000. (Photo courtesy of Edward Schlenk)

charge, which could be seen going in one finger and out the other hand. Schlenk was thrown to the floor, but revived and finished the lecture.

With the death of Emil Fischer in 1919 the Chair at the Friedrich Wilhelms (now Humboldt) University in Berlin became vacant. This was the most prestigious chair in Germany, Richard Willstätter, the first choice for the position, declined to leave Munich.^[10c] Fritz Haber was also considered as a successor, but the influential industrialist Carl Duisberg argued strenuously that an organic chemist should occupy the position, as this was vital to the interests of German industry. The German economy was heavily dependent upon the manufacture of organic chemicals, and was suffering from the ravages of the war and the large reparations which had been imposed afterwards. In 1921 the Chair was offered to Schlenk, who became Director of the Chemical Laboratory. Haber was Professor at the Kaiser Wilhelm Institute at Dahlem, a suburb of Berlin, and a friend of Schlenk's, but was also immensely ambitious, and was given a Chair of Industrial Chemistry at the University. In Berlin the Schlenk family lived in quarters attached to the Chemical Laboratory on Hessische Strasse (Figure 6), erected in 1900 for Emil Fischer. Schlenk's three sons would visit the laboratory,^[10b] which evidently stimulated their interest in chemistry, as all three (Figure 7) became successful chemists: Wilhelm, Jr. (1907–1975, Ph.D. 1929, Technical University of Berlin, with Robert Pschorr), Fritz (1909–1998, Ph.D. 1934, Berlin, with Wilhelm Schlenk, Sr.), and Hermann (born 1914, Ph.D. 1939, Munich, with Heinrich Wieland).

In the aftermath of the First World War Germany was largely excluded from international scientific activities by the victorious allies. However in June, 1921, there was a meeting in Utrecht in the Netherlands, which had been neutral in the

war, to plan for an international conference, and Schlenk along with Paul Walden from Germany and Rudolph Wegscheider from Austria participated in the organizational meeting. This conference, the *Réunion Internationale de Chimie* was duly held in Utrecht June 21–23, 1922, with extensive participation from Europe and the United States, and the lecturers included Schlenk,^[10d] Paul Walden, and Heinrich Wieland from Germany, and William Albert Noyes from the U.S.A.

Also in 1922 Schlenk became a Vice President of the Deutsche Chemische Gesellschaft, the German Chemical Society, and was President from 1926–1928. Increasingly he was involved in administration and in international science, and in 1927 he attended the centennial jubilee of the birth of Berthelot in Paris, along with Willstätter, Wieland, Haber, and Walther Nernst.^[10e,f] Not since the war had German chemists been invited to such an event in France. Then in 1928 Schlenk along with Haber and Alfred Stock attended the International Congress of Pure and Applied Chemistry (IUPAC) in the Hague.^[10e] As the German Chemical Society was still not a member of (IUPAC) at that time, they came not with official but with personal invitations. However in 1930 at the 10th IUPAC Conference in Liège Schlenk was part of an official German delegation. In 1931 he was a lecturer at the Solvay Conference on Chemistry in Brussels, along with Robert Robinson and Christopher K. Ingold from Britain, and Hermann Staudinger from Germany.^[10g]

In 1924 Schlenk authored a chapter on organometallic chemistry in *Die Methoden der Organischen Chemie*^[3a] describing the techniques of handling sensitive materials in glass apparatus, and these techniques were incorporated in many later books and reviews.^[3] Some of his innovative designs are illustrated in Figure 8, and it is for this apparatus

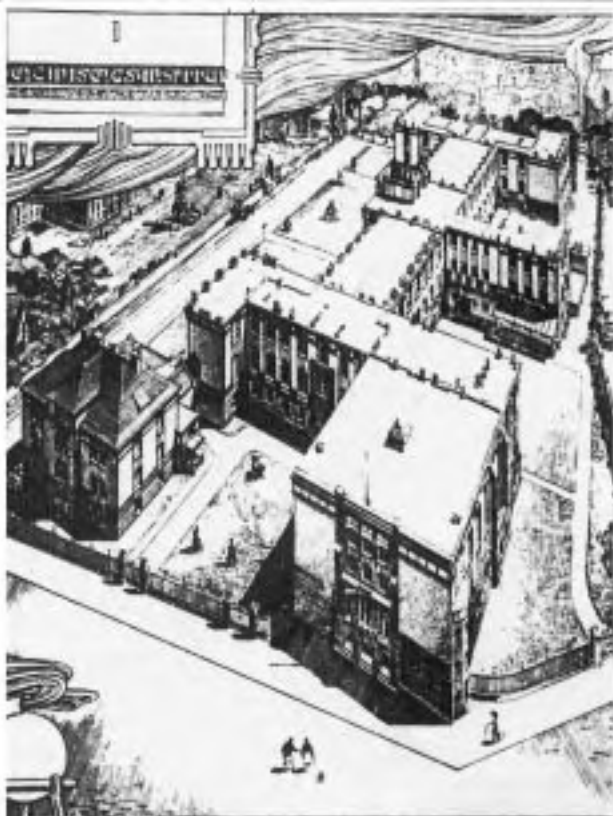


Figure 6. Top: Director's house. Note passageway to private laboratory in Institute (Photo by Wilhelm Schlenk). Bottom: the chemical laboratory on Hessische Strasse in Berlin, for which there was a centennial celebration in June, 2000. The Director's house is on the left corner.



Figure 7. Schlenk's children: Wilhelm, Hermann, Fritz, with Wilhelm, Sr., and Mathilde, about 1922 (courtesy of Gertrude Lenzer).

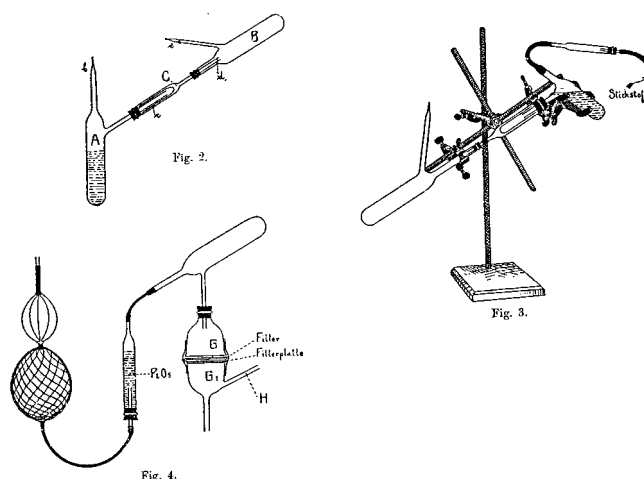
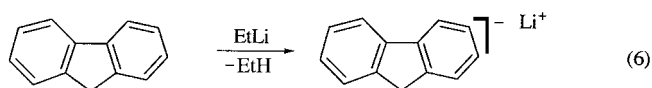


Figure 8. Schlenk glassware (from reference [7d]).

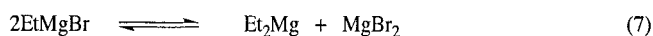
Schlenk's name is most widely known. The pivoting device for transfers was known as a "Schlenk Kreuz", or Schlenk cross.^[3e]

From 1921–1925 Ernst Bergmann was a doctoral student with Schlenk, and remained in Berlin as a Privatdozent from 1928. Together with a sizeable group of students Schlenk and Bergmann engaged in comprehensive studies of the reactions of aromatic alkenes with alkali metals. One important result of this work was the discovery of the direct lithiation of hydrocarbons by organolithiums, as in the reaction of fluorene

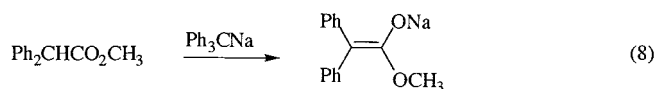
with ethyllithium [Eq. (6)].^[11a] With his son Wilhelm, Jr., Schlenk proposed the equilibrium of Grignard reagents with



diethylmagnesium, known thereafter as the "Schlenk equilibrium" [Eq. (7)].^[11b] Another major discovery was the



preparation and study of crystalline enolates [Eq. (8)].^[11c] Eugen Müller (1905–1976)^[11d] was one of Schlenk's students at this time, and later as Professor at Heidelberg and Tübingen became well known for his own research on free radicals.



There was competition with Karl Ziegler at Heidelberg on the reactions of alkali metals with allenes. Ziegler was a younger man rising to prominence who made important contributions in free radical chemistry of the Gomberg type as well as in organometallic chemistry. Later this was to lead to the discovery of the polymerization of olefins by organometallic compounds, for which Ziegler was awarded the Nobel Prize in 1963.

Schlenk published with Bergmann in 1932 the first volume, of 805 pages, of a comprehensive textbook on organic chemistry.^[12a] In his last scientific paper Schlenk was a coauthor with Bergmann of a paper regarding the structure of steroid derivatives.^[12b] At this stage Bergmann was pursuing research independently, but he left Germany in 1933 and achieved great prominence not only as the founder of organic chemistry in Israel but also as a scientific advisor to the government.^[12c,d]

With the ascension to power of the National Socialist Party under Adolf Hitler in January, 1933, the position of Schlenk became tenuous, as he made his democratic ideals known, for example refusing to begin his lectures with the expected "Heil Hitler".^[10b] He offered his position in Berlin to Willstätter when the latter resigned his Chair in Munich in 1925 because of the increasing anti-Jewish sentiment,^[13a] and in 1932 published a 60th birthday tribute to Willstätter.^[13b] He also remained close to Haber, and authored a prominent memorial to Haber on his death in 1934.^[13c] Haber had suggested in 1933 that Schlenk should take his place as Vice-President of IUPAC,^[10f] but this was anathema to the Nazis. With his close association with Jews such as Haber, Willstätter, and Bergmann, and his outspoken convictions Schlenk's influence was finished. He was conspicuously absent from an important international conference on free radicals organized by the Faraday Society in Cambridge in September, 1933, although others from Germany including Ziegler were in attendance, as well as some who were already émigrés, such as Friedrich Paneth and Michael Polanyi.^[13d]

In 1935 Schlenk was removed from his Chair in Berlin and became Professor at Tübingen, where there was a more tolerant atmosphere. There he was a visible symbol of resistance and demonstrated that one could dare to take risks on matters of principle and still survive. The Berlin Chair remained vacant for the next 10 years.

Schlenk remained in Tübingen for the remainder of his career, but was heavily involved in teaching and administration and published no more research papers, not even from the thesis of his son Fritz.

In 1939 the second large volume of his textbook appeared,^[14a] although for reasons of expediency without Bergmann

as coauthor, to his great displeasure, as he had written much of the text.^[12d, 14b] A third volume was reported to be almost complete, but this never appeared. There was some mention of a possible position in Istanbul, but this did not materialize.^[14c] In 1942 he was expelled from the Deutsche Chemische Gesellschaft,^[2c] and suffered ill health before his death in 1943.^[15] His son Wilhelm, Jr., also ended his academic career and went into industry at BASF, and his other sons Fritz and Hermann emigrated to the United States. Fritz was at the University of Illinois in Chicago, and Hermann at the Hormel Institute of the University of Minnesota. All three sons published extensively.

Schlenk was eulogized in a 60th birthday tribute in Tübingen,^[15] and in a notice on his death,^[15] but these were not published. These emphasized his devotion to science and to his students, and describe his unassuming character and quest for scientific truth not personal acclaim or power. He personally devoted long hours to cleaning the glassware from the lecture demonstrations, and after his early morning walks in Tübingen was in the laboratory at 6 am and available for the students. Schlenk was a tall man, characterized as "long Schlenk" in a memoir^[15] and was noted for his devotion to the arts. Wieland's brief testament to Schlenk^[2c] also describes a courageous and humane individual.

Returning to the questions posed earlier the identity of Wilhelm Schlenk is available in the published record, and he was one of the most talented chemists of the first third of the 20th Century. His work was widely recognized early in his career, for example both tris(4-biphenyl)methyl radical **2c**^[7a] and sodium benzophenone ketyl **3**^[7b] played a prominent role in the development by Gilbert N. Lewis of his theory of the electron pair bond.^[16a] One of the Schlenk diradicals was used by Erich Hückel in considering the application of Hund's rule to diradicals.^[16b] The answer to why the promised detailed memorial has never appeared is open to speculation. It is even somewhat surprising that his death was prominently mentioned in 1943^[2a] in view of the animosity of the Nazis.

He has been commemorated in the Arfvedson–Schlenk Prize in Lithium Chemistry of the GDCh sponsored by Chemetall GmbH, which was awarded for the first time in 1999, to Paul von R. Schleyer. If Schlenk had survived the war and continued his career he may have received further honors, as did Wieland and Paneth. His two most prominent students, Mark and Bergmann, had emigrated, and thus his personal history has been largely forgotten, although his work with free radicals and organometallics, and especially his techniques for handling air-sensitive compounds, still remain prominent. Extensions of his work include the determination of the crystal structures of ethyllithium,^[16c] ester enolates,^[16d] and sodium benzophenone ketyl.^[16e] There is great interest in "high spin" molecules inspired by the Schlenk diradical **4**; and continued prominence for the "Schlenk equilibrium",^[16f] which has recently been extended to lanthanide(II) aryls.^[16g]

He also deserves to be remembered as a man of courage and integrity who dared to risk his high position in opposition to tyranny. He is an example to scientists of all countries that the pursuit of knowledge does not preclude the duty to defend moral principles.

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Diversity-Based Organic Synthesis in the Era of Genomics and Proteomics**

Prabhat Arya,* Doug T. H. Chou, and Myung-Gi Baek

Dedicated to Dr. David Thomas

Synthetic organic chemistry has always been a frontier area of research due to its impact on the materials and biological sciences. The scientific community involved in this area is constantly being challenged to develop efficient methodologies, novel reactions, and processes that will lead to the synthesis of desired target molecules and their derivatives.^[1] Not only is synthetic organic chemistry a tool for obtaining compounds that can be utilized for understanding biological functions or the behavior of materials, but it also leads to the creation of novel drug/drug-like candidates and of novel materials with interesting properties.

During the last few decades, there has been a great push for the development of novel synthetic methodologies that lead to complex natural products, natural product like molecules, and simpler analogues of natural products in an efficient manner. Tremendous progress has been made in asymmetric synthesis for the development of stereo- and enantioselective reactions. Combinatorial chemistry dealing with organic synthesis emerged during the last decade.^[2] This was largely due to the extensive time period required for the identification of drug-like candidates and novel materials. In a classical manner, lead compounds are derived from the extraction of natural products from plants, animals, insects, or microorganisms. Following positive responses from several fractions, the next challenge is identification of the chemical entities responsible for the biological activity. Synthesis is then undertaken to obtain specific compound(s) in large quantities or to obtain simpler analogues that may exhibit similar biological response. Overall, traditional medicinal chemistry approaches toward these goals have been very time consuming and very expensive. By applying combinatorial chemistry, it is possible to obtain large sets of organic/bioorganic compounds over short periods of time, either by applying parallel high-throughput synthesis or by a “mix and split”

technology. In the coming years, it is expected that combinatorial chemistry will play a crucial role in understanding the biological functions of new targets or in the identification of novel targets in the area of genomics and proteomics research. Over the past few years, we have observed the impact of combinatorial chemistry in the development of high-throughput synthesis of focused libraries. It is anticipated that the next era will involve diversity-based synthesis of natural product like compounds to explore their applications in emerging genomics- and proteomics-related research activities. Although very recent, these efforts are already in action within the combinatorial chemistry community and are highlighted in this article.

Recently, Schreiber has given an elegant description of the differences between target-oriented synthesis and diversity-based synthesis.^[3] As Schreiber explains, in a drug discovery process, target-oriented synthesis of small molecules is undertaken on the basis of retrosynthetic analysis. In general, this approach requires preselection of the protein target(s) which are then utilized for developing small molecules as selective binding agents, either by traditional methods or by solid-phase combinatorial chemistry based on organic synthesis. This can further be applied in a parallel manner or by using a mix and split technology for developing high-throughput organic synthesis. Using a mix and split method, it is possible to synthesize a large set of compounds which are then screened as mixtures. The identification coding technique helps to identify the positive lead compounds in mixtures. Parallel synthesis generally does not result in higher numbers as it provides only one compound per well.

In contrast, and as described by Schreiber, diversity-based organic synthesis is not focused toward a given target. Rather, it is used for identifying new targets or for understanding biological functions of new targets. Moreover, it does not rely upon retrosynthetic analysis and is aimed at developing novel methodologies for obtaining small molecules with structural complexity and diversity. Schreiber compares this to the random mutation approach, which is a well-established technique for modulating specific, cellular, biological responses. Schreiber further defines this technique as a “chemical genetics approach” in which small-molecule libraries are used for probing cellular responses in search of “therapeutic target validation” and “chemical target validation”.^[4] Given

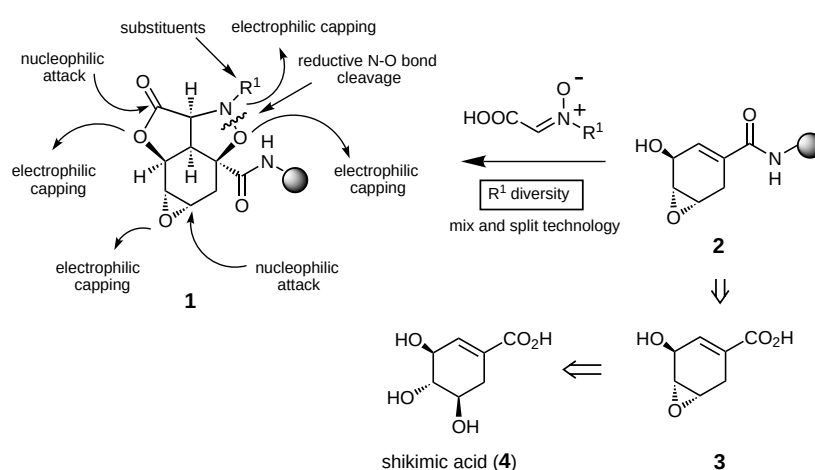
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that genomics and proteomics research will provide rapid information on the discovery of novel genes and proteins, we are faced with the challenge of understanding their functions in a timely fashion. Diversity-based synthesis leading to small-molecule libraries will play a crucial role in this area, and it will likely rival the mutational or gene knock-out experiments commonly carried out in biological laboratories. Instead of carrying out labor-intensive gene knock-out experiments, the use of chemical-based small-molecule libraries would provide similar answers with relative ease. In particular, natural product like libraries will be in great demand, complementing the available natural products that are utilized for modulating (that is, activating or inactivating) protein function(s).

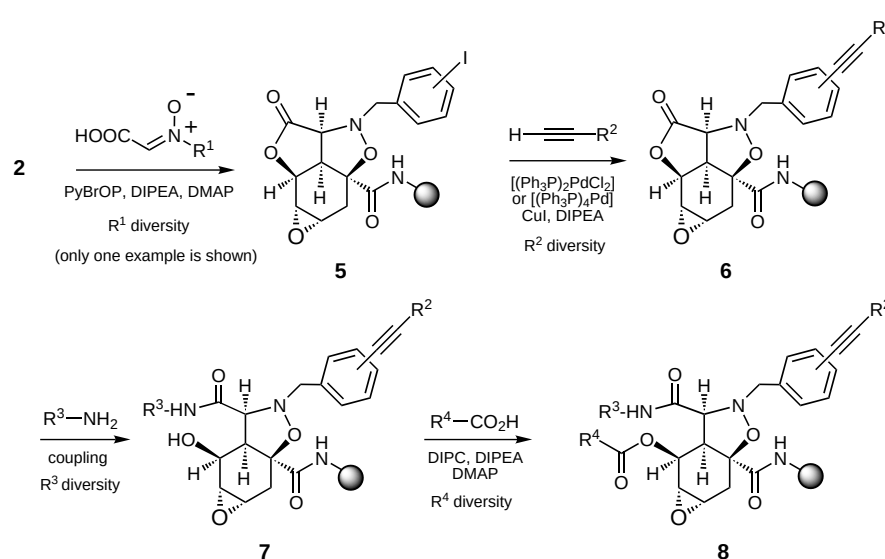
It is well known that several, small-molecule, complex natural products interfere with protein–protein, carbohydrate–protein, and DNA–protein interactions. For example, in the area of protein–protein interactions, it is generally believed that the size and the rigidity of the structural elements within a small molecule tend to provide better binding/interfering agents. This is largely due to flat surfaces that are involved in most protein–protein interactions, although this may not be valid for the active sites for individual enzymes. The two approaches of Schreiber and co-workers for developing diversity-based high-throughput syntheses are summarized as follows.

Using a mix and split solid-phase approach, combined with the encoding technology, Schreiber et al.^[5] synthesized a diversity-based small-molecule library on a tetracyclic template **1** (see Scheme 1 for various diversity-based reactions on the template) which is attached to a TentaGel-S NH₂ [poly(ethyleneglycol)–polystyrene copolymer resin]. This template, anchored onto the solid support, was prepared from the epoxide derivative **2** of shikimic acid on reaction with various nitron carboxylic acid derivatives. The tandem acylation, followed by intramolecular 1,3-dipolar cycloaddition, gave the product with complete stereo- and regioselectivity. 4,5-Epoxy-3-hydroxy-1-cyclohexene-carboxylic acid (**3**) was synthesized from shikimic acid (**4**). Template **1** possesses a high degree of rigidity and is highly functionalized (with the isoxazolidine, lactone, and epoxide). This could further be subjected to a variety of organic and organometallic reactions for the generation of small-molecule libraries. It is interesting to note that the synthetic plan used by Schreiber does not require use of protective groups. Validation of several key reactions was thoroughly carried out, before the sequence of steps was applied with the mix and split encoded tech-



Scheme 1. Shikimic acid derived tetracyclic template for the synthesis of small-molecule libraries.

nology for a full-scale library synthesis. The validation steps involved the repetition of the reaction sequence for suitability, with testing of potential building blocks at every step, the generation of a small library, and the investigation of unforeseen complications. For example, the lactone and the epoxide moiety from template **1**, reacted readily with nucleophiles such as BuNH₂, PhNCO, Et₂NH, and PhCN in a typical organic solvent to obtain the hydroxyl derivatives. Subsequently, the alcohols generated were coupled with carboxylic acids or acid halides to form the ester derivatives. The thioacidolysis of the epoxide was successfully performed using thioacetic acid to yield another hydroxyl adduct. Since the isoxazolidine nitrogen could have various substituents, a number of nitron acids containing reactive functional groups were synthesized. For example, a number of iodoaryl nitron acids were selected for synthesis of the iodoaryl tetracyclic templates (**5**; Scheme 2). Iodo substituents could further be subjected to palladium-catalyzed, cross-coupling reactions to obtain compound **6**, or could be subjected to amination, etherification, or carbonylation. Moreover, the iodo func-

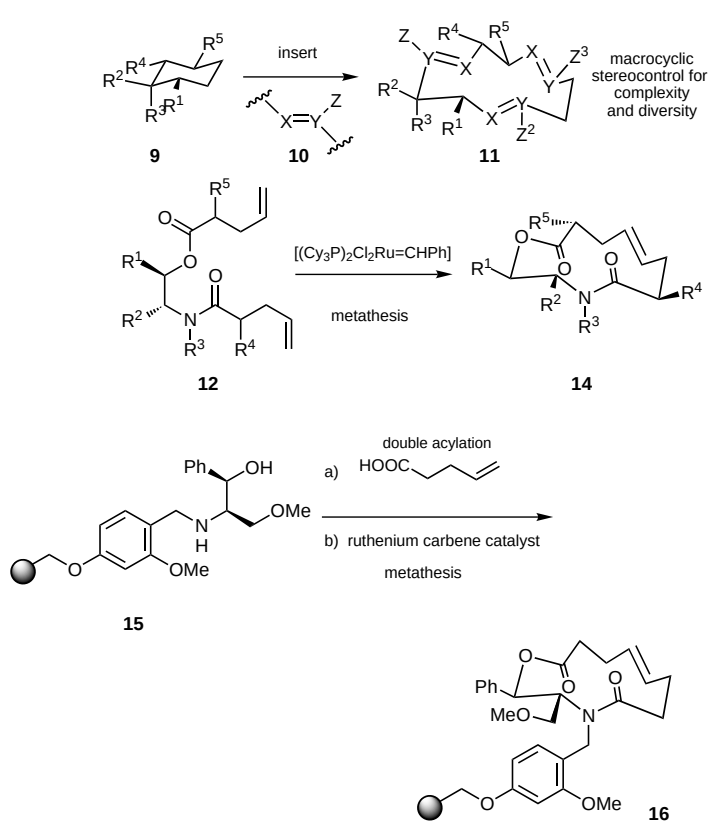


Scheme 2. The synthesis of small-molecule libraries from the tetracyclic template. DIPEA = diisopropylethylamine, DMAP = 4-dimethylaminopyridine, DIPC = diisopropylcarbodiimide.

tional group could be further substituted to alkenes, alkynes, and chloroformates for the generation of highly diverse templates. After optimization of a series of reactions, lactone aminolysis (to form **7**) and esterification (to form **8**), led to the synthesis of a full-size library (approximately 2.18 million compounds) with a high degree of complexity and diversity. The library was analyzed for its inhibitory activity toward a *Xenopus laevis* oocyte extract assay, mink lung cell proliferation, and rapamycin-based growth inhibition in *Saccharomyces cerevisiae*.^[6] Interestingly, several library members were identified as activators of the reporter gene in mink lung cells. It is remarkable that the library design strategy relied upon the use of highly mild reagents and efficient stereoselective synthetic methods. This indeed is a very good lesson for the combinatorial chemistry community. Examples of library synthesis that utilize a simple, chiral starting material for obtaining structurally complex and diverse building block templates are likely to appear in the literature in coming years.

Another interesting example of a similar approach appeared in 1999. In this communication,^[7] Schreiber and co-workers reported an efficient approach to the synthesis of macrocyclic libraries. A key step in their strategy involved the application of a well-known ring-closing metathesis reaction,^[8] which is then followed by exploring macrocyclic-based stereocontrol reactions. It is well-known that several biologically active natural products bear medium to large rings. A number of antibiotics (for example, erythromycin) belong to this category of macrocyclic-base, highly functionalized compounds. Complex small-molecule libraries having medium to large size ring derivatives can provide biologically enriched compounds. Successful strategies will largely depend upon the structure of the acyclic precursors having optimized conformational features suited for the ring closure. In general, six-membered ring cyclization reactions are highly efficient and high yielding. Macrocyclic ring closure could also exhibit similar properties by introducing the structural and the functional elements that would favor the ring cyclization. Schreiber et al. envisioned that inserting *trans*-olefinic moieties **10** into the alternative sp^3 bonds of a six-membered ring **9** would favor the macrocyclic ring cyclization that yields **11** due to the release of the *trans* annular effects and the torsional strains (Scheme 3). For the successful cyclization metathesis, it is important that the reactive termini in both acyclic precursors are oriented in a close proximity suitable for the ring closure. Olefinic and carbonyl groups in a macrocycle could then undergo various macrocyclic-based stereocontrolled reactions (such as epoxidation or enol ether chemistry).

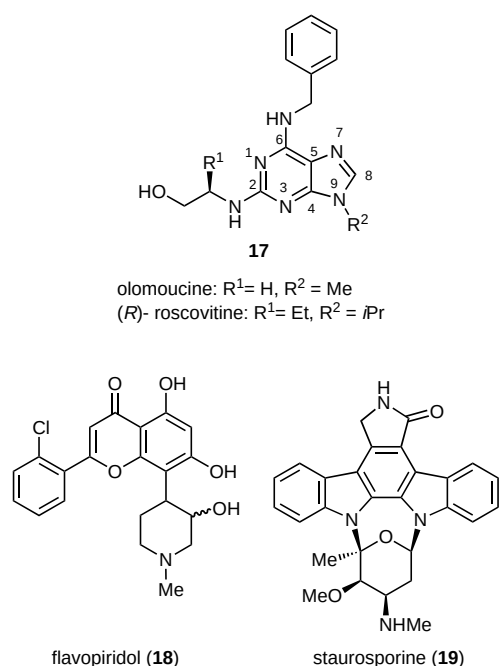
Before library synthesis, the ring-closing metathesis reaction was tested in the solution phase with the model compound. Compound **12** was obtained from the sequential acylation of a 1,2-amino alcohol derivative. Ring-closing metathesis was carried out in the presence of Grubbs' catalyst (**13**; 5–15 mol %) to give the desired product **14** in average to excellent yields. Further, it was shown that epoxidation and enol ether alkylation reaction with the macrocycle gave the epoxide product and the alkylated derivative with complete stereocontrol. At this stage, the ring closing metathesis based macrocyclization was tried on the solid phase. A chiral amino



Scheme 3. Schreiber et al.'s macrocyclic ring formation approach for the potential synthesis of small-molecule libraries. Top: theoretical reaction; middle: model solution-phase system; and bottom: solid-phase reaction.

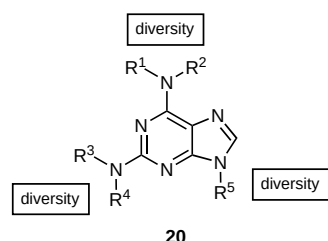
propanol derivative was anchored onto the solid support using a traceless linker yielding compound **15**. This was first subjected to double acylation followed by ring-closing metathesis that gave the chiral macrocyclic derivative **16**. This sets the stage to carry out a mix and split encoded process toward the synthesis of stereochemically complex, chiral macrocyclic compound libraries. The biological outcome from this class of libraries will be seen in coming years.

With a similar goal of using small-molecule libraries in genomics and proteomics research, the Schultz group is developing purine-based small-molecule libraries. In combination with the structural features of several kinases and genomics research, these libraries are tested for the identification of kinase inhibitors. The purine ring constitutes a common structural motif in molecules that play vital roles in many biological processes. For example, it is an important component in proteins such as cellular kinases, specifically cyclin-dependent kinases (CDKs).^[9, 10] These enzymes regulate many biological processes such as cell growth, DNA replication, and cell division.^[9] As such, the synthesis of kinase inhibitors has grown rapidly over the last few years. Some of the earlier CDK inhibitors are shown in Scheme 4 (**17–19**).^[11] These compounds displayed reasonable inhibition, but still lacked the potency and selectivity to be ideal drug candidates. In order to facilitate the synthesis of purine derivatives with greater affinity for CDK enzymes, it was postulated, based on several X-ray crystallographic studies, that the synthesis of



Scheme 4. Natural product based compounds which are CDK inhibitors.

structurally diverse purine analogues (with diversity at the C2, C6, and N9 positions) might lead to the identification of more potent CDK inhibitors (Scheme 5; **20**).^[12]

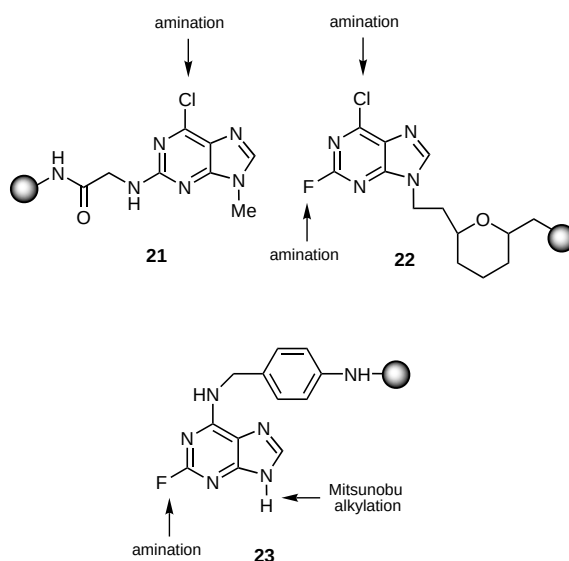


Scheme 5. General structure of the purine-based compounds to be synthesized in libraries for testing as CDK inhibitors.

However, traditional synthetic methodologies involving solution-phase chemistry often prove to be difficult and time-consuming processes if a large number of diverse molecules are desired. On the other hand, combinatorial chemistry offers a practical solution to produce compound libraries for their biological significance. Libraries of natural products or collections of small organic molecules are being explored for their ability to affect particular pathways in cells or organisms. These libraries will enable the identification of new targets for their effectiveness against particular pathways, in the hope of discovering new drugs. The rapid screening of these libraries is now possible with modern technologies. Several strategies have been employed by Schultz and co-workers for solution/solid-phase synthesis of purine derivatives.^[11] These initial targets will allow a primary determination of structure–activity relationships (SARs) against CDK enzymes.

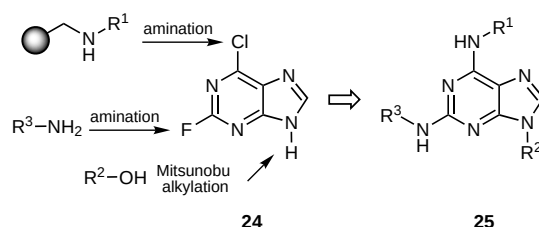
The solid-phase synthesis developed by Schultz and co-workers involves the attachment of a solid support to one of the purine positions (C2, N9, or C6) with glycinamido, ethyl

tetrahydropyran ether, or 4-aminobenzyl amino groups (Scheme 6; **21–23**, respectively).^[11b,c] The main drawback of this strategy is the loss of a potentially useful site for



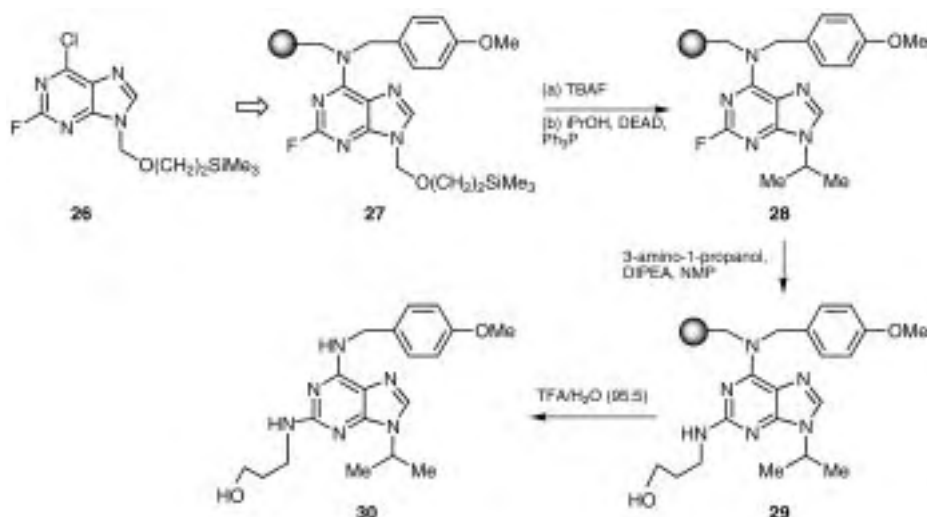
Scheme 6. Solid-phase approaches by Schultz et al. for the synthesis of purine-based libraries.

structural variation. A combination of solid- and solution-phase chemistry was utilized to overcome this problem. This strategy involves immobilization of the purine ring at the C6 position allowing a variety of substitution to occur at the C2, C6, and N9 positions (Scheme 7; **24, 25**). Initially, the solid-

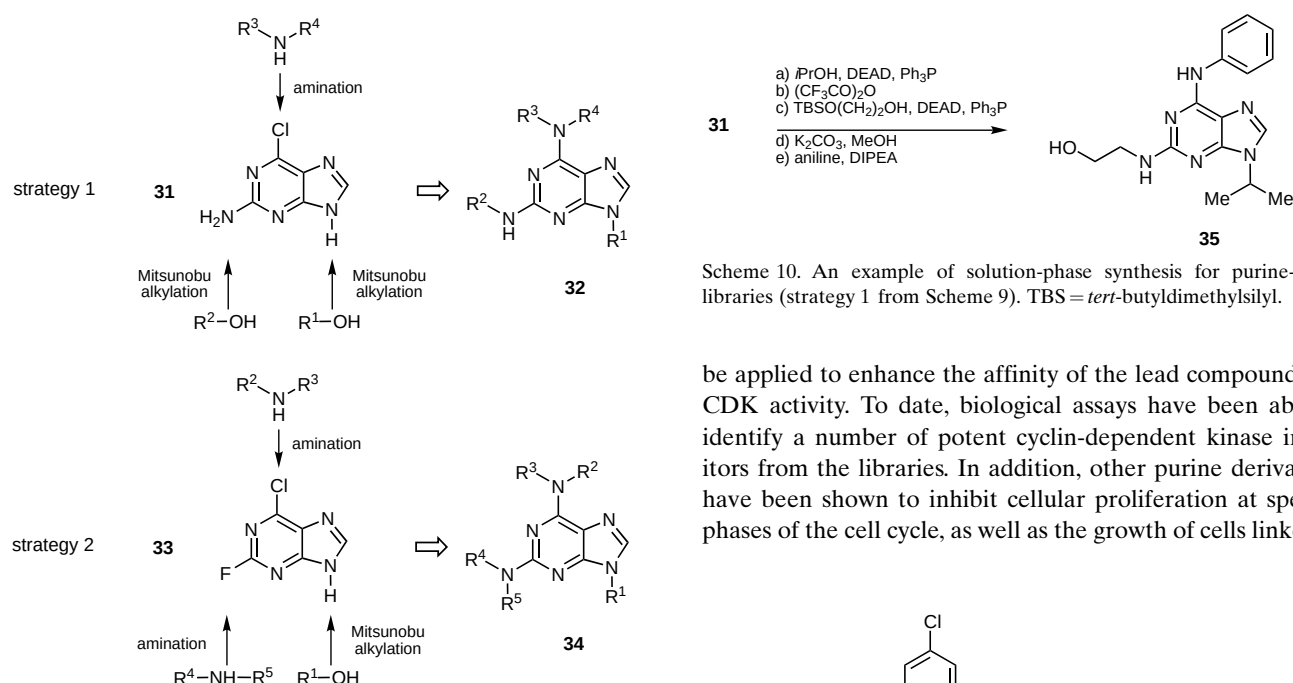


Scheme 7. A combination of solid- and solution-phase chemistry utilized by Schultz et al.

phase synthesis involves the reductive amination of 2,3-dithiol-1-propanol derivatized 4-methylbenzhydrylamine (MBHA) with various primary amines to give resin-bound amines.^[11c] The amines are then reacted with compound **26**, to achieve combinatorial diversity at the C6 position. Mitsunobu and amination chemistry are then applied for further functionalization at the N9 and C2 positions. Scheme 8 illustrates an example of this type of approach. Like the previous strategy, this approach also suffers from two key set backs: 1) direct introduction of a secondary amine at the C6 position is not possible, and 2) amination with bulky groups at the C2 position occurs slowly and in low yields. Schultz and co-workers tackled these difficulties with two new solution-phase strategies, allowing diversification of the trisubstituted purine libraries shown in Scheme 9.^[13]



Scheme 8. Multistep solid-phase synthesis of purine-based small-molecule libraries, developed by Schultz et al. TBAF = tetrabutylammonium fluoride, DEAD = diethylazodicarboxylate, NMP = *N*-methylpyrrolidine, TFA = trifluoroacetic acid.

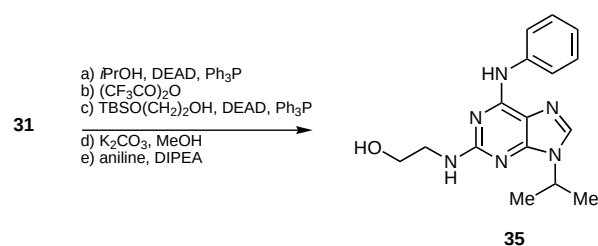


Scheme 9. Solution-phase strategies for the synthesis of purine-based libraries.

The strategies involved the use of 2-amino-6-chloropurine (**31**) and 2-fluoro-6-chloropurine (**33**). Compound **33** can be easily synthesized from commercially available **31**.^[11b] In strategy 1 (Scheme 10), **31** was functionalized in a step-wise fashion at the N9, C2, and C6 positions. Mitsunobu chemistry using primary and secondary alcohols allows the introduction of various substituents at the N9 position. The amino group at the C2 position was acylated with trifluoroacetic anhydride in order for Mitsunobu alkylation to occur efficiently. Lastly, intro-

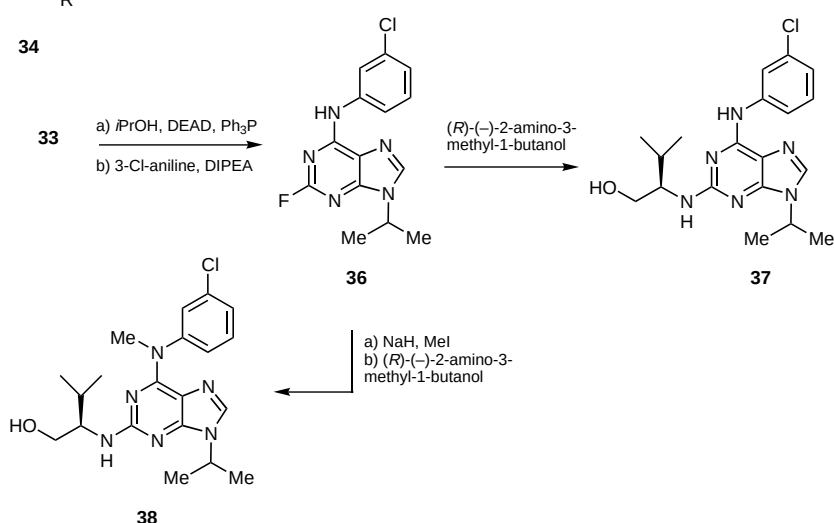
duction of various amine derivatives at the C6 position was accomplished in the presence of *n*-butanol at elevated temperatures (see, for example, compound **35**). Strategy 2 is different from strategy 1 in the order of substitution at various positions, but the main chemistry for both strategies is virtually identical. An example of solution chemistry using this strategy is shown in Scheme 11.

Using a combination of solution/solid-phase approaches, several purine libraries containing hundreds to thousands of purine analogues with structural diversity at the C2, C6, and N9 positions were synthesized. Iterative synthesis can later



Scheme 10. An example of solution-phase synthesis for purine-based libraries (strategy 1 from Scheme 9). TBS = *tert*-butyldimethylsilyl.

be applied to enhance the affinity of the lead compounds for CDK activity. To date, biological assays have been able to identify a number of potent cyclin-dependent kinase inhibitors from the libraries. In addition, other purine derivatives have been shown to inhibit cellular proliferation at specific phases of the cell cycle, as well as the growth of cells linked to

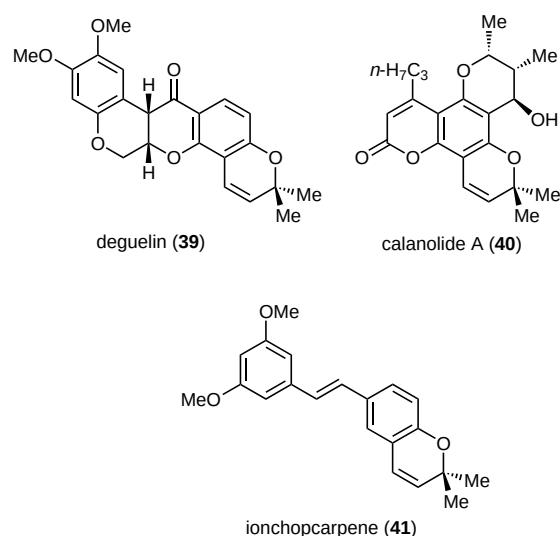


Scheme 11. An example of solution-phase synthesis for purine-based libraries (strategy 2 from Scheme 9).

specific tumors.^[13] Schultz and co-workers have recently isolated, from the purine-based libraries, a compound named myoseverin which has the capability to induce the reversible fission of myotubes (muscle cells) into mononucleated fragments.^[14] This finding has implications in the process of tissue regeneration and wound healing.

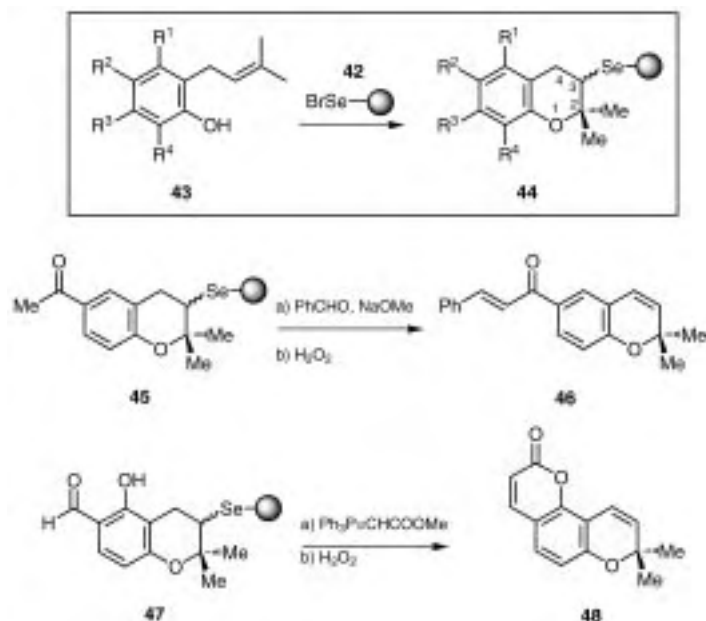
More recently, Bertozzi and co-workers^[15] utilized kinase-based libraries to select for carbohydrate sulfotransferases inhibitors given that both enzymes use a similar substrate. Surprisingly, several purine derivatives were identified as lead compounds with an IC_{50} value of 20–40 μM . These initial compounds will serve as templates for the design of future libraries with greater affinity for carbohydrate sulfotransferase enzymes.

Nicolaou and co-workers are actively involved in the area of solid-phase synthesis leading to natural product like, small-molecule libraries. Recently, they reported a solid-phase selenide resin and its application for the synthesis of benzopyran derivatives.^[16] Several natural products, such as flavonoids, coumarins, rotenoids, stilbenoids, and chromene glycosides contain the dimethylbenzopyran moiety as a part of their core structure. Some representative examples are shown in Scheme 12. A high-throughput synthesis of their



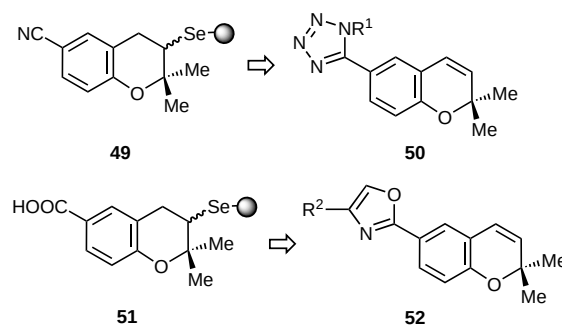
Scheme 12. Examples of dimethylbenzopyran-based natural products.

derivatives could provide interesting lead compounds with a broad spectrum of biological properties. A key step in the approach of Nicolaou et al. is the synthesis of the selenenyl bromide resin, **42** (Scheme 13) prepared from commercially available polystyrene resin. Lithiation, followed by treatment with dimethyl selenide gave the methyl selenide resin. This was then converted into bromide derivative **42** on treatment with bromine. Resin **42** reacted with compound **43** to give the selenyl benzopyran derivative **44**. Under oxidative work-up (33% H_2O_2), it was possible to cleave the benzopyran moiety from the resin with the introduction of the double bond between the C3 and C4 positions. The methodology is highly versatile and could be applied to a variety of substrates bearing different functional groups on the aromatic ring of the



Scheme 13. Nicolaou et al.'s selenide resin based approach for the synthesis of dimethylbenzopyrans.

benzopyran moiety. For example, compound **45** could undergo an enol ether based aldol reaction followed by oxidative work-up to give compound **46** in high yield. Similarly, the selenide resin bound benzopyran derivative **47** could react under Wittig conditions to yield the coumarin derivative **48** after the oxidative work-up. Nicolaou and co-workers have further shown that functional groups from the benzopyran selenide moiety anchored onto a solid support could be converted into useful derivatives. For example, cyano derivative **49** (Scheme 14) was converted into the corresponding

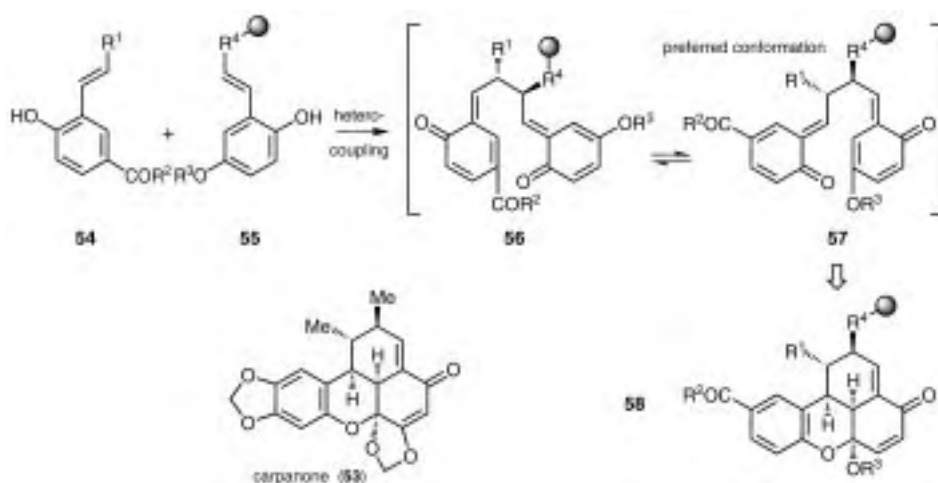


Scheme 14. Examples of functional-group transformation in selenide resin based dimethylbenzopyrans.

tetrazole derivative in a few steps that involve reaction with azidotrimethyl tin followed by N-SnMe_3 cleavage under trifluoroacetic acid (TFA) conditions. In a similar manner, oxazole derivative **52** was obtained from compound **50** in a number of steps. In general, these transformations are high yielding and provide a useful entry to the synthesis of biologically relevant, natural product like compounds. Following success with the use of selenium-based resin for the synthesis of dimethylbenzopyrans, a solid-phase synthesis of indoline-like compounds was also accomplished using sele-

nium chemistry.^[16c] The approaches developed by Nicolaou and co-workers are simple, highly efficient, and could be utilized for obtaining a variety of dimethylbenzopyran- and indole-based small-molecule libraries.

Shair and co-workers are developing solid-phase approaches for the synthesis of natural product like compounds that mimic biosynthetic pathways.^[17] Biomimetic synthesis often requires the use of simple organic precursors and mild reaction conditions. Shair et al. planned to utilize biomimetic-type reactions on the solid phase that could further be combined with the mix and split technology for library synthesis. Carpanone (**53**, Scheme 15), a natural product from the benzoxanthene family, was selected for study. The biomimetic synthesis of carpanone was achieved by Chapman in 1971 and involves a stereoselective, oxidative coupling followed by an intramolecular Diels–Alder reaction.^[18]



Scheme 15. Shair et al.'s biomimetic approach for the synthesis of benzoxanthene-based natural product like compounds.

Following the biomimetic synthesis of carpanone, Shair and co-workers utilized a hetero-coupling reaction followed by an intramolecular Diels–Alder reaction on the solid phase.^[17] The plan was to use two different hydroxystyrenes **54** and **55**, which differ in their electronic configuration. Electron-rich styrene derivative **55** was anchored onto a solid support to avoid any homodimerization. Several oxidizing agents were then tried, to study the cross-coupling reaction, and the use of $\text{PhI}(\text{OAc})_2$ afforded the desired heterocoupled product **58** on the solid phase. It was interesting to note that only a single isomer was detected after cleavage of the product from the support, and the cycloaddition reaction proceeded with a remarkable stereoselectivity. Several examples were tried using this method, and tetracyclic benzoxanthene derivatives were isolated in respectable yields after cleavage from the support. This is the first example in which a biomimetic synthesis has been successfully transferred onto the solid phase. The approach presented by Shair and co-workers is highly unique and it could lead to the library synthesis of structurally complex and diverse natural product like compounds, which would allow exploration of their applications in genomics and proteomics research.

To summarize, in recent years, several interesting approaches leading to the synthesis of structurally complex and diverse compounds have appeared in the literature. Collectively, these methods allow the synthesis of a variety of natural product like compounds in a high-throughput manner. If the last century was the era of focused stereoselective organic synthesis, in the coming years diversity-based organic synthesis will play an important role in understanding the function of biological targets which are emerging from the growing efforts in genomics and proteomics research.

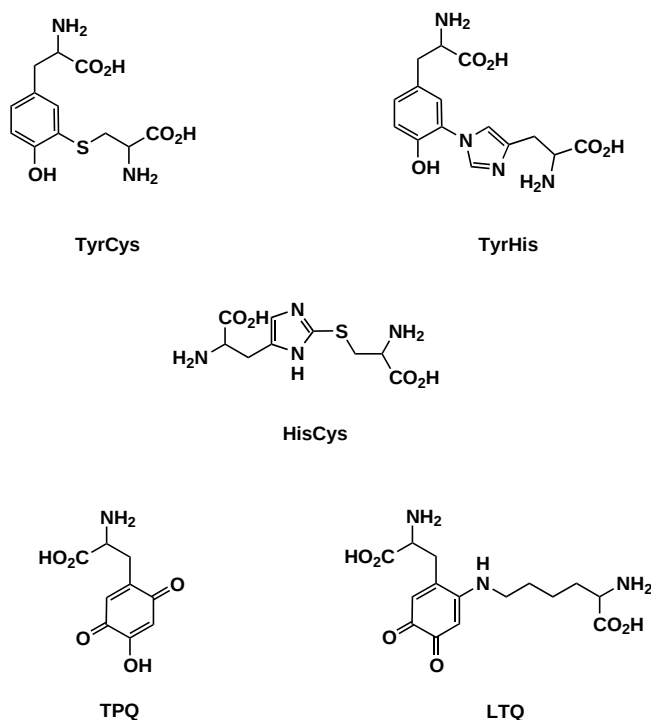
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Chemically Modified Amino Acids in Copper Proteins That Bind or Activate Dioxygen**

Malcolm A. Halcrow*

It is an interesting observation that four of the six classes of copper oxidase or monooxygenase enzymes whose structures are known^[1–3] contain a chemically modified amino acid either ligated to, or in close proximity to, the active-site copper center. Some of these unusual residues, namely the TyrCys, HisCys, and TyrHis moieties, are derived from a cross-linking reaction between two amino acid side chains. Alternatively, the 2,4,5-trihydroxyphenylalaninequinone (topaquinone, TPQ) and lysyl tyrosyl quinone (LTQ) cofactors are generated by monooxygenation of a tyrosine side chain, followed by



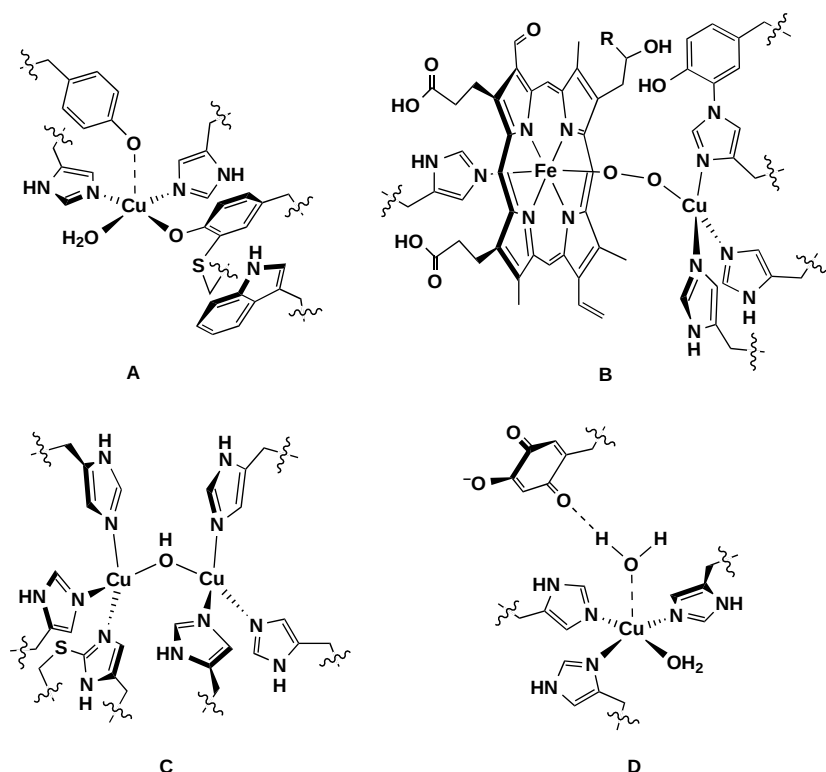
nucleophilic attack at the resultant *ortho*-quinone. The HisCys,^[4] TyrCys,^[5] and TPQ^[6] residues were first detected in their respective proteins between nine and eighteen years ago. However, our understanding of the functional roles of these and the other, more recently discovered,^[7, 8] residues is often still rather limited. Attention has also now begun to focus on the biosynthesis of these cofactors, which in many cases must involve unusual organic transformations that have not been previously characterized in copper biochemistry.

The cross-linked amino acid whose function is best understood is the TyrCys residue found in radical copper oxidases, of which galactose oxidase (GO) is the prototype.^[1] This side chain acts as a ligand to a monocopper center in the enzymatic active site (Scheme 1 A),^[5] and is oxidized to a [TyrCys][•] radical in the active resting enzyme; this phenoxyl radical abstracts a hydrogen atom from the alcohol substrate during turnover.^[1] The oxidation potential of the TyrCys moiety is 0.5 V less positive than would be expected for an unmodified tyrosine residue.^[9] Consistent with this, several model studies have shown that *ortho*-sulfide substitution of a free or coordinated phenoxide will lower its oxidation potential by 250–500 mV.^[10] However, recent calculations have shown that the S atom of an *ortho* sulfide substituted phenoxyl group only accepts up to 15% of the radical unpaired spin, and does not significantly perturb the spin distribution over the rest of the molecule.^[11] In addition, it has also been calculated that the O–H homolytic bond dissociation energy (BDE) of an *ortho* sulfide substituted phenol is identical, to within 2 kcal mol^{–1}, to that of an otherwise identical phenol lacking this substituent.^[12] Hence, the electronic structure of the [TyrCys][•] radical of GO and its reactivity towards H-atom donors are not significantly perturbed by the sulfide substituent, and it appears that the function of this cross-link is purely to lower the oxidation potential of the oxidizable tyrosine ring.

Less is known about the other cross-linked amino acids. The TyrHis cross-link in cytochrome *c* oxidase (CcO) forms part of the heme/copper site of this enzyme (Scheme 1 B),^[7] which catalyzes the reduction of dioxygen to water.^[3] The currently favored mechanism for this reaction implies that 4-electron reduction of O₂ by CcO occurs in one mechanistic step,^[13] and it is thought that the TyrHis residue acts as both as a Brønsted

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Scheme 1. Molecular structures of the active sites of copper oxidases containing modified amino acid residues: A) galactose oxidase;^[5] B) catechol oxidase;^[16] C) the O₂ reduction site of cytochrome c oxidase;^[7] D) copper-containing amine oxidase.^[19–21]

base, and as an H-atom donor to the substrate dioxygen molecule, during this process.^[14] However, a model study has shown that the imidazol-1-yl substituent should lower the oxidation potential of the TyrHis side chain by <100 mV, while barely perturbing its O–H homolytic BDE.^[15] Hence, it is unclear how the TyrHis cross-link should benefit the radical chemistry that this residue is believed to undergo.

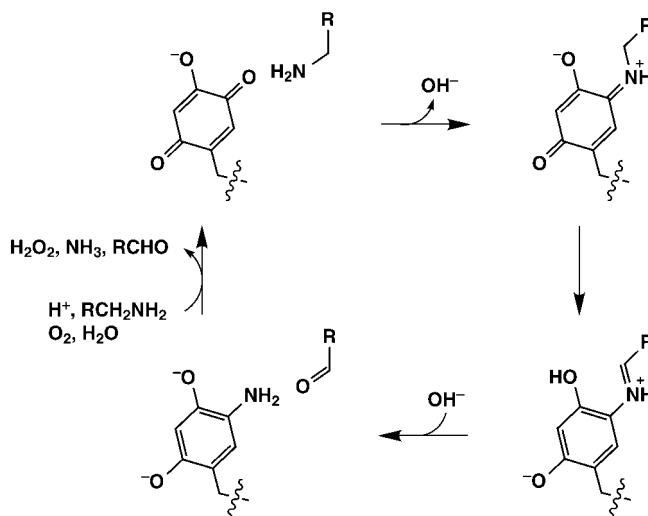
The HisCys side chain is a ligand to many type 3 copper biosites,^[2] and has been crystallographically characterized in a catechol oxidase and a molluscan hemocyanin (Scheme 1C).^[16] There are no model studies relevant to the properties of the HisCys residue, which is *not* oxidized during substrate binding or catalytic turnover by these proteins.^[2] However, since other hemocyanins are known that do not contain a cross-linked histidine side chain,^[17] it has been suggested that the HisCys cross-link serves merely to increase the conformational rigidity of the coordinated Cu ion in these proteins.^[16]

As yet, the biosynthesis of the cross-linked amino acids has been little studied. It has recently been reported that freshly prepared GO is secreted into the medium as a copper-free proprotein, which lacks the TyrCys cross-link and bears a 17-mer N-terminal extension, which is cleaved off during maturation of the polypeptide.^[18] Formation of the TyrCys residue is a self-processing event, which is dependent upon both copper and O₂.^[18] Addition of CuSO₄ to pro-GO initially affords a species showing a Tyr → Cu ligand to metal charge transfer (LMCT) band at 410 nm and a *d–d* absorption at 750 nm,^[18] which can be attributed to a tetragonal Cu^{II}/

tyrosinate species, in which presumably the TyrCys cross-link has not yet formed. Over a period of one hour, this initial species is aerobically converted into active oxidized GO with no observable intermediate at 298 K. Further details of how this is achieved are unknown, however.

Unlike the TyrCys, HisCys, or TyrHis residues, the TPQ cofactor in active copper-containing amine oxidase (CAO) is not directly coordinated to the copper ion in the active enzyme, but lies approximately 5 Å from a [Cu(His)₃(H₂O)_x] (*x* = 1, 2) center (Scheme 1D).^[19–21] The TPQ ring is the site of substrate oxidation, which occurs by a well-understood transamination mechanism involving nucleophilic attack of the substrate amine at the TPQ C-5 carbonyl group, followed by isomerisation and hydrolysis of the resultant Schiff base (Scheme 2).^[1] The reduced amino quinol cofactor is then reoxidized by molecular oxygen, possibly with the involvement of electron transfer to the copper ion although this has not been conclusively demonstrated.

As in GO, the synthesis of the TPQ cofactor in CAO^[22] is a self-processing



Scheme 2. Mechanism of amine oxidation by the TPQ cofactor in copper-containing amine oxidase.^[1]

event and occurs according to the stoichiometry shown in Equation (1).^[23] Aerobic incubation of pro-CAO with Cu^{II}



initially yields two species, which show Tyr → Cu LMCT absorptions at 350 and 380 nm and decay at similar rates.^[24] There are several lines of evidence to suggest that the 380 nm species contains Cu^{II} complexed to amino acids outside the active site, and is irrelevant to cofactor synthesis.^[24] However,

formation of TPQ from the 350 nm intermediate occurs with first-order kinetics,^[24] with concomitant uptake of an equimolar amount of O₂.^[26] The initial reaction of the 350 nm intermediate with O₂ is the rate-limiting step in TPQ synthesis, and does not involve proton transfer.^[26]

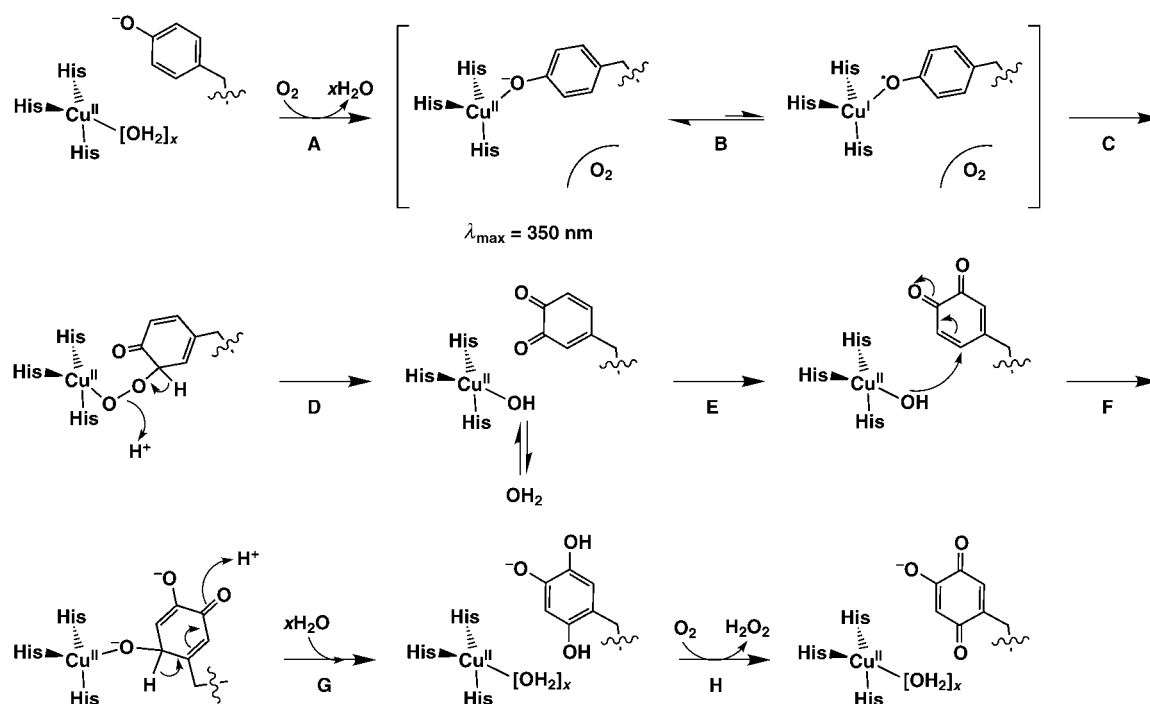
The 350 nm intermediate in TPQ biogenesis is thought to contain a tetrahedral [Cu(His)₃(Tyr)] active-site complex.^[24] Consistent with this, a single crystal structure of an unprocessed bacterial CAO containing zinc instead of copper, shows an isoelectronic tetrahedral [Zn(His)₃(Tyr)]⁺ center, with an unmodified tyrosine cofactor residue ligated to the Zn ion.^[27] Interestingly, the 350 nm species is not obtained if pro-CAO is incubated with Cu anaerobically, although O₂ is not consumed during its aerobic formation.^[24] Since there is no evidence for a Cu–O₂ bond in this species, it was suggested that there must be a separate dioxygen binding site remote from the Cu ion, and that occupation of this site induces a conformational change to force the Tyr residue to coordinate.

On the basis of these measurements, the mechanism shown in Scheme 3 was proposed for TPQ biogenesis.^[26] This mechanism can be considered in two stages: monooxygenation of tyrosine to form 3,4-dihydroxyphenylalanine quinone (DPQ; steps A–D); and hydroxylation and oxidation of the resultant quinone (steps E–H). Chemical precedent has very recently been published for step B of the monooxygenation pathway, namely intramolecular electron transfer with a Cu^{II}/phenoxide complex to yield a Cu^I/phenoxyl species.^[28] The tyrosyl radical thus formed must then be displaced from the Cu ion to allow O₂ to bind to the Cu center (step C). The resultant arylperoxo complex intermediate has no precedent in copper/oxygen chemistry, but is reminiscent of the initial hydroxylation step effected by monoiron centers in catechol dioxygenases.^[29] This species is also structurally similar to the crystallographically characterized substrate–reduced-CAO/

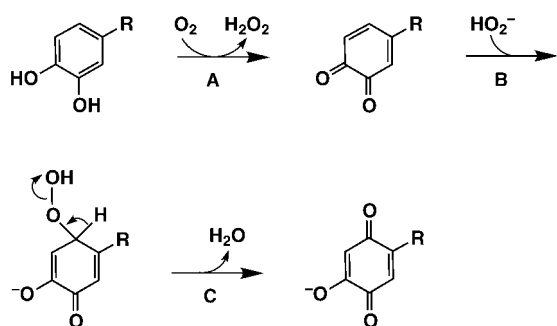
O₂ turnover complex, which shows a monodentate dioxygen species bridging between the Cu ion and cofactor ring.^[21] Hence, the putative arylperoxo complex in Scheme 3 should be sterically feasible within the CAO active site.

A resonance Raman study has shown that the O atom at the C-2 position in TPQ is derived from H₂O rather than O₂.^[30] Since model experiments have shown that aqueous 1,4-hydrolysis of DPQ does not take place at neutral pH values,^[31, 32] a water molecule inside the CAO active site would be insufficiently basic to attack the DPQ ring. However, coordination to a Lewis acidic Cu^{II} ion may well make the water nucleophile acidic enough to be deprotonated and react as shown in step F of Scheme 3. It is noteworthy, however, that rotation of the DPQ ring by approximately 180° about its methylene substituent (step E of Scheme 3) would be necessary to allow a Cu-bound nucleophile to attack both the C-2 and C-5 positions of the precursor tyrosine side chain, as is proposed at different stages of this mechanism. Moreover, steps E and F together must be slow compared to exchange of the Cu-bound hydroxide ion with exogenous water, to permit incorporation of a water-derived O atom into the final product.

There are no known examples of phenol monooxygenation by synthetic mononuclear copper complexes. However, steps F–H of Scheme 3 have been modeled by the aqueous autooxidation of 4-alkylcatechols to 2-alkyl-5-hydroxybenzoquinones (Scheme 4). This occurs slowly under ambient conditions, but is catalyzed by Cu^{II} ions.^[32, 33] The catalyst substantially increases the rate of oxidation of the catechol precursor (step A in Scheme 4),^[32, 33] but does not appear to influence other steps in the reaction.^[32] The rate of conversion of the *ortho*-quinones into the hydroxybenzoquinones (steps B and C in Scheme 4) is increased at higher pH values but is not accelerated in the presence of Cu^{II} salts. By analogy



Scheme 3. The mechanism for TPQ biogenesis proposed by Klinman et al.^[26]



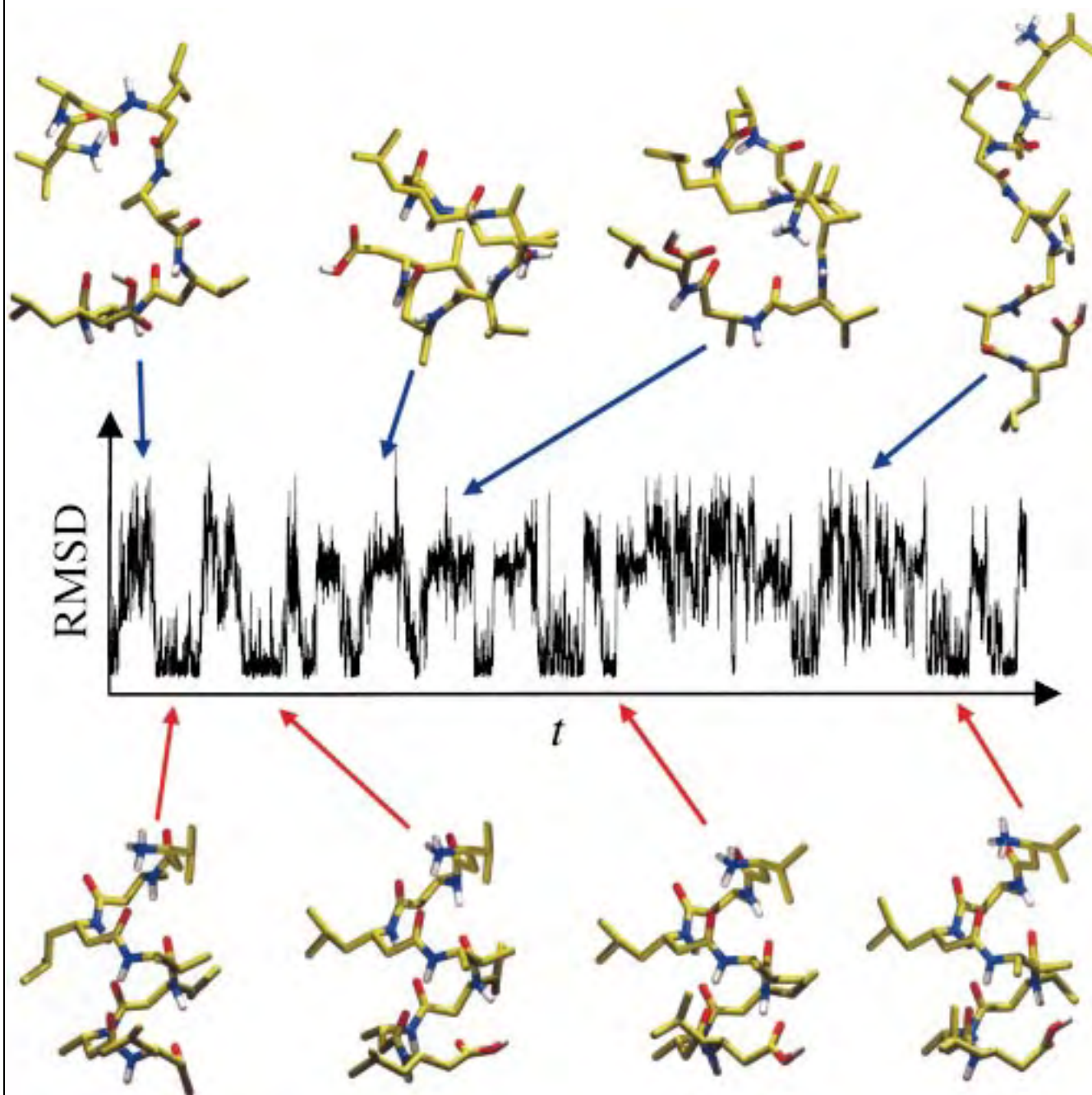
Scheme 4. Mechanism of aerobic catechol autooxidation in vitro.^[34]

with the mechanism in Scheme 3, this was taken to show that the active nucleophile in this reaction is a free, rather than Cu-bound, hydroxide ion.^[32] However, it has recently been demonstrated that, under these conditions, the O atom at the C-2 position is, in fact, derived by conjugate addition of H_2O_2 , which is produced as a by-product of catechol oxidation (Scheme 4).^[34] The preference for nucleophilic attack of HO_2^- rather than OH^- in vitro can be attributed to the lower pK_a of H_2O_2 compared to H_2O .

These results mean that the local environment of the CAO active site has changed the chemistry of *ortho*-quinone hydration from that observed in vitro. This precedent makes it difficult to predict what the detailed synthetic mechanisms for the biosynthesis of the TyrCys, HisCys, or TyrHis moieties might be. Close analogues of all three of these cross-linking reactions have been achieved synthetically, albeit by methods that are unlikely to be biochemically relevant.^[15, 35] Hence, it will be intriguing to see how nature has evolved pathways to couple nucleophilic phenol or imidazole rings, with thiol or imidazole centers that are not electrophiles, under aerobic ambient conditions.

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A 200 ns long simulation of the reversible folding of a β amino acid heptapeptide



The upper series of structures show “snap shots” of the various unfolded conformations at different time points of the simulation, as indicated by the blue arrows. The lower series shows the folded states (red arrows).

The helical conformations that are repeatedly occupied are also evident from the change in the root-mean-square deviation (RMSD) of the backbone atom positions during the simulation of the model structure based on the NMR experiments.

Find out more on the following pages.

The Key to Solving the Protein-Folding Problem Lies in an Accurate Description of the Denatured State**

Wilfred F. van Gunsteren,* Roland Bürgi, Christine Peter, and Xavier Daura

The prediction of the folding process of a protein (that is, its most stable conformer, the relative stability of the different accessible conformations, and the kinetics of folding) as a function of temperature and protein environment (that is, the solvent composition) is one of the fundamental long-standing challenges of molecular biology.^[1, 2] It is still unsolved due to the enormous size of the conformational space of a protein on the one hand, and the relatively small energetic differences between native and denatured conformations on the other.^[3] Looking at three possible conformers per backbone ϕ or ψ angle in an amino acid residue, a 10-residue peptide has about $3^{20} \cong 10^9$ conformers available, a 100-residue protein has about 10^{90} . The conformational space available to a polypeptide grows exponentially with its length, leaving no hope to computationally sample all conformers. Nature does not sample all conformations in the folding process either, but restricts herself to a subset, which forms a folding pathway. These pathways are very difficult, if not impossible, to elucidate experimentally at the atomic level.^[2, 4] Using the ever-increasing power of computers it has become possible to simulate the reversible folding of small peptides.^[5–7] Analysis of the thermodynamic equilibria between folded and unfolded conformers shows that the unfolded or denatured state comprises a relatively low number of conformers,^[8] which does not grow exponentially with the length of the peptide. The simulation of these folding/unfolding equilibria requires not only an accurate description of the folded state but also, most importantly, of the denatured state in order to obtain the correct relative populations of folded and unfolded conformations and their transition rates.

The most stable fold of a protein depends on its amino acid composition, solvent environment (composition, pH value), and thermodynamic state (temperature, pressure). Interactions at the atomic level determine the equilibrium between folded and unfolded conformers. Computer simulation of the statistical mechanical ensemble could be used to calculate the folded/unfolded equilibrium, molecular dynamics (MD) simulation could yield the kinetics of the folding process. However, in view of the huge number of conformations that in principle constitute the denatured state, MD simulation in atomic detail of the folding/unfolding equilibrium was considered to be out of computational reach.^[9] In folding studies, the molecular models used were of a simple nature: one interaction site per residue,^[9, 10] a neglect^[9–12] or a mean-field approximation^[13] of the solvent degrees of freedom, motion

restricted to lattice sites,^[14] etc. Often, force-field parameters were tuned to favor a (particular) fold,^[10, 11] or a particular folding pathway was postulated.^[15]

These studies gave insight into possible folding mechanisms, but could not tell which one corresponds to reality,^[16] due to the simplicity and bias of the models used. On the other hand, protein structure prediction studies^[17] concentrate on predicting the correct, most stable fold, without considering the folding/unfolding equilibrium or kinetics, and disregarding the dependence of the fold on temperature and solvent environment.

Here, we wish to approach the folding problem from a different point of view. Analyzing dynamic simulations of the reversible folding of peptides of different compositions, in various solvents and at different temperatures, into different secondary structure elements or folds, we show that the denatured state of these peptides comprises vastly less conformations than one would think based on the number of conformational degrees of freedom present. For a peptide with about 20 rotatable bonds the denatured state can be characterized by about 10^2 – 10^3 conformers. This small size of the denatured state explains why these peptides fold on a nanosecond time scale.

Extending the argument to proteins which fold on a millisecond time scale, their denatured state will extend over say 10^9 conformers, vastly smaller than the 10^{90} quoted earlier. This makes simulation of protein folding at the atomic level amenable in the near future, provided a force field is available that characterizes the denatured state sufficiently accurately. If the denatured state is wrongly described, one can have no hope of stimulating the correct equilibrium. From this point of view, it does not help to base the force field on a statistical analysis of folded structures; an accurate description of the denatured state is also required. Due to the lack of experimental information regarding the denatured state, the only way is to base the force field on physical principles: the

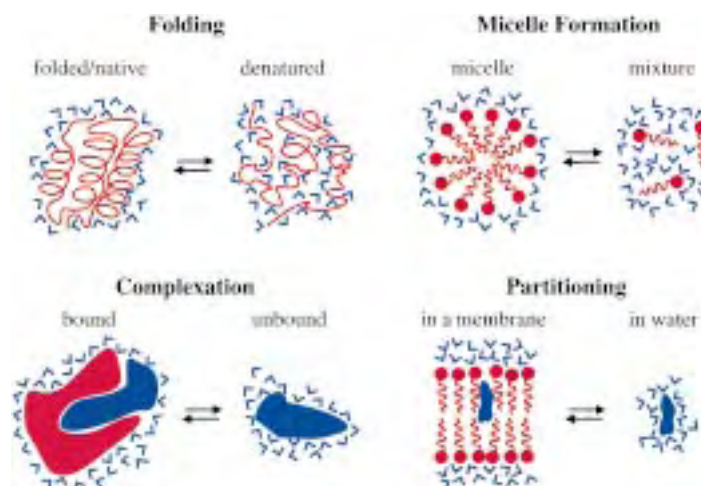


Figure 1. Thermodynamic equilibria that govern key processes in molecular biology. In order to simulate on a computer the correct distribution of, and kinetics between the molecular configurations shown, the general biomolecular force field describing the interatomic interactions^[19] has been calibrated against experimental physico-chemical partitioning data regarding small polar and nonpolar molecules in the condensed phase. Red: protein or lipid molecules. Blue: water molecules or ligand molecules (solid areas) binding to a protein or permeating through a lipid membrane.

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interaction between atoms and molecules in the condensed phase. Here we show that a general atomic-level biomolecular force field whose parameters have been set based on experimental hydrophilic/hydrophobic partitioning data for small molecules in the condensed phase, is able to accurately and reversibly fold a number of peptides into a variety of native folds, and this is not dependent of the starting structure used in the simulations.

Figure 1 illustrates the various thermodynamic equilibria one would like to simulate using a general biomolecular force field.^[18] One of the key factors in these equilibria is the relative strength of polar–polar, polar–nonpolar, and nonpolar–nonpolar interactions. In the GRO-MOS96 force field used,^[19] the nonbonded interaction parameters have been calibrated with solute/solvent partitioning data. The six different peptides studied are shown in Figure 2 with their most stable fold as determined by experiment. The major parameters describing the six systems and simulations are given in Table 1. A successful simulation study of peptide folding would involve the following results:

1. The folded structure should be within a given structural difference from the experimental model structure.
2. The folding should be reversible, more than one folding event should be observed.
3. The distribution of folded versus unfolded conformers in the ensemble should be correct, for example, the free energy of folding ΔG_{fold} and melting temperature T_{m} should be correct.
4. The rate or kinetics of folding should be correct.
5. All this should be achieved using one general force field for a variety of peptides, solvents, and folds.

Figures 2 and 3, and Table 1 show that the six peptides are

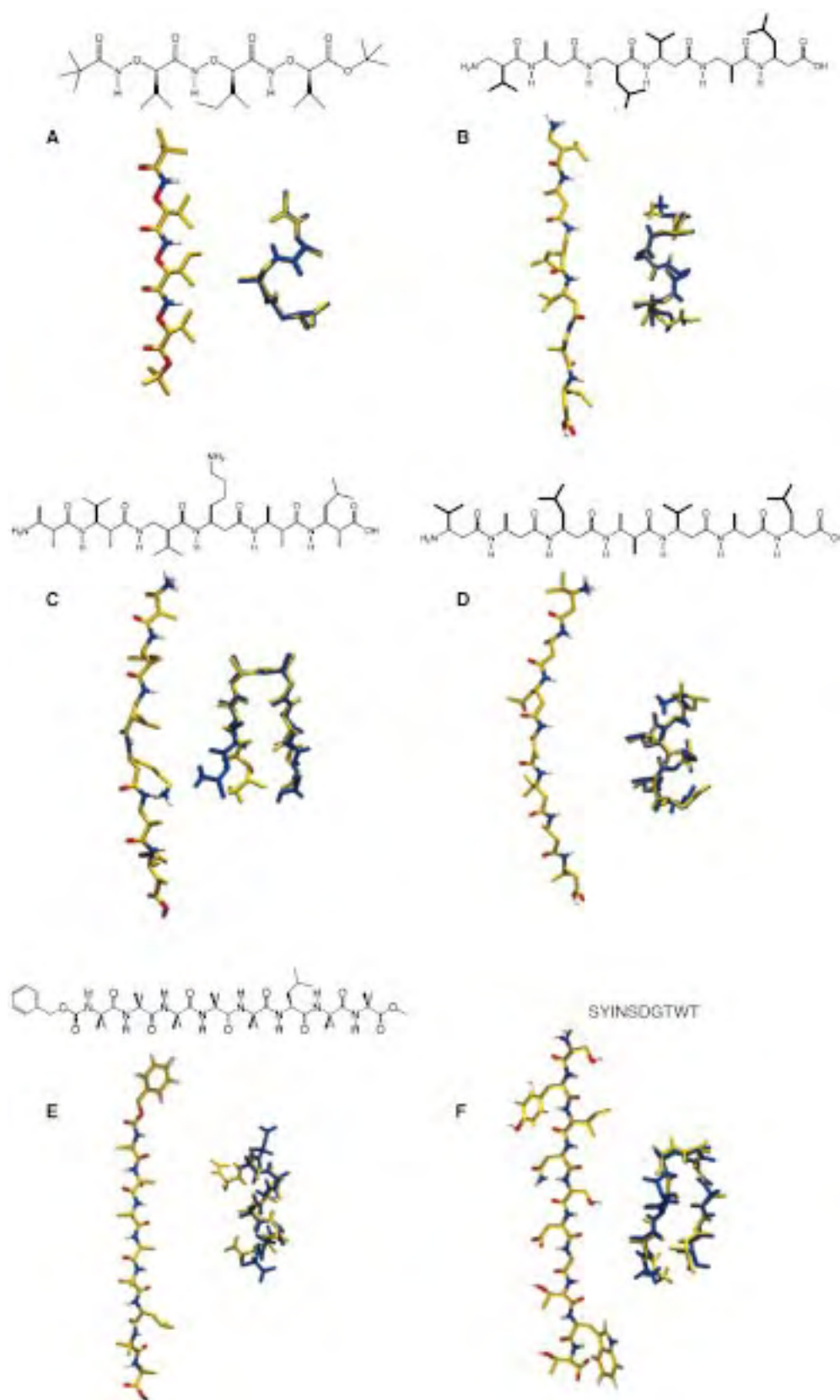


Figure 2. Folding of peptides into different folds. For each of the six different peptides (see Table 1) the following is shown: the chemical formula, an extended structure used as the initial configuration in the MD simulations, a folded structure (yellow) modeled on the available NMR experimental data, and, superimposed on the latter, a folded structure (blue) from the MD simulations of the folding/unfolding equilibrium. For the eight-residue α -amino acid peptide E, both the experiments and the simulation indicate the presence of roughly equally populated conformers (*M* and *P*, α and 3_{10} helices), of which one only is shown.

Table 1. Reversible folding of six peptides.^[a]

System	A	B	C	D	E	F
type of peptide	α -aminoxy		β -amino		α -amino	
stable structure (expt)	helix	helix	hairpin	helix	helix	β -hairpin
type of structure	P-1.8 ₈	P-12/10	10-member turn	M-3 ₁₄	M,P, α ,3 ₁₀	3:5
type of solvent	CHCl ₃	MeOH	MeOH	MeOH	DMSO	H ₂ O
Simulation parameters						
no. of residues	3	6	6	7	8	10
no. of peptide atoms	39	56	64	64	75	110
no. of solvent molecules	672	1435	1453	962	1119	4585
no. of atoms in the system	3399	4361	4423	2950	4551	13865
backbone torsional degrees of freedom	9	18	18	21	16	20
temperature T [K]	340	340	340	340	340	353
simulation length [ns]	72	50	100	200	150	32
Simulated folding process						
folded structure (sim.)	helix	helix	hairpin	helix	helix	β -hairpin
	P-1.8 ₈	P-12/10	10-member turn	M-3 ₁₄	M,P, α ,3 ₁₀	3:5
RMSD between folded structure and experimental model [nm]	0.01	0.01	0.03	0.01	0.03	0.06
RMSD between extended conformation and experimental model [nm]	0.20	0.36	0.40	0.52	0.32	0.70
RMSD criterion folded/unfolded [nm]	0.07	0.08	0.08	0.10	0.10	0.12
no. of unfolded conformers	148	129	286	360	344	57
no. of folding events	40	6	15	23	9	2
estimated free energy of folding ΔG_{fold} [kJ mol ⁻¹]	5	5	6	2	11	14
estimated melting temperature T_m [K]	330 $\pm$ 20	–	–	330 $\pm$ 10	320 $\pm$ 10	–

[a] The upper part of the table shows the type of peptide, the most stable conformation (as determined by NMR experiments; see also Figure 2) and the solvent used in both experiment and simulation. The middle part of the table shows the most important simulation parameters characterizing the different systems. The number of peptide conformational degrees of freedom is indicated by the number of backbone rotatable (i.e. nonpeptidic) torsional angles. Although each peptide was simulated at various temperatures, only results for one temperature (close to the melting temperature of the fold) per peptide are shown. More data can be found in ref. [21] for the α -aminoxy acid peptide, in ref. [6, 22] for the six-residue β -amino acid peptides, in ref. [5] for the seven-residue β -amino acid peptide, in ref. [23] for the eight-residue α -amino acid peptide, and in ref. [24] for the ten-residue α -amino acid peptide. The lower part of the table shows the results of the simulations: the most stable conformation, its backbone atom-positional RMSD value with respect to the experimental NMR model structure, the backbone atom-positional RMSD value of an extended structure from the NMR model structure, the backbone atom-positional RMSD value that is used to distinguish correctly folded conformations from unfolded conformations, the number of unfolded conformations, which form the denatured state of the peptide, the number of (un)folding events (see also Figure 3), very rough estimates of the free energy of folding, ΔG_{fold} , determined by the ratio of folded versus unfolded conformations, and, when sufficient data is available, the melting temperature of the peptide, T_m (defined by a 1:1 ratio of folded and unfolded conformations).

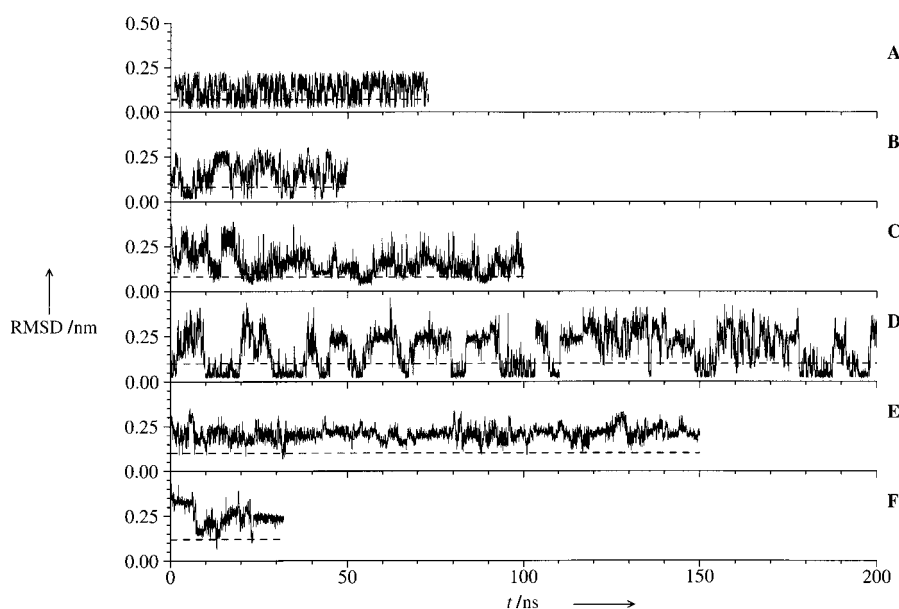


Figure 3. Dynamics of the reversible folding of peptides. For each of the six different peptides (see Table 1 and Figure 2) the backbone atom-positional RMSD of the simulated structures from the experimentally derived NMR model structure is shown as a function of time. Except for the α -aminoxy acid tripeptide A, the atoms of the first and last residues of the peptide chains were excluded when performing the translational and rotational superposition of the structures and when calculating the RMSD values. The dashed horizontal lines indicate the maximum RMSD value which serves as the criterion to identify correctly folded structures.

reversibly folding into the correct fold, with the backbone atom-positional root-mean-square deviations (RMSD) from the NMR-based experimental model structures being smaller than 0.06 nm. No reliable experimental data, either on ΔG_{fold} as function of temperature and on T_m , or on rates of folding, are available for comparison.

Two results stand out in Table 1. The force field used is able to accurately predict the most stable type of secondary structure as function of peptide composition and solvent type. Secondly, the number of different conformers making up the denatured (unfolded) state is very, very low. This leads to the following conclusions. The denatured state of peptides is much smaller than expected, only a tiny fraction of the possible conformers is populated in the temperature range between 300 and 360 K. This implies that it is possible to simulate the equilibrium between folded and

denatured states, given a force field that accurately describes the characteristics of this limited denatured state. Study of only folded states^[20] will be insufficient to solve the folding problem. The key to solving the protein folding problem lies rather in a good understanding of the denatured state.

Methods

The MD simulations were carried out using the GROMOS96 program^[18] and the force field 43A1.^[19] Aliphatic CH_n groups were treated as united atoms, both in the peptides and the solvents. Periodic boundary conditions were applied in a rectangular or truncated octahedron box. The nonbonded interactions were cutoff at a distance of 1.4 nm, and a Poisson–Boltzmann reaction field force was used to approximate electrostatic interactions beyond the cutoff in water, DMSO, and chloroform. Bond lengths in both peptides and solvents and bond angles in the solvent molecules were kept fixed. The integration time step was 2 fs and systems were kept at constant temperature and pressure (1 atm) by weak coupling to temperature and pressure baths.

The results of the simulations are independent of the various initial structures used because of the relatively long lengths of the simulations. The trajectory structures (at 0.01 ns intervals) of the peptides were clustered into conformations as follows:^[8] The number of neighbors (that is, the number of structures satisfying the similarity criterion) was determined for each trajectory structure, with the criterion of similarity between two structures being the positional RMSD value of their main chain atoms. The structure with the highest number of neighbors was then taken as representing the first (most populated) conformation or cluster of structures. After removing the structures belonging to the first cluster from the trajectory, the procedure is repeated to find the second cluster or conformation, and so on.

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Electronic Insight into an Antithrombotic Agent by High-Resolution X-Ray Crystallography**

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In medicinal chemistry it is generally accepted that steric and electronic properties play a dominant role in drug–target recognition processes. Molecular activity, similarity, and recognition, which are ambiguously defined properties, are therefore most often screened in terms of their relationship to a definite and readily accessible property, the molecular structure. However, all of these properties can be deduced unambiguously from the distribution of the electronic charge,

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which is a physical property that can be observed and derived from the first principles of quantum mechanics.^[1, 2] Despite recent dynamic advances in theoretical methods, the modeling of drug–receptor interactions at the electronic level is not yet a feasible approach. Owing to the complexity of biochemical systems and to the lack of information on the receptor site, practical models are limited to drug molecules with properties that are established, at most, at the semi-empirical level of theory.

The charge or electron density $\rho(\mathbf{r})$ can be obtained theoretically from high level ab initio quantum chemical calculations and also experimentally from a high-resolution X-ray diffraction experiment at low temperature ($T \leq 100$ K). The charge density extracted from the X-ray diffraction data of a crystalline sample does not correspond to the pure quantum state. Although the applied pseudoatom formalism^[3] is a density model which is formally equal to a one-center representation of $\rho(\mathbf{r})$, it does not allow for the reconstruction of the wave function, hence, orbitals, for example, are not observable in the deformation density.^[4, 5]

The rationalization of the experimental charge density has been made possible through their comparison with theoretical densities. In this respect topological analyses have played a major role.^[2] Such studies have demonstrated that the experimental density is homologous not only to that derived from the ground-state periodic wave function but also to that calculated for the isolated molecule with the experimental geometry.^[6–8] The experimental charge density obtained after multipole refinement^[3] is affected by experimental errors and model inadequacies. The quality of the theoretical counterpart, on the other hand, depends primarily on the approximations involved and the basis set used in the calculation. The comparison of experimental and theoretical bond topological descriptors for chemically analogous bonds reveals that the spread of these parameters, as changing conditions, is narrower for the former than for the latter method.^[9]

By making use of recent technical developments in X-ray crystallography^[10–12] we were able to investigate the charge density^[13] and related topological properties of an antithrombotic drug molecule of more than 50 atoms. The comparison of experimental and theoretical properties suggests that those extracted from X-ray data, and thus referring to the crystalline environment, are substantially better suited to simulate physiological conditions than those calculated for the isolated molecule.

Terbogrel (Figure 1) is a new antithrombotic agent which is in the course of clinical development. It has recently been introduced as the first compound with a guanidine moiety to combine antagonism to the thromboxane A_2 receptor and synthase inhibition.^[14, 15] The experimental results presented here are based on an X-ray data set of almost 220 000 reflections up to a resolution of $d = 0.4$ Å that were collected in 5 days by using area detection.^[16] This is to be compared with approximately 200 days of exposure time that would have been needed for the corresponding experiment performed with conventional scintillation detection, or to over 85 days of CPU time on a SGI Origin 2000 (R10000 processor) that would be needed to calculate the corresponding results for the isolated molecule at the

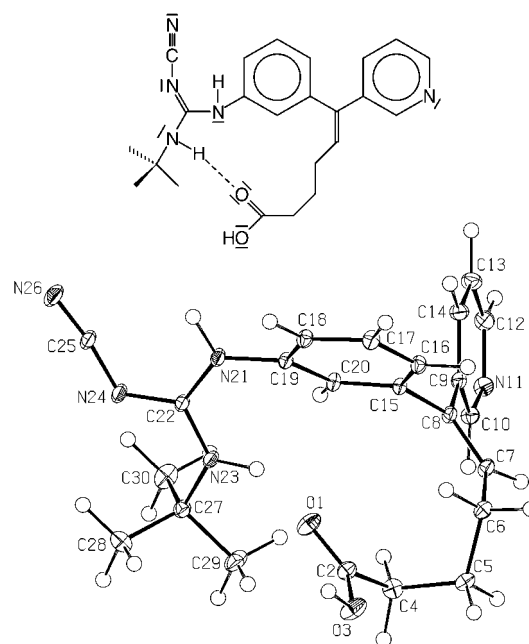


Figure 1. Chemical formula of Terboogrel and its molecular structure as obtained by this X-ray study (ORTEP representation,^[23] the displacement ellipsoids are plotted at a 50% probability level).

HF/6-311++G(3df,3pd) level of theory with the GAUSSIAN94 program package.^[17] The resulting intensity data were interpreted in terms of the Hansen and Coppens multipole formalism,^[3] which allows the modeling of an aspherical distribution of electron density. The multipolar refinement with the program package XD^[18] led to a crystallographic agreement factor of 1.8%. This value shows the excellent quality of the crystal and diffraction intensities. Hence, even the use of a conventional X-ray source is suited for these types of investigations.

From the analytic charge density obtained it is possible to perform a topological analysis according to Baders theory of “atoms in molecules”.^[2] This analysis provides the definition of molecular structure, an atomic partitioning of the molecule, and the characterization of atomic interactions in terms of local topological indices—such as the value of the electron density $\rho(\mathbf{r}_b)$ and its Laplacian function $\nabla^2\rho(\mathbf{r}_b)$ at the bond critical point (BCP, located at $\mathbf{r}_b$, where $\nabla\rho(\mathbf{r}_b) = 0$), as well as the bond ellipticity ϵ ^[19] (see also Table 1).

Table 1 shows a comparison of theory and experiment in terms of quantitative bond topological data for various C–N bonds in the guanidine group, the cyano group, and the pyridine ring of Terboogrel (Figure 1). The weakest bond strength, as given by $\rho(\mathbf{r}_b)$, is found for the bond N23–C27 with an experimental value of $1.76(2) \text{ e Å}^{-3}$, which indicates an almost pure single bond. This result is supported by the bond ellipticity which is close to zero and shows a cylindrical density distribution along the bond. A $\rho(\mathbf{r}_b)$ value of 2.05 e Å^{-3} for the bond N21–C19 is lower and higher, respectively, than that expected for a double and single bond, which suggests there is conjugation with the phenyl ring. The topological equivalence of the N11–C10 and N11–C12 bonds may be attributable to the aromatic character of the pyridine ring. High charge concentrations are found for the formally single

Table 1. Bond topological indices for the various N–C bonds.^[a]

Bond	$\rho(r_b)$	$\nabla^2\rho(r_b)$	d	ϵ
N23–C27	1.61	– 10.3	0.996	0.02
	1.65	– 14.3	0.986	0.03
	1.76(2)	– 8.8(1)	0.831	0.03
N21–C19	1.91	– 15.7	0.941	0.05
	1.97	– 20.8	0.931	0.04
	2.05(2)	– 13.8(1)	0.799	0.10
N21–C22	2.17	– 23.4	0.895	0.05
	2.24	– 28.9	0.886	0.10
	2.35(2)	– 16.4(1)	0.758	0.12
N11–C10	2.30	– 19.9	0.883	0.10
	2.37	– 26.2	0.874	0.13
	2.47(2)	– 21.2(1)	0.755	0.14
N11–C12	2.29	– 19.4	0.885	0.08
	2.37	– 25.9	0.876	0.12
	2.51(1)	– 22.3(1)	0.763	0.13
N24–C22	2.42	– 30.5	0.838	0.14
	2.50	– 34.4	0.823	0.17
	2.53(2)	– 20.9(1)	0.725	0.08
N24–C25	2.46	– 30.1	0.827	0.04
	2.52	– 32.9	0.827	0.04
	2.60(2)	– 18.7(1)	0.726	0.04
N23–C22	2.36	– 27.2	0.868	0.13
	2.44	– 32.9	0.858	0.18
	2.62(2)	– 24.3(1)	0.742	0.19
N26–C25	3.15	– 9.6	0.757	0.03
	3.25	– 12.3	0.760	0.03
	3.54(2)	– 35.5(1)	0.685	0.08

[a] $\rho(r_b)$ [$e \text{ Å}^{-3}$] and $\nabla^2\rho(r_b)$ [$e \text{ Å}^{-5}$] are calculated from the corresponding bond critical point (BCP); d [Å] gives the distance of the BCP from the first listed atom; and the bond ellipticity ϵ indicates the aspherical nature of the charge in the bond.^[19] For each bond the first line corresponds to HF/6-311++G(d,p), the second line to HF/6-311++G(3df,3pd), and the third line to experimental results.

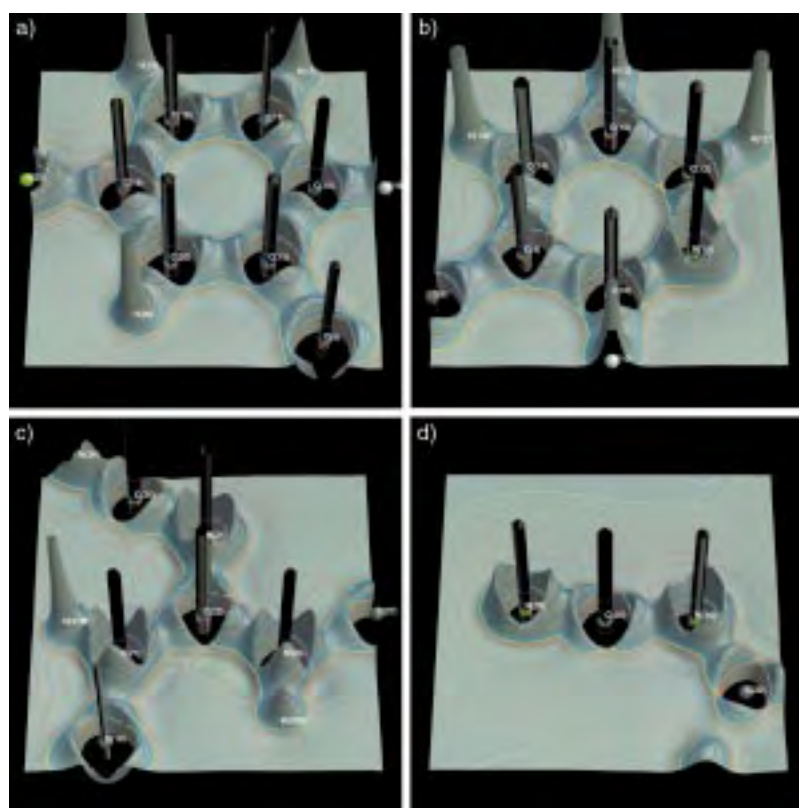
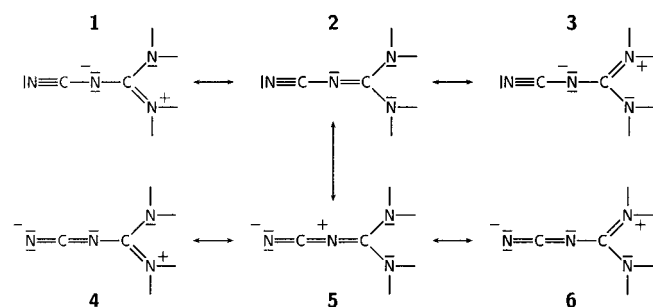


Figure 2. Comparison of the negative Laplacian distribution in four different molecular sections: a) the phenyl ring, b) the pyridine ring, c) the guanidine group, d) the terminal cyano group. The Laplacian function is a very sensitive indicator of local charge accumulations ($\nabla^2\rho(r) < 0$) or depletions ($\nabla^2\rho(r) > 0$). The saddle-shaped features in the bonding regions are typical indicators of the charge concentrations on a covalent bond. The lone pairs on the nitrogen atoms are also all signaled.

bonds N23–C22 and N24–C25 in the guanidine residue. In terms of their $\rho(r_b)$ values, the other two bonds to C22 appear to have strong double bond character. The overall trend found here can be rationalized on the basis of the resonance forms depicted in Scheme 1. The bond orders of the different C–N bonds, as revealed by the $\rho(r_b)$ values, suggest the resonance forms **4** and **6** to have considerable weight.

The Laplacian distribution of the charge density yields valuable chemical information on the reactive sites of the molecule and on the sites where intermolecular interactions are favored. Figure 2 displays this function in a few selected



Scheme 1. Different resonance forms of the guanidine fragment. On the basis of the results from the topological analysis the resonance forms **4** and **6** have considerable weight.

molecular planes, and shows features such as bonded valence shell charge concentrations (VSCCs, with local maxima at $-\nabla^2\rho(r_b)$) on all the covalent bonds and nonbonded VSCCs in the lone-pair regions of the nitrogen and oxygen atoms. Figure 3 displays the zero-Laplacian isosurface (the reactive surface) and shows a high depletion of the VSCC at C2 and C22. These two atoms are therefore the most likely sites for a nucleophilic attack. On the basis of the nonbonded VSCCs

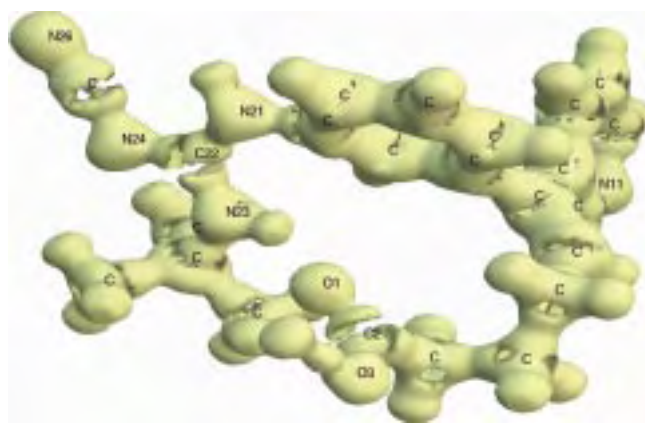


Figure 3. Zero-Laplacian isosurface ($\nabla^2\rho(r)=0$, reactive surface). The labels for the H atoms are omitted. The VSCC at atoms C2 and C22 is reduced, as shown by the open regions in this surface. These are the most likely sites for nucleophilic attack.

(Table 2), the oxygen atoms, as well as atoms N11 and N26 appear to be the most likely sites for an electrophilic attack since $\nabla^2\rho(r_b)$ shows the most negative values, and hence local charge concentration at these sites. This result is in excellent

Table 2. Nonbonded valence shell charge concentrations.^[a]

Atom	$\rho(r_b)$		$\nabla^2\rho(r_b)$		R	
N11	4.02	4.08	-74.1	-83.9	0.388	0.389
N21	3.27	-	-39.9	-	0.411	-
	3.28	-	-40.4	-	0.411	-
N23	3.20	-	-37.7	-	0.413	-
	3.20	-	-37.6	-	0.414	-
N24	3.65	3.64	-57.1	-57.4	0.398	0.397
N26	3.63	3.85	-60.2	-70.5	0.396	0.391
O1	6.27	6.39	-124.0	-133.1	0.344	0.340
	6.31	6.50	-125.1	-133.8	0.344	0.339
O3	6.33	6.77	-124.2	-152.5	0.343	0.336
	-	6.30	-	-129.5	-	0.342

[a] In each column the entries on the left correspond to the theoretical calculation (HF/6-311++G(3df,3pd)), and the entries on the right to the experiment. $\rho(r_b)$ [$\text{e}\text{\AA}^{-3}$] and $\nabla^2\rho(r_b)$ [$\text{e}\text{\AA}^{-5}$] are the values found at the (3,+3) critical point of the Laplacian. R [$\text{\AA}$] is the distance from the corresponding atom to this point.

agreement with that derived from the wave function. On the other hand, the analysis of the experimental $-\nabla^2\rho(r_b)$ function reveals the lack of (3,-3) critical points at the N21 and the N23 sites. This finding also supports the suggestion that the nonbonded electrons of these atoms are, to some extent, involved in the bonding as suggested by the resonance forms 4 and 6.

The electrostatic potential (EP), which can be derived directly from the electron density, is an analytical tool which is used extensively to predict the reactive behavior of chemical systems and to study biological recognition processes, such as drug-receptor or enzyme-substrate interactions. Figure 4 displays positive (blue) and negative (red) isopotential surfaces of the EP derived from the monomolecular charge density extracted from the crystal field according to the method of Su and Coppens,^[20] and compared to that calculated from the HF/6-311++G(d,p) wave function. Both maps show distinct regions of negative potential that are especially pronounced at the cyano-substituted guanidine residue and, to a lesser extent, at the pyridine nitrogen and carboxylate oxygen atoms. These features are considerably enhanced in the experimental potential and indicates the polarization effects of the crystal field. The enlargement of the dipole moment on going from the isolated molecule (11.2 D, HF/6-311++G(3df,3pd)) to that in the crystalline environment (21.9(16) D) has the same origin. These observations are in line with several results published recently on experimental electronic properties.^[21, 22]

The experimental EP extracted from the crystalline state can be assumed to be better suited for the simulation of a physiological situation, which are characteristic of drug-receptor interactions, than the potential calculated from an isolated stationary state. This occurs because it includes effects of intermolecular interactions arising from a given crystal packing in which molecular recognition is realized to a high degree. To obtain comparable results theoretically,

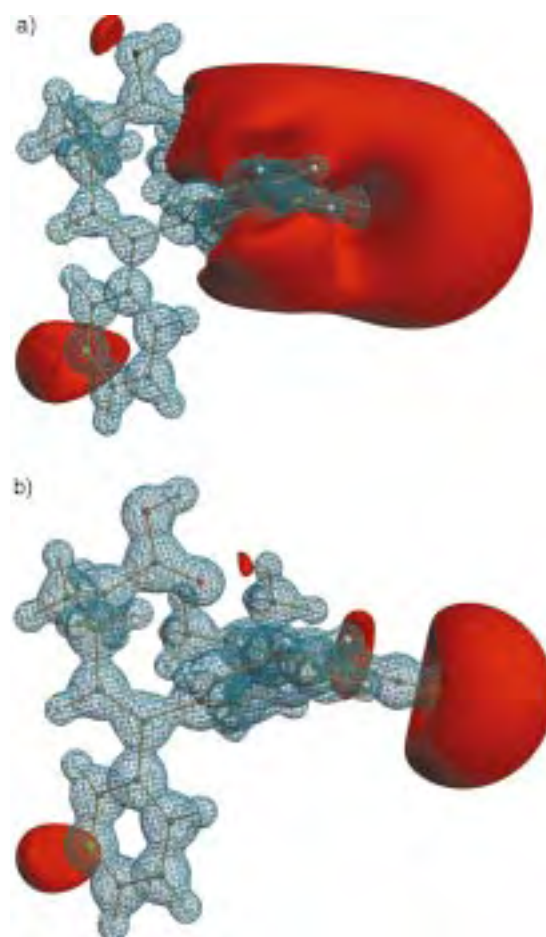


Figure 4. Representation of the isosurface of the electrostatic potential: a) Experimental, extracted from the crystal field by the method of Su and Coppens,^[20] b) calculated from HF/6-311++G(d,p) wave function for the isolated molecule. The values of the isosurface in both representations are: red = $-0.1\text{ e}\text{\AA}^{-1}$, blue = $+1.0\text{ e}\text{\AA}^{-1}$.

calculations need to be carried out on periodic systems, which is hardly feasible with current CPU power and definitely impossible for larger systems. This fact encourages the use of experimentally derived electronic properties in the modeling of biochemical processes since purely geometric considerations are certainly not sufficient for their description. Only steric and electronic complementarity will lead to a successful drug-receptor interaction, hence the accurate determination of the electronic charge density serves as a basis for a better understanding of such interactions. Since this study has proven that charge-density work on medium-sized drug molecules can be performed even with common laboratory equipment in a short time, this method has the potential to improve drug-finding processes.

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Polyol-Mediated Preparation of Nanoscale Oxide Particles**

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Nanoscale oxide particles with a mean particle diameter of 30 to 300 nm are gaining increasing technical importance for classic areas of application such as catalysts, passive electronic components, or ceramic materials.^[1] However, they also contribute in an essential way to the realization of completely new concepts such as transparent solar cells^[2] or photonic crystals.^[3] In addition, they play an important role in the selective surface modification (e.g. passivation, hardening, coloration) of various substrates in the form of coatings.^[4] With regard to all of the applications mentioned, in addition to the particle size a low degree of agglomeration and a monodisperse size distribution are desirable to enable a homogeneous arrangement of particles in thin films or as coatings. The polyol method applied herein provides a promising preparative approach to such oxide particles.

The polyol method was initially described for the preparation of elemental metals and alloys,^[5] in which the reducing properties of a high-boiling alcohol (e.g. glycerol, glycol) towards a suitable metal precursor were utilized. With regard to oxidic materials, only a few insights have been gained so far, namely for ZnO, Fe₂O₃, CoAl₂O₄, and Bi₂O₃.^[6] Our investigations show that the polyol method, which can also be understood as a sol–gel process carried out at elevated temperatures in the case of oxides, is suitable for the preparation of a host of binary and ternary oxides.

By heating suitable metal salts and a defined amount of water in diethylene glycol (DEG), suspensions of various materials are obtained in a simple manner (Figure 1, Table 1). These oxide particle suspensions are colloidally stable and can contain up to 20 wt % of solids. A detailed characterization of the oxide particles obtained is exemplified for Cu₂O, TiO₂,



Figure 1. Various oxide particle suspensions in DEG.

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Table 1. Nanoscale oxide particles obtained with the polyol method.

Cu ₂ O	CoO	Al ₂ O ₃	SiO ₂	V ₂ O ₅	MoO ₃	MgAl ₂ O ₄
	ZnO	Bi ₂ O ₃	SnO ₂	Nb ₂ O ₅	WO ₃	BaAl ₂ O ₄
	CdO	Y ₂ O ₃	TiO ₂	Ta ₂ O ₅		CoAl ₂ O ₄
		La ₂ O ₃	ZrO ₂			ZnCo ₂ O ₄
		Cr ₂ O ₃				
		Fe ₂ O ₃				

and Nb₂O₅. Monodisperse and nanoscale TiO₂ particles can also be obtained by other preparative methods;^[7] Cu₂O and Nb₂O₅, on the other hand, have so far only been described as unstructured or amorphous films, respectively, or as particles with a very inhomogeneous size distribution. Moreover, the preparation was carried out at comparatively high temperatures (500–1000 °C) in both cases.^[8, 9]

The oxide particles prepared with the polyol method can be investigated more closely after separation from the suspension by centrifugation. The resulting powders are highly crystalline (Figure 2) immediately after their synthesis at a

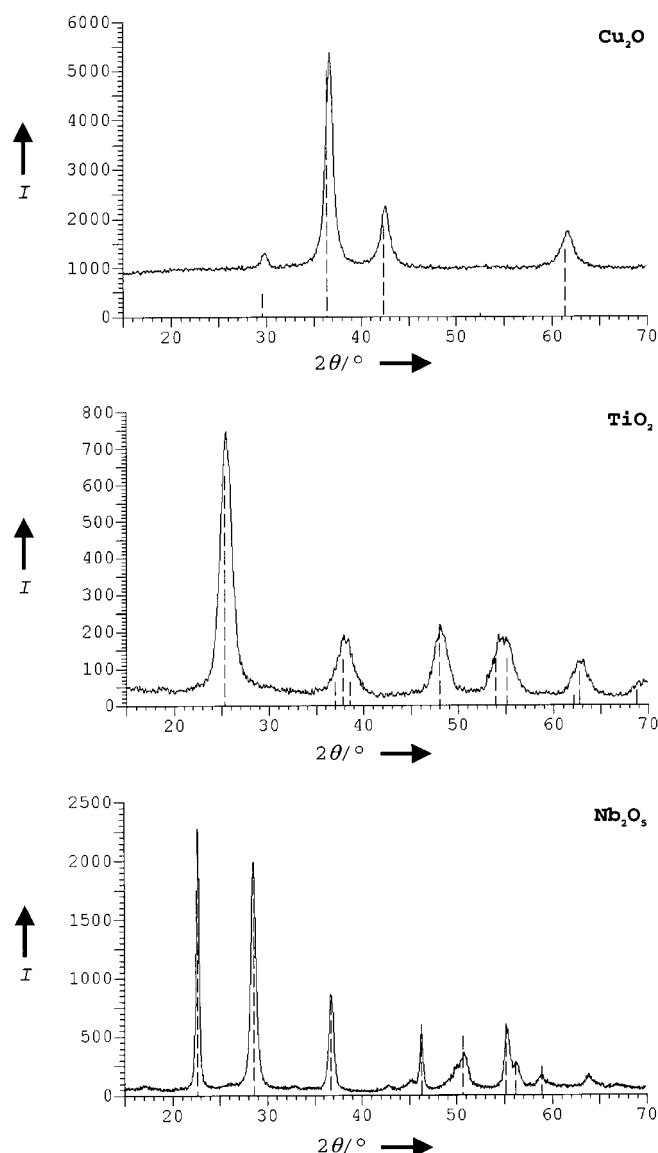


Figure 2. Powder diffractograms of Cu₂O (ICDD-Ref. 05-0667/cuprite), TiO₂ (ICDD-Ref. 21-1272/anatase), and Nb₂O₅ (ICDD-Ref. 28-0317).

maximum temperature of 180 °C (e.g. Cu₂O, TiO₂) or after short heating to surprisingly low temperatures (e.g. Nb₂O₅, 15 min at 300 °C). Electron micrographs show spherical, nanoscale and largely monodisperse oxide particles (Figure 3). By modifying the experimental conditions, especially

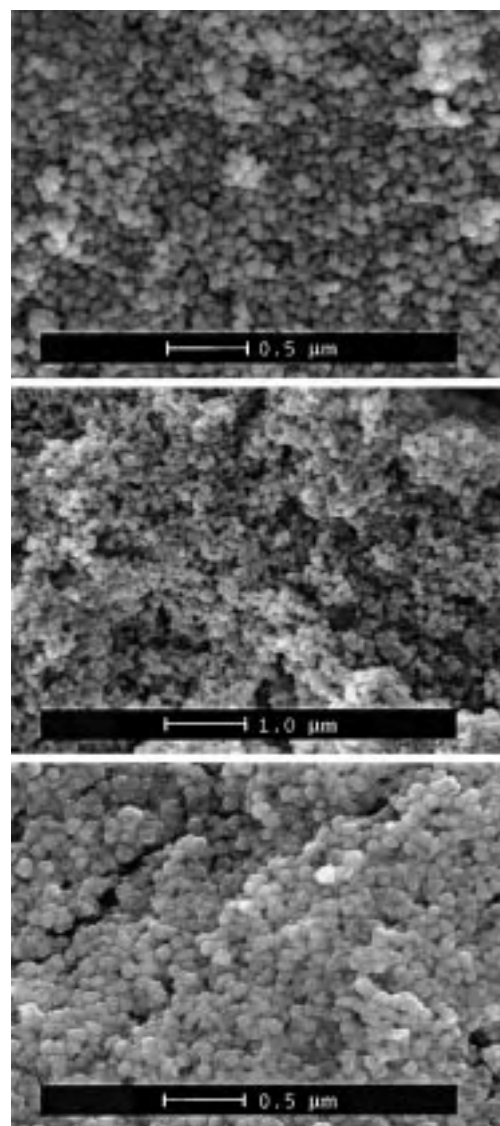


Figure 3. Electron micrographs of Cu₂O (top), TiO₂ (middle), and Nb₂O₅ particles (bottom).

the concentrations of the metal precursor and of water, a mean particle diameter between about 30 and 200 nm can be realized.^[6] The spherical habit of the oxide particles is attributed predominantly due to the coverage of the growth areas with the chelating agent diethylene glycol. This suppresses an inhomogeneous growth of the nuclei. Differential thermal analysis (DTA)/thermogravimetric (TG) studies prove that the DEG film adhering to the particle surfaces can be removed completely by heating to 250 °C. The powdered materials then show Brunauer–Emmett–Teller (BET) surfaces of around 100 m² g⁻¹.

Laser diffraction investigations of oxide particle suspensions confirm the mean particle diameters determined by

scanning electron microscopy (SEM) of powders (Figure 4). Thus, individual, non-agglomerated oxide particles are present in the suspension. This is all the more remarkable as no

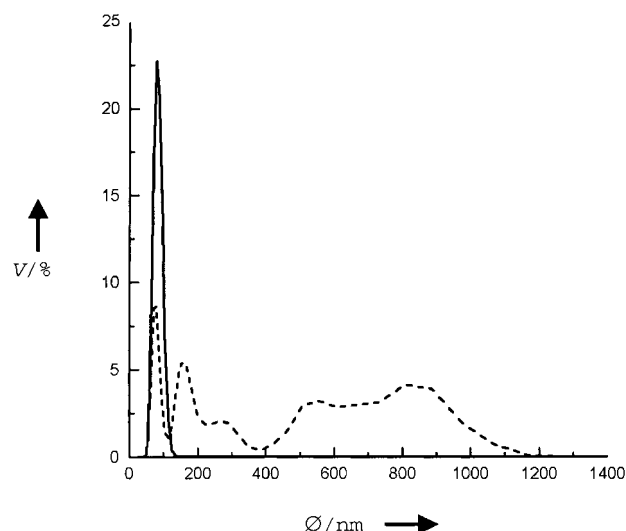


Figure 4. Particle diameters ($\varnothing$) of Nb_2O_5 particles in DEG (—) and 30 min after mixing with water (---).

further stabilizing agents apart from DEG are required. If, however, the DEG suspension is mixed with water, the colloid breaks down and rapid agglomeration of the oxide particles occurs (Figure 4). In the presence of a suitable substrate, the destabilization of the colloid can be used for the selective adhesion of oxide particles to the surface of the substrate. With common methods such as dipping or spin-coating, thin and homogeneous oxide particle layers can be applied to planar substrates, for example a glass plate (Figure 5). In addition, substrates with a curved surface can be coated homogeneously. Thus, the substrate itself, for example Al_2O_3 powder, can consist of particles (Figure 5). Taking the relevant parameters (e.g. polarity and charge of the surface) into consideration,^[10] a virtually immediate and reliable adhesion between substrate and oxide particles is obtained. The coverage of the Al_2O_3 surface with individual, nanoscale Nb_2O_5 particles achieved in the example shown here can be considered as further support for the presence of non-agglomerated oxide particles in the DEG suspension.

The broad applicability and the opportunity to produce nanoscale and crystalline oxides at moderate temperatures are the key features of the polyol method. The comparatively high solid content coupled at the same time with the absence of additional stabilizers makes the oxide particle suspensions in diethylene glycol of technical interest for the coating and modification of surfaces. Preliminary investigations have now also shown that, besides oxides, sulfides (e.g. ZnS) and phosphates (e.g. LaPO_4) can be produced in the form of nanoscale particles with the polyol method.^[11]

Experimental Section

To prepare Cu_2O , TiO_2 , and Nb_2O_5 oxide particles, DEG (50 mL; 99.9%; Merck) was placed in a 250 mL round-bottomed flask. A solution of $\text{Cu}(\text{CH}_3\text{COCHCOCH}_3)_2$ (2.3 mm; 99%; Alfa), $\text{Ti}(\text{O}i\text{Pr})_4$ (2.3 mm;

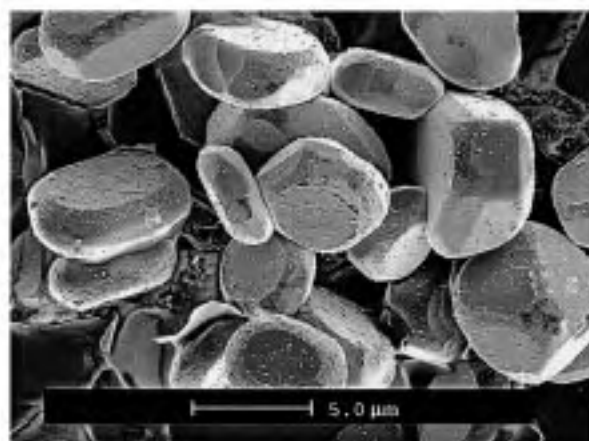
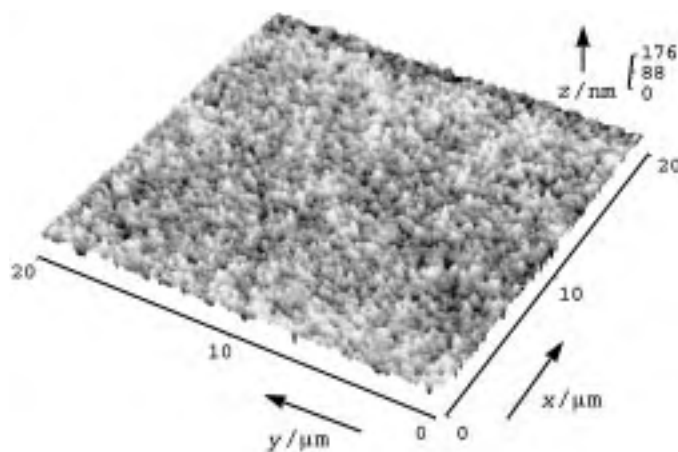


Figure 5. Coverage of a glass plate (top) and an Al_2O_3 powder (bottom) with Nb_2O_5 particles.

99.999%; Aldrich), or $\text{Nb}(\text{OC}_2\text{H}_5)_5$ (2.3 mm; 99.95%; Heraeus) was added, under vigorous stirring, and the clear solution was heated to 140 °C. Subsequently, demineralized water (2 mL) was added and the mixture was heated to 180 °C for 2 h. After the mixture had been cooled, the solid was separated by centrifuging the suspension. It was then resuspended twice in ethanol and centrifuged again to remove any remaining DEG. For the coverage of planar substrates (e.g. glass plates), the oxide particle suspensions in DEG were mixed with water in ratios of 1:1 to 1:10. These mixtures were applied to the substrates by dipping or spin-coating. Powdered substrates (e.g. Al_2O_3 particles) were suspended in water, and the DEG suspension was slowly added dropwise.

The powder diffraction spectra were recorded with a Philips goniometer PW1050 with Bragg-Brentano geometry (graphite monochromator, proportional counter, $\text{CuK}\alpha$ radiation). The electron micrographs were obtained with a Philips/FEI-scanning electron microscope XL30 (samples treated with carbon vapor, accelerating potentials 5–10 kV). The particle sizes in suspension were determined with a Coulter LS230 instrument (Laser power 5 mW at 750 nm, halogen lamp with 150 lm at 2900 K, detector with 126 photodiodes). A Topometrix Explorer was used for the atomic force microscopy (AFM) experiments (Si_3N_4 tip, vertical distance < 2 μm , lateral distance < 150 μm).

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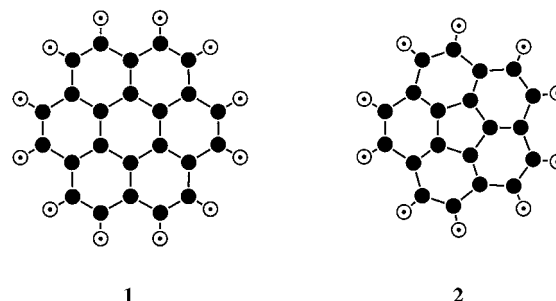
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Counter-Rotating Ring Currents in Coronene and Corannulene**

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Ring currents are intimately linked with the concept of aromaticity in organic chemistry and are essential ingredients of the interpretation of physical and chemical properties of conjugated π systems.^[1–7] The currents themselves are not directly observable, but are inferred through their manifesta-

tations in NMR spectroscopy and measurements of magnetic anisotropy (“exaltation of diamagnetism”).^[8] In monocyclic systems, diamagnetic circulations are associated with the magic Hückel count of $4n + 2\pi$ electrons. In fused polycyclic systems such as the planar coronene (**1**) and the bowl-shaped corannulene (**2**; Scheme 1), it is traditional to invoke an



Scheme 1. ● = carbon; ○ = hydrogen.

“annulene-within-an-annulene” model,^[9, 10] in which both rim and hub attain the aromatic Hückel count (18 and 6 in **1**, and 14 and 6 in **2** if the transfer of one electron to the central pentagon is invoked), which implies there are conrotatory diamagnetic ring currents in the two cycles. Against this picture, calculated populations^[11] show no significant redistribution of electron density from rim to hub in **2**, and the “nucleus-independent chemical shift” (NICS), proposed as a criterion of aromaticity by Schleyer et al.,^[12] indicates that both **1** and **2** have outer aromatic (diamagnetic, diatropic) but inner non-aromatic or anti-aromatic (paramagnetic, paratropic) circuits.^[13]

Fortunately, distributed-origin methods developed in recent years^[14–19] allow the accurate calculation of magnetic response properties and, in particular, direct visualization of induced current densities in conjugated systems.^[20–22] They are used here to confront the discrepant models of **1** and **2** with an ab initio computation of the ring currents, and, additionally, to discuss the question of the applicability of π -only pictures to the nonplanar, bowl-shaped corannulene systems, and hence to fullerenes.^[23, 24] Thus, computational comparisons are made between coronene (**1**, D_{6h}) and corannulene (**2**) in both the equilibrium C_{5v} bowl configuration and the planar D_{5h} transition state for bowl-to-bowl conversion.

Computed current-density maps (see Experimental Section) are shown in Figure 1 for the σ , π , and total ($\sigma + \pi$) electrons at $1 a_0$ above the molecular planes of **1** and planar **2**. The σ maps at this height do not show the detail of the current density close to the nuclei but they do demonstrate characteristic superpositions of diamagnetic circulations centred on σ bonds, with a cumulative effect within each ring of a net central paramagnetic circulation. In both molecules **1** and **2** the π currents combine to give a clear diamagnetic circulation around the outer rim with a paramagnetic counter-circulation on the inner hub. In detail, slight differences can be found between the two molecules: in **1** the outer circulation is stronger than the inner, whereas in **2** it is the inner that is stronger and residual circulation within radial C–C bonds is evident in **2**. This latter effect is not observed in **1**.

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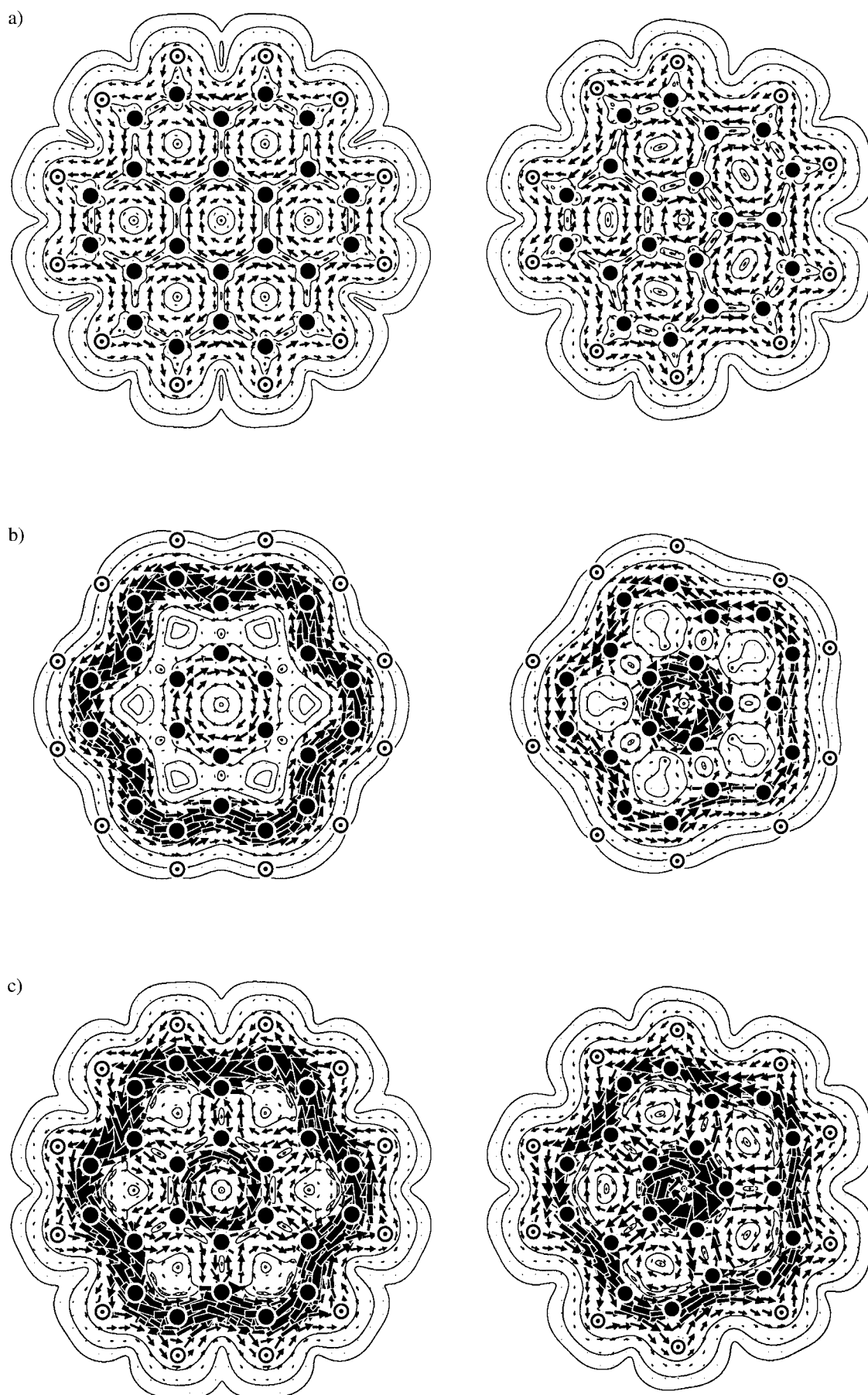


Figure 1. Maps of current density in coronene (1; left) and planar corannulene (2; right): a) σ , b) π , c) total ($\sigma+\pi$) current

This broad overall pattern is insensitive to the curvature of the corannulene π system. Strict σ/π separation no longer applies in the optimal bowl-shaped geometry of **2**, but the qualitative appearance of the total current map is preserved. Figure 2 shows the total current densities induced by a field

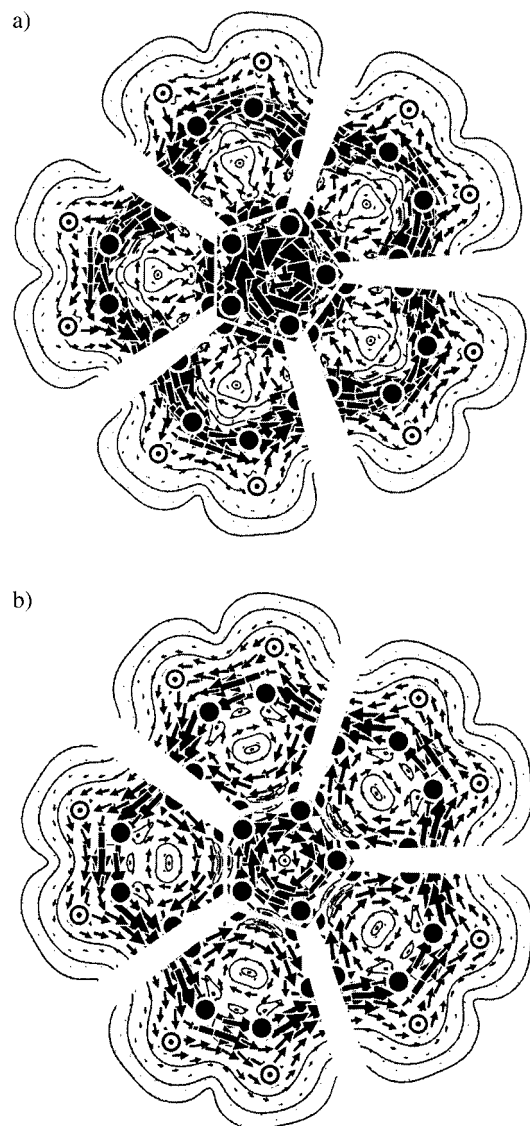


Figure 2. Current density maps in the bowl geometry of corannulene (**2**): a) total current inside the bowl, b) total current outside the bowl.

along the fivefold axis, plotted in an exploded view where the current vectors are projected locally in a plane parallel to the individual ring, at a distance of $1 a_0$ from it. Maps are shown for the current density inside and outside the bowl. Counter-rotating currents are again seen, even though the vectors of the outer rings now have significant components out of the planes of projection. In the planar corannulene (**2**) the central current is similar in magnitude but opposite in sign to that in benzene, as is expected from π -only models.^[24] When curvature is included, the central paramagnetic circulation is strongly enhanced inside the bowl but depleted on the outside, as might be expected from orbital-overlap arguments. The outer diamagnetic circulation is less sensitive but shows the same trends.

Thus, the central result of the ab initio calculations is established: both coronene (**1**) and corannulene (**2**) when placed in a perpendicular magnetic field have *counter-rotating* ring currents, with a diamagnetic rim and paramagnetic hub, which contradicts the predictions of the annulene-within-an-annulene model. A precisely similar motif is predicted in both π -only^[24] and all-electron^[25] calculations of the ring currents induced on pentagonal sites in C_{60} , which shows that corannulene (**2**) is an appropriate model for fullerene magnetism. Counter-rotation of currents can also be expected to have a characteristic chemical-shift signature in strapped cyclophane derivatives of (**2**).^[26]

Other properties from CTOCD calculations (see Experimental Section) are consistent with previous calculations and experiments, and serve to validate our approach. Thus, NICS values (Table 1) are negative and similar to that of benzene ($\delta = -12.7$ in the present basis) for the outer rings of **1** and **2**, negative but smaller for the central ring of **1**, and positive for

Table 1. Computed absolute shielding constants [ppm] at the ring centers in coronene (**1**), corannulene (**2**; planar (D_{5h}) and bowl (C_{5v}) forms).^[a]

	Ring	$\sigma_{\parallel}$	σ
coronene (1)	inner	-22.0	2.4
	outer	14.4	14.8
corannulene (2 , planar)	inner	-58.5	-9.4
	outer	1.6	9.7
corannulene (2 , bowl)	inner	-52.8	-6.9
	outer	4.0	10.1

[a] $\sigma_{\parallel}$ is the component of the absolute shielding out of the plane of the ring and σ is the mean value. NICS^[12] values are obtained by changing the sign of σ .

the hub of **2**. These values are consistent with the sense and strength of the calculated currents shown in Figure 1. Use of the out-of-plane shielding $\sigma_{\parallel}$ at the ring center, which is opposed in sign for the rim and the hub in both **1** and **2** (Table 1), gives an even better indication of the ring currents, and is more systematic than NICS values for points positioned out of the ring plane.^[27]

The computed magnetizability anisotropy for coronene (**1**, Table 2) matches the correlation with conventional exaltation of isotropic susceptibility that can be observed for related molecules. (For example, within the same computational approach, $\Delta\xi$ [a.u.] = -16.5 (benzene), -30.5 (naphthalene), -45.1 (fluoranthene), -55.9 (pyrene), compared with the diamagnetic exaltations $\mathcal{A}$ [$10^{-6} \text{ cm}^3 \text{ mol}^{-1}$] = 13.7, 30.5, 42, 57, respectively (a.u. = arbitrary units.^[8]) In line with its smaller size and larger paramagnetic current, corannulene (**2**) has a

Table 2. Computed molecular magnetizabilities [a.u. = $e^2 a_0^3 / m_e = 7.89104 \times 10^{-29} \text{ JT}^{-2}$] of coronene (**1**) and corannulene (**2**; planar (D_{5h}) and bowl (C_{5v}) forms).^[a]

	$\xi_{\parallel}$	ξ	$\Delta\xi$	$\mathcal{A}$
coronene	-118.8	-51.1	-101.6	103
corannulene (planar)	-75.8	-34.6	-61.8	
corannulene (bowl)	-73.5	-37.1	-54.6	

[a] $\xi_{\parallel}$ is the component of magnetizability parallel to the principal rotational axis, ξ is the mean value, and $\Delta\xi$ is the anisotropy. $\mathcal{A}$ is the diamagnetic exaltation.^[8]

smaller mean magnetizability and anisotropy, with some variation between the planar and dome forms. Computed carbon shieldings and shifts are shown in Table 3. Excellent agreement with experiment is found for the isotropic shifts,^[28, 29] whereas component shifts, as also noted for the GIAO calculations reported in reference [28], are in only

Table 3. Computed ¹³C chemical shifts for coronene (**1**) and the bowl form of corannulene (**2**).^[a]

Site	δ_{11}	δ_{22}	δ_{33}	δ
coronene				
hub	207.3 (199)	181.4 (199)	−13.9 (−38)	124.9 (120/122.6)
rim	210.0 (204)	190.1 (193)	−11.2 (−28)	129.6 (123/128.7)
rim (protonated)	238.0 (225)	130.4 (137)	+12.8 (+7)	127.1 (123/126.2)
corannulene (bowl)				
hub	235.5 (224)	168.4 (177)	+9.4 (+6)	137.8 (136/135.8)
rim	226.2 (214)	145.7 (189)	+22.6 (−10)	131.4 (131/130.8)
rim (protonated)	230.5 (215)	137.5 (145)	+13.3 (+17)	127.1 (126/127.2)

[a] δ_{11} , δ_{22} , and δ_{33} are principal components of the shift tensor, and δ is the isotropic average, obtained from the computed absolute shieldings σ ($\delta = 185.6 - \sigma \times 10^6$).^[17] The values in parentheses are experimental shift components and mean (isotropic) shifts derived from low-temperature, solid-state NMR measurements.^[28] The second set of experimental mean values for coronene^[29] and corannulene^[32] refers to solution (CDCl₃) data. For comparison, the CTOCD computed isotropic shifts for the three sites in planar corannulene are $\delta = 132.8$, 129.4, and 128.1, respectively.

qualitative agreement with those extracted from solid-state ¹³C NMR measurements; tensor components are generally more sensitive than mean shieldings to basis and level of theory.^[30] In the calculated shifts for **2**, the main change observed on going from planar to bowl shapes is a shift downfield of the hub carbon atoms, which is compatible with the expected re-hybridization on bending.^[23, 31] Calculated mean proton shielding σ of 22.2 ppm (**1**) and 23.6 ppm (**2**) imply shifts of $\delta = 8.6$ and $\delta = 7.2$ ($\bar{\sigma} \times 10^6 + \delta = 30.8$ ^[17]), which is in good agreement with the experimental shifts $\delta(\text{CDCl}_3) = 8.90$ (**1**)^[29] and 7.81 (**2**).^[32]

The overall quality of the calculated properties reinforces the conclusion that the CTOCD maps, of which NICS, magnetizability, and nuclear shieldings are all integrals, are physically correct visualizations of the ring currents in these systems. There is therefore a sound theoretical basis for rejecting the annulene-within-an-annulene model as a general picture of coronene (**1**) and corannulene (**2**). This is not to say that conrotatory currents can never occur in such molecules. For example, addition of four electrons to **2** to produce the tetraanion is sufficient to reverse the hub current in the CTOCD-computed current density map, and give concentric, strongly diamagnetic ring currents, which is in agreement with experimental ¹H NMR data.^[33] Similar reversals of current, with consequences for the ¹³C shift, are predicted for hexaanions of C₆₀ and C₇₀.^[34]

Experimental Section

Methods: The magnetic properties of **1** and **2** were computed using distributed-origin methods, originally produced by Keith and Bader^[14, 16] and developed at the coupled Hartree–Fock level by Zanasi,^[17] with the Exeter version of SYSMO.^[35] For current density maps, well converged results are given by the DZ (diamagnetic zero) variant of the CTOCD

(continuous transformation of origin of current density) method,^[14, 17] where the current density at any point in space is calculated with that point as origin. The method has the usual advantages of distributed-origin approaches:^[16, 17] superior convergence with basis size and physically realistic current maps with modest basis sets (here 6-31G++). Integral properties, that is, the magnetizability and shieldings at nuclei and centers of rings, are computed in the PZ2 (paramagnetic zero) variant of the CTOCD method,^[36] which is more accurate for this purpose. Optimized geometries are computed for **1** and both forms of **2** in the 6-31G++ basis set by using CADPAC.^[36] Total SCF energies are −915.9741 (**1**), −763.1926 and −763.2071 E_h (**2**), which implies there is a barrier to inversion of 38 kJ mol^{−1} (compare with 42.7 kJ mol^{−1} obtained from low-temperature NMR measurements on a derivative^[32]). The computed bowl has a depth of 0.82 Å in the optimal geometry (0.87 Å from an X-ray study^[37]). For the planar systems, current densities induced by a unit magnetic field acting along the principal axis are plotted in a plane 1 a₀ above that of the nuclei (that is, close to the maximum π density, with current essentially perpendicular to the inducing field). The plotting area is 24 × 24 a₀², the contours denote the modulus of the current density at values 0.001 × 4ⁿ e_h/m_ea₀ for n = 0, 1, 2, ..., and the vectors represent in-plane projections of current. In all plots the diamagnetic circulation is anticlockwise and the paramagnetic circulation clockwise.

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Towards the Development of Antitumor Vaccines: A Synthetic Conjugate of a Tumor-Associated MUC1 Glycopeptide Antigen and a Tetanus Toxin Epitope**

Stefanie Keil, Christine Claus, Wolfgang Dippold, and Horst Kunz*

Since it was recognized that tumor cells and normal cells are distinctly different in the glycoprotein profile of their outer cell membranes,^[1] numerous efforts have been made to develop tumor-selective antigens for vaccinations against tumors.^[2] First investigations focused on glycolipids.^[3] Since 1977, Springer et al.^[1b] have described glycoproteins carrying the Thomsen–Friedenreich antigen (T- or TF-antigen: $\text{Gal}\beta(1,3)\text{-GalNAc-O-Ser/Thr}$) as being tumor-associated surface structures on epithelial cells. A close structural relation between T-antigen glycoproteins and asialoglycophorins was supposed because of cross reactivities of antibodies induced by these components. Based on these results, we synthesized T_N - and T-antigen glycopeptides 15 years ago in order to obtain antigens for vaccinations against tumors.^[4] To this end, synthetic T-antigen glycopeptides with the N-terminal sequence of the M blood group glycophorin were coupled to bovine serum albumin (BSA) and used for vaccination of

mice. A monoclonal antibody (82-A6) obtained by hybridoma techniques was selectively directed against the T-antigen glycopeptide. It exhibited affinity to epithelial tumor cells in enzyme-linked immunosorbent assays (ELISAs), but did not show sufficient tumor selectivity. Further characterizations of this antibody disclosed no affinity for glycophorin, but binding to asialoglycophorins was observed,^[5, 6] which confirms specificity towards the T-antigen structure. Interestingly, the antibody proved to be distinctly more reactive to asialoglycophorins of the M blood group than those of the N blood group. The former contains an N-terminal peptide sequence identical to the one in the synthetic T-antigen glycopeptide. Thus, the antibody differentiated between the two glycoproteins which both carry numerous identical T-antigen saccharides but are slightly different in their peptide sequences. This observation implies that the specificity of an antibody directed against a carbohydrate epitope is distinctly modulated by the peptide sequence in the linkage region.^[4–6] We conclude that a tumor-selective antigen not only requires a tumor-associated saccharide epitope but also a tumor-selective peptide structure.

During recent years, amino acid sequences of tumor-associated mucins have been elucidated.^[7] Our syntheses are now aimed at glycopeptides of the tumor-associated mucin MUC1.^[8] MUC1 is overexpressed up to tenfold on epithelial tumors and is incompletely glycosylated because of a prematurely occurring sialylation. The low glycosylation rate of the polymorphic epithelial mucin (PEM) MUC1 influences its conformation. Peptide epitopes located in its tandem repeat region become accessible to the immune system. They should constitute tumor-selective peptide-structure information. Therefore, we have synthesized T_N -,^[9] T -,^[10] and sialyl- T_N -antigen glycopeptides^[11] from the tandem repeat region of MUC1.^[12] As only one of these glycopeptides exhibited a proliferating effect on peripheral blood lymphocytes, we have developed a novel concept for the antigen construction of antitumor vaccines. According to this strategy, the tumor-associated MUC1 glycopeptide antigen is combined with a T-cell epitope of tetanus toxin using a flexible spacer to give a conjugate **1** (Figure 1).

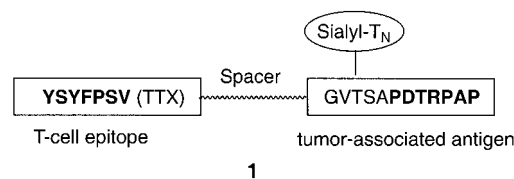


Figure 1.

The peptide motif PDTRPAP was incorporated into the target structure as the immunodominant domain^[13]. The neuraminic acid was protected as its benzyl ester,^[14] and the whole construct **1** was formed from two large portions in a solid-phase fragment condensation. The sialyl- T_N building block was synthesized from a T_N -threonine conjugate and a neuraminic acid donor.^[11] The O-acetylated sialic acid benzyl ester **2**^[14] was treated with acetyl chloride to give the glycosyl chloride which, with potassium O-ethylxanthogenate, was

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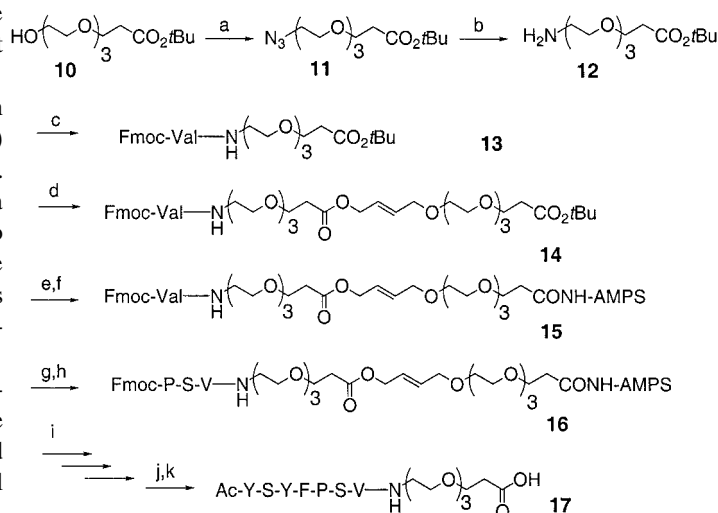
converted into the sialyl xanthogenate **3**;^[15] this had already been demonstrated as a favorable glycosyl donor in the case of the sialic acid methyl ester.^[11] Reaction of **3** with the partially protected T_N-threonine precursor **4**^[11] regioselectively furnished the desired ST_N-threonine conjugate **5** (ST_N = Sialyl-T_N). Low temperature and intermediate acetonitrile conjugates favor the formation of the α-sialoside (Scheme 1).

After O-acetylation of **5**, the *tert*-butyl ester was removed from **6** by careful acidolysis. The obtained ST_N-threonine building block **7**^[16] was used in the solid-phase synthesis of the glycododecapeptide sequence of the MUC1 tandem repeat region.

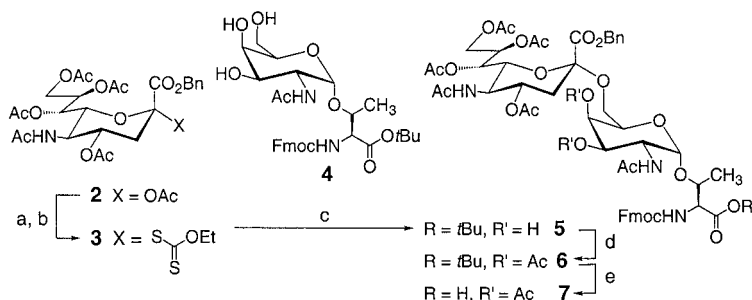
The synthesis of the ST_N-glycododecapeptide started with Fmoc-proline linked to the aminomethylpolystyrene (AMPS) resin **8** through the allylic HYCRON anchor^[9] and β-alanine. In order to avoid the formation of a diketopiperazine, a change to the Boc strategy was chosen for the second amino acid (Ala). This is possible because of the stability of the allylic anchor to both acids and bases.^[9] The further synthesis of the resin-bound ST_N-glycododecapeptide **9** was performed according to the Fmoc strategy (Scheme 2).

Parallel to this, *tert*-butyl 12-hydroxy-4,7,10-trioxa-dodecanoate^[17] (**10**) was converted through the 12-azido derivative **11** into the 12-amino derivative **12**, which was then condensed with Fmoc-valine to give **13**; after cleavage of the *tert*-butyl

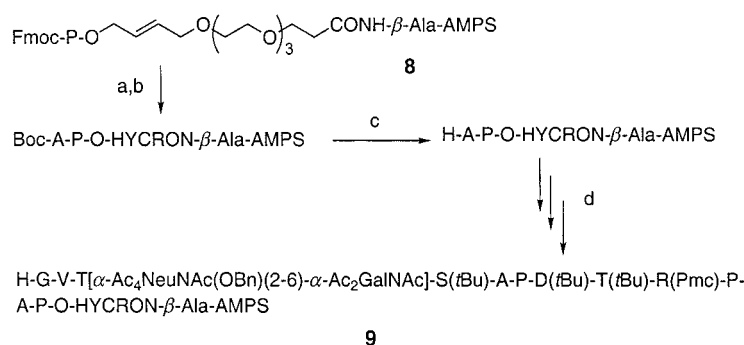
ester, **13** was coupled to the HYCRON linker.^[9] The Fmoc-Val-spacer-HYCRON conjugate **14** was coupled to the polymer (→**15**) and then the tetanus toxin peptide-spacer conjugate was assembled according to the Fmoc strategy. In the first chain extension, a dipeptide was coupled^[18] to furnish **16** in order to avoid formation of a diketopiperazine. Finally, the Fmoc group was exchanged for an acetyl group (Scheme 3).



Scheme 3. a) 1. MesCl, NEt₃, CH₂Cl₂, 20 °C, 3 h, 2. NaN₃, DMF, 60 °C, 18 h; b) Raney-Ni, H₂, 2-propanol, 20 °C, 12 h, 73%; c) Fmoc-Val-OH, EEDQ, CH₂Cl₂, 20 °C, 12 h, 70%; d) 1. TFA, 20 °C, 2 h, 2. Br-HYCRON-OrBu (ref. [9]), NBu₄Br, NaHCO₃/CH₂Cl₂, 20 °C, 12 h, 75%; e) TFA, 20 °C, 2 h, 95%; f) H-AMPS, TBTU, HOBT, NMM, DMF, 20 °C, 18 h, 74%; g) morpholine/DMF (1/1); h) Fmoc-Pro-Ser(*t*Bu)-OH, TBTU, HOBT, NMM, DMF; i) 4 times [1. coupling: Fmoc-AS-OH, TBTU, HOBT, NMM, DMF; 2. capping: Ac₂O/pyridine (1/3); 3. Fmoc-removal: morpholine/DMF (1/1)]; j) Ac₂O/pyridine (1/3); k) [Pd(PPh₃)₄], morpholine, DMF/DMSO (1/1) 44% based on **15**. Mes = β-morpholinylethanesulfonic acid, EEDQ = 2-ethoxy-*N*-ethoxycarbonyl-1,2-dihydroquinoline.



Scheme 1. a) AcCl, 20 °C, 3 d, quant.; b) KCS₂OEt, EtOH, 20 °C, 4 h, 73%; c) CH₃SB⁺Br⁻/AgOTf, CH₃CN/CH₂Cl₂ (2/1), -62 °C, 3 h, 60%; d) Ac₂O, pyridine, 0 °C, 4 h, 84%; e) TFA/CH₂Cl₂ (1/1), anisole, 20 °C, 6 h, quant. Ac = acetyl, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid.

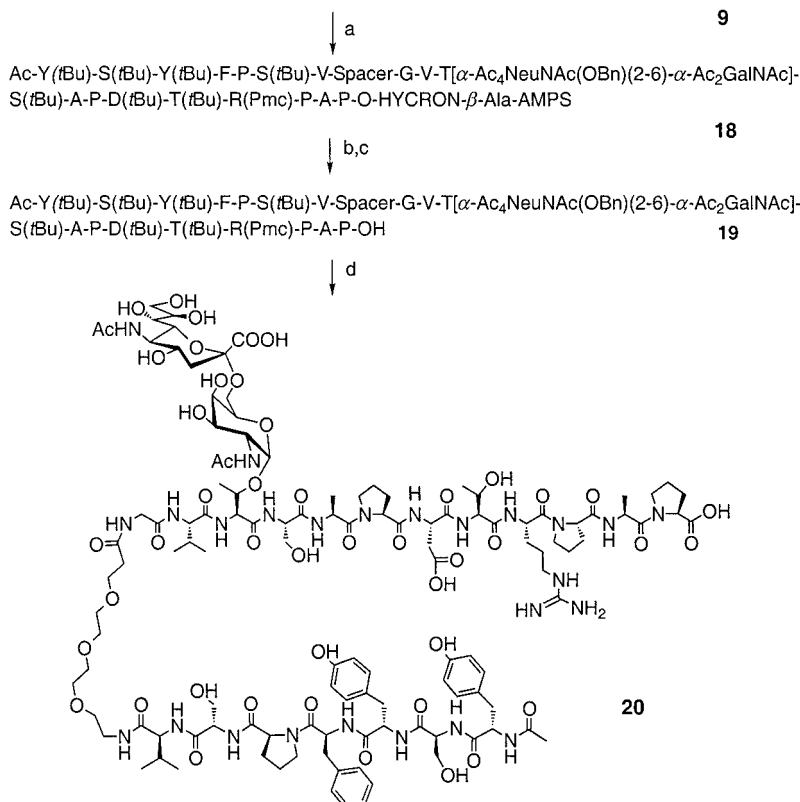


Scheme 2. a) Morpholine/DMF (1/1); b) Boc-Ala-OH, TBTU, HOBT, NMM, DMF; c) 1. CH₂Cl₂/TFA (1/1) 2. DIPEA, CH₂Cl₂; d) ten times [1. 2.-8., 10., and 11. coupling: Fmoc-AS-OH, TBTU, HOBT, NMM, DMF; 9. coupling: **7**; 2. capping: Ac₂O/pyridine (1/3); 3. Fmoc-removal: morpholine/DMF (1/1)]. Boc = *tert*-butoxycarbonyl, HOBT = hydroxybenzotriazole, TBTU = *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate, NMM = *N*-methylmorpholine, DIPEA = diisopropylethylamine, Pmc = 2,2,5,7,8-pentamethylchroman-6-sulfonyl, Fmoc = 9-fluorenylmethoxycarbonyl.

The TTX-T cell epitope-spacer conjugate **17** was obtained by Pd⁰-catalyzed cleavage of the allylic anchor.^[9] This fragment was coupled to the solid-phase-bound MUC1 glycododecapeptide after carboxy-group activation using HATU/HOAT^[19] to furnish the T-cell epitope-spacer-MUC1 antigen conjugate **18** (Scheme 4).

After Pd⁰-catalyzed cleavage of the HYCRON anchor and purification by means of preparative HPLC, the protected T cell epitope-spacer-MUC1 antigen conjugate **19** was isolated in pure form (as judged by NMR spectroscopy).^[20] Hydrogenolysis of the sialic acid benzyl ester, acidolysis of the side-chain protecting groups, and mild methanolysis of the O-acetyl groups gave the pure conjugate **20** (as analyzed by HPLC and NMR spectroscopy)^[21] in 47% yield. Compound **20** corresponds to the delineated construct **1** containing the tetanus toxin epitope, a spacer, and the tumor-associated MUC1 glycopeptide antigen.

H-G-V-T[α -Ac₄NeuNAc(OBn)(2-6)- α -Ac₂GalNAc]-S(*t*Bu)-A-P-D(*t*Bu)-T(*t*Bu)-R(Pmc)-P-A-P-O-HYCRON- β -Ala-AMPS



Scheme 4. a) **17**, HOAT/HATU/NMM, DMF, 20 °C, 2 d, 42 %; b) Ac₂O/pyridine (1/3); c) [Pd(PPh₃)₄], morpholine, DMF/DMSO (1/1) 20 % based on **8**; d) 1. Pd/C (10 %), H₂, MeOH, 20 °C, 1 h 2. CH₂Cl₂/TFA/thioanisole/ethanedithiol (10/10/1/1), 20 °C, 2 h 3. NaOMe, MeOH, pH 8.5, 20 °C, 18 h, 47 % over 3 steps. HOAT = 7-aza-1-hydroxy-1*H*-benzotriazole, HATU = *N*-(dimethylamino)-1*H*-1,2,3-triazol[4,5-*b*]-pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate.

For immunological evaluation, conjugate **20** and, for comparison, the MUC1 dodecapeptide, the MUC1 ST_N glycododecapeptide of identical sequence, the ST_N threonine conjugate, and the tetanus toxin–spacer conjugate (all in completely deblocked form) were applied to approximately 10⁵ peripheral blood lymphocytes (PBL) from four healthy donors in concentrations of 0.1 µg and 1 µg per 200 µL. Since a primary stimulation of the cells did not occur, restimulation with the same antigen was carried out after seven days until centers of proliferation appeared. According to an ELISA with murine antihuman IFN γ antibodies, cells from three of the four donors produced interferon- γ after the second restimulation with all these substances and before the T-cell growth factor interleukin 2 was added. After the fourth restimulation, the proliferation of the PBLs was measured by [³H]thymidine incorporation. Proliferation was found to a different extent for the cells from each donor with all of the five substances, and also in a medium free of fetal calf serum. However, the proliferation only proceeded in the presence of antigen-presenting cells (APCs) and was not found for purified T-cells. This is considered as distinct proof of an antigen-specific reactivity. The proliferating lymphocytes were characterized using monoclonal antibodies directed against surface antigens in a fluorescence-activated cell sorter

(FACS analysis). The analyses showed that conjugate **20** induces proliferation of up to 100 % for CD3-positive T-cells, and amongst those for 53 % of CD8-positive T-cells. The other substances also induced proliferation of CD3-positive T-cells, but a much lower extent of proliferation for the desired cytotoxic CD8-positive T-cells. These preliminary results justify the anticipation that conjugates of T cell epitopes and tumor-associated MUC glycopeptide antigens such as **20** can induce cytotoxic T-cell response^[22] and that on this basis efficient synthetic antitumor vaccines can be developed.

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- [16] Trihydrate of **7**: [α]_D²⁰ = 29.1 (*c* = 1.0, MeOH). MALDI-MS (MeOH, dihydroxybenzoic acid (DHB)): *m/z*: 1239.1 [*M* - H⁺ + K⁺ + Na⁺], 1223.3 [*M* - H⁺ + 2Na⁺], 1217.0 [*M* + K⁺], 1201.5 [*M* + Na⁺]; ¹H NMR (¹H-¹H COSY) (400 MHz, CD₃OD, TMS): δ = 4.99 (dd, 1H, J_{2,3} =

Synthesis and Membrane-Binding Properties of a Characteristic Lipopeptide from the Membrane-Anchoring Domain of Influenza Virus A Hemagglutinin**

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Key events in the establishment and progression of viral infection are attachment and fusion of the virus with the cell and budding of new virus particles from the infected cell. This complex multistep process is decisively influenced and determined by posttranslationally modified proteins embedded in the viral lipid bilayer. For instance, hemagglutinin from influenza virus A is glycosylated in the extracellular domain^[1, 2] and S-palmitoylated next to the transmembrane region (Figure 1).^[3, 4] The glycoprotein part is responsible for initiation of viral infection through selective binding to sialic acid receptors on the surface of the host cell. The lipid residues are required for the interaction between the cell membrane and the free capsid during budding of viral offspring^[5, 6] and are thought to mediate protein–protein and protein–lipid interactions in the viruses.^[7] In addition, the lipidated regions may play an important role in fusion processes of the viral membrane with the endosome after entry of the viral particle into the cell.^[8, 9] However, this proposal is controversial, since other investigations indicated that the lipidated cytoplasmic tail of the complex viral lipoglycoproteins is not essential for its membrane fusion activity.^[10]

For the study of these and related processes in precise molecular detail, lipidated peptides which represent the characteristic linkage region between the protein backbone and the lipid groups and which additionally carry a marker by which they can be traced in biological systems may be employed as efficient molecular probes.^[11] However, their synthesis is complicated by the pronounced base lability of the palmitic acid thioesters which hydrolyse spontaneously at pH > 7.^[12] For the synthesis of such labile peptide conjugates enzymatic methods may open up viable alternatives to classical chemical techniques.^[11] In this paper we report on the development of the *p*-phenylacetoxymethyl (PAOB) ester, a new enzyme-labile protecting group for carboxyl function-

- 11.7 Hz, $J_{3,4} = 3.2$ Hz, H-3), 4.90–4.84 (m, 2H, H-1, H-4'), 4.69 (dd, 1H, $J = 6.2$, 10.9 Hz, OCH₂Fmoc), 4.51 (dd, 1H, $J = 5.9$, 10.9 Hz, OCH₂Fmoc), 4.10 (dd, 1H, $J = 5.3$, 12.3 Hz, H-9'b), 3.84 (dd, 1H, $J_{5,6a} = 7.5$ Hz, $J_{6a,6b} = 10.3$ Hz, H-6a), 3.15 (dd, 1H, $J_{5,6b} = 4.4$ Hz, $J_{6a,6b} = 10.3$ Hz, H-6b), 2.69 (dd, 1H, $J_{3'e,3'a} = 12.6$, $J_{3'e,4} = 4.4$ Hz, H-3'e), 1.22 (d, 3H, $J = 6.5$ Hz, T^γ); ¹³CNMR (DEPT) (100.6 MHz, CD₃OD): δ = 100.77 (C-1), 99.93 (C-2'), 38.83 (C-3'), 19.32 (T^γ).
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- [20] **19**: $[\alpha]_D^{25} = -20.8$ (c = 1.0, CH₃CN). FAB-MS (nitrobenzyl alcohol (nba), positive ion): *m/z* (%): 3754.4 (62.3) [$M(2 \times {}^{13}\text{C}) - 4 \times (\text{tert-butyl}) + 2 \times \text{Na}^+$], calcd: 3753.74, 3755.1 (100) [$M(3 \times {}^{13}\text{C}) - 3 \times (\text{tert-butyl}) + 2 \times \text{Na}^+$], 3755.8 (82.7) [$M(4 \times {}^{13}\text{C}) - 4 \times (\text{tert-butyl}) + 2 \times \text{Na}^+$], 3757.2 (49.1) [$M(5 \times {}^{13}\text{C}) - 4 \times (\text{tert-butyl}) + 2 \times \text{Na}^+$]; ¹HNMR (400 MHz, [D₆]DMSO, TMS): δ = 8.48–7.41 (m, 18H, NH), 7.38 (m, 5H, H_A-Bn), 7.28–7.16 (m, 5H, H_A-F), 7.11 (d, 2H, $J = 7.9$ Hz), 7.03 (d, 2H, $J = 7.6$ Hz, 2 × (H2-Y, H6-Y)), 6.82–6.76 (m, 4H, 2 × (H3-Y, H5-Y)), 6.70, 6.55 (S_{br}, R^{NH}(ε,δ,γ)), 5.22–5.14 (m, 5H, H-4, H-7', H-8', CH₂Bn), 4.92–4.85 (m, 2H, H-1, H-3); 4.78–4.69 (m, H-4'), 4.65–3.24 (m, 58H, F^α, 2 × Y^α, 2 × V^α, 3 × S^α, 3 × S^β, CH₂CH₂(OCH₂CH₂CH₂)₂=CH₂CH₂, R^α, D^α, 2 × A^α, 4 × P^α, 2 × T^α, G^α, V^α, H-2, H-5, H-6', H-9', 2 × T^β, 4 × P^β, H-6a, H-5'), 3.22–2.60 (m, 10H, F^β, 2 × Y^β, H-6b, R^β, H-3'e), 2.57–2.38 (m, 4H, D^β, CH₂CH₂Pmc), 2.38–2.35 (m, 2H, CH₂CONH-G-V), 2.49, 2.46 (s, 6H, *o,o'*-CH₃Pmc), 2.18–1.58 (m, 18H, 4 × P^β, 4 × P^γ, CH₂CH₂Pmc), 2.03, 2.00, 1.99, 1.93, 1.91, 1.85, 1.82, 1.75, 1.71, 1.66 (10 × s, 30H, m-CH₃Pmc, 6 × OAc, 3 × NHAc), 1.53–1.02 (m, 9H, 2 × V^β, R^β, R^β, H3'a, 2 × A^β), 1.35, 1.23, 1.20, 1.15, 1.11, 1.08, 1.06, 1.05, (s, 69H, 7 × C(CH₃)₃, C(CH₃)₂Pmc), 0.98–0.90 (m, 3H, T^γ), 0.89–0.83 (m, 3H, T₂'), 0.82–0.78 (m, 12H, V^γ); ¹³CNMR (DEPT) (100.6 MHz, [D₆]DMSO): δ = 98.40 (C-1), 98.01 (C-2'), 41.18, 40.97, 38.40, 36.95, 35.87 (2 × Y^β, F^β, C-3', D^β, R^β, CH₂CONH), 32.12 (CH₂CH₂Pmc), 19.05, 18.98, 18.75, 18.75, 18.16, 18.07, 17.95 (2 × V^γ, T₁'), *o,o'*-CH₃Pmc), 16.77, 16.72, 16.00 (T₂'), 2 × A^β), 11.82 (m-CH₃Pmc).
- [21] **20**: $[\alpha]_D^{25} = -76.9$ (c = 1.0, H₂O); FAB-MS (nba + LiBr, positive ion): *m/z* (%): 2770.7 (0.62) [$M + \text{Li}^+$], calcd: 2770.30; ¹HNMR (¹H-¹H COSY) (400 MHz, D₂O): δ = 7.37–7.24 (m, 3H), 7.23, 7.16 (m, 2H, H_A-F), 7.08–6.97 (m, 4H, 2 × (H2-Y, H6-Y)), 6.81–6.72 (m, 4H, 2 × (H3-Y, H5-Y)), 4.90 (m, 1H, H-1), 4.72–4.66 (m, 1H, D^α), 4.64–4.59 (m, 2H, F^α, R^α), 4.57–4.50 (m, 1H, A₁'), 4.49–4.42 (m, 6H, A₂'), 2 × S^α, 2 × Y^α), 4.41–4.33 (m, 6H, 4 × P^α, S₃'), 4.32–4.29 (m, 2H, V₁'), 4.28–4.23 (m, 1H, T₁'), 4.22–4.17 (m, 1H, T₂'), 4.12–4.03 (m, 3H, H-2, V₂'), 4.01–3.27 (m, 40H, H-3, H-4, H-5, H-6, H-4', H-5', H-6', H-7', H-8', H-9', NH(CH₂CH₂O)₃CH₂CH₂CONH, 2 × S^β, G^α, 4 × P^β), 3.17 (m, 2H, R^β), 3.10–2.99 (m, 1H, F^β), 2.90–2.77 (m, 7H, 2 × Y^β, D^β, F^β), 2.67 (dd, 1H, H-3'e), 2.60–2.54 (m, 2H, CH₂CONH-G-V), 2.33–2.18 (m, 4H, 4 × P^β), 2.11–1.77 (m, 15H, 2 × V^β, 4 × P^β, 4 × P^γ, R^β), 2.03, 2.01, 1.93 (s, 9H, 3 × NHAc), 1.76–1.59 (m, 4H, H-3'a, R^β, R^γ), 1.34 (m, 6H, $J = 6.5$ Hz, 2 × A^β), 1.30–1.21 (m, 3H, T₁'), 1.15 (d, 3H, $J = 6.2$ Hz, T₂'), 0.97–0.85 (m, 12H, 2 × V^γ); ¹³CNMR (DEPT) (100.6 MHz, D₂O): δ = 99.62 (C-1), 99.20 (C-2'), 22.14, 21.94, 21.49, (3 × NHAc), 18.73, 18.39, 18.22, 17.54 (2 × T^γ, 2 × V^γ), 15.11, 14.92 (2 × A^β).
- [22] For the importance of this key property, see Section 2 in ref. [2a], p. 885.

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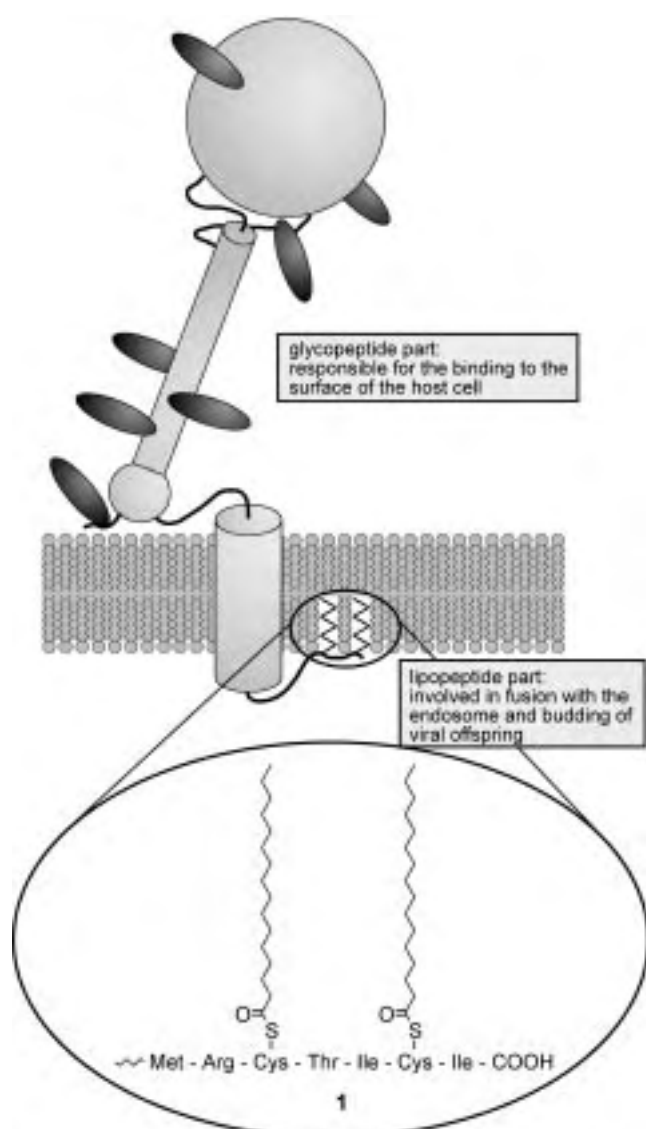
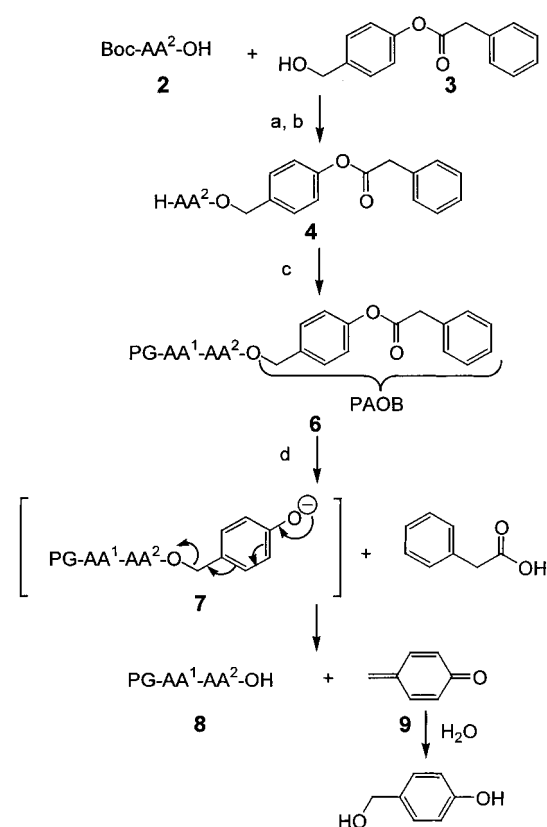


Figure 1. Schematic drawing of the glycosylated and lipidated influenza virus hemagglutinin A and the double-palmitoylated target peptide **1**.

alities, and its application in the construction of a fluorescent-labeled lipopeptide **1** from influenza virus A hemagglutinin.

In developing an enzyme-labile ester group that can be removed selectively under conditions that are mild enough for lipopeptide synthesis we resorted to the principle of fragmentation after cleavage of a suitable enzyme-labile bond. To this end, N-protected dipeptide PAOB esters **6** were synthesized (Scheme 1). The PAOB group embodies a phenylacetate which is specifically recognized and cleaved by the enzyme penicillin G acylase. Upon enzymatic hydrolysis a phenolate **7** is formed that fragments spontaneously to a quinone methide **9** and the desired carboxylic acids **8**. The quinone methide is trapped by water or added nucleophiles. This principle of deprotection by enzyme-induced fragmentation has been used for the development of enzyme-labile urethanes before.^[13, 14] We stress, however, that even in the case of the urethanes the success of the enzyme-mediated fragmentation at pH 6–8 was rather surprising. Nonenzymatic induction of the fragmentation reaction requires the use of strong bases



8	PG	AA ¹	AA ²	Yield (%)
8a	Aloc	Val	Ala	80
8b	Boc	Ser	Ile	80
8c	Boc	Thr	Phe	82
8d	Boc	Ala	Pro	82

Scheme 1. Synthesis and selective enzymatic deprotection of N-protected dipeptide PAOB ester **6**. a) DIC/DMAP (cat.), b) HCl/Et₂O, 63–90 % (2 steps); c) PG-AA¹-OH **5**, EEDQ, 71–87 %; d) phosphate buffer (pH 7), 10 % methanol, penicillin G acylase. Boc = *tert*-butoxycarbonyl, PG = protecting group, Aloc = allyloxycarbonyl, DIC = *N,N'*-diisopropylcarbodiimide, DMAP: 4-dimethylaminopyridine, AA = amino acid, EEDQ = 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline.

like ammonia^[15] whereas in the presence of the biocatalysts the unmasking even occurs at neutral pH. In addition, in the case of the urethane protecting groups the entire unmasking is driven by the liberation of CO₂, thus shifting the equilibrium to the product side. This driving force is no longer operative in the case of an ester blocking function. Thus it was highly questionable whether this principle could be transferred successfully from an amino to a carboxy protecting group.

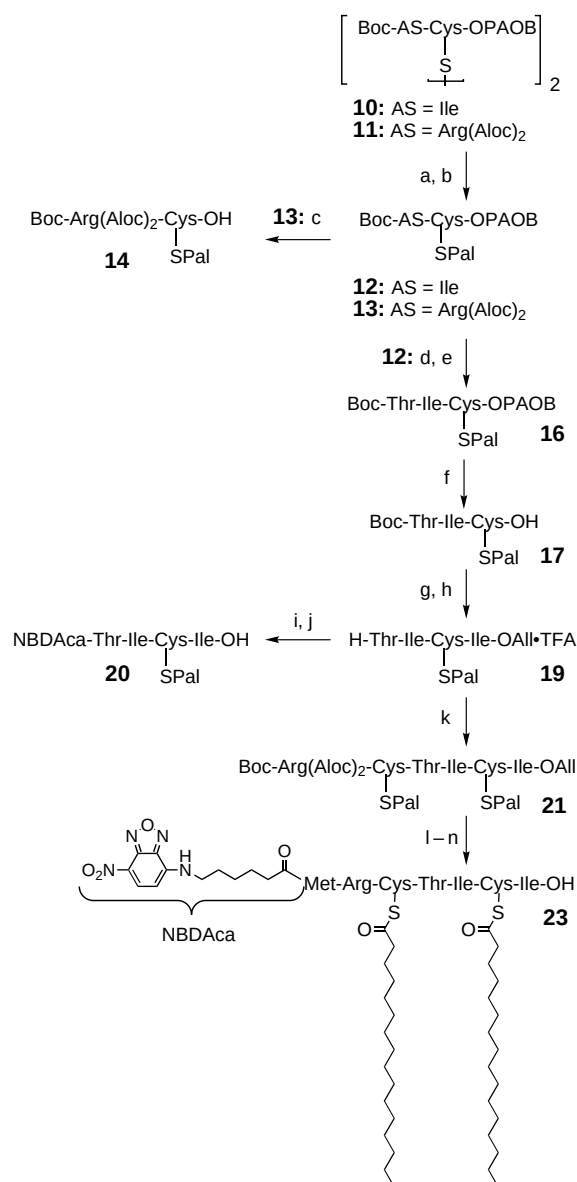
PAOB esters **6** were readily and efficiently synthesized by esterification of Boc-protected amino acids **2** with *p*-phenyl-acetoxybenzyl alcohol **3**, subsequent acid-mediated cleavage of the Boc group, and coupling of the resulting amino acid PAOB esters **4** with differently masked amino acids **5** (Scheme 1). Upon treatment of dipeptide PAOB esters **6** with penicillin G acylase at pH 7 and room temperature, to our delight, the desired selective C-terminal deprotection occurred smoothly. The enzyme saponifies the phenylacetate and, even at pH 7 and without the additional driving force of CO₂ liberation, the intermediately formed phenolates **7** undergo

fragmentation to the desired unmasked dipeptides **8**. Quinone methide **9** is efficiently trapped by water, addition of stronger nucleophiles is not necessary. Penicillin G acylase is a readily available (immobilized, native, and as cross-linked enzyme crystals (CLECs)) and very stable enzyme with a broad substrate tolerance which does not attack peptide bonds or urethanes. In addition, in the PAOB group the site of enzyme attack is remote from the differing amino acids of the substrates. Thus the efficiency of the enzyme-induced deprotection is nearly independent of steric bulk and structure (that is, D- or L-amino acids, acyclic or cyclic amino acids, see Scheme 1). The desired peptides **8a–8d** were obtained in high yield.

On the other hand the Boc and Aloc groups can be removed selectively from dipeptide esters **6** without harm to the PAOB esters, that is, the protecting groups are orthogonally stable to each other (data not shown, see also below).

The full capacity of the enzyme-labile PAOB ester became evident in the synthesis of fluorescent-labeled derivatives of virus hemagglutinin peptide **1** (Scheme 2). This synthesis is complicated by the base lability of the thioesters and the need to additionally protect and deprotect the basic arginine side-chain functionality. Thus, a set of three orthogonally stable protecting groups is required, whereby the use of base-labile and hydrogenolytically removable blocking groups is not permitted. This problem was overcome by using the acid-labile Boc group for the N terminus, the enzymatically removable PAOB ester for the C terminus, and the Pd⁰-sensitive Aloc group for the arginine guanidino side-chain function.

The synthetic sequence commenced with the construction of two S-palmitoylated dipeptide PAOB ester building blocks. Thus, cystinyl dipeptides **10** and **11** were synthesized in high yield as described above for other dipeptides. The disulfide bonds were then reduced by treatment with DTT and the liberated cysteine thiols were immediately converted into the corresponding palmitic acid thioesters (Scheme 2). S-Acylated dipeptides **12** and **13** were obtained in high yields. Upon treatment of arginyl peptide PAOB ester **13** with penicillin G acylase at pH 7 and 25 °C the C-terminal protecting group was hydrolyzed smoothly and without any undesired side reaction. The mildness of the reaction conditions and the substrate specificity of the biocatalyst guarantee that neither the thioester nor the bis-acylated guanidino group are attacked, and the selectively unmasked S-palmitoylated dipeptide **14** was isolated in high yield. The Boc group was removed selectively from isoleucyl peptide PAOB ester **12** and the peptide chain then was elongated with Boc-threonine to yield fully protected lipotriptide **16**. Once again treatment of S-palmitoylated tripeptide PAOB ester **16** with the enzyme penicillin G acylase at pH 7 and 25 °C resulted in a smooth and completely selective removal of the C-terminal enzyme-labile blocking function. Selectively deprotected tripeptide thioester **17** was isolated in high yield. The enzyme-catalyzed transformations proceed only if dimethyl-β-cyclodextrin is added to the reaction mixture. In the absence of this cyclic hexasaccharide PAOB ester **16** was not hydrolyzed at all. The cyclodextrin has a hydrophobic core with which it can slip over the hydrophobic palmitic acid group. Thereby it solubilizes the peptide and renders it accessible to the biocatalyst.



Scheme 2. Chemoenzymatic synthesis of **23**. a) DTT, NEt₃; b) 2 Pal-Cl, NEt₃, **12**: 83 %, **13**: 81 % (2 steps); c) penicillin G acylase, dimethyl-β-cyclodextrin, 0.05 M phosphate buffer (pH 7), 25 °C, 77 %; d) TFA; e) Boc-Thr-OH (**15**), EEDQ, NEt₃, 74 % (2 steps); f) penicillin G acylase, dimethyl-β-cyclodextrin, 0.05 M phosphate buffer (pH 7), 25 °C, 81 %; g) H-Ile-OAll-TosOH (**18**), EEDQ, NEt₃; h) TFA, 71 % (2 steps); i) NBDaca-OH, EDC, HOBT, NEt₃; j) Pd(PPh₃)₄, DMB, 69 % (2 steps); k) **14**, EEDQ, NEt₃, 46 %; l) TFA; m) NBDaca-Met-OH (**22**), EDC, HOBT, NEt₃; n) Pd(PPh₃)₄, DMB, 69 % (3 steps). Pal = palmitoyl, All = allyl, NBDaca = depicted in the scheme, DTT = dithiothreitol, TFA = trifluoroacetic acid, Tos = 4-toluenesulfonyl, EDC = N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride, HOBT = 1-hydroxybenzotriazole, DMB = dimethylbarbituric acid.

lyst. In addition, the formation of this inclusion complex may prevent the thioester from being hydrolyzed.

Next S-palmitoylated tripeptide carboxylic acid **17** was condensed with isoleucine allyl ester **18** and the Boc group was removed to deliver lipotetrapeptide **19** in high overall yield. Compound **19** was blocked as allyl ester at the C terminus to allow for simultaneous Pd⁰-catalyzed deprotection of both the arginine side-chain function and the

C-terminal carboxylic acid towards the end of the synthesis. C-terminal deprotected and S-palmitoylated dipeptide building block **14** and N-terminally unmasked lipotetrapeptide **19** were then condensed to give double-palmitoylated lipohexapeptide **21**. The N-terminal Boc group was removed from **21** and the fluorescent 7-nitrobenz-2-oxo-1,3-diazole (NBD) label was introduced. Finally, the three allyl-type blocking functions were cleaved by Pd⁰-catalyzed allyl transfer with *N,N'*-dimethylbarbituric acid as the accepting C nucleophile.^[16] Similarly, introduction of the NBD label followed by selective removal of the allyl ester yielded lipopeptide **20**. The desired fluorescent and palmitoylated influenza virus hemagglutinin lipopeptides **20** and **23** were obtained in high overall yield.

These compounds may, for instance, be applied advantageously to determine the membrane binding properties of the viral proteins. In order to demonstrate this possibility lipidated peptides **20** and **23** were subjected to an assay determining a kinetic value which characterized their binding to liposome model membranes.^[17]

For this assay methanolic solutions of the fluorescent-labeled lipopeptides **20** and **23** were mixed with a hundredfold molar excess of lipid (here: palmitoyl oleoyl phosphatidylcholine, POPC) and a twofold excess of a nonexchangeable fluorescence quencher (*N*-(lissamine rhodamine sulfonyl)phosphatidylethanolamine, Rho-DHPE). Both, lipid and quencher were dissolved in methanol. Buffer was added to generate mixed vesicles corresponding to a POPC concentration of 1 mM. Vesicles are trimmed by freeze–thaw cycles and extruder treatment^[18] to generate vesicles of a defined size distribution (approximately 100 nmØ). If the NBD fluorophore of the lipopeptide incorporated in such a vesicle is excited at 460 nm its fluorescence emission at 535 nm is directly absorbed by the rhodamine dye of the quencher when Rho-DHPE is close to the lipopeptide. Mixing those vesicles with an excess of pure POPC vesicles allows mobile lipopeptides to leave their original environment. They enter the quencher-free vesicles where their NBD fluorescence is not quenched any longer resulting in an increase in fluorescence emission at 535 nm (Figure 2a).

Mixed vesicles were generated containing 1 mol% of peptide **20** and **23** respectively and 2 mol% of Rho-DHPE. Only tetrapeptide **20** with a single palmitoyl-thioester showed an increase in fluorescence after mixing a solution of 5 µM POPC (mixed vesicles) with a 20-fold excess of pure POPC vesicles. This indicates the transfer of the lipopeptide to the vesicles free of Rho-DHPE, showing that one lipid modification is not sufficient for irreversible membrane insertion. In contrast the NBD emission of the heptapeptide **23** with two palmitoyl residues was not affected by the dilution with quencher-free vesicles (Figure 2b). This observation demonstrates that two C16 anchors are sufficient to fix the lipopeptide in its original environment.

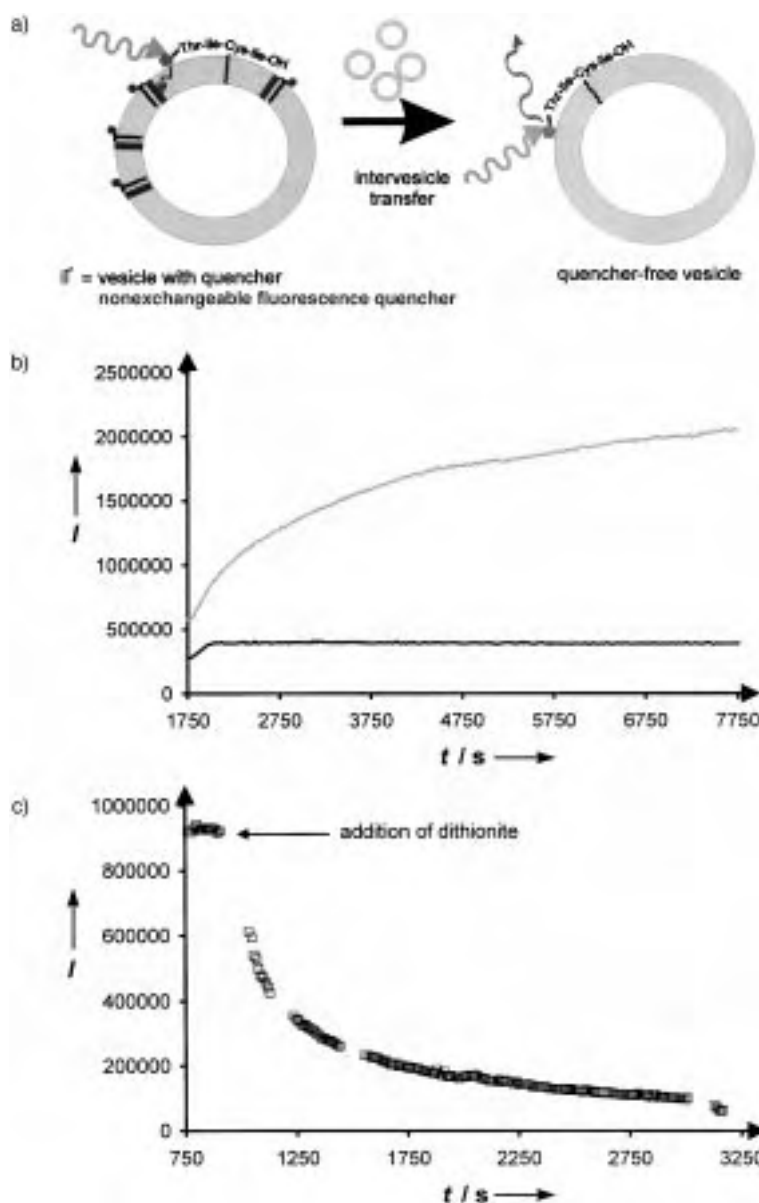


Figure 2. a) Principle of the intervesicle transfer of lipopeptides and the fluorometric detection employing a nonexchangeable fluorescence quencher; b) intervesicle transfer of the monopalmitylated tetrapeptide **20** (gray line) and the double-palmitylated heptapeptide **23** (black line); c) flip-flop diffusion of monopalmitylated tetrapeptide **20**. *I* = relative fluorescence.

The intervesicle transfer of lipopeptide **20** is composed of two separate processes. Peptides anchored at the outer face of the vesicle can directly migrate to the acceptor vesicle by diffusion. This step can be described as an irreversible first order mechanism if the acceptor vesicles are present in high excess. Depending on their distribution between inner and outer face of the vesicles the intravesicular lipopeptides have to perform a reversible flip-flop diffusion to appear on the outer face of the vesicles. In a first estimation we fitted the overall change in fluorescence for the tetrapeptide by a monoexponential function including a linear term for the flip-flop process. Best fits were obtained for a dissociation rate of $1.3 \times 10^{-3} \text{ s}^{-1}$ and a linear drift of 1.8×10^2 units of fluorescence s^{-1} . The drift corresponds to approximately 45 % of the fitted amplitude.

The separated analysis of the flip-flop exchange can be monitored by dithionite treatment of vesicles loaded with lipopeptide but without quencher. The addition of sodium dithionite resulted in fast reduction of all accessible NBD fluorophors at the outer face of the vesicles. This first loss of emission signal was followed by a slower decay, indicating the flip-flop of the intravesicular lipopeptides to the outside (Figure 2c).

The apparent rate constant for the intervesicle transfer of tetrapeptide **20** and heptapeptide **23** between POPC vesicles can be compared with data for lipopeptides with a single farnesyl modification or two hydrophobic residues (farnesyl thioether and palmitoyl thioester).^[19] Here half-times of 21 s for a peptide with the sequence NBD-GCMGLPC(Far)-OMe and 155 h for the peptide NBD-GC(Pal)MGLPC(Far)-OMe were calculated for experiments at 37 °C, while tetrapeptide **20** has a half-time of about 9 min at 20 °C. Thus, in comparison to a farnesyl thioether, a single palmitoyl group confers a significantly enhanced stability of membrane insertion, however desorption from the model membrane still occurs at a relatively fast rate. Combination of a farnesyl thioether with a palmitic acid thioester results in a very slow but still detectable intervesicle transfer, but in the presence of two palmitoyl groups desorption of membrane-bound lipidated peptides cannot be detected at all. Thus, a bis-palmitoyl membrane anchor will lead to quasi irreversible membrane-anchoring of doubly palmitoylated proteins which can only be reversed by hydrolysis of the palmitic acid thioester bonds.

These values correspond well to data recorded for model peptides, which are derived from other lipidated proteins (such as Rho) and which have been used to predict the membrane binding properties of their parent proteins.^[19, 20] Thus, determining a full set of data for several different hemagglutinin-derived lipopeptides in a detailed biophysical analysis should allow for an extrapolation to the membrane binding properties of this lipoglycoprotein as well.

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First Use of a Mineral Liquid Crystal for Measurement of Residual Dipolar Couplings of a Nonlabeled Biomolecule**

Hervé Desvaux,* Jean-Christophe P. Gabriel,* Patrick Berthault, and Franck Camerel

Dedicated to Professor Fred Wudl
on the occasion of his 60th birthday

The classic NMR strategy for determining the conformation of a biomolecule^[1] involves exploiting the combination of the scalar coupling ^3J , to obtain dihedral angle information, and the ^1H – ^1H dipolar cross-relaxation rate, which has a $(1/r^6)$ dependence where r is the internuclear distance. The limitation of this approach is that only short range structural information is obtained (a few bonds for the scalar coupling

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and distances of less than 5 Å for the relaxation). The consequence is that only a few constraints per nucleus can be detected so the accumulation of errors (for example, in multidomain proteins, oligosaccharides, or oligonucleotides) can lead to an imprecise overall structure. In order to circumvent this problem, a different approach has recently been proposed in which structural data that are defined relative to an absolute molecular frame are also used.^[2, 3] Methods that exploit residual dipolar couplings are particularly interesting.^[3, 4] However, as dipolar couplings are almost averaged to zero (values of tenths of Hertz) because of the almost isotropic overall tumbling of the solute molecule, it is necessary to render this tumbling more anisotropic. This can be achieved by replacement of the aqueous phase with an anisotropic medium such as a magnetically oriented mesophase.^[4] As a consequence new couplings, *D*, add to the usual scalar couplings, *J*, to split the signals by a few Hertz.^[5] By studying pairs of spins separated by well-known distances (any C–H or N–H bond) one can finally extract more precise and longer range structural information.^[5]

There are currently four types of organic/biologic liquid crystals (LCs) used successfully for this purpose: surfactant-based bicelles,^[4, 6, 7] purple membranes,^[8] phages,^[9] and cellulose microcrystals.^[10] Here, we propose the use of mineral liquid crystals (MLCs)^[11] to generate an anisotropic medium. The inherent advantages of this approach are numerous: (1) some MLCs can be well-aligned when a magnetic field is applied,^[12] even with only very small amounts of mineral materials (1–3% w/w, to be compared with 5–30% w/w for bicelles, 10% w/w for purple membranes, 5% w/w for phages, and 8% w/w for cellulose); (2) these MLCs, which are sometimes formed using polar solvents other than water, present nematic phases that are stable on a very long timescale (few years) and over a wide temperature range (the liquid-state temperature range of the solvent), in stark contrast with the organic LC systems whose stability is often an experimental problem for this type of NMR spectroscopic method;^[15] (3) the dissolved biomolecule can simply be recovered after the experiment by flocculation of the mineral colloid; and finally, (4) whereas, in the case of organic LCs, the NMR signal is strongly dominated by the liquid-crystal resonances due to the high ratio of LC molecules to biomolecules, in MLCs the absence of ¹H and ¹³C nuclei renders isotope labeling of the studied molecule unnecessary. This is obviously a major improvement especially for systems such as oligosaccharides or oligonucleotides for which labeling is chemically challenging and particularly expensive. In this communication, the potential of such MLCs for NMR spectroscopic structural characterization is demonstrated by reporting the residual C–H dipolar couplings observed for a nonlabeled pentasaccharide containing the Lewis^x motif (Figure 1), dissolved in a readily synthesized and handled aqueous suspension of V₂O₅.

Davidson and co-workers, in their study of the behavior of V₂O₅ aqueous suspensions in a magnetic field, have shown that the phase diagram of such suspensions presents a domain of concentration (0.13 < *c* < 0.2 M) in which the nematic phase flows and is easily oriented in a magnetic field.^[14, 16] We

therefore decided to work at a V₂O₅ concentration just slightly above 0.13 M, and at a pH value of 2.5. Once dissolved in a V₂O₅ aqueous suspension, the ¹H and ¹³C NMR shifts of the pentasaccharide were found to be identical to those in pure D₂O. The dynamic properties of the sugar in the nematic medium are affected in the expected fashion. The increase of the local correlation times, which is deduced from off-resonance proton dipolar cross-relaxation rates,^[17] results from the higher viscosity of the solution and this leads to the expected increase of the proton longitudinal and transverse self-relaxation rates; this indicates that the presence of paramagnetic impurities in V₂O₅ (V^{IV}) is of little importance. The differences between the ¹H,¹³C couplings (*J* + *D*) of the pentasaccharide dissolved in the MLC and the corresponding *J* values observed in pure D₂O at the same pH value are illustrated in Figure 1; they range between –4.4 Hz and

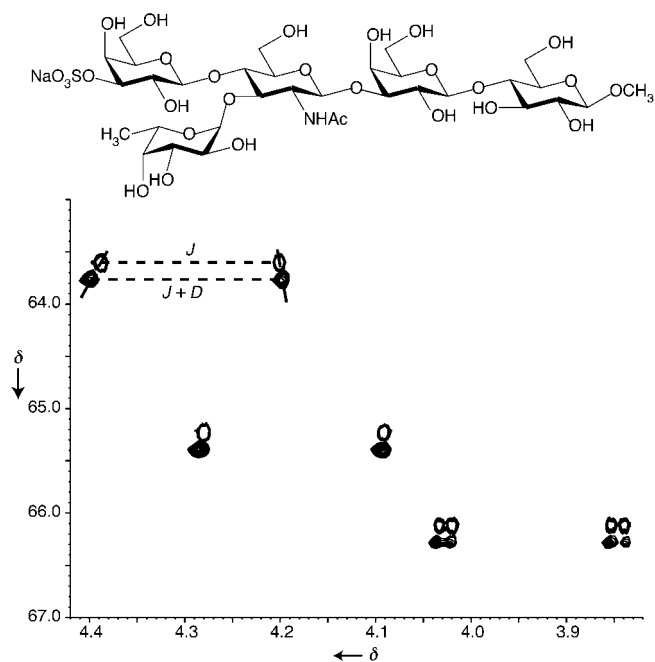


Figure 1. Overlay of a region of the ¹³C–¹H correlation maps of the pentasaccharide acquired in pure D₂O (light cross-peaks; this spectrum is shifted along the ¹³C dimension by 0.15 ppm for clarity) and in the MLC medium (dark cross-peaks). Since no decoupling is applied during the acquisition time, the *D* values can be extracted. For the three C–H pairs shown, which correspond to the C4 of the sulfated galactose unit, the C4 of the galactose unit, and the C3 of the fucose unit (from top left to bottom right), the *D* values are equal to 8.3, 2.0, and –0.4 Hz, respectively.

15.7 Hz.^[18] These *D* values are much larger than the experimental uncertainties in the measurement.^[19] They cannot be assigned to a relaxation mechanism, since this would also affect the natural linewidth of the peaks by at least the same order of magnitude.^[20, 21] We can therefore safely assign these additional splittings to the presence of residual dipolar couplings. This interpretation is substantiated by the similar *D* values found for all axial C–H bonds of each pyranoside unit.^[18, 22]

It is remarkable that at this low MLC concentration (<2.4% w/w) a relatively large variation in the peak splittings is observed for such a small molecule in both the ¹H and

^{13}C NMR spectra. This can be compared with the systems of Bolon and Prestegard^[23a] or Martin-Pastor and Bush,^[23b] who used about 20 % w/w of DHPC/DMPC in water to detect the orientation of oligosaccharides of similar size (DHPC and DMPC = 1,2-dihexanoyl- and 1,2-ditetradecanoyl-*sn*-glycero-3-phosphocholine, respectively). In these cases, the orientation of the biomolecule is induced by an excluded volume effect,^[24] because, since the anisotropy of the biomolecule is usually small, it requires a large volume fraction of bicelles to induce its partial orientation.^[24, 25] For V_2O_5 , the mechanism responsible for its orientation is expected to be more similar to that of the purple membrane, namely a highly charged surface that orients the biomolecule predominantly by electrostatic interactions, together here with numerous possible hydrogen bonds. The orientation tensors of the biomolecules in these two mediums (V_2O_5 and bicelles) are consequently expected to be different, which represents another reason for the development of new anisotropic media with the aim of ultimately obtaining more accurate structures.^[7]

We have shown that the use of MLCs at low concentrations ($\sim 2\text{--}3\%$ w/w), which are easy to handle, opens the way to the measurement of residual dipolar couplings of biomolecules without requiring isotopic labeling. This represents, to our knowledge, the first application of the mesogenic properties of an MLC. Finally, since V_2O_5 ribbons are stable in the pH range between 1 and 3, it is important to find other MLCs that could be used at more basic pH values. We are currently developing new MLCs that work at higher pH values as well as investigating known MLCs, such as clays of the montmorillonite (smectite) family,^[26] imogolite nanotubes (aluminosilicate),^[27] boehmite rods ($\gamma\text{-Al(OH)}_3$),^[28] and gibbsite disks (Al(OH)_3),^[29] either in their pure forms or doped with traces of paramagnetic metals in order to favor magnetic alignment.

Experimental Section

Synthesis: Various pathways for synthesizing V_2O_5 aqueous suspensions exist and have recently been described.^[30] However, for our NMR experiments, where we have studied nonexchangeable protons, it was relevant to use deuterated water ($\text{D}_2\text{O} > 95\%$). To limit the volume of D_2O needed, we scaled down the ion-exchange synthesis.^[30, 31] In a typical synthesis, sodium metavanadate (6.5 mL) dissolved in pure D_2O (99.90 % D, Euriso-Top; $[\text{NaVO}_3] = 1.0\text{ M}$) was passed through a column (inner diameter 1.1 cm, height 19.5 cm) filled with proton-exchanging resin (Dowex 50 W-X2, 50–100 mesh, 6.15 g) and eluted with pure D_2O (ca. 40 mL).

The resin was previously prepared by successively passing the following solutions through the column: 1) an aqueous NaOH solution (1.0 M, 10 mL); 2) pure H_2O (Millipore (18.2 M Ω cm), ca. 100 mL) until pH 7 was achieved; 3) an aqueous HCl solution (1.0 M, 10 mL); and finally, 4) pure H_2O (ca. 100 mL) until the pH value returned to 7. This treatment was repeated three times, with pure D_2O (ca. 100 mL) being used for the final rinse.

Once the eluent became colored, it was collected in fractions of 2.0 mL. After 24 h of aging, fractions 5 and 6 were homogeneous, viscous, birefringent, dark red gels of concentration, $\text{V}_2\text{O}_5 \cdot 128\text{D}_2\text{O}$ (6.64 % w/w, 0.43 M) and $\text{V}_2\text{O}_5 \cdot 320\text{D}_2\text{O}$ (2.77 % w/w, 0.17 M), respectively (measured by thermogravimetric analysis (TGA) up to 180 °C). The NMR sample is obtained by dilution of fractions 5 or 6 with D_2O , until the concentration of $\text{V}_2\text{O}_5 \cdot 380\text{D}_2\text{O}$ (2.34 % w/w, 0.15 M) was reached, which is very close to the boundary of the biphasic phase (2.22 % w/w, 0.13 M).^[16] From proton NMR spectra, we could estimate the enrichment to be approximately 95–96 %

D_2O . Since V_2O_5 suspensions have been reported to take about two weeks to reach chemical equilibrium,^[30] they were allowed to age for about a month prior to use in the NMR experiments. The ^2H splitting of the bulk water due to the orientation of the MLC was 91 Hz, in agreement with ref. [14a].

NMR experiments were performed at 293 K on a Bruker DRX spectrometer (18.6 T; 800 MHz for ^1H spectra) with an inverse 5 mm triple resonance probehead. Two samples containing 0.31 mg of the pentasaccharide^[32] were used, one dissolved in 400 μL D_2O and the other in 400 μL of the MLC medium (0.8 mm). ^1H , ^{13}C 2D maps were acquired using the HSQC sequence with sensitivity enhancement and gradient selection.^[34] No decoupling was applied during the 0.95 s acquisition time (resolution 0.53 Hz). The precision on the ^1H , ^{13}C dipolar splitting, D , was estimated to be in the order of 1 Hz.

The recovery of the biomolecule from the MLC can be readily achieved since most MLCs are based upon suspensions of charged colloids. Their flocculation can be induced, as predicted by the DLVO theory,^[35] by increasing the ionic force of the medium.^[36] The flocculus can be removed by centrifugation or filtration, and the biomolecule can then be extracted from the supernatant by methods such as chromatography, dialysis, or by extraction with organic solvent.

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- $$D_{ij} = S \frac{\gamma_i \gamma_j \hbar}{r_{ij}^3} \left[A_a \left(\frac{3}{2} \cos^2 \theta - \frac{1}{2} \right) + A_r \frac{3}{4} \sin^2 \theta \cos^2 \phi \right] \quad (1)$$
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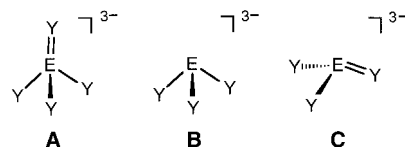
Novel Approach to Mixed Group 15/16 Element Ligands—Formation of Unusual Trichalcogenophosphonato Ligands in Mixed Fe/Cr Clusters**

Manfred Scheer,* Shubhangi B. Umbarkar, Saurav Chatterjee, Rajiv Trivedi, and Pradeep Mathur*

Dedicated to Professor Henri Brunner on the occasion of his 65th birthday

Complex chemistry of “naked” main group element ligands has been a fascinating area of research over the last few decades. Within this field, ligands consisting of different main group elements are scarce and are only well established between Group 15 and Group 16 elements.^[1] Known synthetic approaches for obtaining such complexes make use of E_4Y_n cages (*E* = element from Group 15, *Y* = element from Group 16, *n* = 3, 4) or their metal salts, such as $M_3^+AsS_3$; another method is the chalcogenation of pnictogenido complexes. Recently Fenske et al. have used $SP(SSiMe_3)_3$ as a precursor to $(PS_4)^{3-}$ and $(P_2S_6)^{4-}$ ligands.^[2]

While EY_4^{3-} (type **A**; *E* = P, As; *Y* = S, Se) is established as a ligand in some complexes, the molecular structure of the complexed EY_3^{3-} ligand (type **B**) has only been observed for *E* = As in $[Cp'_2Ti_2(\mu-O)(\mu-AsS_3)]$ ($Cp' = \eta^5-C_5H_4Me$)^[3] and for *E* = P in $[Pd_3(PS_4)(PS_3)(PEt_3)_4]$.^[2b] So far complexes of type **C** ligands are unknown.

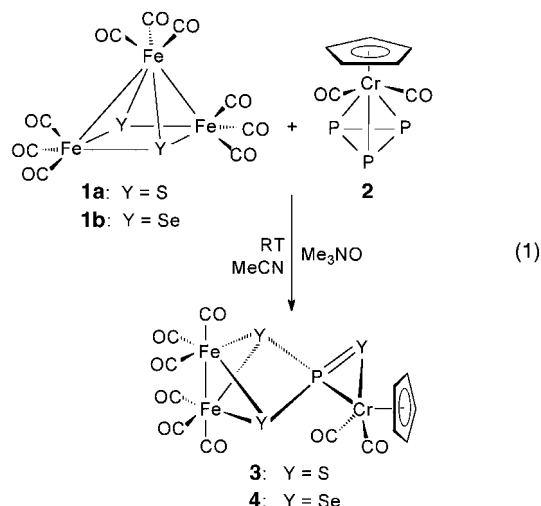


We report here a novel synthetic approach to mixed Group 15/16 element ligands by using the reaction of Group 15 element complexes with those of Group 16. This method leads to novel trichalcogenophosphonato ligands of type **C** (*Y* = S, Se). Our initial attempts to prepare mixed-metal clusters containing mixed chalcogenide/phosphorus bridging ligands centered on thermolysis and photolysis reactions between $[Fe_3(CO)_9(\mu_3-Y)_2]$ (*Y* = S (**1a**) or Se (**1b**)) and $[CpCr(CO)_2(\eta^3-P_3)]$ (**2**). Under such conditions, no new product was obtained; either the starting materials were

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recovered intact or, after extended reaction periods, complete decomposition of **1** occurred. We therefore resorted to the use of trimethylamineoxide (Me_3NO) for labilization purpose, and from the reaction of **1** with **2** in acetonitrile, in the presence of Me_3NO , we could isolate the new complexes, $[\{\text{Fe}_2(\text{CO})_6\}(\mu_3\text{-Y}_3\text{P})\{\text{CpCr}(\text{CO})_2\}]$ ($\text{Y}=\text{S}$ (**3**) or Se (**4**)) [Eq. (1)].



The IR spectra of the products indicate the presence of only terminally bonded carbonyl groups, and the ^1H NMR spectra for both compounds show the signal for the Cp protons split into a small doublet due to coupling with the P atom. The ^{31}P NMR spectra show a singlet and, for **4**, two pairs of satellites due to different $^{31}\text{P}/^{77}\text{Se}$ couplings are also revealed. Mass spectra of both compounds showed molecular ion peaks and fragments arising from CO loss.

Single-crystal X-ray structure analyses were carried out for **3** and **4**. They are isostructural and crystallize with two independent molecules in the unit cell. Both molecules are similar in their structural parameters and a representative molecular structure of one of the molecules is shown in Figure 1.^[4] The structure consists of a butterflylike $[\text{Fe}_2(\text{CO})_6\text{Y}_2]$ unit and a $[\text{CpCr}(\text{CO})_2\text{Y}]$ moiety; these are connected by a $\mu_3\text{-P}$ bridge which is bonded to the three chalcogenides and one Cr atom. The structures of **3** or **4** can be considered as the metal-substituted derivatives of a trithio- or triselenophosphonate, respectively, in which the P atom is bonded to a Cr atom and reveals two different chalcogen bonding modes. One P–Y bond in both compounds is shorter than the other two (P–S: 1.9761(10) in contrast to 2.1152(10) and 2.1202(10) Å; P–Se: 2.132(13) in contrast to 2.286(16) and 2.282(16) Å) and comparable to the P–Y double bond distances reported in the literature: 1.949 Å (av) in P_4S_5 ,^[5] 1.949 Å (av) in $[\text{Cp}_4\text{Fe}_4(\text{P}_2\text{S}_2)_2]$,^[6] 2.116 Å (av) in P_4Se_5 ,^[7] and 2.101 Å (av) in $[\text{Cp}_4\text{Fe}_4(\text{P}_2\text{Se}_2)_2]$.^[6] The other P–Se bond lengths in **4** are also comparable to the P–($\mu_2\text{-Se}$) and P–($\mu_3\text{-Se}$) bond lengths in $[\text{Fe}_4\text{Se}_2(\mu\text{-Se}_2\text{PCtBu})(\text{CO})_{11}]$.^[8] The three-membered Cr–P–Y subunit in **3** and **4**, which arises from the side-on coordination of the trithio- or triselenophosphonate ligand has been observed in the compounds $[\text{Cp}_4\text{Cr}_4(\text{CO})_9(\text{P}_4\text{Y}_3)]$, which were obtained from the thermolysis of

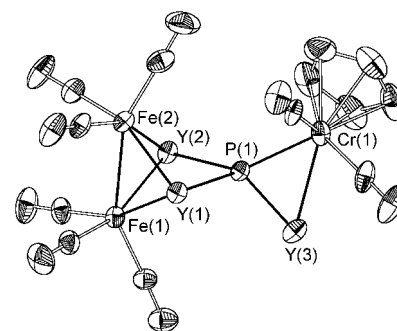


Figure 1. Representative molecular structure from the X-ray crystal structure analyses of **3** and **4** (molecule A, showing 30% probability ellipsoids; hydrogen atoms are omitted for clarity). Selected bond lengths [Å] and angles [°]: **3** ($\text{Y}=\text{S}$): Cr(1)–P(1) 2.2125(9), Cr(1)–S(3) 2.5514(12), P(1)–S(3) 1.9783(10), P(1)–S(1) 2.1188(10), P(1)–S(2) 2.1204(10), Fe(1)–S(1) 2.2706(9), Fe(1)–S(2) 2.4704(9), Fe(2)–S(1) 2.2801(9), Fe(2)–S(2) 2.2790(8); Cr(1)–P(1)–S(3) 74.77(4), P(1)–S(3)–Cr(1) 56.80(3), P(1)–Cr(1)–S(3) 48.43(3), S(1)–P(1)–S(2) 85.84(4), P(1)–S(1)–Fe(1) 89.86(4), P(1)–S(1)–Fe(2) 86.66(4), P(1)–S(2)–Fe(1) 86.66(4), P(1)–S(2)–Fe(2) 86.65(4). **4** ($\text{Y}=\text{Se}$): Cr(1)–P(1) 2.218(2), Cr(1)–Se(3) 2.6859(18), P(1)–Se(3) 2.132(2), P(1)–Se(1) 2.2815(19), P(1)–Se(2) 2.2861(18), Fe(1)–Se(1) 2.3887(12), Fe(1)–Se(2) 2.3915(13), Fe(2)–Se(1) 2.3936(12), Fe(2)–Se(2) 2.4024(11); Cr(1)–P(1)–Se(3) 76.22(7), P(1)–Se(3)–Cr(1) 53.33(6), P(1)–Cr(1)–Se(3) 50.44(6), Se(1)–P(1)–Se(2) 85.31(7), P(1)–Se(1)–Fe(1) 89.97(5), P(1)–Se(1)–Fe(2) 86.43(6), P(1)–Se(2)–Fe(1) 89.79(6), P(1)–Se(2)–Fe(2) 86.12(5).

$[\text{Cp}_2\text{Cr}_2(\text{CO})_6]$ with P_4Y_3 ($\text{Y}=\text{S}$,^[9] Se ^[10]). The structures of $[\text{Cp}_4\text{Cr}_4(\text{CO})_9(\text{P}_4\text{Y}_3)]$ also feature a $\text{CpCr}(\text{CO})_2$ fragment connected to a P–Y subunit ($\text{Y}=\text{S}$, Se) with comparable P–Y bond lengths but longer Cr–P bond lengths (2.282 Å (av) for $[\text{Cp}_4\text{Cr}_4(\text{CO})_9(\text{P}_4\text{S}_3)]$ and 2.29 Å (av) for $[\text{Cp}_4\text{Cr}_4(\text{CO})_9(\text{P}_4\text{Se}_3)]$) than those in **3** (2.2148(9) Å) and **4** (2.218(8) Å). Assuming that the PY_3 ligand contributes three electrons to the Cr atom and six electrons to the Fe_2 unit, the 18-electron count for all three metal centers in **3** and **4** is satisfied.

Formation of the new clusters formally involves the following: conversion of $[\text{Fe}_3(\text{CO})_9(\mu_3\text{-Y})_2]$ into an open $[\text{Fe}_2(\text{CO})_6(\mu_2\text{-Y})_2]$ butterfly unit and loss of a P_2 unit from $[\text{CpCr}(\text{CO})_2\text{P}_3]$ to form a $[\text{CpCr}(\text{CO})_2\text{P}]$ fragment, which abstracts one Y atom from $[\text{Fe}_3(\text{CO})_9(\mu_3\text{-Y})_2]$ such that an intermediate of the form $[\text{CpCr}(\text{CO})_2\text{PY}]$ is obtained. New bond formation between the two Y atoms in another $[\text{Fe}_2(\text{CO})_6(\mu_2\text{-Y})_2]$ moiety and the P atom in the $[\text{CpCr}(\text{CO})_2\text{PY}]$ unit yields **3** and **4**.

The results show the high synthetic potential of the novel approach to the production of mixed Group 15/16 element ligand complexes. Through the reaction between complexes of Group 15 and Group 16 elements complexes revealing novel coordination modes can be obtained. We are presently extending this approach to obtain different mixed Group 15/16 ligand complexes as well as investigating other methods for the activation of the starting materials, such as photolysis and ultrasonic activation.

Experimental Section

3 and **4**: In a typical preparation, a solution of trimethylamineoxide (44 mg, 0.6 mmol) in acetonitrile was added dropwise to an acetonitrile solution (50 mL) of $[\text{CpCr}(\text{CO})_2(\eta^3\text{-P}_3)]^{[12]}$ (0.052 g, 0.2 mmol) and either $[\text{Fe}_3(\text{CO})_9(\mu_3\text{-S})_2]^{[11]}$ (0.290 g, 0.6 mmol) or $[\text{Fe}_3(\text{CO})_9(\mu_3\text{-Se})_2]^{[11]}$ (0.34 g, 0.6 mmol) with constant stirring at room temperature under an argon

atmosphere. The solution was stirred for 30 min at room temperature and was closely monitored by thin layer chromatography. The solvent was removed under vacuum and the residue was dissolved in dichloromethane. The solution was filtered through Celite to remove the insoluble material and the solution was subjected to chromatographic workup using silica gel thin layer chromatography plates. Elution with *n*-hexane yielded a single brown band which contained **3** (30 mg, 25%) or **4** (46 mg, 32%).

Compound **3**: IR (*n*-hexane): $\tilde{\nu}(\text{CO}) = 2083(\text{s}), 2050(\text{vs}), 2014(\text{vs}), 1999(\text{m}), 1919(\text{m}) \text{ cm}^{-1}$; EI-MS (70 eV, 180 °C): m/z (%): 579.7 (6) [M^+], 523.7 (24) [$M^+ - 2\text{CO}$], 439.9 (26) [$M^+ - 5\text{CO}$], 411.6 (9) [$M^+ - 6\text{CO}$], 383.7 (22) [$M^+ - 7\text{CO}$], 355.7 (100) [$M^+ - 8\text{CO}$], 292.7 (52) [$M^+ - 8\text{CO} - \text{PS}$], 227.7 (25) [$M^+ - 8\text{CO} - \text{PS} - \text{Cp}$]; ^1H NMR (250.113 MHz, 298 K, CDCl_3 , TMS): $\delta = 4.90$ (d, $^3J(\text{P,H}) = 1.8 \text{ Hz}$, 5H); ^{31}P NMR (101.256 MHz, 298 K, CDCl_3 , 85% H_3PO_4 ext.): $\delta = 260.7$; m.p. 136–137 °C; elemental analysis (%) calcd for $\text{C}_{13}\text{H}_5\text{CrFe}_2\text{O}_8\text{PS}_3$: C 26.9, H 0.86; found: C 26.2, H 1.3.

Compound **4**: IR (*n*-hexane): $\tilde{\nu}(\text{CO}) = 2075(\text{s}), 2042(\text{vs}), 2006(\text{vs}), 1991(\text{m}), 1985(\text{s}), 1920(\text{m}) \text{ cm}^{-1}$; EI-MS (70 eV, 180 °C): m/z (%): 721.8 (7) [M^+], 665.8 (20) [$M^+ - 2\text{CO}$], 581.7 (21) [$M^+ - 5\text{CO}$], 497.8 (100) [$M^+ - 8\text{CO}$], 432.7 (12) [$M^+ - 8\text{CO} - \text{Cp}$], 321.8 (34) [$M^+ - 2\text{Fe} - 8\text{CO} - \text{Cp}$]; ^1H NMR (250.113 MHz, 298 K, CDCl_3 , TMS): $\delta = 4.88$ (d, $^3J(\text{P,H}) = 2.01 \text{ Hz}$, 5H); ^{31}P NMR (101.256 MHz, 298 K, CDCl_3 , H_3PO_4 ext.): $\delta = 235.1$ (s, $J(\text{P,Se}) = 95.9$ and 269 Hz); m.p. 142–143 °C; elemental analysis (%) calcd for $\text{C}_{13}\text{H}_5\text{CrFe}_2\text{O}_8\text{PSe}_3$: C 21.6, H 0.69; found: C 21.5, H 1.15.

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- [4] Crystal structure analysis of **3** and **4**: STOE IPDS area-detector diffractometer with $\text{AgK}\alpha$ radiation ($\lambda = 0.56087 \text{ \AA}$) for **3** and $\text{MoK}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$) for **4**. The structures were solved by direct methods using SHELXS-86,^[13a] and refined by full matrix least squares on F^2 using SHELXL-93,^[13b] with anisotropic displacement for non-H atoms. H atoms were placed in idealized positions and refined isotropically using a riding model. **3**: $\text{C}_{26}\text{H}_{10}\text{Cr}_2\text{Fe}_4\text{O}_{16}\text{P}_2\text{S}_6$, $M_r = 1160.04$, crystal size $0.40 \times 0.20 \times 0.03 \text{ mm}$, monoclinic, space group $P2_1/n$, $a = 7.5570(15)$, $b = 21.477(4)$, $c = 24.213(5) \text{ \AA}$, $\beta = 96.11(3)^\circ$, $V = 3907.5(13) \text{ \AA}^3$, $T = 213(2) \text{ K}$, $Z = 4$, $\rho_{\text{calcd}} = 1.972 \text{ Mg m}^{-3}$, $\mu(\text{AgK}\alpha) = 12.66 \text{ cm}^{-1}$; 14890 independent reflections ($2\theta_{\text{max}} = 52^\circ$, $R_{\text{int}} = 0.0669$), 505 parameters, $wR_2 = 0.1400$; R_1 (10513 with $F_o = 4\sigma(F_o)$) = 0.0483. **4**: $\text{C}_{26}\text{H}_{10}\text{Cr}_2\text{Fe}_4\text{O}_{16}\text{P}_2\text{Se}_6$, $M_r = 1441.44$, crystal size $0.30 \times 0.15 \times 0.01 \text{ mm}$, monoclinic, space group $P2_1/n$, $a = 7.5355(2)$, $b = 21.868(2)$, $c = 24.809(3) \text{ \AA}$, $\beta = 96.16(3)^\circ$, $V = 4172.4(10) \text{ \AA}^3$, $T = 293(2) \text{ K}$, $Z = 4$, $\rho_{\text{calcd}} = 2.295 \text{ Mg m}^{-3}$, $\mu(\text{MoK}\alpha) = 72.31 \text{ cm}^{-1}$; 8095 independent reflections ($2\theta_{\text{max}} = 52^\circ$, $R_{\text{int}} = 0.0816$), 505 parameters, $wR_2 = 0.1164$; R_1 (5107 with $F_o = 4\sigma(F_o)$) = 0.0480. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-148123 and CCDC-146124. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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About the Chemistry of Phosphorus Suboxides**

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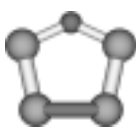
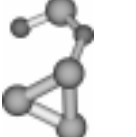
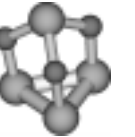
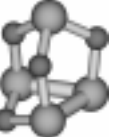
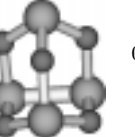
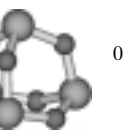
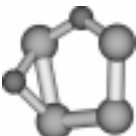
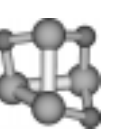
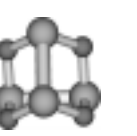
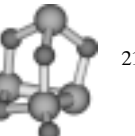
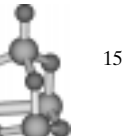
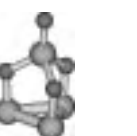
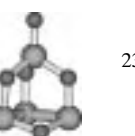
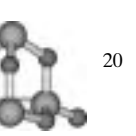
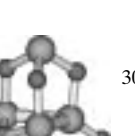
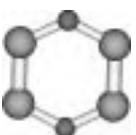
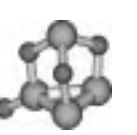
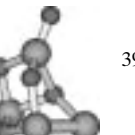
While the molecular phosphorus subsulfides P_4S_3 , P_4S_4 , and P_4S_5 are well known,^[1] various attempts to prepare the corresponding molecular phosphorus suboxides have failed so far. In its polymeric form phosphorus suboxide “ P_4O ” was already mentioned in 1832^[2] but in molecular form P_4O has been detected only in rare gas matrices.^[3] Using IR spectroscopy combined with ab initio calculations^[4] it was possible to identify the geometries of three different isomers of P_4O . The energetically most favorable isomer of P_4O possesses a planar five-membered ring (isomer **I** in Table 1), while a terminal (isomer **III** in Table 1) and a bridged-bonded isomer (isomer **II** in Table 1), which are closely related to the tetrahedral structure of the P_4 molecule, were found to lie much higher in energy.^[4]

While the structure of P_4O is known, very little is known about its chemistry. For the other phosphorus suboxides P_4O_n ($n = 2–5$), even structural information is missing. The question why phosphorus subsulfides have been prepared, but analogous oxides could not be isolated is generally answered by the statement that P–O bonds are more stable than P–S bonds, however, detailed thermodynamical data of phosphorus suboxides are not known. In order to extract a building-up

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Table 1. Structures and calculated energies [kcal mol⁻¹]. The energies are given relative to the lowest lying isomer of the respective summation formula. The dark centers represent oxygen.

Isomer	P ₄ O	P ₄ O ₂	P ₄ O ₃	P ₄ O ₄	P ₄ O ₅	P ₄ O ₆
I	 0	 0	 0	 0	 0	 0
II	 15	 4	 28	 1	 21	 15
III	 32	 6	 29	 9	 23	 20
IV	 31	 15	 29	 15	 30	—
V	—	 25	—	 24	 39	—

principle for phosphorus suboxides the present study determines the geometrical structure and the relative energy of various isomers of compounds with the summation formula P₄O_n (*n* = 1–6); the corresponding heats of formation are computed to gain more insight into the chemistry of phosphorus suboxides.

Due to its unusual bonding a prediction of the most stable isomers of P₄O_n (*n* = 2–5) represents a difficult task. P₄O already illustrates the problem. Its most stable isomer possesses an entirely different structure than that of the tetrahedral P₄, while those isomers structurally related to the tetrahedron lie higher in energy. To ensure that the lowest energy isomer is found in the present study a simulated annealing procedure^[5] is used as a first step to obtain the geometrical parameters of a large number of local minima on the potential energy surface (PES) of the respective summation formula. In the second step the energetically low-lying isomers of this set are determined by single point density functional theory (DFT) calculations.^[6] Finally, the geometries of the lowest lying isomers are refined using the DFT approach.^[7, 8]

Table 1 contains the calculated relative stabilities of various P₄O_n (*n* = 1–6) isomers and includes sketches of the respective geometrical structures.^[9] In addition to the known isomers of P₄O^[4] Table 1 presents data for a structure (isomer

IV) closely related to the most stable isomer of P₄O₂ (see below). For P₄O₆ we included in addition to the well-known cage structure information on two possible low-lying isomers (Table 1). According to our calculations, the most stable isomer of P₄O₂ has an unexpected structure. It is composed of an isosceles P₃ triangle and one O–P–O chain. The base of the triangle has a bond length of 2.05 Å, while the two other bonds are somewhat longer (2.2 Å). The P–O bond connecting the P₃ triangle with the O–P–O fragment is found to be 1.75 Å. The P–O bond lengths within the O–P–O fragment are 1.64 Å (inner) and 1.50 Å (terminal), respectively. The reason for the stability of this isomer may lie in the P₃ triangle which was found in many stable P_n clusters.^[10] Isomer **II** of P₄O₂ is about 4 kcal mol⁻¹ less stable than isomer **I**^[11] according to the present calculations. Its structure is closely related to the most stable isomer of P₄O. Isomer **III** of P₄O₂, which is about 6 kcal mol⁻¹ less stable than the most stable isomer, can be related to the P₄ tetrahedron by replacing two P–P bonds by P–O–P units. Isomer **IV**, which possesses one terminal P–O bond, is less stable by about 15 kcal mol⁻¹. In their study, McCluskey and Andrews^[3] computed further isomers of the type of isomer **V**, but as shown by our computations such structures are even less stable than the structures discussed so far. While the structural relationships between the isomers of P₄, P₄O, and P₄O₂ are quite complicated, the building-up

principle for the higher phosphorus suboxides P_4O_n ($n \geq 3$) is straightforward. The energetically low-lying isomers of these phosphorus suboxides are related to the most stable isomer of P_4O_3 , which is composed of a PO_3 unit and a P_3 ring. The structures of the low-lying isomers of P_4O_n ($n > 3$) are obtained either by inserting the additional oxygen atom into one of the P–P bonds, that is by replacing a P–P bond by a P–O–P unit or by adding an oxygen atom in a terminal position. Energetically, the former isomers are found to be always lower than the latter. Examples for these rules are P_4O_4 (isomer **I** in comparison to isomer **III**) and P_4O_5 (isomer **I** compared to isomers **II–IV**). Similarly, for P_4O_6 only the cage structure (isomer **I**) but not the structure with terminally bonded oxygen (e.g. isomer **II**) is known.^[12] Isomer **II** of P_4O_4 is not directly related to isomer **I** of P_4O_3 but to its isomer **II**. However, while for P_4O_3 isomer **II** is about 28 kcal mol^{−1} higher in energy than isomer **I**, for P_4O_4 the energy gap between isomers **I** and **II** is about zero.

From our computed data, the basis for the structural and energetic rules discussed above become clear. For oxygen-rich compounds P_4O_n ($n > 4$) the stability of the P–O–P unit (i.e. two P–O single bonds) in comparison to the stability of one P–P single and one terminal P=O double bond, determines the structures of the energetically most favorable isomers. According to our calculations isomers possessing terminal oxygen atoms lie about 15–25 kcal mol^{−1} above those isomers with a P–O–P unit. For P_4O_n clusters possessing fewer oxygen atoms the P_3 ring represents an additional stabilizing structural unit, which can be seen from the energy difference between isomer **I** and **II** of P_4O_3 (28 kcal mol^{−1}). Both isomers possess the same number of P–O and P–P bonds but only isomer **I** possesses a P_3 ring. Both, isomers **I** and **II** of P_4O_4 possess also the same number of P–O and P–P bonds; in contrast to P_4O_3 neither of these isomers contains a P_3 ring, and in line with our arguments, both structures are found to be essentially equal in energy. In addition the similar stability of both isomers suggests that the question whether the P–P bonds are adjacent or not is of minor importance.

The P_3 ring stabilizes also isomer **III** of P_4O_4 . Formally isomer **III** is obtained from isomer **I** by replacing one P–O–P unit by one P–P single bond and one terminal P–O bond. While for P_4O_5 and P_4O_6 such a replacement leads to a destabilization of about 20 kcal mol^{−1}, in the case of isomer **I** and **III** of P_4O_4 a destabilization of less than 10 kcal mol^{−1} is computed. Nevertheless, the stabilization effect of the P_3 ring strongly depends on its substituents. One example is the energy difference between isomer **III** and **V** of P_4O_4 (≈ 15 kcal mol^{−1}). In isomer **III** the P_3 ring is an equilateral triangle with P–P bond lengths of about 2.24 Å. In isomer **V** the C_{3v} symmetry is distorted by the terminal oxygen atom. While the P–P bonds adjacent to the terminal P–O bond do not change (2.25 Å) significantly, the base of the triangle elongates by about 0.2 Å. As already discussed, the energetic ordering of oxygen-rich phosphorus suboxides P_4O_n ($n > 4$) is determined by the stability of the P–O–P unit. Nevertheless, in these compounds the stabilizing effect of the P_3 ring is also found. One example is P_4O_5 , which possesses three isomers differing only in the position of the terminal P–O double bond. While the stabilities of isomer **II** and **III** (in

which the P–O bond is adjacent to two or three P–O–P units, respectively) are nearly equal, the energy gap to isomer **IV** (in which the P–O bond is adjacent to one P–O–P unit) is predicted to be 9 and 7 kcal mol^{−1}, respectively. These differences are much smaller than those predicted between isomer **III** and **V** of P_4O_4 underlining again the stability of the P_3 ring. For P_4O_6 the energy difference between the respective isomers (isomer **II** and **III**) is somewhat larger than for P_4O_5 (5 kcal mol^{−1}) and our computations predict the reverse ordering, that is the isomer in which the P–O bond is adjacent to three P–O–P units is more stable than the isomer in which one P–P bond is in the neighborhood of the terminal P–O bond. Besides structural information about larger compounds (i.e. P_mO_n with $m > 4$ and $n = 1 - \frac{3}{2}m$), the thermodynamic and the kinetic stability of the clusters are of great interest. The stability of the various compounds with respect to the most stable elementary form^[13] are summarized in Figure 1. As expected, Figure 1 shows that the thermodynamic stability

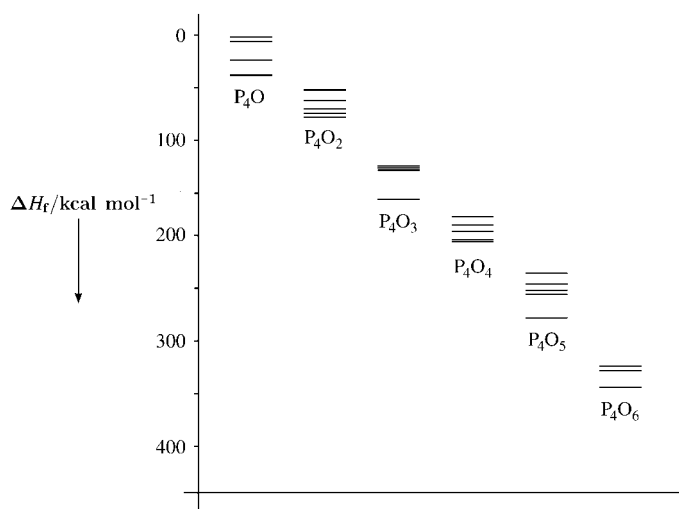


Figure 1. Heat of formation [kcal mol^{−1}] for the computed P_4O_n isomers.

of phosphorus suboxides increases strongly along the series P_4O_n . This strong gain in energy is perhaps one of the main reasons for the difficulties in the attempts to prepare phosphorus suboxides. Besides the increasing thermodynamic stability along the P_4O_n series, we also expect that the polymerization to amorphous phosphorus oxides (i.e. to P_mO_n compounds with $n \gg 4$) is also thermodynamically favorable.

In summary we have discussed energetically low-lying isomers of phosphorus suboxides of the summation formula P_4O_n ($n = 1–6$) and extracted structural factors which determine the relative energy of such compounds. With these data the nature and the stability of various possible bonding types (P–P bonds, P–O single and double bonds, P_3 rings) could be analyzed. In addition, we computed the heat of formation for the various clusters to obtain a key for the experimental difficulties in the preparation of phosphorus suboxides. The findings of the present work are helpful for further investigations of phosphorus suboxides, for example for the study of larger compounds (P_mO_n compounds with $m \gg 4$). The understanding of the chemistry of these compounds is

important to gain insight into polymerization processes which hamper the synthesis of molecular phosphorus suboxides. A comparative study of phosphorus suboxides and phosphorus subsulfide is underway.

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- [6] The DFT computations were performed with the B3LYP functional^[17] in connection with an AO basis of double zeta plus (DZP) polarization quality.^[18] The second step of our procedure is necessary because for phosphorus suboxides the PM3 method gives reasonable geometries but fails in the prediction of reliable heats of formation.
- [7] For the refinement of the geometries an analytical gradient optimization were used. These computations were performed by employing the DFT approach described in reference [6]. Bond lengths obtained from second-order perturbation theory (second-order MBPT theory^[19]) differ by less than 0.01 Å.
- [8] To test the accuracy of the DFT approach we performed CCSD(T) computations in conjunction with the DZP AO basis for selected systems. In addition we checked the basis set dependency of the B3LYP functional. Both computations point to an error bar of about 3 kcal mol⁻¹ for the relative energies of the various isomers. Furthermore the DFT approach always predicted the same energetical ordering as the more sophisticated CCSD(T) method. In addition we found that the DFT calculations predict the correct energetical ordering for the isomers of P_4S_6 and P_4O_6 .
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Alkylating Polymers: Resin-Released Carbenium Ions as Versatile Reactive Intermediates in Polymer-Assisted Solution-Phase Synthesis**

Jörg Rademann,* Joachim Smerdka, Günther Jung, Philipp Grosche, and Dietmar Schmid

*Dedicated to Professor Ivar Ugi
on the occasion of his 70th birthday*

Although combinatorial chemistry was dominated by solid-phase synthesis during its first decade,^[1, 2] the solution-phase synthesis remains to show indisputable advantages, for example, in respect to the versatility of reactions applicable and the accumulated knowledge of synthetic protocols. Ideally, a synthetic strategy should be able to combine these merits with the advantages of solid-phase synthesis protocols, such as the possibility to use reagents in high excess, to remove them by filtration, and to employ automated multiple synthesizers. This combination can be realized in polymer-assisted solution-phase (PASP) synthesis either by using scavenger resins or by the implementation of polymeric reagents.^[3–5] Especially desirable is the substitution of chemicals which are highly toxic, explosive, or difficult to handle during preparation, reactions, work-up, waste disposal, and in large amounts. Many alkylating agents, such as diazoalkanes, sulfate esters, sulfonate esters, and alkyl halogens belong to this group of hazardous compounds.^[6] Solid-supported sulfonate esters have been employed in alkylations of amines and thiols at elevated temperatures under basic conditions.^[7]

Elemental nitrogen is an excellent leaving group in alkylations. Therefore we focused our efforts on introducing a novel concept of alkylating polymers based on the release of carbenium ions and nitrogen from precursors bound to insoluble polystyrene gels. The alkylating species are generated from solid-phase-bound 3-alkyl-1-aryltriazenes under acidic conditions and we demonstrate their use as very reactive, mild, and versatile alkylation reagents.^[8] The chemistry and applications of triazenes have a long history dating back to the 19th century.^[9, 10] Their alkyl derivatives are stable entities unless treated with acid.^[11–14] They fragment into radicals when moderately heated,^[15] under irradiation^[15] or by one-electron oxidation.^[16]

Electron-rich triazenes have higher reactivity,^[17] and therefore *para*-alkoxy-substituted anilines were selected as efficient starting materials. Solid-supported triazenes have been

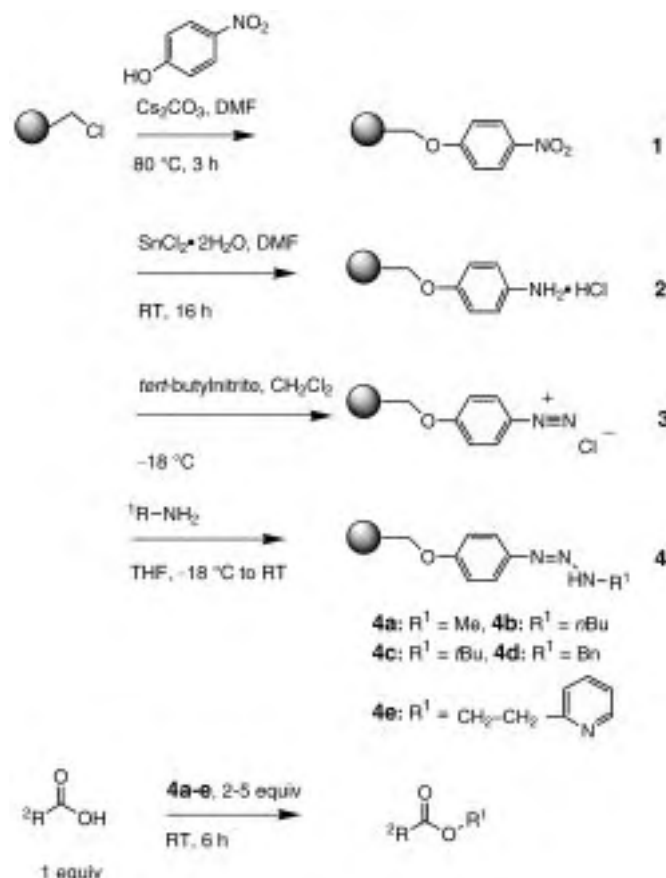
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prepared by two research groups.^[13, 14] We developed a modified procedure (Scheme 1) via the solid-phase bound nitroarene **1**, which was reduced to the polymeric ammonium hydrochloride **2**. The best results in the diazotization reaction



Scheme 1. Preparation of reactive polymers **4a–e** starting from the chloromethyl–polystyrene resin and employing the reaction sequence alkylation, reduction, diazotization, and nucleophilic addition of an amine. For details see the Experimental Section.

were obtained by directly employing the ammonium hydrochloride salt **2** with *tert*-butylnitrite in CH_2Cl_2 at -18°C , no improvement was observed by adding further protic or Lewis acids. The diazonium salt **3** was treated with methylamine, *n*-butylamine, *tert*-butylamine, benzylamine, and 2-(2-aminoethyl)pyridine to furnish triazenes **4a–e**, respectively, which should be useful in the transfer of methyl-, *n*-butyl-, *tert*-butyl-, benzyl-, and 2-(2-pyridylethyl) cations, respectively. Triazene **4a** was obtained with a loading of 1.54 mmol g^{-1} of reactive sites by starting from polystyrene containing 2.0 mmol g^{-1} of chloromethyl groups. When the mass increase during the reaction sequence is taken into account this loading corresponds to an excellent conversion (94%) of chloromethyl groups into triazenes. Completion of the reaction steps could be monitored by following characteristic vibrational bands in the attenuated total reflection IR spectrum (FT-ATR-IR) directly from washed and dried resin samples. Products **4a–e** were stable at room temperature for at least several months when kept in the dark.

Various reactions of the novel polymeric reagents **4a–e** were then investigated. First esterifications were studied with

acids representing a broad range of $\text{p}K_a$ values, size, steric hindrance, as well as chemical lability and additional functionality. As the reaction requires acidic conditions and is initiated supposedly by protonation of the triazene moiety, the $\text{p}K_a$ value is a possible determinant of the reaction. Furthermore, there is evidence pointing to carbenium ion intermediates either as ion pairs in the case of benzyl ions or through a concerted mechanism in the case of primary alkyl ions.^[18]

Sterically demanding benzoic acid (**7**) was used to optimize the reaction conditions in respect to reagent excess and reaction time. Complete conversion (99%) of benzoic acid to the corresponding methyl ester was obtained with two equivalents of alkylating polymer **4a** after 6 h, while 96% conversion was obtained with resin **4b** (Figure 1). The polymer-supported reaction of **4a** (2 equiv) with *p*-nitrophenylacetic acid (**5**, 1 equiv, 2 mg mL^{-1}) in CH_2Cl_2 was analyzed after various reaction times by HPLC. A 53% conversion from the acid to the ester product was observed after 5 min; data analysis^[19] indicated a second-order reaction as observed in homogeneous solution.^[17]

The results of esterifications are summarized in Table 1. A diverse selection of acids was converted into highly pure ester products when treated with five equivalents of the alkylating polymers **4a**, **4b**, **4d**, and **4e** for 2–6 h. Typical yields for the conversion of 5 mg acid were in the range of 80%. In case of

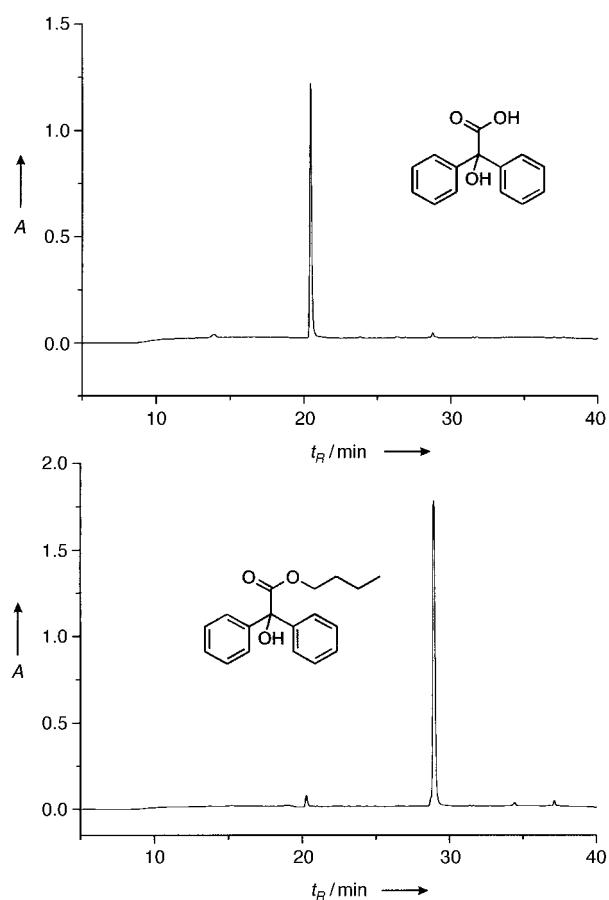
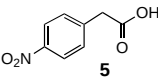
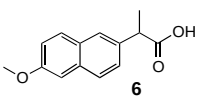
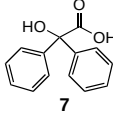
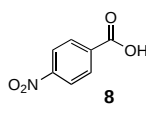
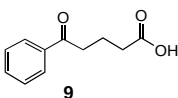
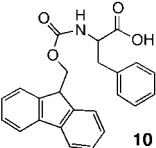
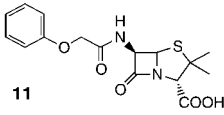
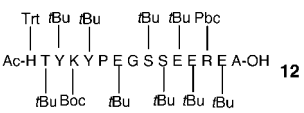
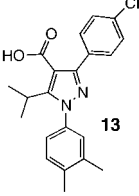
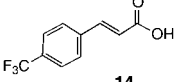


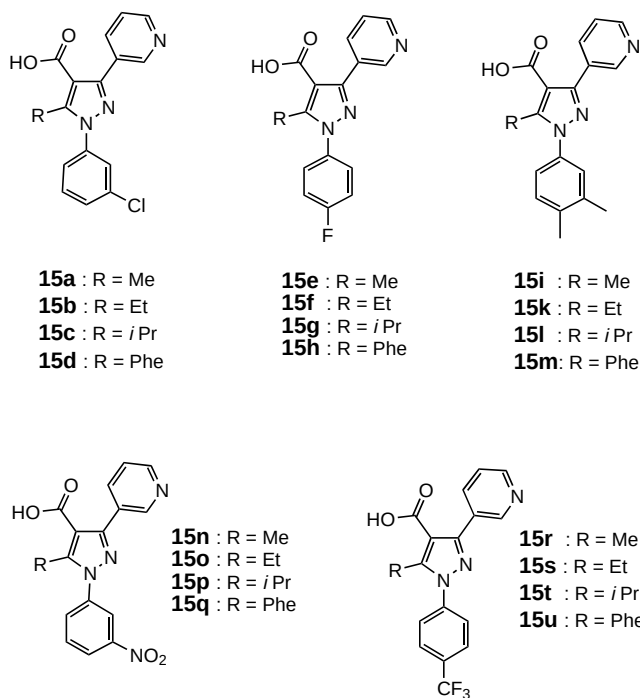
Figure 1. HPLC chromatogram of **7** (top) and after 6 h reaction with five equivalents of **4b** (bottom). The *n*-butyl ester was formed in a purity of 96% (see Table 1).

Table 1. Conversion of a diverse collection of various acids with the alkylating polymers **4a**, **b**, **d**, **e**. The purity was determined by HPLC with UV detection at 214 nm.

Entry	Acid	R ¹ of 4	Purity
1		Me	96
2	5	<i>n</i> Bu	95
3	5	C ₂ H ₄ -C ₅ NH ₄	92
4		<i>n</i> Bu	91
5	6	C ₂ H ₄ -C ₅ NH ₄	91
6		Me	99
7	7	<i>n</i> Bu	96
8	7	C ₂ H ₄ -C ₅ NH ₄	94
9		Me	90
10		Me	86
11	9	<i>n</i> Bu	87
12		Me	96
13		Me	92
14		Me	82
15		Bn	90
16		Me	91

the esterification of acid **5** with resin **4b** NMR analysis was employed to prove the structure of the *n*-butyl ester; the NMR spectrum did not display any signals of an isobutyl ester by-product formed by rearrangement. In contrast, alkylation to the *tert*-butyl ester (**4c**) failed, though the generation of gaseous products indicated decomposition of the triazene moiety. Possibly, the intermediary *tert*-butyl cation reacts under proton abstraction to yield isobutene. The reagents tolerate the presence of non-acidic hydroxy groups (**7**, entries 6–8), enolizable carbonyl functions (**9**, entries 10 and 11), and nitrogen heterocycles with limited basicity such as in pyridine ($\text{p}K_{\text{a}}$ 5.25) and pyrazole systems (**13**, entry 15). The reaction fails in the case of alkylic amines such as the unprotected amino acids. The conversion of acid-sensitive structures is exemplified with penicillin V (**11**, entry 13). Esterification of this especially labile structure failed under acidic and basic conditions as well as with diazomethane.^[20] After conversion of the potassium salt of penicillin V into the free acid by employing ion-exchange resin Amberlyst 15 in dioxane/water, the ion exchanger was removed and the remaining solution was treated immediately with polymeric reagent **4a** to yield the respective penicillin ester. A penta-decapeptide bearing various acid-labile side protecting groups and having a mass of 2924.5 Da (**12**, entry 14) was investigated in the reaction with resin **4a** (5 equiv). After 6 h the starting peptide was consumed and the product was formed as analyzed by HPLC and ESI-MS. The etherification of alcohols was attempted without significant formation of product.^[21]

Finally, the conversion of a collection of druglike molecules was investigated, since this process might be useful for lead optimization in a medicinal chemistry program. An equimolar mixture of 20 pyrazolecarboxylic acids **15a–u**^[22] was synthesized by a split-and-combine approach via solid-phase-bound β -dicarbonyl compounds that were cyclized regioselectively with various aldehydes and arylhydrazines. One portion of



this mixture was treated with resin **4a** (5 equiv) for 6 h to yield the methyl esters of the pyrazolecarboxylic acids. Both the mixtures of acids and esters were analyzed by electrospray ionization Fourier transform ion cyclotron mass spectrometry (ESI-FT-ICR-MS) using both direct infusion measurements and coupling to micro-HPLC. All 20 pyrazolecarboxylic acids (**15a–u**) could be assigned in the starting mixture (Figure 2, top) as well as the corresponding 20 methyl esters (Figure 2, bottom) in the product mixture. Assignment was based on accurate mass determination with a relative mass error of less than 2.2 ppm.

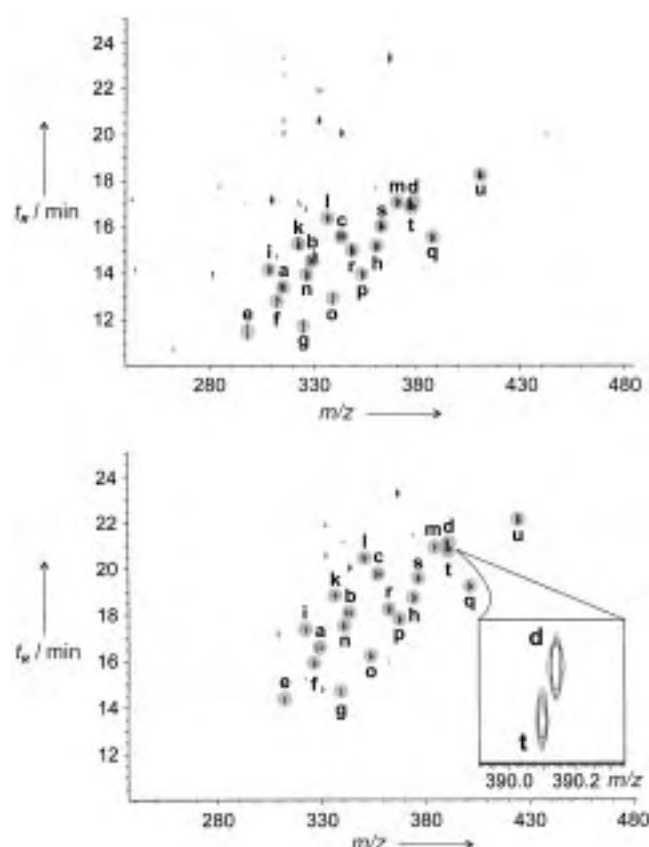


Figure 2. LC-MS contour plots (mass-to-charge ratio versus retention time) using HPLC-ESI-FT-ICR-MS. A collection of 20 pyrazole acids **15a–u** (top) were converted into their corresponding methyl esters **16a–u** (bottom) by treatment with resin **4a**. Coeluting compounds **16d** and **16t** were resolved having a mass difference of 0.042 Da.

In summary, we have demonstrated that the alkylating polymers **4a**, **b**, **d**, and **e** are very efficient and versatile esterification reagents that allow the conversion of diverse, highly functionalized substrates under extremely mild reaction conditions. The novel reagents might be of value especially in the parallel conversion of mixtures of highly functionalized compound collections such as those used in lead-optimization efforts. Alkylating polymers should be useful as well in flow-through applications allowing in situ conversions, for example, in gas chromatography. Further potential applications of the presented alkylation reagents can be expected for other nucleophiles besides carboxylates, such as for alcohols, phenols, amines, thiols, and various C-nucleophiles including the cyanide ion.

Experimental Section

Attachment of *para*-nitrophenol to Merrifield resin: Chloromethylated polystyrene resin (0.5 g, 1.0 mmol, 200–400 mesh cross-linked with 1% divinylbenzene, loading 2.0 mmol g⁻¹) was suspended in a solution of *para*-nitrophenol (5 mmol, 696 mg) in DMF (5 mL). Cs₂CO₃ (2 mmol, 652 mg) was added and the reaction mixture was agitated for 3 h at 80 °C. The resin was washed at RT with DMF, CH₂Cl₂, MeOH, CH₂Cl₂, and MeOH (each five times) and dried in vacuo to furnish resin **1**. IR: ν = 1339, 1495, 1592 cm⁻¹.

Reduction of the nitro group and diazotization: Resin **1** was treated with a 2 M solution of SnCl₂ · 2 H₂O in DMF (450 mg per mL solution) for 16 h at RT and subjected to the washing and drying procedure described above to furnish resin **2** (IR: ν = 2581 cm⁻¹ (NH₃⁺)) with a loading of 1.63 mmol g⁻¹ (elemental analysis). Resin **2** (1.0 mmol) was suspended in CH₂Cl₂ and cooled to –18 °C. *tert*-Butylnitrite was then added (10 mmol, 988 μ L). After 4 h the diazonium resin **3** was washed with cold CH₂Cl₂ (five times) and cooled again to –18 °C. IR: ν = 2238 cm⁻¹ (N₂⁺).

Triazene formation: The intermediate diazonium resin **3** was treated with a 2 M solution of an amine in THF at –18 °C and warmed to RT. After 4 h, washing and drying furnished resins **4a–e** with a loading of 1.54 mmol g⁻¹ for resin **4a** starting from 2.0 mmol g⁻¹ of chloromethyl groups. For further loadings of **4a–e** consult the Supporting Information.

Representative example of the alkylation of acids: Acid **5a** (5 mg) was dissolved in CH₂Cl₂ (5 mL) (or CH₂Cl₂/MeOH 9/1, or THF, or dioxane) and treated with resin **4b** (5 equiv) for 6 h. The resin was washed with CH₂Cl₂, MeOH, and CH₂Cl₂ (each two times with 2.5 mL) and the solvent was removed by evaporation to furnish 5.3 mg of the *n*-butyl ester (79.5% yield). HPLC analysis was conducted to determine the purity of the products (see Table 1).

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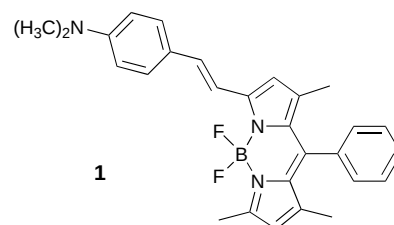
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Molecular Switching in the Near Infrared (NIR) with a Functionalized Boron–Dipyrromethene Dye**

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Recent developments in supramolecular chemistry and nanotechnology have stimulated interest in the design and the construction of molecular signaling systems capable of performing photo- and substrate-induced logic functions or redox-based switching actions.^[1] At the molecular level, photons, that is their absorption or emission, often are the vehicle of choice for transduction of an electrochemically^[2] or photochemically^[3] generated signal. Examples range from photonic switches^[4] to photo- or electrochromic devices^[5] and to advanced micro- or nanomachines.^[6] In particular, multifunctional dyes that are sensitive toward both external physical and chemical triggers provide a versatile basis for the construction of sophisticated switches that communicate, for instance, through changes in electrochromic and/or fluorescence properties. Over the past few years, the boron–dipyrromethene (BDP) chromophore has gained in importance in the design of such systems^[2c, 3b, 7–9] since the BDP core is comparatively readily oxidized and reduced,^[2c] a prerequisite for fluorescent switches relying on electron or charge transfer (CT),^[3b, 7, 8] as well as for the generation of stable radical ions that show electrogenerated chemiluminescence upon charge recombination.^[2c] In these systems, the *meso*-substituted BDP chromophore acts as in donor(D)–acceptor(A)-substituted biaryls so that the switching process hardly influences the absorption and emission wavelengths. However, for the design of more advanced molecular ensembles it would be highly desirable to generate signal changes by substrate interaction at a site conjugated to the BDP core. Since experience has shown that creation of an

extensively delocalized amino radical cation would result in strong electrochromism, introduction of a proton-sensitive amino donor group seemed most suitable for the construction of such a multifunctional electro- and photochemical molecular switch. Here, we report the synthesis and spectroscopic and electrochemical properties of the 3-dimethylaminostyryl-substituted dye **1**, which, to the best of our knowledge, is the first example of an unsymmetrically substituted BDP dye carrying an analyte-sensitive (donor) group conjugated to the core.



Compound **1** was synthesized by condensation of the tetramethyl derivative^[7b] with *p*-dimethylaminobenzaldehyde using piperidinium acetate as catalyst.

Owing to the introduction of a donor-styryl-spacer group at the 3-position the spectroscopic behavior of **1** is more reminiscent of D–A stilbenes^[10a,b] or styryl bases,^[10c] in contrast to *meso*-donor-substituted BDP dyes, where no direct electronic conjugation exists between both aryl subunits.^[3b, 7b] As follows from Table 1 and Figure 1, the absorp-

Table 1. Spectroscopic data of **1** and **1-H⁺** in different solvents at 298 K.^[a]

	Solvent	λ_{abs} [nm]	ϵ_{max} [M ⁻¹ cm ⁻¹]	λ_{f} [nm]	Φ_{f}	τ_{f} [ns]	$k_{\text{f}}^{\text{[b]}}$ [10 ⁸ s ⁻¹]	$k_{\text{nr}}^{\text{[b]}}$ [10 ⁸ s ⁻¹]
1	MeCN	597	75 000	731	0.13	0.94	1.4	9.2
1	THF	603	89 000	672	0.58	3.21	1.8	1.3
1	Et ₂ O	594	98 000	638	0.83	3.88	2.1	0.4
1	Bu ₂ O	598	101 000	630	0.87	3.73	2.3	0.3
1	hexane	596	n.d. ^[c]	611	0.97	3.84	2.5	0.1
1-H⁺	MeCN	553	100 000	563	0.97	4.38	2.2	0.1
1-H⁺	THF	558	100 000	566	0.85	4.02	2.1	0.3
1-H⁺	Et ₂ O	556	101 000	563	0.90	4.24	2.1	0.2

[a] Experimental conditions: $c(\mathbf{1}) = 1 \times 10^{-6}$ M, $\lambda_{\text{exc}} = 545$ and 595 nm for steady-state, 500 and 578 nm for time-resolved fluorescence measurements, proton source HClO₄. [b] $k_{\text{f}} = \Phi_{\text{f}}/\tau_{\text{f}}$, $k_{\text{nr}} = (1 - \Phi_{\text{f}})/\tau_{\text{f}}$. [c] Not determined due to low solubility.

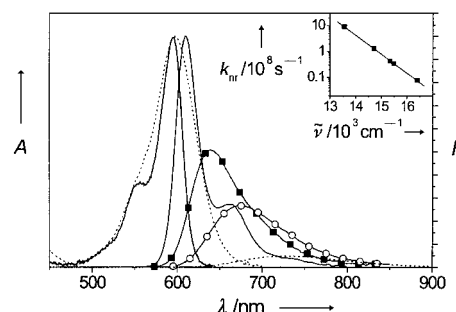


Figure 1. Absorption (normalized; absorption *A*) and emission spectra (fluorescence intensity *F*) of **1** at 298 K (—: in hexane, ■: in Bu₂O, ○: in THF, ---: in MeCN; absorption spectra in THF and Bu₂O omitted for better clarity, experimental conditions, see Table 1). In the inset, a plot of $\ln k_{\text{nr}}$ versus the emission maximum is shown (— fit; $r = 0.999$).

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tion band is centered at 598 ± 5 nm and shows no solvent-dependent shifts which suggests that the ground-state dipole moment is rather small.^[11] The BDP-like shape for **1** (narrow and structured, with high ϵ , Table 1, Figure 1),^[7, 9a] is only seen in hexane and the band slightly broadens (while maintaining high ϵ) as the solvent polarity increases. On the other hand, the fluorescence of **1** is strongly dependent on the polarity of the solvent; the band broadens (full width at half maximum (fwhm) increases from 890 cm^{-1} (main band only) in hexane to 2390 cm^{-1} in MeCN) and the maximum λ_f shifts to the near infrared (NIR; from 611 nm in hexane to 731 nm in MeCN, Figure 1, Table 1), indicative of an intramolecular CT process. Only the emission spectrum in hexane displays the typical BDP features, that is a slightly Stokes-shifted, mirror-symmetrical band (Figure 1).^[7, 9a] In more polar solvents, the band steadily shifts to the red and no well-separated dual emission is found here as, for example, in the case of some 8-dimethyl-anilino-substituted BDP dyes.^[3b, 7b] Very remarkable behavior is revealed in the inset of Figure 1; the semi-logarithmic plot of the rate constant of nonradiative deactivation k_{nr} versus the emission maximum yields a linear correlation of $r = 0.999$. According to the energy gap rule,^[12] this decrease in fluorescence quantum yield (Φ_f) and lifetime (τ_f , see Table 1) with increasing emission wavelength is attributed to the acceleration of internal conversion (ic) as the energy gap between the excited and the ground state decreases. Thus, the positive solvokinetic effect observed does not arise from the population of differently emitting species during the lifetime of the excited state,^[10a,c] but the quenching of the only emitting, highly polar ^1CT state^[13] is caused by an increase of k_{ic} .^[14] Nonetheless, because of the high intrinsic fluorescence yield of ^1CT , Φ_f of **1** is still comparatively high in acetonitrile (Table 1).^[15]

Protonation drastically alters the electron-donating properties of the dimethylamino group and consequently “switches off” any charge transfer interaction. This results in typical BDP-like narrow, structured and solvent-polarity-independent absorption and emission bands (Figure 2), the latter of

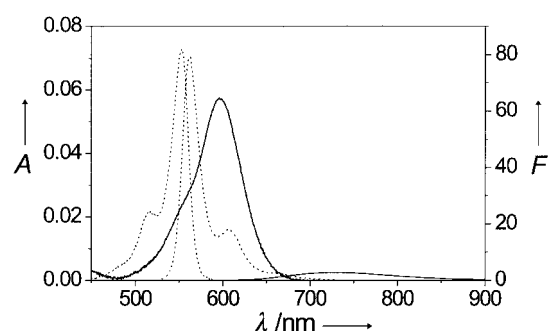


Figure 2. Steady-state spectra of **1** (—) and **1-H⁺** (---) in acetonitrile at 298 K (the emission spectra are normalized at the same optical density at the excitation wavelength 545 nm, experimental conditions, see Table 1).^[19]

high fluorescence yield in all the acidified solvents employed (Table 1). The absorption bands of **1-H⁺** are blue-shifted by about 40 nm compared to those of **1**, and the width of the band is further reduced (fwhm ca. 700 cm^{-1} for **1-H⁺** and 950 cm^{-1} for **1** in hexane), stressing the influence of the conjugated

(unprotonated) dimethylamino substituent on the spectroscopic properties of **1** in solvents of any polarity. This proton-induced spectral switching along with the high fluorescence yields observed in all the experiments qualifies **1** as a very suitable sensor molecule for communicating local environmental properties in solution. By employing pulsed or modulated laser diodes as excitation sources (the fluorescence lifetimes of ≥ 1 ns do not require highly sophisticated equipment), the temporal and spectral information on solvent polarity can be read out in the region between 590 and 750 nm, while the presence of protons can be monitored between 550 and 620 nm. Thus, with a simple single excitation/dual emission wavelength measurement of the fluorescence decay kinetics, solvent polarity and acidity can be probed independently at, for example, 670 and 560 nm, respectively.

Besides chemical switching, **1** can be reversibly reduced to give the radical anion (-1635 mV vs. ferrocene/ferrocenium (Fc/Fc^+)) and be reversibly oxidized to give a radical cation and a dication at 105 and 430 mV, respectively. The oxidations occur at much lower potentials than in other donor-substituted BDP systems^[2c, 9b] which indicates extensive delocalization in the radical cation. Whereas the radical anion shows a strong absorption at 562 nm ($\epsilon = 58000$) but only very weak absorption bands in the NIR ($\epsilon < 1000$ at 788 and 890 nm), the radical cation shows a sharp and very intense ($\epsilon = 130000$) band at 754 nm (Figure 3).

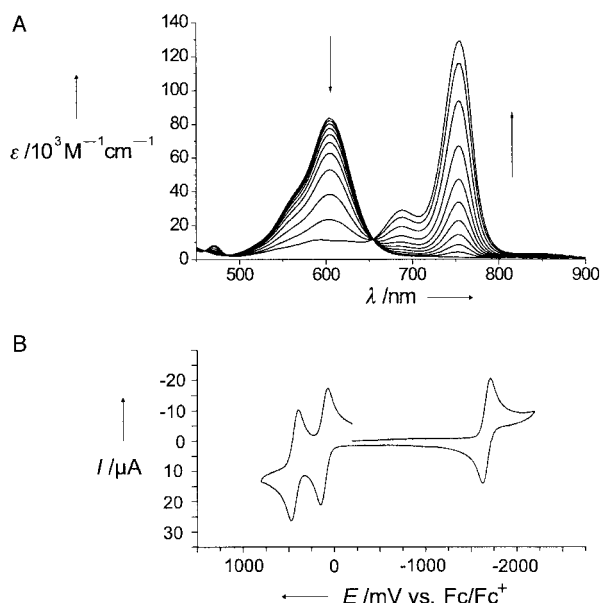


Figure 3. A) Spectra taken during the oxidation of **1** to the radical cation ($\text{CH}_2\text{Cl}_2/0.1\text{M}$ TBAHFP); B) cyclic voltammogram of **1**.

In summary, the first unsymmetrically substituted BDP dye with an analyte-responsive receptor in the polymethinic part of the chromophore presented herein is a multifunctional molecular system that can either be utilized for highly sensitive probing of solvent polarity and acidity through measuring fluorescence or can be employed as an efficient dual-mode chemical (protons)/electrochromic switch in the red/NIR, operating already at very low voltages.

Experimental Section

Steady-state absorption and fluorescence spectroscopy: Bruins Instruments Omega 10 spectrophotometer, Spectronics Instruments 8100 spectrofluorometer; details on the determination of the relative fluorescence quantum yields (Φ_f) and the correction of the fluorescence spectra are given in ref. [7b]; fluorescence standards: cresyl violet in methanol ($\Phi_f = 0.54 \pm 0.03$),^[17a] rhodamine 101 in ethanol ($\Phi_f = 1.00 \pm 0.02$).^[17b]

Time-resolved fluorescence spectroscopy: Unique laser impulse fluorometer with ps time resolution as described in ref. [17c] including a synchronously pumped dye (rhodamine 6G) laser (Spectra Physics); details on detection and temporal calibration are given in ref. [7b, 17c]; fitting procedure: reference convolution of cresyl violet decays (Globals Unlimited V2.2, Laboratory for Fluorescence Dynamics, University of Illinois).

Cyclic voltammetry: Solvent dichloromethane; reversible half-wave potentials $E_{1/2}$ [mV] versus ferrocene/ferrocenium as internal standard; conditions: scan rate 250 mV s⁻¹, supporting electrolyte: 0.1 M tetrabutylammonium hexafluorophosphate (TBAHFP).

Spectroelectrochemistry: Solvent dichloromethane, OTTE transmission cell with a minigrid-gold working electrode.^[18]

Synthesis: 1,3,5,7-Tetramethyl-8-phenyl-difluorobordiazaindacene (65 mg, 0.2 mmol)^[7b] and 4-dimethylaminobenzaldehyde (35 mg, 0.23 mmol) were refluxed for 26 h in a mixture of toluene (5 mL), glacial acetic acid (0.15 mL) and piperidine (0.18 mL) together with a small amount of molecular sieves (3 Å). After cooling to room temperature the mixture was placed on top of a silica column and eluted with CH₂Cl₂/hexane (1/1). The blue fraction was collected and recrystallized from CHCl₃/hexane to give **1** as purple needles (22 mg, 0.048 mmol, 24 %). M.p.: 288–291 °C; IR (KBr, $\tilde{\nu}$ in cm⁻¹): $\tilde{\nu} = 1178$ (B–F); ¹H NMR (250 MHz, CDCl₃): $\delta = 1.38$ (s, 3 H), 1.42 (s, 3 H), 1.54 (s, 3 H), 3.03 (s, 6 H), 5.96 (s, 1 H), 6.59 (s, 1 H), 6.70 (m, 2 H), 7.20 (d, 2 H, $J = 16.3$ Hz), 7.28–7.33 (m, 2 H), 7.45–7.55 (m, 6 H); HR-MS (EI, 70 eV): calcd for C₂₈H₂₈N₃BF₂ 455.2344, found 455.2352.

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- [14] Note that during our studies no *trans*–*cis* isomerization was observed.
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An Efficient Cobalt(II) Catalyst System for the Selective 1,4-Hydrovinylation of 1,3-Dienes**

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The selective 1,4-hydrovinylation of 1,3-dienes with alkenes under mild reaction conditions for the formation of new C–C bonds is of high synthetic interest.^[1] For instance, ethylene and 1,3-butadiene are codimerised under rhodium catalysis on an industrial scale (DuPont synthesis). The resulting 1,4-hexadiene is then transformed into synthetic rubber and other unsaturated polymers.^[2]

Recently we described a catalyst system ([CoBr₂(dppe)]/ZnI₂/Bu₄NBH₄ dppe = ethane-1,2-diylbis(diphenylphosphane)) for the efficient Diels–Alder reaction of acyclic 1,3-dienes with acetylenes.^[3] When we attempted to use this catalyst system for the Diels–Alder reaction of acyclic 1,3-dienes, with substituted alkenes as the dienophile, none of the desired Diels–Alder product could be isolated. Instead the linear 1,4-hydrovinylation product **2** was isolated from the

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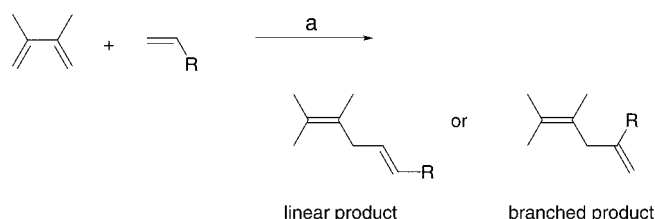
[**] This work was supported by the Deutsche Forschungsgemeinschaft (DFG).

reaction of 2,3-dimethyl-1,3-butadiene (**1**) with *n*-butyl acrylate (entry 1, Table 1). This product is formed by a 1,4-addition of the acrylate to the diene under formal insertion into the (*E*)- β -C–H bond of the acrylate (Scheme 1).

Table 1. Cobalt(i)-mediated reaction of 1,3-dienes with acrylates.

Entry	Substrate	Product	Yield [%]
1			92
2			82
3			88 ^[a]

[a] In addition, 5% of the linear product ethyl 6,10-dimethyl-(*E*)-2,5,9-undecatrienoate was isolated.



Scheme 1. 1,4-Hydrovinylation of 1,3-dienes with substituted alkenes. a) [CoBr₂(dppe)] (1–3 mol %), ZnI₂ (3–9 mol %), Bu₄NBH₄ (1–3 mol %), CH₂Cl₂, 25 °C, 16 h.

The reaction of ethyl acrylate using **3** and **5** as model systems also proceed in high yield under mild reaction conditions (room temperature, 16 h, 1–3 mol % catalyst, 100% conversion). The new C–C single bond is formed predominantly at the disubstituted double bond of the monosubstituted 1,3-dienes (92:8 by GC, 88% isolated yield of **6**, entry 3, Table 1)^[4]. The regiochemistry can be further improved when the reaction temperature is lowered (94:6, 0 °C).

Because of the mild reaction conditions, the 1,4-hydrovinylation products can be isolated in good to excellent yields, while the often encountered polymerization side products are not formed.^[5]

Besides acrylic esters, the longer chain β,γ - and γ,δ -unsaturated carbonic esters **7** and **9** also react well with 1,3-dienes (entries 1 and 2, Table 2). In these cases the new C–C bond is formed at the more substituted carbon of the alkene, which will be referred to as “branched 1,4-hydrovinylation” (compare Scheme 1). The branched 1,4-hydrovinylation products are also formed with allyl ethers **11** and **13** (entries 3 and 4, Table 2), and the products are isolated in excellent yields (98% and 95%, respectively) with a high level of selectivity (>98%). Even unfunctionalized terminal alkenes (**15**, **17**, and **19**; Table 2, entries 5–7) undergo this hydrovinylation to give

Table 2. Cobalt(i)-mediated hydrovinylation of functionalized alkenes with 2,3-dimethyl-1,3-butadiene (**1**).

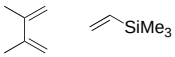
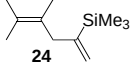
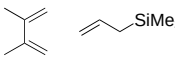
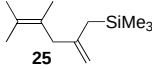
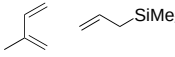
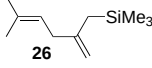
Entry	Substrate	Product	Yield [%]
1			97 ^[a]
2			81 ^[a]
3			98
4			95
5			95
6			97
7			66 ^[a]
8			95

[a] The reaction was performed at 40 °C and with 5 mol % of the cobalt catalyst.

the branched products with high selectivities and good yields. The C–C bond formation of these substrates also proceeds under mild reaction conditions so that with the nonconjugated 1,5-diene **17** no isomerization could be detected. Although, more sterically hindered alkenes such as **19** react more slowly than the unbranched terminal alkenes (e.g. **15** and **17**), the 1,4-hydrovinylation product is still formed exclusively. Allyl phenyl ethers can be used successfully as starting materials (entry 3, Table 2) and these materials can be converted by a Claisen rearrangement into allyl benzene derivatives. The direct conversion of allyl benzene derivatives (like **21**) with 1,3-dienes can also be accomplished under mild reaction conditions by using our catalyst system and the product can be isolated in a very good yield of 95% (entry 8, Table 2).

The 1,4-hydrovinylation reaction of silyl-substituted alkenes (vinyl and allyl silanes) generates the branched, silyl-substituted 1,4-dienes (Table 3),^[6] which are interesting building blocks for further transformations. The branched 1,4-hydrovinylation reactions generally proceed in good yields while the new C–C bond is formed with high regioselectivity at the less-substituted double bond of the diene (**26**, 83%, 94:6). These silyl-substituted derivatives are easily converted under acid catalysis into the conjugated 1,3-dienes. For example, **25** is quantitatively isomerized to (*E/Z*)-trimethyl-(2,4,5-trimethyl-hexa-2,4-dienyl)silane. The chemistry of such

Table 3. Cobalt(II)-mediated hydrovinylation of silyl substituted alkenes with 1,3-dienes.

Entry	Substrates	Product	Yield [%]
1		 24	90
2		 25	92
3		 26	83

masked carbon nucleophiles is well described and very interesting transformations seem possible with these higher-substituted vinyl and allyl silanes.^[7]

In conclusion, interesting linear and branched 1,4-dienes can be generated under very mild reaction conditions with good selectivities and in good to excellent isolated yields from the 1,4-hydrovinylation reactions. The investigation of reactions with higher-substituted functionalized alkenes and non-symmetrical 1,3-dienes are currently underway.

Experimental Section

Representative procedure (synthesis of 4,5-dimethyl-2-methylene-4-hexenyloxybenzene (**12**)): A 50 mL flask was charged with [CoBr₂(dppe)] (40 mg, 65 µmol, 1.8 mol %) and dry zinc iodide (100 mg, 313 µmol, 8.6 mol %) under nitrogen atmosphere and suspended in dry dichloromethane (2.0 mL). After the addition of 2,3-dimethyl-1,3-butadiene (0.5 mL, 363 mg, 4.42 mmol) and allyl phenyl ether (0.5 mL, 489 mg, 3.64 mmol), tetrabutylammonium borohydride (18 mg, 70 µmol, 1.9 mol %) was added, inducing a color change from green to brown. The mixture was stirred overnight at room temperature, then pentane (10 mL) was added and the solution filtered through silica gel with pentane/diethyl ether (10/1) as the eluent. The filtrate was reduced in volume and the product purified by column chromatography on silica gel with pentane/diethyl ether (50/1) as the eluent. The product **12** was obtained as a colorless liquid (772 mg, 3.57 mmol, 98 % yield).

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Subnanomolar Inhibitors from Computer Screening: A Model Study Using Human Carbonic Anhydrase II

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The search for novel lead structures as potential drugs or herbicides is increasingly time consuming and costly. Modern methods of disease characterization at the molecular level, driven in particular by the Genome Project,^[1] promise to deliver a plethora of potential therapeutic targets. How well are we prepared to transform this flood of information into lead structures? Enormous effort has been put into large-scale automation of experimental hi-tech high-throughput screening (HTS). Initial euphoria surrounding this technique as a universal lead generator has subsided as a result of the considerable costs involved, coupled with frequent inadequacies in quality and quantity of the available compounds for screening.^[2] This raises the question: are computer methods sufficiently mature to complement the experimental screening process for new lead structures?

The requirements for computer screening^[3] are opposite to those for HTS. The latter is technology-driven, delivering potentially structurally diverse hits by identifying an interaction with the target. No insights are obtained into why a particular hit interacts, however. In contrast, virtual computer screening is dependent upon prior information about factors necessary for binding to the target; thus, it is knowledge-driven. Computer screening should therefore provide the interactions responsible for binding. The rules governing protein–ligand interactions are, however, complex and are only in part understood.^[4] We decided to investigate whether the rules incorporated in current programs are able to reliably predict novel ligands.

We chose human carbonic anhydrase II for our test study, as its structure has been solved to high resolution. We utilized existing computational tools to analyze the binding pocket in

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detail. To convert the binding pocket properties into a query that could be applied to a database of chemical structures it was necessary to develop a number of new strategies. A variety of (in part new) filters were applied to the hits obtained, reducing the data to an essential core by way of molecular similarity, ligand docking, and estimation of binding affinity.

Three-dimensional molecular candidates were generated by using the program CORINA^[5] from about 90 000 entries of the Maybridge^[6] and LeadQuest^[7] databases. The latter database has been designed to contain molecules that are easily synthesized yet highly chemically diverse.^[8] The 13 best hits from this search were tested for inhibition experimentally; of these, three could be shown to be subnanomolar, one nanomolar, while a further seven were micromolar inhibitors. The structures of two of the best inhibitors could be determined in complex with the human carbonic anhydrase II crystallographically, providing a "proof of concept".

Carbonic anhydrase II (CAII; E.C. 4.2.1.1) is a metalloenzyme that catalyzes the reversible hydration of CO₂ to HCO₃⁻.^[9] The reactive zinc center is coordinated by three histidine groups at the base of a conical amphiphilic binding pocket. One isoform of CAII is concentrated in the ciliary body of the eye, where it is responsible for aqueous production. Glaucoma leads to reduced ocular water removal with subsequent increase in intraocular pressure (IOP) and thereby damage to the optic nerve. Inhibitors of CAII thus offer a possible route to reducing intraocular pressure. The binding modes of acetazolamide (**1**),^[10] dorzolamide (**2**;

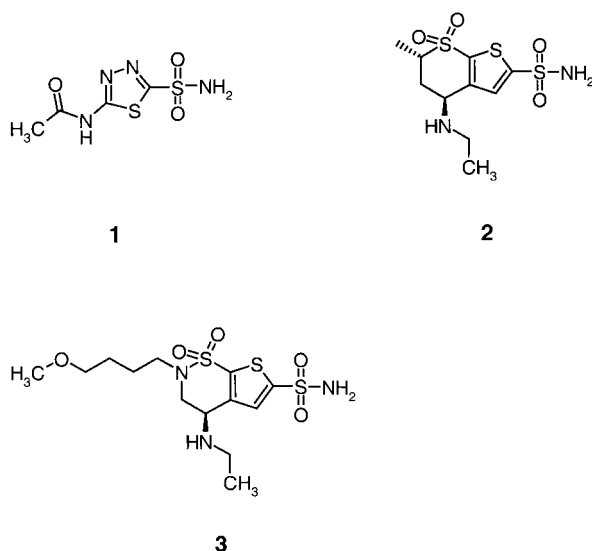


Figure 1),^[11] and brinzolamide (**3**)^[12] have been determined by using crystallographic methods. Derivatives of both sulfonamide and hydroxamate^[13] have been identified as inhibitors, although the latter exhibit much lower affinity for CAII. Initial analysis of the binding pocket entailed multiple superpositioning of the C_α atoms of 24 high-resolution complex crystal structures^[14] by using our modified version of Relibase+.^[15] The pocket is rather rigid, with only His64 exhibiting alternative conformations (Figure 2).^[11]

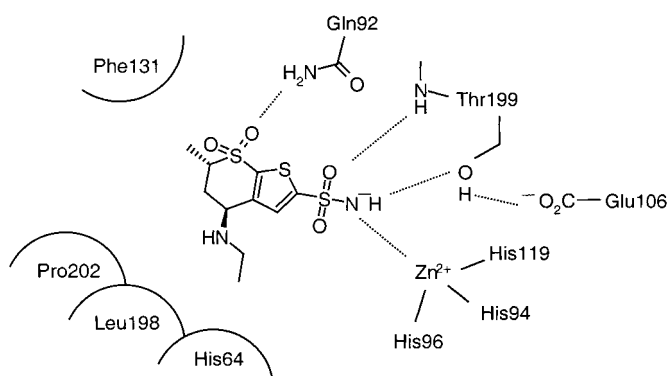


Figure 1. The binding of the zinc ion to a sulfonamide group, which is most probably singly deprotonated, is common to all sulfonamide inhibitors, and results in a tetrahedral coordination geometry at the zinc center. The remaining sulfonamide proton forms a hydrogen bond to the hydroxy oxygen atom of the Thr199. A further hydrogen bond exists between the amide nitrogen atom of Thr199 and one of the two sulfonamide oxygen atoms; the remaining oxygen atom makes no contacts with the protein. For dorzolamide, an additional hydrogen bond is formed between one of the two oxygen atoms of the second sulfone moiety and the side chain nitrogen atom of Gln92.

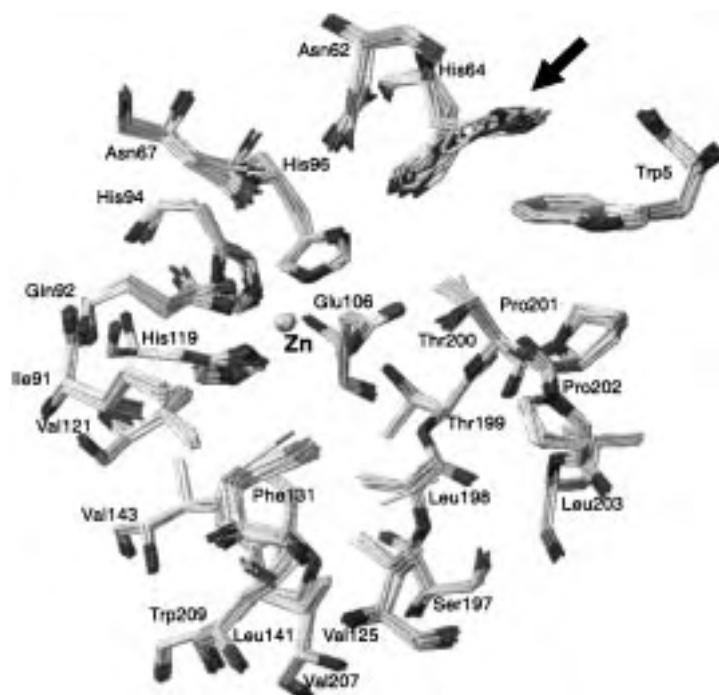


Figure 2. Superposition of 24 protein–ligand complexes of CAII (ligands not shown) calculated in Relibase+ based on C_α positions. With the exception of His64 (arrow), the binding pocket is rather rigid.

The pocket was then investigated by using various probes in GRID,^[16] SuperStar,^[17] LUDI,^[18] and DrugScore.^[19] The pocket was systematically searched for favorable interactions with possible functional groups of a ligand; the probes used were a C=O group (H-bond acceptor), an amide NH group (H-bond donor), and a CH₃ group (hydrophobic probe). Although each method highlighted qualitatively similar regions (hot spots), the maps differed quantitatively due to different relative weightings. Hot spots for the three probes were converted into a pharmacophore model to allow the

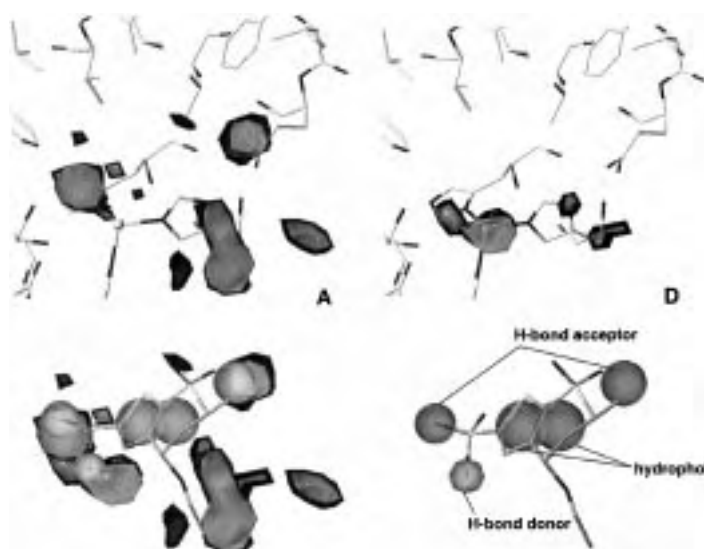


Figure 3. Analysis of preferred interactions for hydrogen-bond acceptors (A; top left) and hydrogen-bond donors (D; top right) within the binding pocket of CAII. These maps were calculated using SuperStar; analogous results were obtained with GRID and DrugScore, albeit with different relative weightings. LUDI generated interaction centers in similar positions for C=O, NH, or aliphatic carbon probe. This “hot spot” distribution was converted into a pharmacophore query for UNITY (bottom right), taking into account the hydrophobic excluded volume according to known inhibitor binding modes. SuperStar calculates probability densities based on contact geometries determined from low molecular weight crystal structures. GRID is based on a force-field approach, allowing calculation of interaction potentials for a large variety of different probes within the binding pocket. DrugScore uses the “inverse Boltzmann principle”, evaluating the binding pocket according to frequency for which a particular atom type of a potential ligand is found in contact with a protein in known protein–ligand complexes. LUDI places potential interaction sites for hydrogen-bond donors, acceptors, and hydrophobic groups within the binding pocket according to a set of empirical rules derived from experimental data.

database search using UNITY.^[20] In addition to matching the thus formatted query, the molecular structures extracted from Maybridge and LeadQuest had also to contain at least one zinc-binding head group.^[21] A total of 35 known inhibitors of CAII were added to the database, whose appearance in the hit list served to calibrate and validate the method at each stage.^[22]

The 2D and 3D searches with UNITY yielded 3314 molecules after taking flexibility into consideration. The resulting compounds were ordered according to their potential binding abilities using the program FlexS.^[23] FlexS flexibly superimposes a test ligand on a reference molecule through optimizing the spatial distribution of various physicochemical parameters. The highly potent inhibitor dorzolamide, in the conformation known from the crystal structure, was used as reference. Scores for the additional test ligands indicated that a size normalization was important to obtain the correct order in the hit list. Use of such a similarity search has the advantage that information on the chemical structures of known inhibitors is implicitly taken into account, information that is ignored in a simple docking strategy. All CAII inhibitors reported to date, for example, possess a sulfonamide anchor as zinc-coordinating element; the superposition using FlexS ensures that this fact is utilized in the ranking of possible

lead structures. Procedures for combining docking and similarity to ligands of known potency have recently been implemented in DOCK^[24] and DrugScore.^[25]

Table 1. Lead structures for CAII inhibitors generated by using the virtual screening procedures described here.

Entry	Compound	FlexX ^[a]	DrugScore ^[a]	IC ₅₀ [nM]	Databank
1		−25.7	−102.2	21	LeadQuest
2		−15.0	−107.1	0.9	LeadQuest
3		−17.3	−116.5	185	LeadQuest
4		−23.4	−100.6	488	LeadQuest
5		−19.9	−100.9	117	LeadQuest
6		−21.6	−112.4	248	LeadQuest
7		−25.7	−105.1	0.6	LeadQuest
8		–	–	> 10 ⁶	LeadQuest
9		−16.0	−83.5	169	LeadQuest
10		−23.4	−88.6	5500	Maybridge
11		−16.5	−97.4	0.8	Maybridge
12		−23.0	−94.1	2300	Maybridge
13		–	–	> 10 ⁶	Maybridge

[a] Large negative scores correspond to high predicted affinities. FlexX and DrugScore values cannot be compared directly with one another, relative comparisons can only be made within each of the methods. No score has been given for the two hydroxamate inhibitors (entries 8 and 13) as these cannot be compared directly due to the different zinc-coordinating groups.

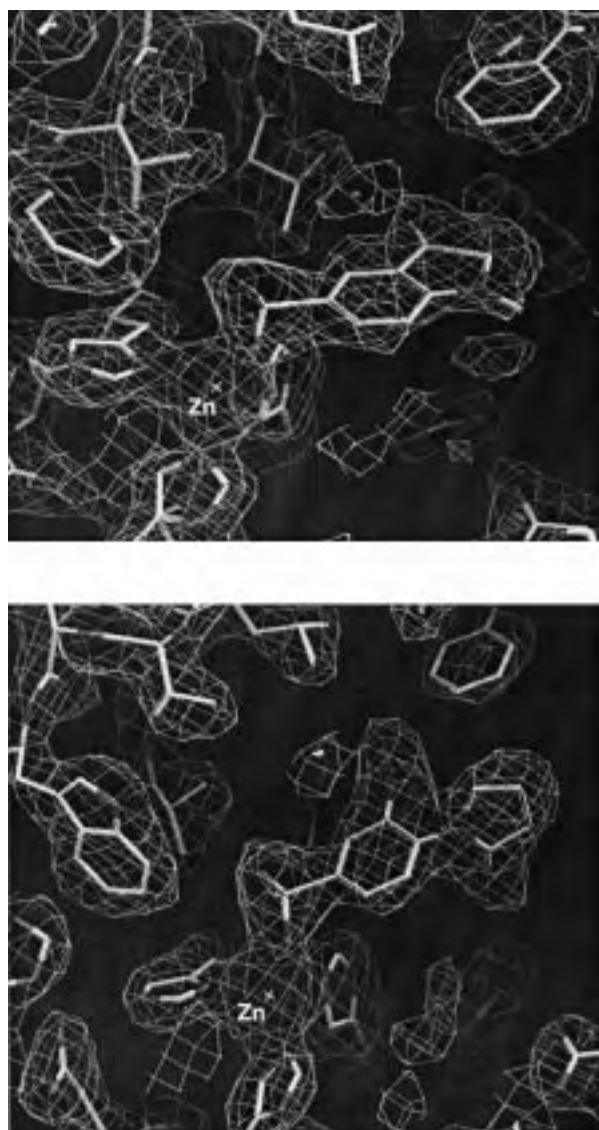


Figure 4. Experimental electron density for the inhibitors given in entries 6 (top) and 7 (bottom) in Table 1 in the binding pocket of CAII.

The best scoring hits derived from this procedure were then docked into the binding pocket using FlexX,^[26] in which the partial hydration of the pocket proved to play an important role. Four conserved water molecules could be identified following superposition of all complex- and apo-structures in Relibase+, taking into account B-factors, local hydrophobicity, and neighboring hydrogen-bonding partners, and backed up by an analysis of the H-bond network using MAB/Moloc.^[27] These solvent molecules added to the steric restriction of the binding pocket.

Following the docking procedure, binding affinity was estimated using FlexX and DrugScore, and the top ranking 13 hits were chosen for experimental testing. These 13 hits were also inspected visually for their FlexX-generated binding modes. The 13 compounds (with 10 from LeadQuest) are shown in Table 1, together with their computer scorings and experimental IC₅₀ values.

Two of the resulting high affinity hits were investigated crystallographically (Figure 4).^[29] In both cases the binding

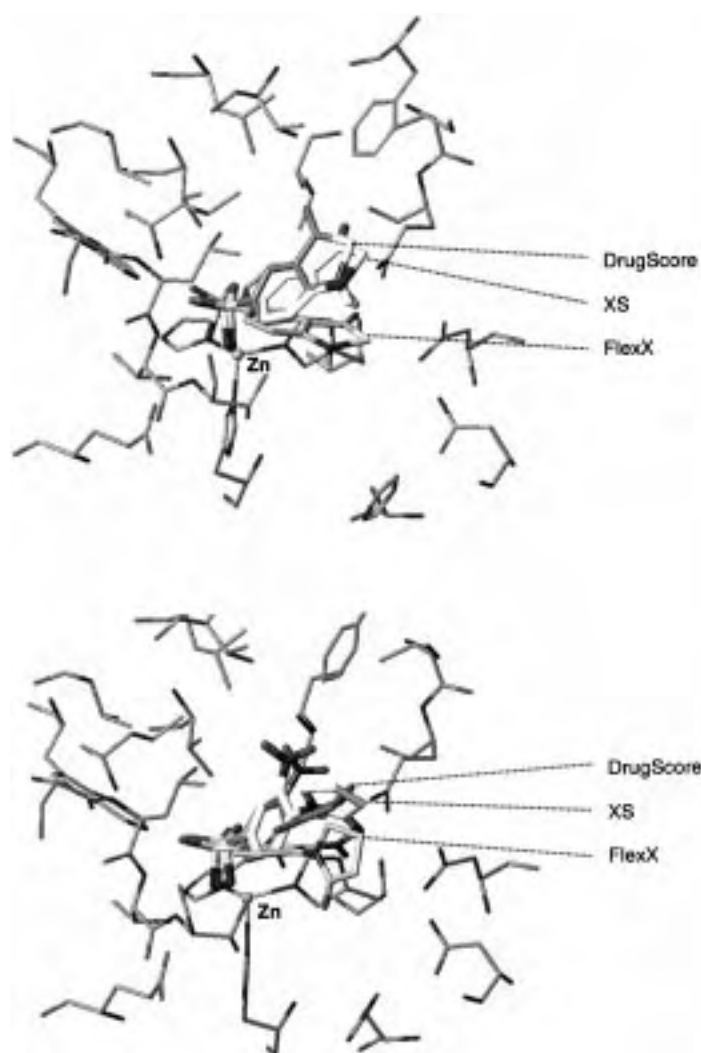


Figure 5. Superposition of the X-ray structure (XS) and docked models for the inhibitors given in entries 6 (top) and 7 (bottom) in Table 1 in CAII. In both cases, DrugScore predicts a binding geometry (generated using FlexX) that is very close to the experimentally observed geometry. The original scoring function in FlexX places a binding geometry as highest ranking that diverges significantly from the experimental one.

mode generated by FlexX and ranked as highest using DrugScore is in good agreement with the experimental structure (Figure 5).

This emphasizes the improvement afforded by the knowledge-based scoring function of DrugScore over the regression-based function implemented in FlexX, which placed these solutions at rank 51 and 61, respectively. Validation using the compounds of known structure also indicated that DrugScore showed a marked improvement in finding the correct binding mode.

The correlation between the IC₅₀ values and the affinities predicted by DrugScore or FlexX is rather disappointing; at best, a correct order of magnitude could be found. Other studies have shown predicted affinities to be accurate to about 1.5 lg units.^[28] Experimental measurements are often only correct to an order of magnitude, however; methods for affinity prediction from structures must be brought to within these limits. The development of a better method to define

native-like binding geometries represents an important first step towards this goal.

Finally, we have shown that the LeadQuest Database provides an ideal source for the discovery of novel lead compounds,^[31] in terms of both structural diversity^[8] and chemical purity.^[30]

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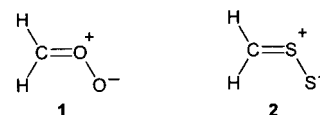
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Thioformaldehyde S-sulfide (Thiosulfine)**

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The elucidation of the course of events in the ozonolysis of olefins by Criegee^[1] was a milestone in the effort to understand the mechanism of organic reactions. As early as in 1949 it was recognized that carbonyl oxides are the decisive intermediates in this process.^[2] However, to date it has not been possible to observe these species directly during the transformation of “primary” into “secondary” ozonides. In contrast, an entry into carbonyl oxides exists in the trapping of carbenes with oxygen under matrix conditions;^[3] however, the unsubstituted formaldehyde *O*-oxide **1** cannot be isolated even upon using this procedure. In the reaction of methylene with oxygen in an argon matrix only formic acid was detected.^[4]

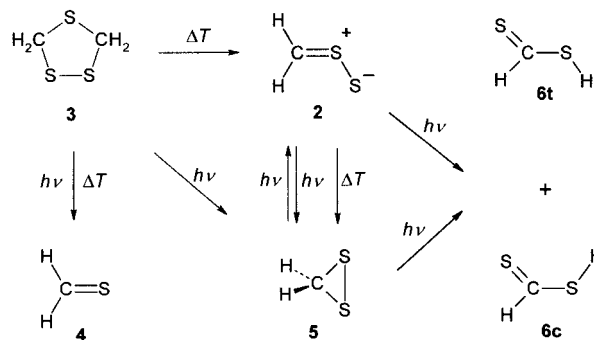


The idea that it might be possible to generate formaldehyde together with its oxide by cycloreversion of 1,2,4-trioxolane has not yet been realized, presumably due to the fact that the required ozonide of ethene is difficult to handle.^[5] As is shown herein,^[6] the situation is completely different in the sulfur series. 1,2,4-Trithiolane (**3**) is a stable, easily accessible

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substance.^[7] There are additional reasons to try the thermal fragmentation of **3** into the title molecule **2**, the analogue of Criegee's "zwitterion", and thioformaldehyde (**4**). On the one hand such a cycloreversion was successfully used by Huisgen and Rapp^[8] for the preparation of substituted derivatives of **2**, on the other hand Bock et al.^[9] identified **4** by photoelectron spectroscopy upon the pyrolysis of **3**.



Indeed, the gas-phase pyrolysis of **3** in combination with matrix isolation of the formed products opens an ideal route for the system thiosulfine (**2**)/dithiirane (**5**)/dithioformic acid (**6**),^[10] which is of importance from the preparative and the theoretical point of view.

We pyrolyzed 1,2,4-trithiolane (**3**) in high vacuum (quartz tube: diameter 8 mm, heating zone 5 cm, ca. 10^{-5} mbar, 950 °C) and condensed the reaction products together with argon on a CsI window at 10 K. In the IR spectrum of the formed matrix besides the known bands of **3** and **4** (**4** generated independently by pyrolysis of allylmethyl sulfide gave an identical IR spectrum) only the absorptions shown in Tables 1 and 2 and in Figure 1 were registered.

Fabian and Senning^[10] calculated the energy and geometry of thioformaldehyde *S*-sulfide (**2**) on the B3LYP/6-311 + G(3df,3pd) level, but its IR spectrum on the B3LYP/6-31G* level. Since especially the position of the S–S stretching vibration strongly depends on the used basis set (6-31G*: 586, 6-311 + G(3df,3pd): 612, exp: 623 cm⁻¹) we additionally calculated the IR spectra with the first mentioned method. As the comparison shows the theoretical IR spectrum

Table 1. Calculated (B3LYP/6-311 + G(3df,3pd), harmonic approximation; intensities [kmol⁻¹] in parentheses) and experimental (argon matrix, 10 K) IR spectrum of thioformaldehyde *S*-sulfide (**2**).

Mode ^[a]	$\tilde{\nu}_{\text{calcd}}$ [cm ⁻¹]	$\tilde{\nu}_{\text{exp}}$ [cm ⁻¹]
ν_1 a'	CH ₂ str. 3264 (2)	3126.3 (vw)
ν_2 a'	CH ₂ str. 3140 (3)	3010.4 (w)
ν_3 a'	CH ₂ sciss. 1416 (12)	1366.4 (m)
ν_4 a'	CS str. 1019 (23)	970.9 (m)
ν_5 a'	CH ₂ rock. 934 (13)	910.2 (m)
ν_8 a''	CH ₂ wag. 809 (59)	756.8 (s)
ν_6 a'	SS str. 612 (47)	622.8 (s)
ν_9 a''	CH ₂ twist. 575 (3)	–
ν_7 a'	def. 310 (1)	–

[a] str. = stretching vibration, sciss. = scissoring vibration, rock. = rocking vibration, wag. = wagging vibration, twist. = twisting vibration, def. = deformation vibration.

Table 2. Calculated (B3LYP/6-311 + G(3df,3pd), harmonic approximation; intensities [kmol⁻¹] in parentheses) and experimental (argon matrix, 10 K) IR spectrum of dithiirane (**5**).

Mode ^[a]	$\tilde{\nu}_{\text{calcd}}$ [cm ⁻¹]	$\tilde{\nu}_{\text{exp}}$ [cm ⁻¹]
ν_6 b ₁	CH ₂ str. 3215 (0)	–
ν_1 a ₁	CH ₂ str. 3118 (9)	2986.7 (m)
ν_2 a ₁	CH ₂ sciss. 1461 (2)	1412.0 (w)
ν_7 b ₂	CH ₂ wag. 1072 (2)	1053.0 (m)
ν_5 a ₂	CH ₂ twist. 952 (0)	–
ν_8 b ₁	CH ₂ rock. 944 (3)	928.3 (m)
ν_3 a ₁	ring str. 856 (1)	–
ν_9 b ₂	ring str. 588 (9)	581.0 (s)
ν_4 a ₁	SS str. 501 (1)	–

[a] See footnote [a] in Table 1.

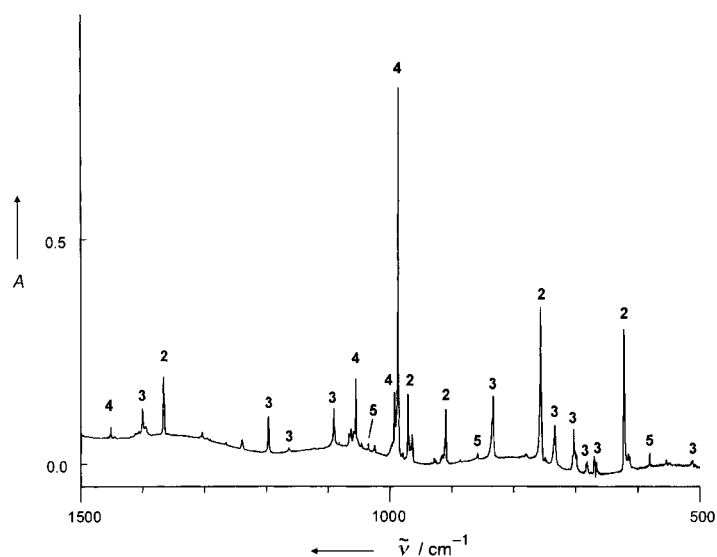


Figure 1. Selected region of the experimental IR spectrum (Ar, 10 K) of the products of the pyrolysis of 1,2,4-trithiolane (**3**).

obtained in this manner fits quite well with the experimental one of **2** (Table 1).

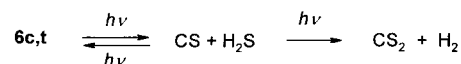
As the calculation indicates, the IR bands of dithiirane (**5**) should be much less intense than those of **2**. In accordance with this prediction the experimental spectrum of **5** shows a very weak but clearly visible band at 581 cm⁻¹. On the basis of the calculated band intensities it can be estimated that the cycloreversion of **3** at 950 °C leads to a ratio **2**:**5** of about 2:1. At 850 °C a minor amount of dithiirane **5** (ratio **2**:**5** ca. 3.5:1) is found. At even lower temperatures (650 °C) the starting molecule **3** remains intact. That means, in the thermal fragmentation of **3** a considerable barrier must be passed. If a fragmentation occurs, a thermal ring closure of **2** to **5** partly takes place already during the pyrolysis.

In the UV spectrum **2** shows an intense band at 356 nm. Since a photoisomerization of **2** is even possible with light of very long wavelengths ($\lambda > 570$ nm; see below), the compound has to have a second, bathochromically shifted absorption; however, its intensity is too low for a direct observation under the applied experimental conditions. This finding fits to the calculations of Fabian and Senning,^[10] which predict an intense $\pi \rightarrow \pi^*$ transition at 300 nm and a very weak $n \rightarrow \pi^*$ absorption at 373 nm for **2**. For dithiirane (**5**) no

distinct absorption maximum could be found. The photochemical behavior of **5** discussed below demands, however, also an absorption in the long-wavelength region (at ca. 500 nm) for this molecule.

Depending on the applied wavelength the products of the pyrolysis of **3** undergo various photoreactions. Light of wavelength >385 nm leads to *s-cis*- and *s-trans*-dithioformic acid **6c** and **6t**, respectively, as indicated by the comparison with the known^[11] matrix IR spectra and with the theoretical spectra calculated on the B3LYP/6-311 + G(3df,3pd) level (Figure 2). If the pyrolysis products are irradiated with light of

and H_2S are generated. Changing the wavelength to 254 nm induces a partial recapture within the matrix cage and **6** is reformed. After longer irradiation only CS_2 can be detected, probably under elimination of H_2 .



Remarkably, upon direct irradiation ($\lambda = 313$ nm) of tri-thiolane **3** no IR bands of thioformaldehyde *S*-sulfide (**2**) but only those of thioformaldehyde (**4**), dithiirane (**5**), and dithioformic acid (**6**) can be observed. It has to be assumed that thiosulfine **2**, which is generated photochemically from **3**, is photoisomerized immediately to the isomers **5** and **6**.

Conclusion: a) The expectation by Fabian and Senning^[10] that the calculated spectroscopic data of **2** may lead to its detection under matrix conditions has been fulfilled. Here-with, a thiosulfine—and even better, the unsubstituted parent compound—has been directly identified. The existence of thiosulfines had been illustrated using trapping reactions by Huisgen and Rapp^[8] already in 1987. b) The good agreement between the experimental and calculated IR spectra is an indication that the geometry (planar, bent) and the electronic structure of **2** is correctly expressed by the calculations. Consequently, thioformaldehyde *S*-sulfide (**2**) should be regarded more as a dipole (ylide form) and less as a singlet diradical.^[10] c) After the isolation of sterically hindered dithiiranes, which has been achieved recently,^[12] now the existence of the unsubstituted parent molecule **5** is also proven. d) The calculated^[10] high barrier of $28.6 \text{ kcal mol}^{-1}$ for the isomerization of **2** into more stable dithiirane **5** (by $5.9 \text{ kcal mol}^{-1}$; the global minimum is represented by **6**) explains why the ring closure $\text{2} \rightarrow \text{5}$ needs a relatively high temperature (kinetic control; the higher the temperature of pyrolysis, the more **5**) or photoexcitation. The thermal threshold for the transformation $\text{2/5} \rightarrow \text{6}$ is evidently too high to be passed under the applied pyrolysis conditions. e) This observation provides new insight on the question whether substituted thiosulfines can be isomerized in solution into esters of dithiocarbonic acid via the corresponding dithiiranes, which is controversially discussed in the literature.^[8, 13]

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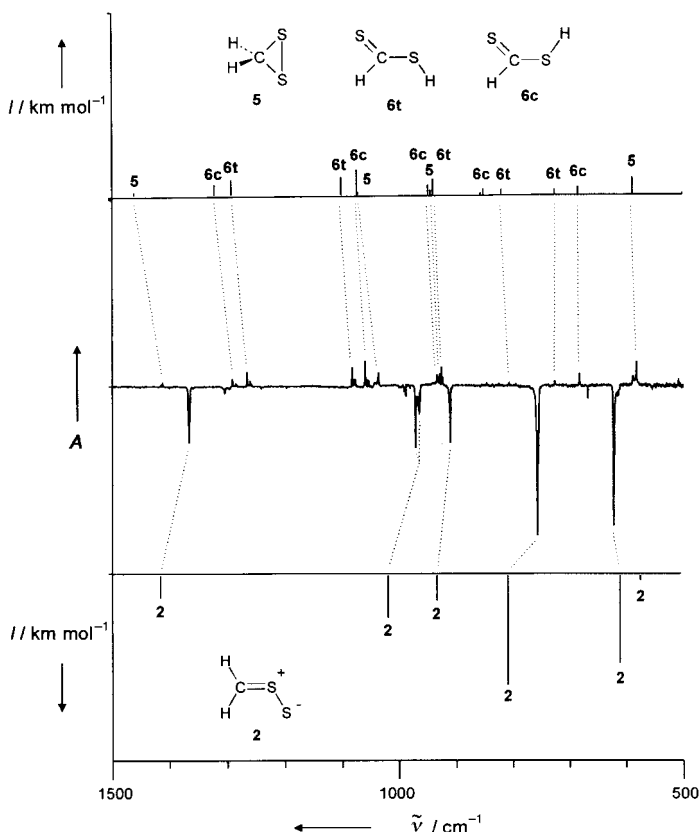


Figure 2. Selected region of the experimental (Ar, 10 K) and calculated (B3LYP/6-311 + G(3df,3dp)) IR spectra of the CH_2S_2 isomers thioformaldehyde *S*-sulfide (**2**), dithiirane (**5**), *s-cis*- and *s-trans*-dithioformic acid (**6c/6t**). Middle: Experimental difference spectrum before and after irradiation of the matrix isolated pyrolysis products of **3** with light of the wavelength >570 nm (the positive bands grow, the negative ones disappear during irradiation). Top: Calculated spectrum of a 10:1:1 mixture of **5**, **6c**, and **6t**. Bottom: Calculated spectrum of **2**, related to the same scale.

even longer wavelengths ($\lambda > 570$ nm), the IR spectra show initially a selective rearrangement of *S*-sulfide **2** into dithiirane **5**. If the irradiation is continued with light of wavelength $\lambda > 570$ nm the bands of **2** decrease further and one registers besides absorptions of **5** those of **6c** and **6t** (Figure 2). If the secondary irradiation is carried out with monochromatic light ($\lambda = 500 \pm 10$ nm) the reaction starts with a partial back reaction $\text{5} \rightarrow \text{2}$. A photoequilibrium $\text{5} \rightleftharpoons \text{2}$ is established, from which the final conversion into **6c** and **6t** originates.

If the mixture of the dithioformic acids **6c** and **6t** is irradiated in the matrix with light of wavelength 313 nm CS

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A Scandium Carbide Endohedral Metallofullerene: (Sc₂C₂)@C₈₄**

Chun-Ru Wang, Tsutomu Kai, Testuo Tomiyama, Takuya Yoshida, Yuji Kobayashi, Eiji Nishibori, Masaki Takata, Makoto Sakata, and Hisanori Shinohara*

The recent discovery of single-wall carbon nanotubes with C₆₀^[1] inside the tubular hollow space has demonstrated that such a large empty space can actually encapsulate fullerenes and carbon-related molecules. However, in the fullerene size range, only metal atoms,^[2] metal clusters,^[3] metal nitrides,^[4a] nitrogen atoms,^[4b–d] and noble gas atoms^[5] are observed to be encaged inside C₆₀, C₇₀, or higher fullerenes. Experimental evidence that carbon atoms or metal–carbon clusters (carbides) can be encapsulated inside fullerenes has not yet been reported. Here we report the production, isolation, and structural and spectroscopic characterization of the first scandium carbide endohedral fullerene (Sc₂C₂)@C₈₄.^[6] The endohedral nature and detailed molecular/crystal structure of the carbide Sc₂C₂ in the D_{2d}-C₈₄ cage were revealed by both ¹³C NMR and synchrotron X-ray structural analyses.

The relative yield of (Sc₂C₂)@C₈₄ is about 2 % of that of C₆₀, which is lower than those of the most abundant discandium metallofullerenes Sc₂@C₈₄ and Sc₂@C₈₂, but higher than those of all other metallofullerenes. We were able to isolate 3.5 mg of (Sc₂C₂)@C₈₄ as a black powder for spectroscopic and structural studies. Purified (Sc₂C₂)@C₈₄ is stable in air and soluble in normal organic solvents such as toluene and carbon disulfide. It has a light green color in CS₂ solution. Figure 1 shows the UV/Vis/NIR absorption spectrum of (Sc₂C₂)@C₈₄ between 400 and 2000 nm in CS₂ solution. A strong absorption band is observed around 600 nm, and the absorption onset is at 1410 nm. The overall absorption spectrum is quite different from those of the seven empty C₈₄ fullerene isomers^[7] and the three Sc₂@C₈₄ isomers^[2].

To obtain structural information on (Sc₂C₂)@C₈₄, ¹³C NMR measurements were performed using a Varian Inova-600 spectrometer at a ¹³C frequency of 125 MHz (CS₂ solution, [Cr(acac)₃] relaxant, [D₆]acetone lock). Figure 2 shows a typical ¹³C NMR spectrum of (Sc₂C₂)@C₈₄ obtained after

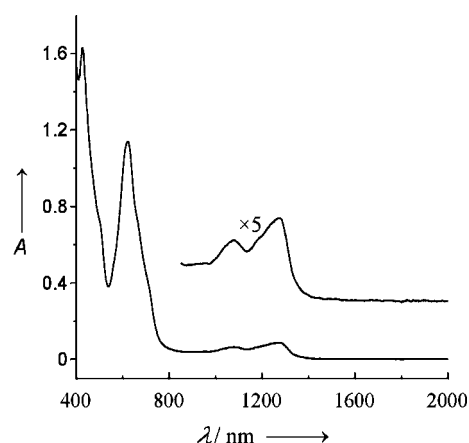


Figure 1. UV/Vis/NIR spectrum of purified (Sc₂C₂)@C₈₄ in CS₂ solution. The strong absorption band at around 600 nm results in a light green color. A = absorbance.

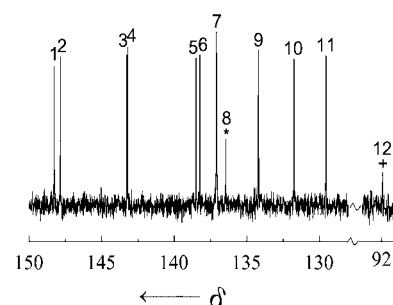


Figure 2. ¹³C NMR spectrum (171000 scans, 240 h) of (Sc₂C₂)@C₈₄ in CS₂ solution (2.5 mg [Cr(acac)₃] (acac = acetylacetonate) as relaxant, and [D₆]acetone as reference). The measured chemical shifts δ and relative intensities *I*_{rel} are: 1 (δ = 148.27, *I*_{rel} = 18.0), 2 (147.85, 19.3), 3 (143.27, 19.6), 4 (143.21, 20.6), 5 (138.50, 19.2), 6 (138.24, 19.6), 7 (137.09, 22.6), 8* (136.50, 8.5), 9 (134.20, 20.3), 10 (131.75, 19.1), 11 (129.55, 19.5), 12⁺ (91.99, 4.5). Lines 8 and 12 have 1/2 and 1/4, respectively, of the intensity of the other ten lines.

171000 scans (240 h) at room temperature. The spectrum consists of a series of ten distinct lines of nearly equal intensity, one line with half the intensity, and an additional line with 1/4 the intensity. The ¹³C NMR pattern is thus assigned as (10 × 8; 1 × 4; 1 × 2), where (a × b) indicates ([number of NMR lines] × [relative intensity]).^[8] A wider spectral range revealed no other peaks besides these 12 signals, and this confirms the high purity of the sample. C₈₆ has 19 isomers satisfying the isolated pentagon rule (IPR).^[9] However, even the most symmetrical isomer of D_{3h}-C₈₆ requires 15 (1 × 2; 14 × 6) ¹³C NMR signals. The current ¹³C NMR spectrum with only 12 lines can not be assigned to Sc₂@C₈₆.

Eleven of the 12 ¹³C NMR signals are in the range for sp²-hybridized fullerene C atoms (δ = 129.55–148.27), and the other is in the range for a sp-hybridized carbon atom (δ = 92). The presence of such an NMR line indicates that this metallofullerene is not a normal C₈₆-based metallofullerene. In fact, the observed NMR spectrum in the sp² fullerene range is quite similar to that of D_{2d}-C₈₄,^[9] which exhibits eleven NMR lines with a (10 × 8; 1 × 4) pattern. This observation strongly suggests that the present metallofullerene is not Sc₂@C₈₆ but (Sc₂C₂)@C₈₄, in which a Sc₂C₂ cluster is encaged

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by a D_{2d} - C_{84} fullerene. The NMR lines 1–11 in Figure 2 are due to the D_{2d} - C_{84} (no. 23)^[9] cage, and line 12 results from the Sc_2C_2 cluster (^{13}C NMR pattern: 2×1).

We performed synchrotron X-ray diffraction on the powder sample to confirm the endohedral structure of $(Sc_2C_2)@C_{84}$. The space group of the crystal was assigned as cubic $Fm\bar{3}m$ ($a = 15.8644(4)$ Å). The experimental data were analyzed by the MEM/Rietveld method, which was successfully applied to the structure determination of metallofullerenes such as $Y@C_{82}$,^[10a] $Sc@C_{82}$,^[10b] $Sc_2@C_{84}$,^[10c] and $Sc_3@C_{82}$.^[3] The number of structure factors derived in this analysis was 36. The reliability factors are $R_1 = 0.024$ and $R_{wp} = 0.021$, which are much better than those of previous studies on the metallofullerenes. The MEM analysis was carried out with $128 \times 128 \times 128$ pixels per unit cell. The reliability factor of the final MEM charge density was $R = 0.017$.

The MEM charge density is shown in Figure 3 as an equicontour surface for a section of the molecular structure. Several maxima in the charge density were found inside the

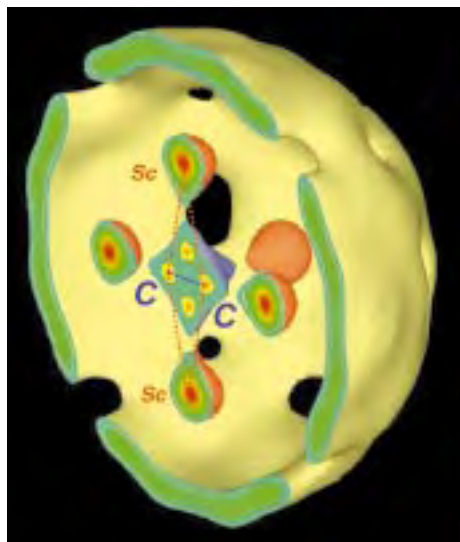


Figure 3. Half section of the equicontour (1.9 e Å^{-3}) surface of the MEM charge density for $(Sc_2C_2)@C_{84}$. The cross section corresponds to the $\langle 100 \rangle$ plane. The charge-density surfaces of the Sc and C atoms are colored red and blue, respectively. The Sc_2C_2 cluster is emphasized by dotted red lines and a solid blue line. In the cubic symmetry, the $(Sc_2C_2)@C_{84}$ molecules exhibit merohedral disorder in the unit cell, and an Sc_2C_2 cluster thus represents the disordered feature along the $[100]$, $[010]$, and $[001]$ directions with respect to the fullerene cage.

carbon cage. The MEM charge density also reveals that the C_{84} cage has D_{2d} (no. 23) symmetry and that the C_2 axis is parallel to the $\langle 100 \rangle$ fcc direction of the unit cell. As a result of the site symmetry of $4mm$, the C_2 axis of $(Sc_2C_2)@C_{84}$ is oriented in six equivalent $\langle 100 \rangle$ directions and show a merohedral disorder. From Figure 3, which exhibits the section through the Sc atoms and C atoms in four positions among the six equivalent positions, it is concluded that the Sc_2C_2 cluster is encapsulated in the D_{2d} - C_{84} fullerene cage.

The observation of a single NMR line due to a sp-hybridized carbon atom ($\delta = 92$) for Sc_2C_2 (see Figure 2) suggests that the Sc_2C_2 cluster is in a rapid rocking motion along the Sc–Sc axis between two mutually orthogonal

positions. This is consistent with the moderate smearing of charge density of the central C_2 moiety around the Sc–Sc axis in Sc_2C_2 (see Figure 3). Figure 4 shows a one-dimensional section of the charge density along the center axis of the

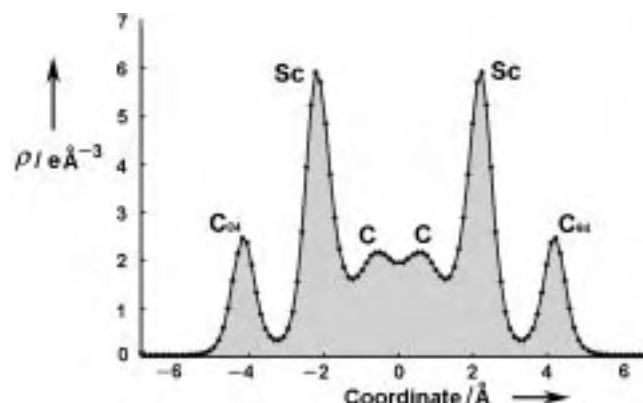


Figure 4. One-dimensional MEM charge density along the $\langle 100 \rangle$ direction, which passes through the center of the $(Sc_2C_2)@C_{84}$ molecule. Because of the merohedral disorder (see text), two carbon density maxima are seen along this bisecting axis (see Figure 3).

molecule, which passes through the density maxima. The four internal maxima are identified from the charge density concentration at the density maxima as Sc and C atoms. This assignment reveals that a Sc_2C_2 carbide cluster is indeed encapsulated in a C_{84} cage. The Sc_2C_2 form of scandium carbide has not been found in solid scandium carbides. The composition of the known scandium carbides in the solid state are Sc_4C_3 , $Sc_{13}C_{10}$, and $Sc_{15}C_{19}$.^[11]

The molecular structure based on the above analysis is presented in Figure 5. The $Sc \cdots Sc$ and $C \cdots C$ distances of the Sc_2C_2 cluster are $4.29(2)$ Å and $1.42(6)$ Å, respectively. The C–C distance lies between those of typical single and double bonds, and is very similar to that of the C–C bond (1.43 Å) that connects two pentagons on a C_{60} molecule.^[12] The Sc–C

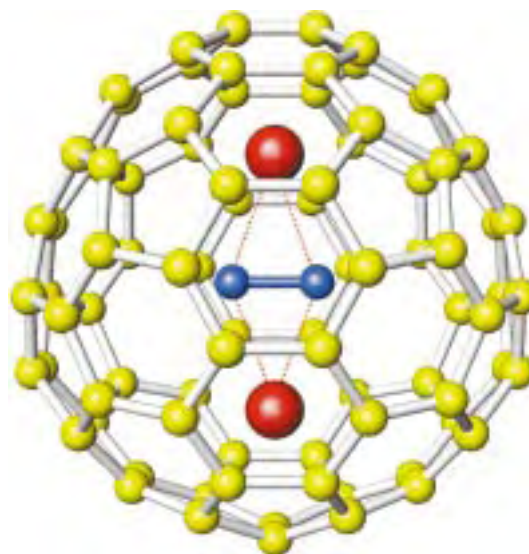


Figure 5. Schematic representation of the $(Sc_2C_2)@C_{84}$ molecule based on the results of the synchrotron X-ray powder diffraction and ^{13}C NMR experiments.

distance is 2.26(3) Å, which is qualitatively the same as an ab initio theoretical Sc–C bond length (2.135 Å) of a ScC₂ cluster.^[13] The number of electrons belonging to the Sc₂C₂ cluster is estimated to be 51.9(2) e from the MEM charge density; hence, the Sc₂C₂ species is in the divalent charge state in the C₈₄ fullerene cage. The formal electronic structure of (Sc₂C₂)@C₈₄ can thus be described as (Sc₂C₂)²⁺@C₈₄²⁻. The nature of the bonding between Sc and C₂ might be highly ionic as in the case of the ScC₂ cluster.^[13a] As one of the two major isomers of C₈₄ (namely, D₂ and D_{2d}), D_{2d}-C₈₄ not only has much higher abundance than the other C₈₄ isomers,^[7] but also has an unique ability to encage both metal atoms to form Sc₂@C₈₄,^[10c] and metal carbide clusters to form (Sc₂C₂)@C₈₄.

Experimental Section

The details of the production, separation, and isolation of endohedral scandium fullerenes has been described elsewhere.^[2, 14, 15] Briefly, soot containing (Sc₂C₂)@C₈₄ and other scandium metallofullerenes such as Sc₂@C₈₄^[15] and Sc₂@C₈₂^[14] was generated in a direct-current (350 A, 21 V) arc discharge of Sc₂O₃/graphite composite rods (12 × 12 × 300 mm, 0.8 atom %, heat treated at 1600 °C, Toyo Tanso Co.) under a 17 L min⁻¹ flow of helium at 50–100 Torr. The soot was Soxhlet-extracted with carbon disulfide for 12 h. (Sc₂C₂)@C₈₄ was isolated by multistage high performance liquid chromatography (HPLC)^[2, 14, 15] with two complementary 5PYE (21 × 250 mm) and Buckyclutcher (21 × 500 mm) columns. Stage 1 was HPLC on a 5PYE column, which was used primarily to remove C₆₀ and C₇₀. In stage 2, the (Sc₂C₂)@C₈₄-containing fraction (yellow) collected in stage 1 was re-injected into the 5PYE column, and recycling HPLC was performed. After a few cycles, the (Sc₂C₂)@C₈₄ sub-fraction containing some Sc₂@C₈₂ and C₉₀ was collected. In stage 3, recycling HPLC on a Buckyclutcher column was employed to completely separate (Sc₂C₂)@C₈₄ from the other fullerenes. Stages 2 and 3 were repeated several times to increase the sample purity to 99 %, as confirmed by laser-desorption time-of-flight (LD-TOF) mass spectrometry.

Solvent-free (Sc₂C₂)@C₈₄ powder sample was sealed in a silica-glass capillary (0.3 mm inside diameter). To collect an X-ray powder pattern with good counting statistics, a synchrotron radiation (SR) X-ray powder experiment with an imaging plate (IP) as a detector was carried out at SPring-8 BL02B2. The exposure time on the IP was 80 min. The wavelength of incident X-rays was 0.75 Å. The X-ray powder pattern of (Sc₂C₂)@C₈₂ was obtained in 0.02° steps in the range 3.0 ≤ 2θ ≤ 30.5°, which corresponds to 1.45 Å resolution in the d spacing.

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- [6] In fact, the isolation (but not structural characterization) of (Sc₂C₂)@C₈₄ had been already achieved by us, but it was then erroneously assigned as one of the three isomers of the normal metallofullerene Sc₂@C₈₆ (isomer I).^[14]
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A Two-Dimensional Polyrotaxane with Large Cavities and Channels: A Novel Approach to Metal–Organic Open-Frameworks by Using Supramolecular Building Blocks**

Eunsung Lee, Jaheon Kim, Jungseok Heo, Dongmok Whang, and Kimoon Kim*

Dedicated to Professor James A. Ibers
on the occasion of his 70th birthday

Mechanically interlocked supermolecules such as rotaxanes and catenanes have received much attention because of their intriguing structures as well as their potential applications.^[1, 2] We have been interested in the self-assembly of such

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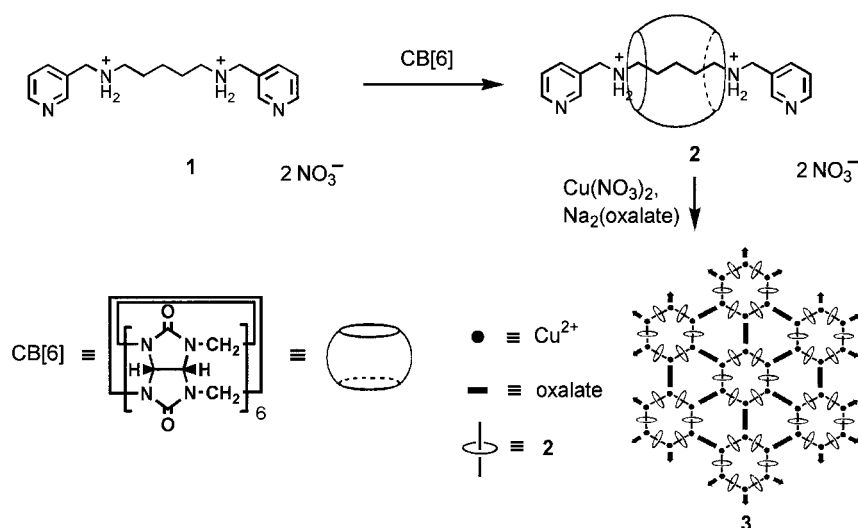
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 Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

interlocked supramolecular species, particularly polyrotaxanes and molecular necklaces, through the use of coordination bonds.^[3] Our approach to the interlocked structures involves reaction of a pseudorotaxane, composed of a cucurbituril (CB[6])^[4,5] “bead” threaded on a short “string”, with a transition metal ion or metal complex to form an infinite chain coordination polymer or a discrete supramolecular species. The large two- and three-dimensional networks^[3c,h] found in some of the polyrotaxanes suggest that this building principle can also be applied to the construction of metal–organic open-framework materials, which is another subject of intense current investigation.^[6] For example, we have reported a 2D polyrotaxane net consisting of large edge-sharing chair-shaped hexagons with an Ag^I ion at each corner and a pseudorotaxane unit at each edge.^[3c] Although interpenetration of two independent nets prevents formation of large voids in this structure, the large 2D net suggests that such pseudorotaxanes can be used as large, rigid supramolecular building blocks for the construction of metal–organic open-frameworks. We now report a novel 2D polyrotaxane network with large cavities and channels which demonstrates that this is indeed a viable approach to modular porous solids.

The pseudorotaxane **2** is prepared by threading CB[6] with *N,N'*-bis(3-pyridylmethyl)-1,5-diaminopentane dihydronitrate (**1**).^[3d] The 2D polyrotaxane **3** is then obtained by reaction of pseudorotaxane **2** with Cu(NO₃)₂ in the presence of oxalate ions (Scheme 1). The X-ray crystal structure of **3** reveals a 2D polyrotaxane in which CB[6] beads are threaded on a 2D coordination polymer network (Figure 1). A close inspection of the structure reveals that hexagonal, seven-membered molecular necklaces [7]MN^[3e,f] composed of six copper ions and six pseudorotaxanes behave as a secondary building block of the 2D polyrotaxane (Figure 1). Each corner of the supramolecular hexagon is occupied by a copper ion that is coordinated by two pyridyl units of **2**, a bidentate oxalate anion, and two water molecules in a distorted octahedral geometry. The Cu···Cu distances are approximately 13.9 Å for the side and approximately 27.8 Å for the diagonal. The molecular necklaces are connected to each other through coordination of the oxalate anion to the copper corners to form a large 2D hexagonal array of the hexagon. There are two different types of cavities (A and B) as shown in Figure 1. Cavity A is surrounded by six CB[6]s whereas cavity B is surrounded by three CB[6]s; therefore, the latter cavity is much larger than the former (see below).

The 2D layers stack along the *c* axis in the crystal, with a mean interlayer separation of 12.88 Å, in such a way that the cavities are aligned vertically to form 1D channels along the *c* axis (Figure 2). Each channel has an identical repeating unit consisting of a type A cavity and two type B cavities (Figure 3). Cavity A provides the 1D channel with a small aperture having an effective diameter of about 5 Å. The



Scheme 1. Synthesis of the 2D polyrotaxane **3**.

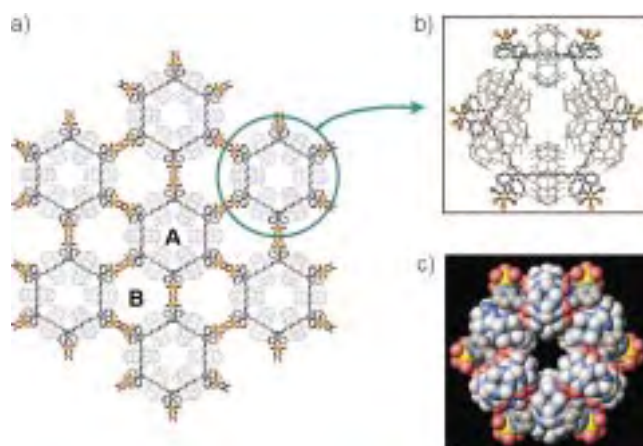


Figure 1. The 2D polyrotaxane layer in **3** built with a molecular necklace [7]MN as a secondary building block (a), which is highlighted in a ball and stick representation (b), and in a space-filling representation (c). Two different types of cavities A and B exist in the 2D network as noted. Color: copper: yellow; oxygen: red; nitrogen: blue; carbon: gray.

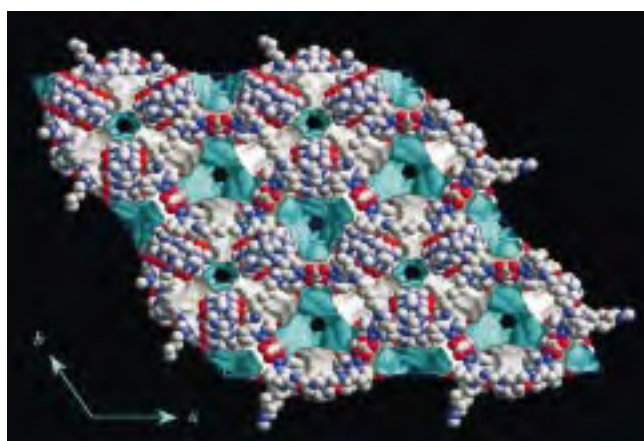


Figure 2. Structure of **3** showing the 1D channels along the *c* axis. The red, blue, and gray spheres represent oxygen, nitrogen, and carbon atoms, respectively. The accessible surface in the channels is shown in light blue. Each channel has a small aperture (shown in black) with an effective diameter of approximately 5 Å.

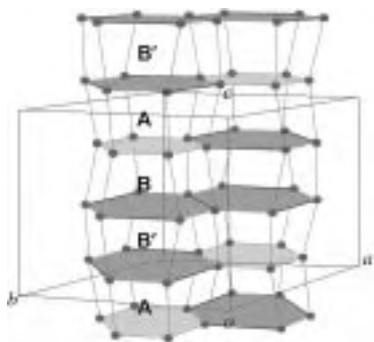


Figure 3. Schematic representation of how the cavities A and B are aligned to form 1D channels along the *c* axis.

fusion of two B cavities generates a long cylindrical void in the channel with a diameter of approximately 14 Å and a length of about 20 Å (Figure 4a). The 1D channels are interconnected to form a 3D channel network as seen in the cross-sectional view on the *ab* plane (Figure 4b): two neighboring A cavities are interconnected through another cavity (type C) with dimensions of approximately $14 \times 14 \times 7$ Å³. The channels are filled with nitrate counterions and water molecules.

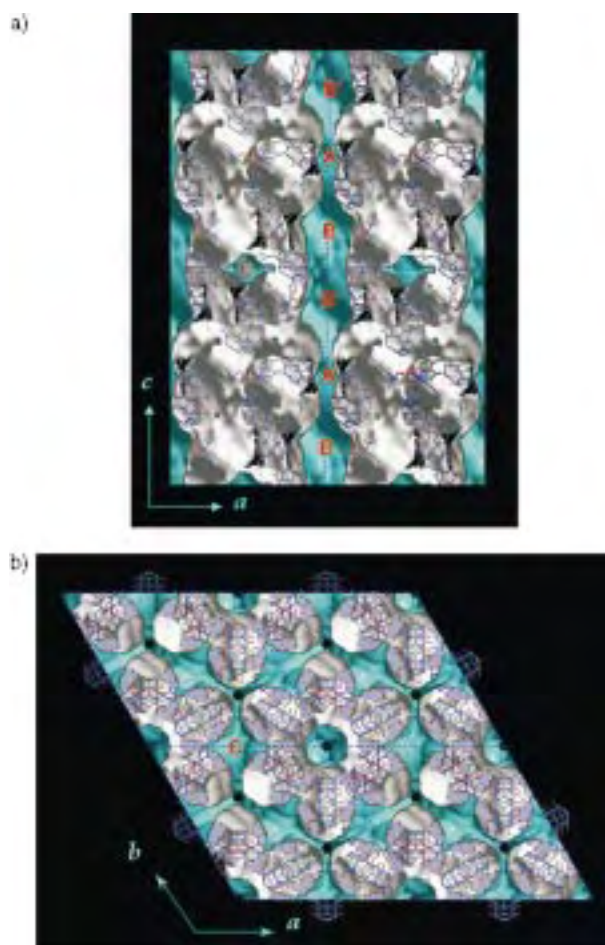


Figure 4. Cross-sectional views of **3** in the *ac* plane (a) and in the *ab* plane (b) showing the channels (in blue) formed with three different types of cavities A, B, and C: a) shows the 1D channels along the *c* axis and b) shows how they are interconnected to form 3D channels.

The total and accessible^[7] void volumes are estimated to be 48 and 22 %, respectively, of the total volume.

The layer structure appears to be stabilized by efficient van der Waals interactions arising from the self-complementarity between the 2D layers. The framework of **3** is stable indefinitely in air and in nonpolar organic solvents, and only slightly soluble in water. Upon removal of the guest water molecules by evacuation, however, **3** loses its crystallinity,^[8] but restores it upon exposure of the evacuated sample to water vapor, as judged by powder X-ray diffraction patterns. A similar behavior has been observed before,^[6] but is not fully understood yet.

The ion-exchange properties of **3**, which has a cationic framework, have been studied. Stirring a suspension of **3** in an aqueous solution containing a slight excess of NaPF₆ at room temperature results in the exchange of NO₃[−] with PF₆[−] ions. The IR and elemental analysis data indicate that nearly 80 % of the anions are exchanged after 6 h (see the Supporting Information). The larger tosylate anion is also exchanged with NO₃[−] ions, but the exchange rate is slower than that of PF₆[−] ions: only approximately 20 % of the anion is exchanged after 6 h. Larger anions such as tetraphenylborate are not exchanged with NO₃[−]. These results demonstrate the size selectivity in anion exchange in **3**. X-ray powder diffraction studies (see the Supporting Information) show that the crystallinity of **3** is maintained during the anion exchanges.

The aqua ligands coordinated to the copper centers in **3** can be replaced by other ligands. For example, treatment of a suspension of blue crystalline **3** in dichloromethane with NH₃ gas for five minutes results in a color change to deep blue. The X-ray powder diffraction pattern of the crystalline solid remains essentially the same. The elemental analysis of the new solid (**3'**) is consistent with the idea that the coordinated aqua ligands are replaced by NH₃ during this process (see the Supporting Information). However, no evidence was found for replacement of the aqua ligands with pyridine, which may be too large to be coordinated to the metal center. The exchangeable aqua ligands suggest the metal centers in **3** may be used for recognition, binding, and activation of specific substrates. Further studies along this line are in progress.

In summary, we have synthesized a novel 2D polyrotaxane with large cavities and channels. The metal–organic framework is built with a seven-membered molecular necklace which behaves as a secondary building block. This cationic framework allows size-selective anion exchange as well as coordinated ligand exchanges. Most importantly, this work demonstrates a new synthetic strategy to modular porous solids that utilizes large, rigid, interlocked supermolecules as primary or secondary building blocks.

Experimental Section

3: Sodium oxalate (24 mg, 0.18 mmol) and **2** (500 mg, 0.36 mmol) were added to a solution of Cu(NO₃)₂·3H₂O (86 mg, 0.36 mmol) in water (15 mL). The solution was then heated in air until its volume had reduced to about 5 mL. Cooling the solution to room temperature produced blue, hexagonal, X-ray-quality crystals which were collected, washed with water, and dried in air (340 mg, 51 %). Elemental analysis (%) calcd for C₁₀₈H₁₃₂N₆₀O₄₆Cu₁₂·28H₂O: C 35.38, H 5.17, N 23.69; found: C 35.53, H 5.13, N 23.62. Crystal data of **3**: [Cu(C₁₇H₂₆N₄)·(C₃₆H₃₆N₂₄O₁₂)·(C₂O₄)_{0.5}·2H₂O]·(NO₃)₃·

20H₂O, M_r = 1973.24, trigonal, $R\bar{3}m$, $a = b = 33.2194(3)$, $c = 38.9594(4)$ Å, $V = 37232.8(6)$ Å³, $Z = 18$, $\rho_{\text{calc}} = 1.584$ g cm⁻³, $T = 188$ K, Siemens SMART CCD diffractometer, MoK α radiation ($\lambda = 0.71073$ Å), $\mu = 3.84$ cm⁻¹. The structure was solved by Patterson methods (SHELXS-86). Of the three nitrate ions, only 1.5 were found because of disorder. Solvent molecules were also badly disordered. All non-hydrogen atoms were refined anisotropically (SHELXL-93). Final block-diagonal matrix least-squares refinement on F^2 with all 6888 reflections and 653 variables converged to $R1$ ($I > 2\sigma(I)$) = 0.129, $wR2$ (all data) = 0.418, and GOF = 1.77. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-147742. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Design of a Molecular Beacon DNA Probe with Two Fluorophores**

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DNA/RNA analysis is of great importance in molecular biology, genetics, and molecular medicine. DNA hybridization is a major tool for the diagnosis of genetic disease, of which the clinical symptoms are linked to alterations in DNA. Identifying the mutations in the human genome has become the focus of many research efforts. One recent development is that of a novel class of oligonucleotide probe: molecular beacons (MBs).^[1] Molecular beacons are single-stranded oligonucleotide probes with a hairpin structure. A fluorophore and a quencher are linked to the two ends of the strand. The five to seven bases at both ends of the beacon are complementary to each other, forming the stem, which keeps the fluorophore and the quencher in proximity to each other. The fluorescence of the fluorophore is thus quenched by the quencher through energy transfer. The loop portion of the molecule beacon is so designed that it is complementary to a target oligonucleotide of interest.^[1-8] When the probe encounters the target DNA molecule it forms a hybrid and forces the stem apart. Such a conformational change moves the fluorophore and the quencher away from each other, which leads to the restoration of fluorescence. Therefore, molecular beacons emit an intense fluorescent signal at room temperature only when hybridized to their target molecules. Molecular beacons have been shown to have very high selectivity in regards to the identification of a single base-pair mismatch.^[1,2] Also, since the signal transduction mechanism is built within the MB molecules, no DNA intercalation reagent or labeling of the target molecule is needed. There have been a number of different applications of molecular beacons, such as real-time monitoring of polymerase chain reactions,^[1,2] detection of DNA/RNA hybridization in living cells,^[3] DNA/RNA biosensors,^[4] bacterial detection,^[5] monitoring of enzymatic cleavage,^[6] investigation of the progression of HIV-1 disease,^[7,8] and the study of DNA-protein interactions.^[9] Molecular beacons hold great promise in studying genetics and disease mechanisms, in disease diagnostics, and in new drug development.

While MBs have been used successfully in DNA assays, their utility for quantification is limited. Currently, MBs use a

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fluorophore and a quencher attached to both ends of the stem. The sensitivity and dynamic range of MBs as probes are determined mainly by two parameters: the residual fluorescence intensity when the MBs are in the stem-closed form (incomplete quenching); and the fluorescence intensity when they are in the stem-open form. In principle, the fluorophore should be quenched completely by the quencher in the stem-closed form. In reality, however, the residual fluorescence varies greatly, because of factors such as the selection of the fluorophore/quencher pair, the synthesis of MBs, and the way the fluorophore/quencher groups are attached to the oligonucleotide. Such residual fluorescence greatly limits the detection sensitivity of MBs. In addition, MBs of this fluorophore/quencher type can rarely be used to detect the target quantitatively.

To address these problems we have developed a new strategy to design MBs with two fluorophores instead of one fluorophore and one quencher. We attach two different fluorophores (F_1 and F_2) to the two ends of the stem (Figure 1). F_1 and F_2 are chosen such that fluorescence

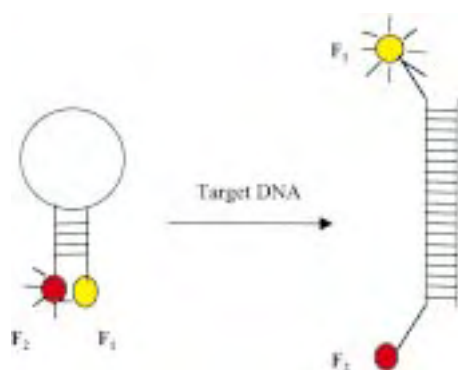


Figure 1. A schematic representation of the MB with two fluorophores. The molecular beacon was designed as a loop sequence flanked with shorter complementary sequences on the 5'- and 3'-ends. F_1 and F_2 represent the two fluorophores.

resonance energy transfer (FRET) will occur when they are in proximity. When the MB is in the stem-closed form and excited at the absorption band of F_1 , the fluorescence of F_1 is quenched by F_2 , while that of F_2 is observed (so-called sensitizing F_2).^[10] When the MB forms a hybrid with the target, FRET is reduced or eliminated and the fluorescence of F_1 will rise while that of F_2 will diminish or disappear. Thus, the change of two fluorescence intensities can be monitored, instead of only one as in the case of a MB with a quencher and a fluorophore.

The utilization of the ratio of the intensities of the fluorescence of F_1 and F_2 (I_{F1}/I_{F2}) should provide significant advantages over measurement of I_{F1} only. First, the MBs with two fluorophores are more sensitive to the concentration of the target DNA than the current MBs. For the fluorophore/quencher MBs, the enhancement factor of the fluorophore intensity f upon hybridization with the target

is defined as $I_{F1,o}/I_{F1,c}$, where subscripts o and c denote the stem-open and stem-closed forms of MB, respectively. However, the enhancement factor for the MBs with two fluorophores is defined as the change of the ratio I_{F1}/I_{F2} . This ratio is equal to $(I_{F1,o}/I_{F2,o})/(I_{F1,c}/I_{F2,c})$, which can be rewritten as $(I_{F1,o}/I_{F1,c}) \times (I_{F2,c}/I_{F2,o})$. According to the aforementioned mechanism, the fluorescence intensity of F_1 will increase upon hybridization, while that for F_2 will decrease. $I_{F2,c}/I_{F2,o}$ will always be larger than one, and, therefore, the change of I_{F1}/I_{F2} will always be larger than $I_{F1,o}/I_{F1,c}$. This means an improvement in the fluorescence detection sensitivity. Second, the MBs with two dyes will have the advantages which a ratiometric intracellular dye would have, such as better quantitation, less dependence on optical geometry, and less influence from photobleaching as well as other environmental factors that affect optical measurements.^[10]

We have applied this strategy by synthesizing a two-fluorophore MB with a coumarin group (excitation 350 nm/emission 447 nm) on one end of the stem as a donor and a 6-carboxyfluorescein group (6-FAM, excitation 492 nm/emission 518 nm) as an acceptor on the other. The sequences of the MBs and different target DNAs used in this work are summarized in Table 1. All MBs and target DNA1 were synthesized by Trilink BioTechnologies, Inc. (San Diego, CA), and DNA2 was purchased from Integrated DNA Technologies, Inc. (Coralville, IA). All MBs were synthesized using standard phosphoramidite coupling procedures. The 5'-termini of the MBs were modified with 6-FAM and 4-(4-dimethylaminophenylazo)benzoyl (DABCYL) phosphoramidites. Each sample was deprotected with concentrated ammonium hydroxide at room temperature for 30 hours, and then purified on a polyacrylamide gel. After recovery of the full-length product, the amine-modified oligonucleotides were treated with the succinimidyl ester of 6-((7-amino-4-methylcoumarin-3-acetyl)amino)hexanoic acid (succinimidyl ester of AMCA-X), and the coumarin-labeled oligonucleotide was isolated on reversed-phase HPLC.

In the absence of a target sequence MB1 adopts a hairpin structure containing a stem of 6 base pairs (Table 1 underlined segment) and a loop of 16 bases. The stem keeps the two fluorophores in proximity, which causes a quenching of the coumarin fluorescence and an emission of FAM fluorescence

Table 1. MB and target DNA sequences.

MB 1	5'-(6-FAM)- <u>GCTCGTCCATGCCAGGAAGGAACGAGC</u> -(C6NH)-(coumarin)-3'
MB 2	5'-(DABCYL)- <u>GCTCGTCCATGCCAGGAAGGAACGAGC</u> -(C6NH)-(coumarin)-3'
MB 3	5'-(6-FAM)-GCTCGT GG CCATGCCAGGAAGGA TT ACGAGC-(C6NH)-(coumarin)-3'
DNA 1	5'-TCCTTCCTGGGCATGG-3'
DNA 2	5'-AATCCTTCCTGGGCATGG CC -3'

The underlined bases indicates the stem sequence of the MB. Bold bases indicate the mismatched bases.

as a result of energy transfer. A conformational change that opens the stem leads to the separation of the two fluorophores, and therefore restores the fluorescence of coumarin while depressing that of FAM. Figure 2 shows fluorescence spectra of MB 1 before (a) and after (b) hybridization with its target DNA1. Fluorescence spectra were collected on a

Perkin–Elmer luminescence spectrometer (Model LS50B) with excitation at 350 nm. All fluorescence experiments were performed at room temperature. The buffer solution consists of 5 mM Mg^{2+} ions, 50 mM KCl, 20 mM tris(hydroxymethyl)-aminomethane-HCl (Tris-HCl; pH 8.0). As expected, the emission of coumarin is significantly quenched in the stem-closed form while the FAM fluorescence is strong (a), which indicates energy transfer is quite efficient for the coumarin/FAM pair. Once MB1 hybridizes with the target DNA1, the two fluorophores are pulled apart, and the coumarin fluorescence is largely restored (b).

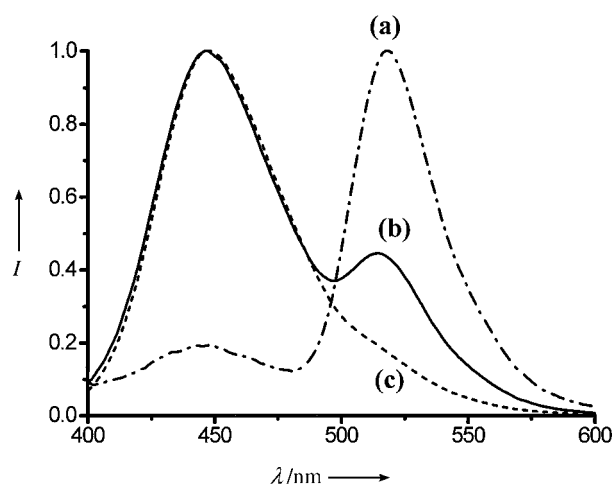


Figure 2. Normalized fluorescence spectra of MB1 with excitation at 350 nm: a: MB1 alone (1×10^{-7} M); b: MB1 (1×10^{-7} M) and complementary DNA1 (5×10^{-7} M); c: solution (b) digested by deoxyribonuclease I into mononucleotides and shorter oligonucleotide fragments. F_1 and F_2 are completely disassociated after enzymatic digestion.

We have determined the sensitivity of the MB by using different concentrations of target DNA1. The ratio of $I_{\text{coumarin}}/I_{\text{FAM}}$ is used to report the amount of DNA1 present. The ratio increases linearly with target oligonucleotide concentration (Figure 3 top). The excellent linear relationship indicates that a MB of this design can be used to detect the target quantitatively over a large dynamic range (1 nM to 1 μM). For a comparison, we synthesized MB2, a conventional fluorophore/quencher (coumarin/DABCYL) molecular beacon with the same stem and loop sequence. The response of MB2 towards different concentrations of the same target DNA1 is shown in Figure 3 bottom, where I_{coumarin} is used to report the amount of DNA1 present. Although I_{coumarin} can report DNA1 concentration linearly over the range of 1 to 10 nM, it is clear that the increase of I_{coumarin} is far from linear against the increase of DNA1 concentration above 10 nM.

The MBs with two fluorophores are also more resistant to fluctuations caused by the experimental environment and allow quantitative determination of the target. The $I_{\text{coumarin}}/I_{\text{FAM}}$ measurement is a fluorescent ratiometric measurement with self-calibrating characteristics.^[10] Since the fluctuation in fluorescence is a major source of noise in the signals, especially when the target concentration is low, the $I_{\text{coumarin}}/I_{\text{FAM}}$ measurement will not only increase the sensitivity but

also make it more reliable for measurements. We carried out a statistical determination of the detection limit of DNA1 by MB1. The ratio of $I_{\text{coumarin}}/I_{\text{FAM}}$ for MB1 is 0.164 ± 0.002 . Based on a signal/noise ratio of 3/1, the detection limit for DNA1 was determined to be 0.17 nM, which is one order of magnitude lower than that for many other DNA probes.^[11, 12] It is worth noting that this detection limit is achieved with a conventional spectrometer with a mercury lamp and can be further improved with a more efficient optical detection

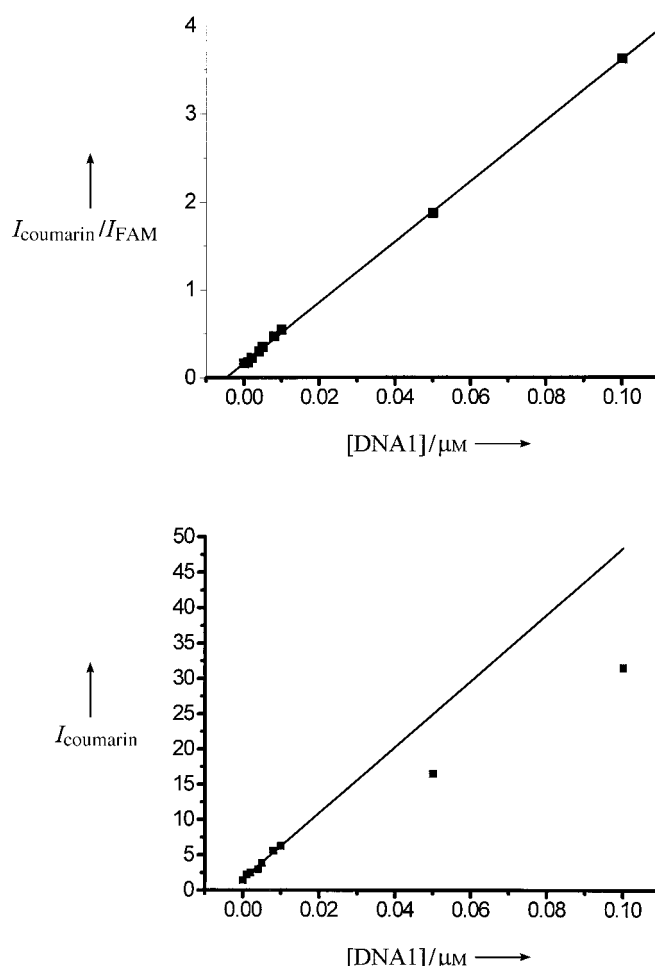


Figure 3. Top: $I_{\text{coumarin}}/I_{\text{FAM}}$ ratio for MB1 versus [DNA1]; bottom: I_{coumarin} for MB1 versus [DNA1] (the intensity is given in arbitrary units). Both were excited at 350 nm. $[\text{MB1}] = 1 \times 10^{-7}$ M.

system and a better optical excitation by using lasers. Moreover, the loop and the stem of the MB can be optimized to achieve higher fluorescent enhancement, thus higher sensitivity, in DNA/RNA studies.^[2]

It is worthwhile pointing out the fact that the fluorescence intensity of coumarin increased further upon addition of deoxyribonuclease I to the hybrids of MB and complementary DNA. This indicated that the emission of the donor is not completely restored even in the open form of MB. A similar

phenomenon was also observed for a MB with a fluorophore/quencher design. While having not been reported previously, this observation can be understood considering that the distance between donor and acceptor when MB is in the open form (usually 20–30 mer in length) is not significantly larger than the Förster distance (around 65 Å in this case). Thus there is considerable FRET between the donor and acceptor for MBs in the open form. This process is also manifested by the appearance of a fluorescence spectrum of MB in the open form (Figure 2b), where the FAM emission is still significant. The design of the MB with two fluorophores also provides an easy and effective way of measuring the Förster energy transfer distance for a given donor/acceptor pair. The efficiency of energy transfer can be calculated from the quenching of the donor emission in the presence of the acceptor. By designing two-fluorophore MBs with different lengths (number of bases as shown in MB1 and MB3 in Table 1), Förster energy transfer distance for a given donor/acceptor pair can thus be determined using the FRET efficiency with these different MBs.

In conclusion, we have proposed a new strategy of designing MBs which uses two fluorophores instead of one fluorophore and one quencher as the donor and acceptor. Such MBs display high sensitivity and a large dynamic range. Molecular beacons of this new design with coumarin and 6-FAM as the fluorophores can quantitatively detect the target DNA up to 1×10^{-7} M with a detection limit of 1.7×10^{-10} M with a basic spectrometer. It could also be very useful for studying protein–DNA/RNA interactions,^[8] where the fluorophores are as likely to be pulled apart as to be squeezed closer. We were also able to determine for the first time the Förster distance for the coumarin/FAM pair, which was estimated to be 65 ± 1 Å. We expect MBs of this design to be effective for applications in both DNA/RNA and protein–DNA/RNA interaction studies as well as in genetic analysis based on better linearity, larger dynamic range, higher sensitivity, and less dependence on optical geometry and photobleaching.

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An Exceptionally Stable Ti Superoxide Radical Ion: A Novel Heterogeneous Catalyst for the Direct Conversion of Aromatic Primary Amines to Nitro Compounds**

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Superoxide ion ($O_2^{\cdot-}$), an active oxygen species, plays important roles in various diseases caused by oxygen toxicity such as ischemia, carcinogenesis, inflammation, diabetes, and aging.^[1] Superoxide dismutases act as a defense system against oxygen toxicity in living cells by catalyzing the dismutation of $O_2^{\cdot-}$ into H_2O_2 and O_2 .^[2] Although it is normally reduced to H_2O , O_2 may diffuse out of the electron-transport enzyme system and interact with important biological molecules.^[3] In spite of much research, neither the mode nor the site of damage due to $O_2^{\cdot-}$ in biological systems is known. Investigations on the organic chemistry of $O_2^{\cdot-}$ with simple model substances have shown that $O_2^{\cdot-}$ is a versatile species^[4] and can behave as a base, as a nucleophile, and as an oxidizing or reducing agent,^[5] but none of this provides an explanation for its toxicity. While the debate regarding the importance of $O_2^{\cdot-}$ in vivo continues, the chemistry of the radical remains to be completely characterized. Consequently, it is of interest to study the reactions of $O_2^{\cdot-}$ with simple organic molecules such as amines to build up a picture of its possible biological effects.

A literature search^{[2a, 4], [6]} reveals that the generation of $O_2^{\cdot-}$ is achieved by electrolytic reduction of O_2 in DMF or by enzymes such as xanthine-xanthine oxidase. Recently, the generation of $O_2^{\cdot-}$ was described on the lattice of metal oxides such as MgO/CaO, ZnO, ZrO₂, and TiO₂ by using a photo-induced electron-transfer process.^[7] However, these methods

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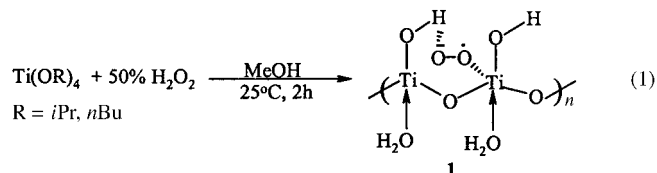
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Supporting information for this article is available from the author.

are not suitable for large-scale synthesis. Here we report a new and practical method for the generation of $\text{O}_2^{\cdot-}$ on a solid hydrated titanium matrix and its catalytic activity towards N–H bonds of aromatic and aliphatic primary amines.

The light yellow Ti superoxide catalyst **1** was prepared by the action of 50% H_2O_2 on $\text{Ti}(\text{OR})_4$ in anhydrous MeOH at 25 °C [Eq. (1)]. It was characterized by FTIR, ESR, and Raman spectroscopy, X-ray diffraction (XRD), thermogravimetric/differential thermal analysis (TG/DTA), and elemental analysis. Its IR spectrum shows characteristic absorption bands at 3720 (w), 3665 (w), and 3450 cm^{-1} (s) that indicate the presence of vibrational modes of coordinated water molecules on a Ti^{4+} site and of surface TiOH groups.^[8] The other IR absorption bands at 1027 (s) and 1157 cm^{-1} (m) indicate the presence of superoxide radical ion on the solid material.^[7b, 9] It also has IR bands in the range of 900–538 cm^{-1} (m) corresponding to the presence of Ti–O–Ti linkages. An intense line at 900 cm^{-1} in the Raman spectrum of the catalyst further confirmed the presence of Ti–O–Ti linkages. The other weak Raman lines observed in the range of 1025–1119 cm^{-1} were assigned to $\text{O}_2^{\cdot-}$.



The XRD pattern of **1** shows that it is amorphous, as there are no sharp peaks in the spectrum. A sample of **1** dried at 25 °C (3 mm Hg) shows characteristic ESR signals at $g_1 = 2.024$, $g_2 = 2.009$, and $g_3 = 2.003$ (Figure 1), which strongly

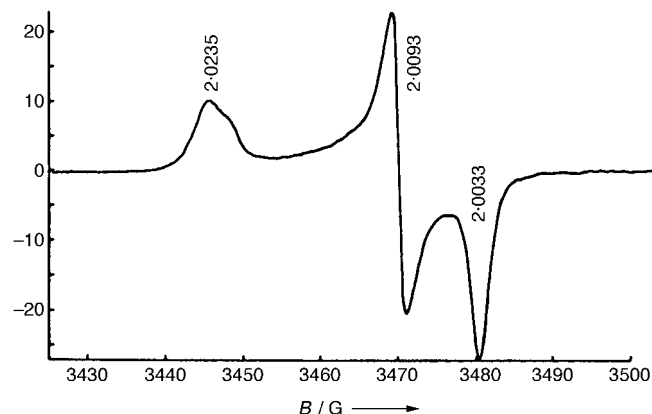


Figure 1. ESR spectrum of **1** at 298 K.

suggest the presence of unpaired electrons of the stable superoxide radical anion generated by the decomposition of H_2O_2 on the Ti matrix.^[7c,f, 10] However, when **1** was dried at 90 °C (3 mm Hg), the characteristic ESR signals were absent, that is, the superoxide radical anions are lost at higher temperature.

The TG/DTA analysis of **1** (Figure 2) shows a weight loss of 22.59% at 114 °C and of 10.84% at 291 °C due to the loss of

coordinated H_2O molecules and superoxide radical anion, respectively. Volumetric analysis^[11] of **1** gave Ti content of 41.7%, and the surface area, determined by the Brunauer–Emmett–Teller method, was 310 m^2g^{-1} .

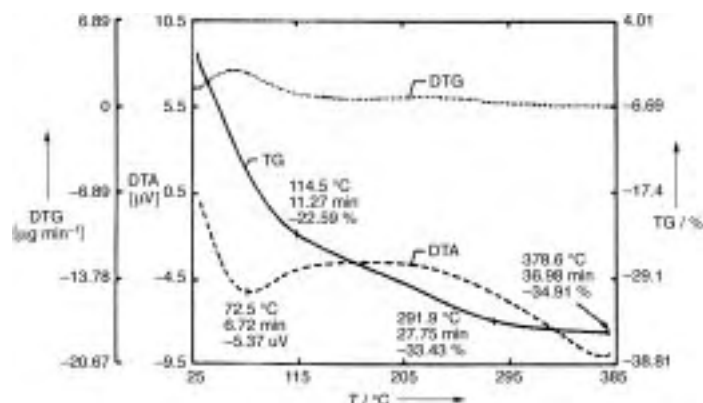
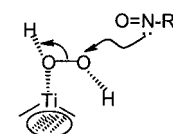


Figure 2. TG/DTA spectrum of **1**.

To evaluate the catalytic activity of **1**, various primary amines were subjected to oxidation with 50% H_2O_2 at 25 °C (Table 1). In the case of aromatic amines, the reaction selectively afforded the corresponding nitro derivatives in high yields. This result is particularly interesting because oxidation of amines is generally complicated by several other competing reaction pathways that yield a range of products.^[12] Product selectivity depends on the H_2O_2 /amine molar ratio, and at higher ratios (H_2O_2 /amine = 6/1) the selectivity for nitro derivatives is high. Remarkably, even arylamines with electron-withdrawing groups such as COOH and NO_2 are efficiently oxidized to the corresponding nitroarenes (entries 11 and 12), which otherwise may be difficult to obtain by conventional nitration methods. The high selectivity for nitrobenzenes may be rationalized by the high Ti content (41.7%) of the solid catalyst.

Under similar oxidation conditions, aliphatic primary amines with α -CH bonds are selectively converted to oximes along with the ketone formed by partial hydrolysis thereof. It can be reasoned that the α -CH protons of species **C** (see Scheme 2) undergo prototropic migration to give a more stable enol form. It is also possible that attack of nitroso species **C** on the electrophilic oxygen atom of the peroxide associated with the Ti matrix is preferred due to the higher basicity of the nitroso compound compared to its oxime counterpart (Scheme 1).

To obtain more information on the nature of the reactive intermediate in the oxidation of amines, the following experiments were carried out: 1) The oxidation of aniline with 50% H_2O_2 and **1** as catalyst was monitored by ESR spectroscopy. When the catalyst **1** was added to a solution of aniline in methanol, the characteristic ESR signal of the catalyst disappeared. However, the ESR signal reappeared on the addition of a small



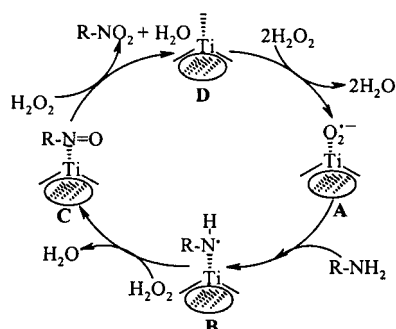
Scheme 1. Attack of nitroso species on the electrophilic oxygen atom of the peroxide associated with the Ti matrix.

Table 1. Oxidation of amines with **1** as catalyst.^[a]

Entry	Substrate	Time [min]	Conversion [%]	ArNH ₂ $\xrightarrow[25^\circ\text{C}, 0.5\text{ h}]{\text{1, H}_2\text{O}_2, \text{MeOH}}$ ArNO ₂			
				NB	Product ^[b] selectivities [%] ^[c]	NSOB	AB
Aromatic amines							
1	aniline	30	100	98.18	1.82	–	–
2	2-methylaniline	30	100	97.35	1.50	–	1.15
3	3-methylaniline	35	100	90.00	6.60	1.50	1.90
4	4-methylaniline	30	100	98.00	1.57	–	0.43
5	2-methoxyaniline	30	100	97.15	1.00	0.80	1.05
6	2-methoxy-5-nitroaniline	35	100	95.60	3.05	–	1.35
7	4-methoxyaniline	30	100	97.05	1.13	0.37	1.45
8	4-hydroxyaniline	45	100	89.22	3.01	3.62	4.15
9	2-methyl-6-ethylaniline	35	100	90.98	4.50	1.87	2.65
10	4-chloroaniline	35	100	91.22	5.00	1.50	2.28
11	4-nitroaniline	45	100	82.50	9.01	3.19	5.31
12	2-aminobenzoic acid	45	100	85.05	8.05	4.09	2.81
Aliphatic amines					Oxime		Ketone
1	cyclohexyl amime	45	90		88.88		11.11
2	benzylamine	45	85		94.11		5.88
3	ethylenediamine	45	80		87.5		12.5

[a] Catalyst was recovered and reused without any loss of activity and selectivity. [b] Products were characterized by m.p., IR, ¹H NMR, MS, and GC-MS. [c] Selectivities are based on gas chromatographic analysis; NB = nitrobenzene, NSOB = nitrosobenzene, AB = azobenzene, AZOB = azoxybenzene.

quantity of 50 % H₂O₂. As the reaction progressed, this signal again became weak and finally disappeared. 2) The oxidation of primary amines did not take place when a radical quencher was added to the reaction mixture. To explain these results, the catalytic cycle shown in Scheme 2 is proposed.



Scheme 2. Proposed catalytic cycle for the oxidation of amines.

The first step is the abstraction of a hydrogen atom from the amine by the superoxide radical anion **A** to generate the transient RNH[•] radical **B**,^[13] which is oxidized by H₂O₂ to nitroso species **C**. Further oxidation of **C** with 1 mol of H₂O₂ generates nitrobenzene and liberates **D**. Finally the superoxide catalyst **A** is regenerated by decomposition of hydrogen peroxide on the Ti⁴⁺ surface [Eqs. (2) and (3)].^[7f,g, 14]



To determine whether the catalyst behaves in a truly heterogeneous manner, it was filtered off at the end of the reaction, and an additional amount of aniline and H₂O₂ was added to the reaction mixture. No nitrobenzene was obtained, and aniline was completely recovered. Further, the catalyst

recovered by simple filtration was successfully reused for the oxidation of aniline.

In conclusion, we have demonstrated a novel method for the preparation of a stable Ti superoxide catalyst **1** from readily and cheaply available Ti(OiPr)₄. Catalyst **1** is heterogeneous and very effective for the selective oxidation of amines, particularly of anilines and aliphatic primary amines, to the corresponding nitrobenzenes and oximes. We are currently investigating the use of this novel material for other oxidations such as epoxidation and dihydroxylation of olefins, sulfoxidation, and hydroxylation of phenol.

Experimental Section

1: 50 % H₂O₂ (5.98 g, 0.175 mol) was added slowly to a solution of Ti(OiPr)₄ (5.0 g, 0.0175 mol) in anhydrous MeOH (50 mL) over 40 min under N₂ with stirring at room temperature. The yellow precipitate that formed was collected by filtration on a sintered funnel, washed with anhydrous methanol, and dried under reduced pressure (3 mmHg) at 25 °C for 1 h. Yield: 3.94 g (98 %). EPR spectra were recorded on a Bruker EMX spectrometer at 9.76 GHz and 298 K, and *g* values were determined relative to a standard marker: *α,α'*-diphenyl-*β*-picryl hydrazyl (DPPH, *g* = 2.0036). TG/DTA was performed on a TG/DTA 22, TG/DTA 32 system (Seiko Instruments) in the range of 30–400 °C at 10 °C min^{−1}.

Oxidation of aniline: 50 % aqueous H₂O₂ (2.19 g, 0.064 mol) was added slowly to a mixture of aniline (1.0 g, 0.011 mol), **1** (0.25 g, 25 wt %), and anhydrous methanol (15 mL) under N₂ with stirring over 10 min. The reaction was exothermic, and the color changed from yellow to reddish brown during addition of H₂O₂. The reaction was monitored by TLC (15 % ethyl acetate in petroleum ether (60–80 °C)) and after completion, catalyst **1** was filtered off, and methanol evaporated under reduced pressure. The crude product (1.3 g) was analyzed by gas chromatography.

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Parallel Synthesis of ZSM-5 Zeolite Films from Clear Organic-Free Solutions**

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High-throughput synthesis and screening (“combinatorial”) techniques have been recently introduced to the discovery and optimization of solid-state materials,^[1–3] such as phosphors,^[4] superconductors,^[5] dielectrics,^[6] and heterogeneous catalysts.^[7–11] In this study parallel synthesis is applied to prepare supported ZSM-5 zeolite films. Identifying compositions that produce a microscopically continuous zeolite film usually constitutes the first step in zeolite membrane synthesis,^[12, 13] an area that has attracted considerable attention in the last decade due to prospective gas separation applications.^[13–17] Zeolite films are also of interest for sensor and nonlinear optical material applications.^[18, 19] Zeolite film

synthesis, in which film thickness, composition, and even crystallite orientation can be controlled,^[19–22] offers an interesting approach to the preparation of catalytic libraries.

There are several reports on the parallel synthesis of zeolite powders.^[23–25] Akporiaye and co-workers developed a convenient multiwell autoclave wherein one hundred or more distinct reaction mixtures could be treated hydrothermally. The solid products were washed in situ and transferred to individual sample holders for X-ray analysis.^[23] Other groups employed post-synthetic treatment to attach the powder products to a silicon wafer or filter paper to eliminate the need for individual sample handling. X-ray microdiffraction was then used to identify individual sample members. Klein et al.^[24] used a silicon wafer as the bottom of a multiwell autoclave and, after reaction, heated the precipitates to bond them to the wafer. They also applied this technique to produce zeolite libraries for catalytic investigation.^[26] Bein and co-workers designed a centrifuge apparatus that allowed quantitative product recovery onto filter paper without manipulation of individual samples.^[25]

Parallel film synthesis in the present study was carried out in a multiwell reactor similar to that used in reference [24]. The reactor, shown schematically in Figure 1, contains twenty-one wells of approximately 3 mm diameter and 5 mm depth

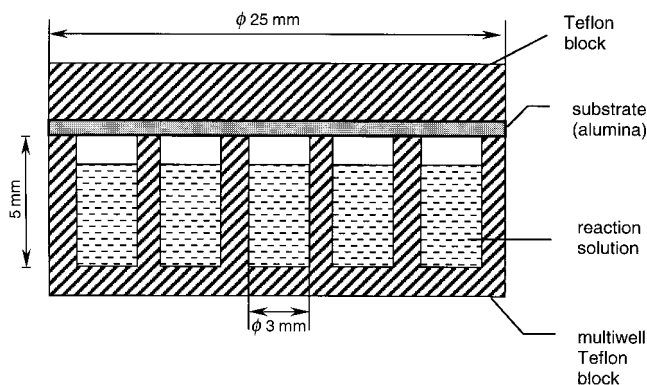


Figure 1. Cross-section of the multiwell reactor.

drilled in a Teflon block. After the solutions had been introduced, the substrate alumina disk was placed on top of the wells and was covered by a cylindrical Teflon block. The sandwich was enclosed in a Parr reaction bomb, with the Teflon cap of the bomb applying the necessary pressure for sealing the wells. No additional water was added into the bomb. The diameter of the substrate disk was 2.5 cm, chosen to fit in the sample holder of the scanning electron microscope (SEM). The volume of solution in each well was 35 μL , a little less than the 40 μL volume of the wells. To ensure full contact of the substrate with the solution, the bomb was inverted and gently shaken several times with the substrate at the bottom of the solution and then placed in the oven either with the substrate placed horizontally at the bottom of the synthesis solution, or was rotated by 90° to fix the substrate in a vertical position. Upon opening the autoclave at the completion of the reaction no loss of liquid from the wells was observed and all zeolite films were found firmly attached to the substrate. The morphology of the films was examined by scanning electron

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microscopy (SEM). X-ray diffraction (XRD) analysis of the films ideally should be carried out by a microdiffractometer. Such an instrument was not available and, instead, a conventional powder XRD diffractometer was used, with a lead foil covering all but one film at a time.

Initial experiments were carried out to test the effectiveness of sealing and the effect of substrate orientation. Figure 2

the slightly higher gravity potential at such a small volume-to-surface ratio.

Another issue of interest is how the film morphology compares with that produced at higher volume-to-surface ratios under conventional conditions. In the present experiments, the ratio of solution volume to substrate surface was about 0.5 cm, less than one-tenth of the ratio 5–20 cm used

previously in our laboratory for zeolite film synthesis.^[12, 13, 22] The zeolite films shown in Figure 2 were about 5 μm thick, and were well crystallized. They displayed morphology similar to that of films prepared conventionally from the same composition on porous or dense alumina but in larger autoclaves using 10–150 mL solution.^[12] On the other hand, the X-ray diffraction pattern of the films prepared by parallel synthesis differs somewhat from the pattern of the conventionally grown films in relative peak intensities, indicating lesser orientation of crystallites in the films grown in the wells. Preferred orientation of seeded growth is known to result from competitive growth of the fastest growing crystallographic axis, usually the *c* axis,^[20, 21] and depends on the extent of film growth. The lesser orientation of the films grown in the wells is then consistent with the lower volume-to-surface ratio of the wells.

Substrate orientation had an obvious effect on zeolite film morphology. Figure 4 shows a ZSM-5 film prepared by

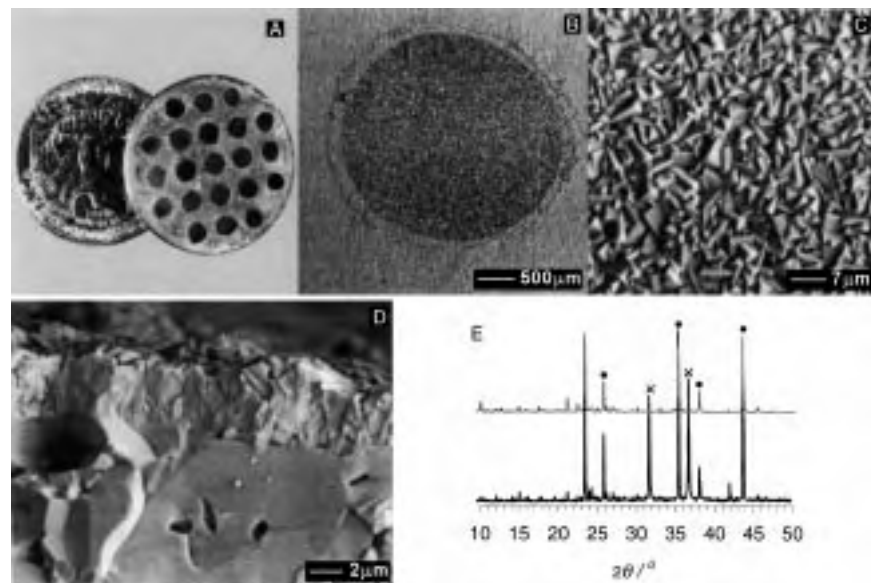


Figure 2. An array of ZSM-5 zeolite films grown on an alumina disk. The hydrothermal reaction was carried out on a seeded alumina disk for 16 h at 150 °C with the substrate held vertically during synthesis. A) The disk is displayed alongside a quarter coin in the background; B, C) one of the films under magnification; D) SEM image of a film cross-section; E) X-ray diffraction patterns of one of the array films (bottom) and a conventionally grown film (top). The dots mark peaks from the alumina substrate, and the crosses mark peaks from the lead mask.

displays a 21-member array of zeolite films prepared by using identical composition in all wells ($\text{SiO}_2\text{:}0.15\text{TPABr:}0.7\text{NaOH:}98\text{H}_2\text{O}$; TPA = tetrapropylammonium) with the substrate held in the vertical position. Figure 2 B and C show one member of the array under higher magnification and indicate that the sealing was effective in confining the hydrothermal reaction inside each of the reaction wells. The film shown in Figure 2 B is circular and of uniform appearance, suggesting that the substrate surface covered by the well was uniformly wetted despite the incomplete filling of the well (Figure 3). A simple experiment conducted at room temperature showed that the liquid assumes the configuration of Figure 3 a in preference to the alternative shown in Figure 3 b, evidently due to a lower surface energy more than balancing

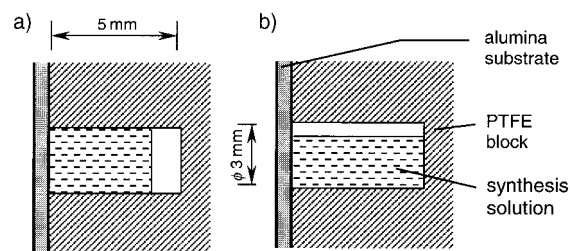


Figure 3. Liquid position for the vertically oriented substrate. a) Horizontal solution column formed following the adopted loading procedure. b) Position not realized.

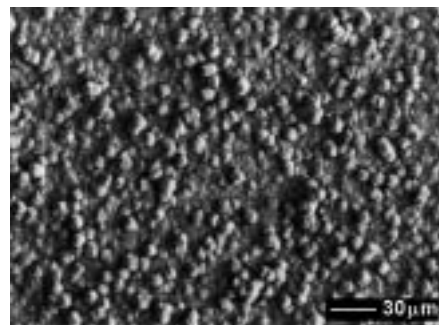


Figure 4. A ZSM-5 film prepared with the seeded alumina disk placed at the bottom of the solution.

placing the substrate horizontally at the bottom of the solution during parallel synthesis under otherwise identical conditions to those of Figure 2. While the vertical synthesis geometry yielded a smooth and well-intergrown film, the horizontal geometry produced a continuous film with larger embedded particles, evidently as a result of precipitation of homogeneously grown crystals. At the larger volume-to-surface ratios used in standard autoclaves, precipitation of homogeneously grown species is more extensive when the substrate is placed at the bottom of the solution.^[12]

After the preliminary experiments, parallel synthesis was further applied to explore zeolite ZSM-5 film preparation from clear, organic-free synthesis solutions. Compared to the standard ZSM-5 synthesis that involves organic tetrapropylammonium (TPA⁺), the organic-free synthesis employs chemicals of lower cost and toxicity. More importantly from the standpoint of film or membrane synthesis, it renders unnecessary the calcination employed to remove the TPA⁺ ions, during which lattice changes often produce microcracks in the films.^[27–29] Organic-free synthesis of ZSM-5 in either powder^[30–32] or film^[33] form invariably employed hydrogel reaction mixtures, but clear solutions containing organic templates have been widely used in ZSM-5 membrane synthesis to minimize spatial inhomogeneity. They have also been quite popular in mechanism investigations of zeolite powder synthesis owing to the ease of product separation.

Exploration of clear, organic-free solutions for ZSM-5 film growth in the range SiO₂:xNaOH:yAl₂O₃:80H₂O by parallel synthesis using 20 different compositions is summarized in Figure 5. As expected, alkalinity was the major factor in the formation of a clear solution, and for NaOH/SiO₂ ≥ 0.5:1 the solutions were clear. Figure 5 indicates that NaOH was also the most important factor affecting film morphology and that a NaOH/SiO₂ ratio of <0.8:1 was required to form a continuous film. Interestingly, within the composition space 0.5:1 ≤ NaOH/SiO₂ ≤ 0.7:1 and 300:1 ≤ SiO₂/Al₂O₃ ≤ 700:1 the film morphology appeared insensitive to solution composition. Energy dispersive spectroscopy (EDS) gave for all films the estimate Si/Al ~ 20:1 (atomic ratio), close to the lower bound allowed for ZSM-5. This ratio is much lower than the ratio Si/Al = 150–350:1 in the solution, indicating that aluminum-rich species are predominantly involved in the growth of the ZSM-5 crystals in the absence of TPA⁺ templates. The Si/Al ratio of these films is comparable to the Si/Al ~ 15:1 ratio of ZSM-5 membranes prepared by using TPA⁺-free hydrogels,^[33] and much lower than the Si/Al ratio of 100–200:1 often measured for ZSM-5 films prepared by using TPA⁺ templates.

ZSM-5 films were also prepared conventionally from 10 mL solution to compare with the films synthesized in parallel. Figure 6 shows a conventionally grown film that displays morphology similar to that obtained by parallel synthesis. Additional films were prepared conventionally varying SiO₂/Al₂O₃ ratios in the synthesis solution from 200:1 to 600:1. There was little effect of the SiO₂/Al₂O₃ ratio

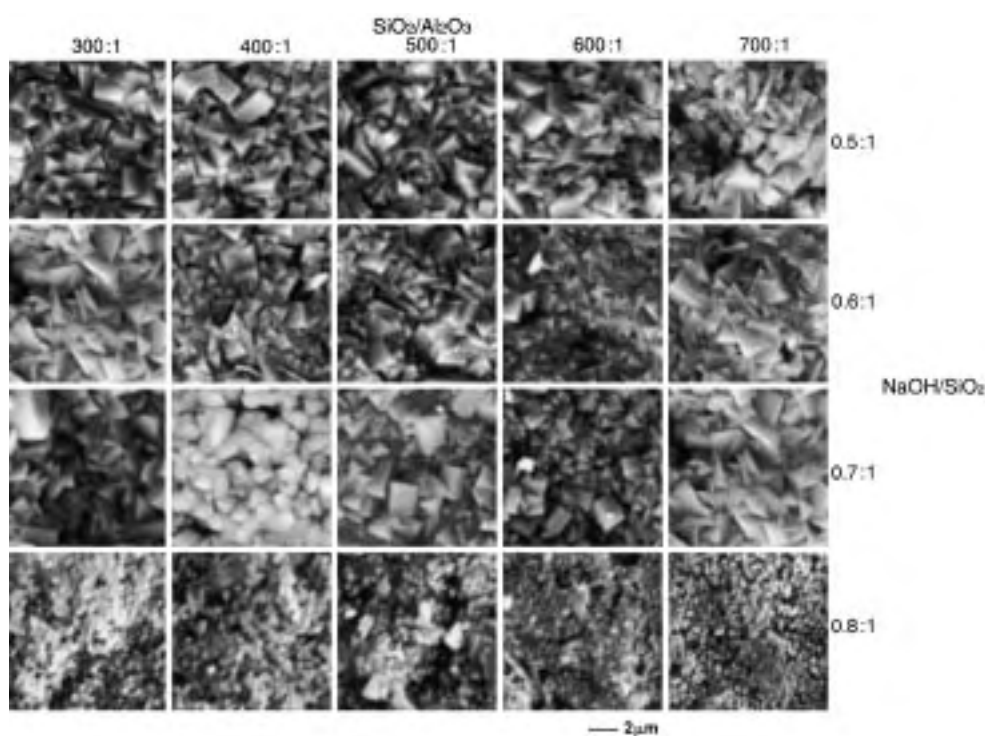


Figure 5. ZSM-5 films prepared from clear synthesis solutions of composition SiO₂:xNaOH:yAl₂O₃:80H₂O. The reaction was carried out at 180 °C for 16 h on a seeded alumina disk held vertically.

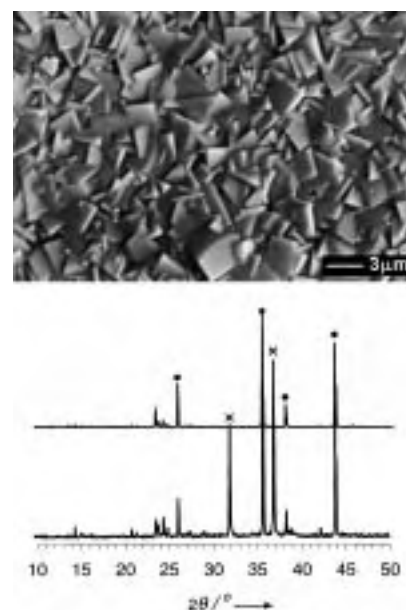


Figure 6. Top) SEM image of a ZSM-5 film prepared conventionally on a seeded alumina substrate placed in a 10 mL reactor. The reaction was carried out for 16 h at 180 °C in a clear solution of composition SiO₂:0.5NaOH:1/300Al₂O₃:80H₂O. Bottom) X-ray diffraction pattern of the film (top curve), compared with that of a film prepared by parallel synthesis (bottom curve). The peaks marked with a dot originate from the alumina substrate, and the peaks marked with a cross from the lead mask.

on morphology. The X-ray diffraction patterns of films grown in parallel and conventionally had some differences as noted previously.

In summary, parallel synthesis of ZSM-5 zeolite films was demonstrated using a 21-well reactor. Holding the substrate

vertically provided uniform wetting of the substrate in the well area and favored heterogeneous film growth. The films prepared by parallel synthesis were shown to have similar morphology to those synthesized under conventional conditions but their X-ray diffraction patterns indicate lesser orientation of crystallites. Parallel synthesis was used to screen the composition space of organic-free clear synthesis solution for ZSM-5 film growth. The composition $\text{SiO}_2:(0.5-0.7)\text{NaOH}:(1/300-1/700)\text{Al}_2\text{O}_3:80\text{H}_2\text{O}$ resulted in continuous ZSM-5 films of $\text{Si}/\text{Al} \sim 20:1$.

Experimental Section

Two types of silicon sources were used: sodium silicate solution (14% NaOH and 27% SiO_2), and tetraethylorthosilicate (TEOS). Sodium silicate was filtered by using a Buchner funnel with a coarse fritted disc immediately before use. When TEOS was used as the silicon source, it was first dissolved in tetrapropylammonium hydroxide (TPAOH) to form a clear solution of composition $\text{TEOS}:0.15\text{TPAOH}:0.7\text{NaOH}:98\text{H}_2\text{O}$, which was then filtered before use with a PTFE filter (0.45 μm). Tetrapropylammonium bromide (TPABr) solution (25 wt %) was prepared and filtered with 0.45 μm cellulose acetate membranes.

The synthesis mixture was prepared by mixing a measured amount of chemicals in a transparent LDPE vial of volume 1 mL (Nalgene). When sodium silicate solution was used, H_2SO_4 (5N, VWR) was added to adjust the alkalinity of the final solution. After thorough shaking, a clear synthesis solution was formed and aged for one day at room temperature without stirring before being introduced into the well for reaction. Occasionally, the synthesis mixtures turned turbid immediately after mixing, but the solution became clear after standing for several hours.

The substrates employed were nonporous α -alumina disks of diameter 2.5 cm. Prior to seeding the substrates were cleaned by a procedure described in reference [22]. Seeding of the entire substrate surface with a monolayer of silicalite particles was carried out using a previously developed protocol.^[12, 33] The seeds about 0.4 μm in size were finer than the substrate roughness and did not cause problems in sealing under pressure against the Teflon surfaces.

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Bowl-Shaped Tris(2,6-diphenylbenzyl)tin Hydride: A Unique Reducing Agent for Radical and Ionic Chemistry**

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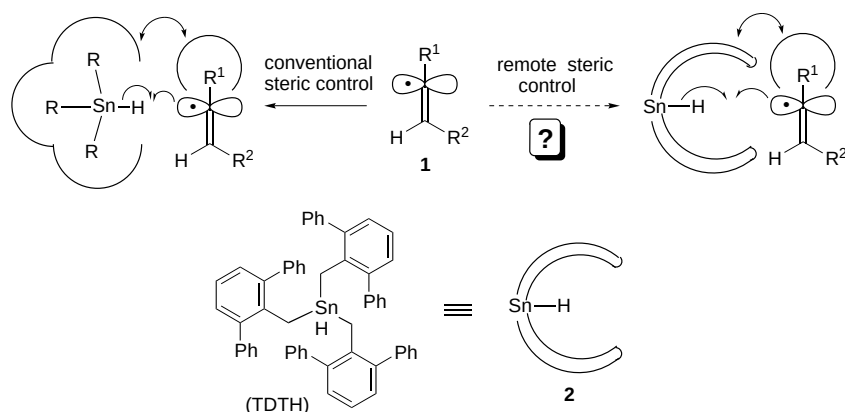
Trialkyltin hydrides (R_3SnH) are widely utilized in numerous radical reactions including reductive dehalogenations,^[1, 2] desulfurizations,^[3] and radical cyclizations.^[4] Among several R_3SnH ($\text{R} = \text{Me}, \text{Bu}, \text{Ph}$), Bu_3SnH is the most popular reagent in radical chemistry. The Bu_3SnH -mediated radical reactions exhibit high regio- and stereoselectivity by changing radical initiators (azobisisobutyronitrile (AIBN), benzoyl peroxide (BPO), $h\nu$, Et_3B , etc.) and/or the reaction conditions.^[5] Alternatively, such stereoselectivity is also achievable by replacing Bu_3SnH or Ph_3SnH ^[6] with the sterically more hindered $(\text{Me}_3\text{Si})_3\text{SiH}$.^[7] However, it is apparent that there

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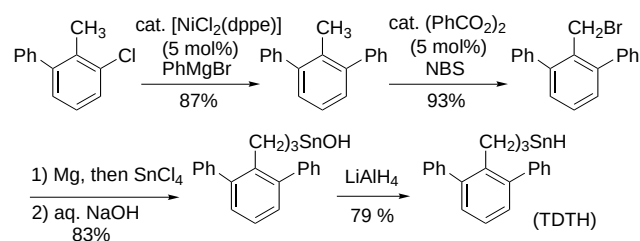
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is a limit to such steric approaches due to the troublesome introduction of sterically hindered alkyl groups in the preparation of bulky R_3SnH . In this context, we have focused on the possibility of using a bowl-shaped trialkyltin hydride of type **2** to obtain high stereoselectivity by remote steric control as illustrated by the stereoselective reduction of vinyl radical **1** (Scheme 1). Herein we report that the bowl-shaped tris(2,6-diphenylbenzyl)tin hydride (TDTH) can be successfully utilized as a new reducing agent, and in particular achieves a unique selectivity not observable in ordinary radical and ionic reactions involving previously known R_3SnH and $(Me_3Si)_3SiH$.^[8–11]

The requisite TDTH can be conveniently prepared from commercially available 2-chloro-6-phenyltoluene in the four-step sequence shown in Scheme 2. The structure of TDTH,



Scheme 1. Bowl-shaped tris(2,6-diphenylbenzyl)tin hydride (TDTH) (**2**) allows the remote stereochemical control in vinyl radical reductions.



Scheme 2. Four-step synthesis of TDTH from commercially available 2-chloro-6-phenyltoluene. dppe = 1,2-bis(diphenylphosphanyl)ethane; NBS = *N*-bromosuccinimide.

which was determined by single-crystal X-ray diffraction analysis (Figure 1),^[12] reveals the presence of a molecular pocket about the tin atom.

Intramolecular radical cyclization of the *o*-halophenyl ether, *o*-iodophenyl 3-phenylpropynyl ether (**3**) under standard radical reaction conditions (catalytic AIBN (0.2 equiv), Bu_3SnH (1.1 equiv), benzene reflux) gave rise to an *E/Z* mixture of cyclic ether **4** in 99% yield (*E/Z* = 1:37; Scheme 3).^[13] Reaction of **3** in CH_2Cl_2 with Bu_3SnH or Ph_3SnH (1.1 equiv) and catalytic Et_3B (0.4 equiv) as radical initiator at $-78^\circ C$ yielded **4** in 88–99% yield with moderate stereoselectivity (*E/Z* = 3.1–5.1:1). Switching R_3SnH ($R = Bu, Ph$) to bulky $(Me_3Si)_3SiH$ (1.1 equiv) further enhanced

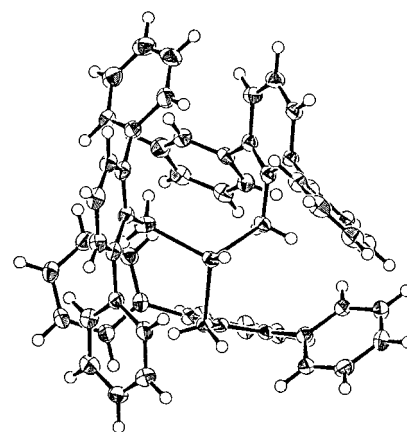
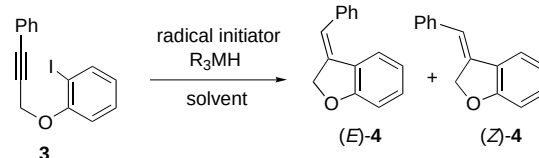


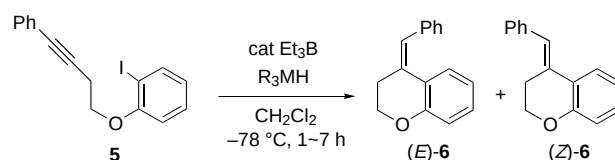
Figure 1. Structure of TDTH (ORTEP representation).

the selectivity to *E/Z* = 10.8:1 at the expense of chemical yield (38%). In marked contrast, however, radical reduction of **3** with TDTH (1.1 equiv) and catalytic Et_3B (0.5 equiv) in CH_2Cl_2 afforded **4** in 97% yield with excellent stereoselectivity (*E/Z* = 46.5:1), implying the importance of our new strategy on remote stereochemical control to achieve high selectivity of the radical cyclization.^[14]

We also examined the intramolecular cyclization of the one-carbon elongated *o*-halophenyl ether, *o*-iodophenyl 4-phenylbutynyl ether (**5**), which can be categorized as a heptynyl radical cyclization (Scheme 4). Interestingly, radical cyclization of **5** with Bu_3SnH gave the target cyclic ether **6** with low selectivity (*E/Z* = 1.5:1),



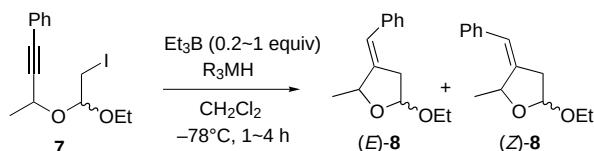
Scheme 3. Influence of R_3MH on the radical cyclization of **3** to **4**. Reagents, conditions, and selectivities: cat. AIBN/ Bu_3SnH /benzene, $80^\circ C$, 1 h: 99% (*E/Z* = 1:37); cat. Et_3B / Bu_3SnH / CH_2Cl_2 , $-78^\circ C$, 2 h: 99% (*E/Z* = 5.1:1); cat. Et_3B / Ph_3SnH / CH_2Cl_2 , $-78^\circ C$, 2 h: 88% (*E/Z* = 3.1:1); cat. Et_3B / $(Me_3Si)_3SiH$ / CH_2Cl_2 , $-78^\circ C$, 3 h: 38% (*E/Z* = 10.8:1); cat. AIBN/TDTH/benzene, $80^\circ C$, 2.5 h: 57% (*E/Z* = 22.8:1); cat. Et_3B /TDTH/ CH_2Cl_2 , $-78^\circ C$, 2.5 h: 97% (*E/Z* = 46.5:1).



Scheme 4. Influence of R_3MH on the radical cyclization of **5** to **6**. Reagents, conditions, and selectivities: cat. Et_3B (0.2 equiv)/ Bu_3SnH (1.1 equiv): 71% (*E/Z* = 1.5:1); cat. Et_3B (1 equiv)/ $(Me_3Si)_3SiH$ (1.1 equiv): 57% (*E/Z* = 44:1); cat. Et_3B (0.6 equiv)/TDTH (1.1 equiv): 76% (*E/Z* = >100:1).

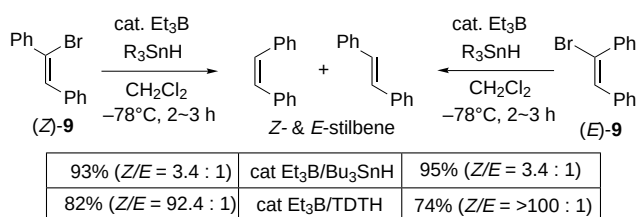
whereas use of TDTH afforded **6** with virtually complete stereoselectivity ($E/Z = >100:1$).

A similar tendency is also observed in the stereoselective radical cyclization of iodoacetal **7** (diastereomeric ratio = 1:1) to cyclic acetal **8** (diastereomeric ratio = 1:1) with high Z selectivity using TDTH (Scheme 5).



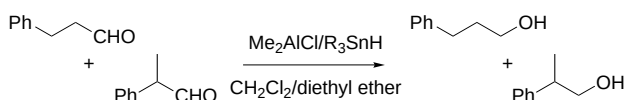
Scheme 5. Influence of R_3MH on the radical cyclization of **7** to **8**. Reagents, conditions, and selectivities: cat. Et_3B (0.2 equiv)/ Bu_3SnH (1.2 equiv): 92% ($E/Z = 1:3.1$); cat. Et_3B (0.2 equiv)/ Ph_3SnH (1.2 equiv): 98% ($E/Z = 1:4.3$); cat. Et_3B (1 equiv)/ $(\text{Me}_3\text{Si})_3\text{SiH}$ (1.2 equiv): 76% ($E/Z = 1:6.7$); cat. Et_3B (1 equiv)/TDTH (1.2 equiv): 76% ($E/Z = 1:65.8$).

Such selectivity in vinyl radical reduction appears feasible in acyclic systems. For example, E -bromostilbene is transformed to Z -stilbene with excellent stereoselectivity ($Z/E = >100:1$) on treatment with TDTH (1.1 equiv) and catalytic Et_3B (0.2 equiv) in CH_2Cl_2 at low temperature, while the selectivity is only moderate ($Z/E = 3.4:1$) in the case of Bu_3SnH under similar reduction conditions (Scheme 6).



Scheme 6. Influence of R_3MH on the selectivity in the vinyl radical reduction of acyclic systems.

The synthetic power of TDTH has been further demonstrated in ionic reactions by the chemoselective, electrophilic reduction of structurally similar aldehyde substrates with trialkyltin hydride. For example, treatment of one equivalent each of hydrocinnamaldehyde and α -phenylpropionaldehyde in CH_2Cl_2 /diethyl ether (v/v, 7/1) with R_3SnH ($\text{R} = \text{Bu}, \text{Ph}$; 1 equiv) under the influence of Me_2AlCl (2.2 equiv) as Lewis acid at low temperature afforded a mixture of less hindered 3-phenyl-1-propanol and more hindered 2-phenyl-1-propanol with only moderate selectivity (Scheme 7).^[15] However,



Scheme 7. Influence of R_3MH on the chemoselective, electrophilic reduction of similar aldehyde substrates. Reagents, conditions, and selectivities: Bu_3SnH , -78°C , 0.5 h: 81% (43:57); Ph_3SnH , -78°C , 1 h: 93% (38:62); TDTH, $-78 \sim -20^\circ\text{C}$, 1.5 h: 82% ($>100 : <1$); L-Selectride , -78°C , 0.5 h: 99% (45:55).

virtually complete discrimination of two structurally different aldehyde carbonyl groups can be realized with TDTH as hydride donor. Notably, an ordinary selective reducing agent, L-Selectride gave a disappointing result in terms of the chemoselectivity.

Experimental Section

Radical cyclization of **3** with TDTH: To the solution of TDTH (280.4 mg, 0.33 mmol) in CH_2Cl_2 (2.5 mL) was added **3** (100.2 mg, 0.3 mmol) in CH_2Cl_2 (1 mL) and Et_3B (150 μL , 0.15 mmol of a 1 M solution in hexane) under Ar at -78°C . After the reaction mixture had been stirred at -78°C for 2.5 h, it was poured into an aqueous saturated solution of NaHCO_3 and then extracted with diethyl ether. The combined extracts were dried over Na_2SO_4 . Evaporation of solvents and purification of the residue by column chromatography on silica gel (diethyl ether/hexane (1/20)) gave **4** as a colorless oil and a small amount of **3** which was recovered (**4**: 60.8 mg, 0.292 mmol, 97% yield; **3**: 0.008 mmol, 3% yield). The ratio of $(E)/(Z)$ -**4** was determined by ^1H NMR analysis ($(E)/(Z)$ -**4** = 46.5/1.0). (E) -**4**: ^1H NMR (300 MHz, CDCl_3 , 20°C , TMS): δ = 7.45–7.20 (m, 6H; Ar-H), 7.16 (t, $J(\text{H},\text{H}) = 7.8$ Hz, 1H; Ar-H), 6.86 (d, $J(\text{H},\text{H}) = 7.8$ Hz, 1H; Ar-H), 6.68 (t, $J(\text{H},\text{H}) = 7.8$ Hz, 1H; Ar-H), 6.50 (t, $J(\text{H},\text{H}) = 2.5$ Hz, 1H; $\text{C}=\text{CHPh}$), 5.24 (d, $J(\text{H},\text{H}) = 2.5$ Hz, 2H; $\text{C}=\text{CH}_2\text{O}$); (Z) -**4**: δ = 7.53 (d, $J(\text{H},\text{H}) = 7.6$ Hz, 1H; Ar-H), 7.41 (t, $J(\text{H},\text{H}) = 7.8$ Hz, 2H; Ar-H), 7.32–7.20 (m, 4H; Ar-H), 6.96 (t, $J(\text{H},\text{H}) = 7.6$ Hz, 1H; Ar-H), 6.92 (d, $J(\text{H},\text{H}) = 7.6$ Hz, 1H; Ar-H), 6.85 (t, $J(\text{H},\text{H}) = 3.0$ Hz, 1H; $\text{C}=\text{CHPh}$), 5.43 (d, $J(\text{H},\text{H}) = 3.0$ Hz, 2H; $\text{C}=\text{CH}_2\text{O}$).

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- [13] Treatment of (*E*)-**4** (*E/Z* = 46.5:1) with Bu₃SnH (1 equiv) in benzene under reflux for 2 h gave rise to an *E/Z* mixture (*E/Z* = 2:1) of **4**, suggesting that (*Z*)-**4** is a thermodynamic product.
- [14] TDTH was found to be a slower reducing agent than Bu₃SnH. For example, reduction of benzyl *p*-iodophenyl ether with Bu₃SnH and TDTH (1.1 equiv) in CH₂Cl₂ at -78 °C under the influence of catalytic Et₃B (0.2 equiv) for 20 min afforded benzyl phenyl ether in 88% and 40% (recovery of *p*-iodophenyl ether in 56%) yields, respectively.
- [15] Attempted reduction of the two different aldehydes with (Me₂Si)₂SiH in the presence of Me₂AlCl resulted in recovery of most of these aldehydes.

Chemoselective Iterative Dehydrative Glycosylation**

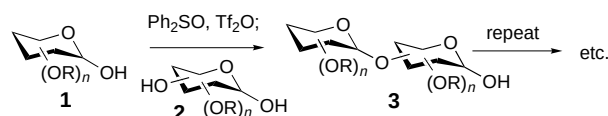
Hien M. Nguyen, Jennifer L. Poole, and David Y. Gin*

The development of strategies for efficient construction of complex oligosaccharides has been a long-standing challenge in organic synthesis.^[1] This is a direct result of the immense structural diversity and biological importance of complex glycoconjugates in nature. In traditional approaches to the assembly of oligosaccharides, a preformed glycosyl donor incorporating an anomeric latent leaving group is coupled with a nucleophilic glycosyl acceptor, and the resulting disaccharide then undergoes either a selective deprotection or anomeric derivatization step prior to the subsequent

coupling event. In order to streamline this process, a number of elegant chemoselective and orthogonal glycosylation strategies have been developed with the goal of circumventing deprotection and anomeric derivatization steps in the iterative glycosylation sequence. Within this context, two key strategies, which use well-established glycosylation methods, have been explored. One approach employs carbohydrate coupling partners with identical anomeric latent leaving groups; the reactivities of each of the leaving groups are differentiated by varying the electronic nature of proximal protective groups.^[2] The success of this approach to oligosaccharide synthesis thus relies on intricate selection of protective groups to establish a suitable reactivity hierarchy among the carbohydrate building blocks.^[2e] In an alternative strategy, the anomeric latent leaving groups in the carbohydrate coupling partners are mutually distinct, possessing chemically orthogonal reactivities; successive glycosylations are performed with a number of different reagents that are specific for a certain latent leaving group.^[3]

We now report a novel approach to iterative oligosaccharide synthesis which employs a chemoselective glycosylation strategy that: 1) is not dependent on the careful selection and placement of specific protective groups in the carbohydrate coupling partners to electronically influence anomeric reactivity; 2) avoids the need for C1-derivatized carbohydrate building blocks with chemically distinct anomeric latent leaving groups; and 3) requires only a single glycosylation method to effect iterative one-pot anomeric bond constructions.

We have recently established a dehydrative glycosidic coupling method whereby a variety of nucleophilic acceptors can be directly glycosylated with C1-hydroxy donors using diphenyl sulfoxide and triflic anhydride.^[4, 5] The fact that our dehydrative coupling is not plagued by self-condensation of the C1-hydroxy donor led us to investigate the possibility of selective glycosylation of an alkyl hydroxy group in the presence of a free hemiacetal functionality. In this context, our dehydrative glycosylation reaction can serve as the basis for a new approach to iterative chemoselective glycosylation in which a hemiacetal donor **1** is activated with diphenyl sulfoxide and triflic anhydride (Scheme 1). A nucleophilic



Scheme 1. Chemoselective iterative dehydrative glycosylation. Tf = trifluoromethanesulfonyl.

acceptor **2**, which incorporates a free alkyl hydroxy group as well as an unprotected C1-hemiacetal functionality, is then introduced. Ideally, the alkyl alcohol is chemoselectively glycosylated in the presence of the hemiacetal hydroxy group to generate, in a one-pot procedure, the hemiacetal-terminated disaccharide **3**, which is immediately poised for another coupling iteration. Thus, the key issue of chemoselectivity in this approach pertains only to the relative nucleophilicities of the alkyl hydroxy group versus the hemiacetal hydroxy group

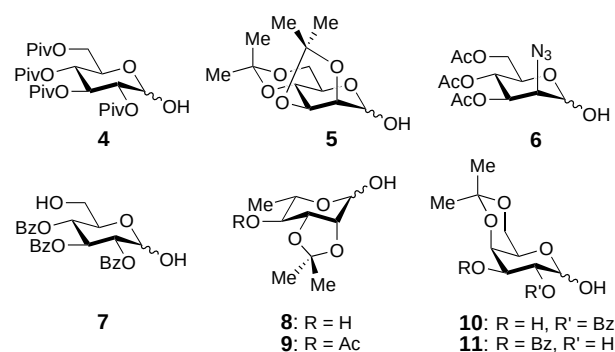
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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

within the acceptor substrate itself, a feature that heretofore has not been successfully exploited in oligosaccharide synthesis with traditional chemical glycosylation methods. As a result, the versatility of this iterative process is not limited to the number of available orthogonal latent leaving groups or activating agents, nor is it limited by the need for extensive manipulation and selection of protective groups to adjust relative reactivities among carbohydrate coupling partners.^[6]

This concept for chemoselective glycosylation (Scheme 1) can only be realized with the use of a controlled dehydrative coupling procedure that does not lead to indiscriminate oligomerization of the carbohydrate diol acceptor. Using the reagent combination of Ph₂SO and Tf₂O as the dehydrating agent, the critical question of chemoselectivity was first addressed by performing a variety of glycosidic couplings with several hemiacetal donors (**4**–**6**, and **9**, Scheme 2) and diol



Scheme 2. Carbohydrate coupling partners. Piv = pivaloyl, Ac = acetyl, Bz = benzoyl.

carbohydrate acceptors (**7**, **8**, **10**, and **11**) incorporating an unprotected C1-hemiacetal functionality. For example, 2,3,4,6-tetra-*O*-pivaloyl-*D*-glucopyranose (**4**, Table 1, entry 1) was coupled with 2,3,4-tetra-*O*-benzoyl-*D*-glucopyranose (**7**) to afford the corresponding 1,6- β -linked disaccharide as the sole disaccharide product. Likewise, entries 2 and 3 clearly demonstrate that the primary hydroxy group within a carbohydrate can be selectively glycosylated in the presence of the free C1-hemiacetal; no evidence of 1,1'-linked disaccharides was detected in these reactions.

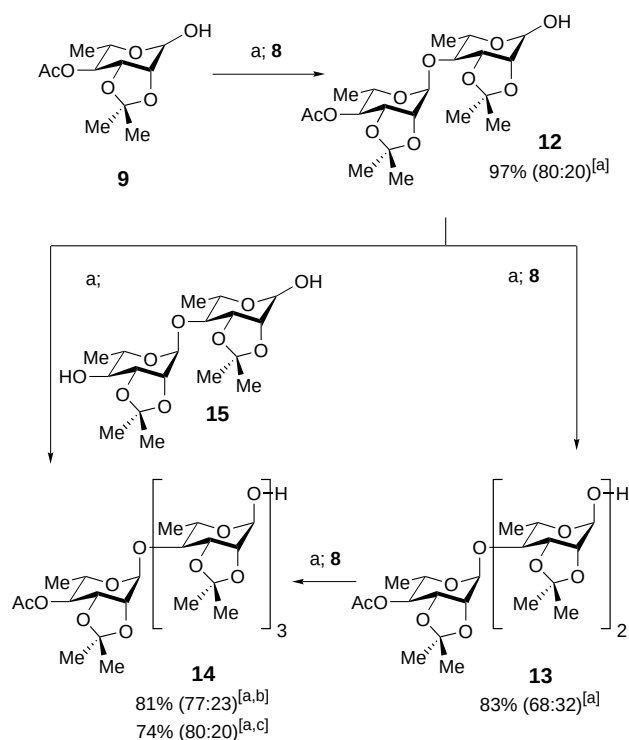
It is notable that secondary alcohols on carbohydrate acceptors are also preferentially glycosylated in the presence of a C1-hemiacetal. For example, the C4- and C3-hydroxy groups of **8** and **10**, respectively, are glycosylated with the carbohydrate donors **5**, **6**, and **9** to generate the hemiacetal-terminated disaccharides in good yield with complete chemoselectivity (entries 4–6). The C2,C1-diol **11** was anticipated to be a challenging substrate in this glycosylation strategy. Not only is the preferred reaction site in **11** a secondary alcohol, but this group is also flanked by both the competing C1-hydroxy nucleophile and the electron-withdrawing acyl group at C3, which can inductively attenuate the nucleophilicity of the C2-hydroxy group. Even with this “difficult” diol acceptor, the glycosylation of **11** with **9** (entry 7) proceeded with good chemoselectivity (5:1 ratio), to afford the desired 1,2'-linked disaccharide as the major product.

Table 1. Results of chemoselective dehydrative glycosylation.

Entry	Donor + acceptor	Product	Yield [%] (α : β) ^[a]
1	4 + 7		71 (β)
2	5 + 7		85 (73:27)
3	9 + 7		81 (71:29)
4	6 + 8		77 (90:10)
5	5 + 8		96 (86:14)
6	9 + 10		86 (α)
7	9 + 11		68 ^[b] (α)

[a] α : β ratios refer to the anomeric distribution in the newly formed glycosidic bond. [b] The corresponding Rham α 1–1' α / β Gal disaccharide was also isolated in 14 % yield.

The efficacy of this approach lies in its ability to function in iterative single-pot glycosylations for the preparation of oligosaccharides. In an illustrative example, the 1,4- α -linked tetrasaccharide **14** (Scheme 3), which is the carbohydrate moiety within the antiserotonic resin glycoside merremoside d,^[7] was prepared by two routes. In the first, the rhamnopyranose donor **9** was iteratively coupled with the diol acceptor **8** in a three-step sequence (**9** $\rightarrow$ **12** $\rightarrow$ **13** $\rightarrow$ **14**) to



Scheme 3. Chemoselective iterative dehydrative glycosylation. Reagents: a) Ph_2SO , TiF_4 , 2,4,6-tri-*tert*-butylpyridine, $-78 \rightarrow -40^\circ\text{C}$. [a] Ratio refers to the anomeric distribution (α : β) in the newly formed glycosidic bond. Only the major (α) anomer was subjected to the subsequent glycosylations. [b] Yield derived from **13**+**8** (three-step route). [c] Yield derived from **12**+**15** (two-step route).

afford the tetrasaccharide **14**. The second route (**9** $\rightarrow$ **12** $\rightarrow$ **14**) highlights the adaptability of this strategy to the block synthesis of oligosaccharides, in which the C4,C1'-dihydroxy disaccharide acceptor **15**^[8] is chemoselectively glycosylated with the hemiacetal donor **12a** to afford tetrasaccharide **14**. In both of these synthetic sequences, it is worth noting that: 1) each one-pot glycosylation proceeds with complete chemoselectivity; 2) all of the carbohydrate acceptor building blocks incorporate the same protective group (that is, isopropylidene ketal); and 3) a single coupling method is used to construct all of the glycosidic bonds.

A new approach to iterative chemoselective glycosylation is reported for the efficient preparation of oligosaccharides. The strategy employs a controlled dehydrative glycosylation method that allows one to capitalize on the inherent difference in nucleophilicity between an alkyl hydroxy group and a free hemiacetal functionality within carbohydrate acceptors. Not only does this approach require just a single glycosylation method for each coupling event, but it also obviates the need for the extensive protective group differentiation that is traditionally required for chemoselective glycosylation. Efforts are currently underway to adapt this strategy to polymer-supported oligosaccharide synthesis.

Experimental Section

Preparation of **12** as a representative chemoselective glycosylation procedure: Trifluoromethanesulfonic anhydride (200 μL , 1.2 mmol, 1.4 equiv) was added to a solution of 4-*O*-acetyl-2,3-*O*-isopropylidene-L-

rhamnopyranose (**9**, 200 mg, 0.81 mmol, 1 equiv), 2,4,6-tri-*tert*-butylpyridine (570 mg, 2.3 mmol, 2.8 equiv), and diphenyl sulfide (470 mg, 2.3 mmol, 2.8 equiv) in a mixture of toluene and dichloromethane (24 mL, 3:1) at -78°C . The reaction mixture was stirred at this temperature for 10 min and then at -40°C for 85 min. A solution of 2,3-*O*-isopropylidene-L-rhamnopyranose (**8**, 320 mg, 1.5 mmol, 2.0 equiv) in a mixture of toluene and dichloromethane (24 mL, 1:1) was then added through a cannula at -40°C . The resulting mixture was stirred at this temperature for 1 h, and then at 0°C for 30 min before the addition of excess triethylamine (1.10 mL, 7.7 mmol, 9.5 equiv). The reaction mixture was diluted with dichloromethane (500 mL) and was washed sequentially with saturated aqueous sodium bicarbonate solution ($2 \times 200\text{ mL}$) and saturated aqueous sodium chloride solution ($2 \times 200\text{ mL}$). The organic layer was dried (sodium sulfate), filtered, and concentrated. The residue was purified by silica gel flash column chromatography (ethyl acetate/benzene (1:3)) to afford the readily separable disaccharides **12a** (270 mg) and **12b** (73 mg) as viscous oils (4.1:1 α : β , 97% total).^[9] **12a**: $R_f = 0.55$ (ethyl acetate:hexane (1:1)); $^1\text{H NMR}$ (500 MHz, CDCl_3): $\delta = 5.32$ (d, 1H, $J = 2.4\text{ Hz}$, H1'), 5.23 (s, 1H, H1), 4.84 (dd, 1H, $J = 10.0, 7.8\text{ Hz}$, H4), 4.74 (dd, 1H, $J = 5.9, 3.7\text{ Hz}$, H3'), 4.57 (d, 1H, $J = 5.9\text{ Hz}$, H2'), 4.12 (dd, 1H, $J = 7.8, 5.4\text{ Hz}$, H3), 4.06 (d, 1H, $J = 5.4\text{ Hz}$, H2), 4.08–4.02 (m, 1H, H5'), 3.94 (dd, 1H, $J = 8.5, 3.7\text{ Hz}$, H4'), 3.85 (dq, 1H, $J = 10.0, 6.4\text{ Hz}$, H5), 3.12 (d, 1H, $J = 2.7\text{ Hz}$, OH), 2.08 (s, 3H), 1.54 (s, 3H), 1.42 (s, 3H), 1.42 (s, 3H), 1.33 (s, 3H), 1.30 (d, 3H, $J = 6.1\text{ Hz}$), 1.29 (s, 3H), 1.13 (d, 3H, $J = 6.4\text{ Hz}$); $^{13}\text{C NMR}$ (126 MHz, CDCl_3): $\delta = 170.2, 112.5, 109.6, 101.2, 98.1, 85.4, 82.9, 79.7, 76.2, 75.7, 74.5, 73.2, 64.2, 27.7, 26.5, 26.1, 24.8, 21.0, 19.4, 16.7$; FT-IR (neat film) 3441, 2985, 2939, 2907, 1743, 1454, 1375, 1222, 1134, 1076, 1046, 1026, 856 cm^{-1} ; HR-MS (FAB): m/z : calcd for $\text{C}_{20}\text{H}_{32}\text{O}_{10}\text{Na}$ [MNa^+] 455.1892, found 455.1893. **12b**: $R_f = 0.38$ (ethyl acetate:hexane (1:1)); $^1\text{H NMR}$ (500 MHz, CDCl_3): $\delta = 5.34$ (d, 1H, $J = 2.4\text{ Hz}$, H1'), 5.09 (dd, 1H, $J = 10.0, 7.1\text{ Hz}$, H4), 4.93 (dd, 1H, $J = 5.9, 3.4\text{ Hz}$, H3'), 4.91 (d, 1H, $J = 2.4\text{ Hz}$, H1), 4.57 (d, 1H, $J = 5.9\text{ Hz}$, H2'), 4.27–4.22 (m, 2H, H2, H5'), 4.19–4.16 (m, 2H, H3, H4'), 3.46 (dq, 1H, $J = 10.0, 6.4\text{ Hz}$, H5), 2.56 (d, 1H, $J = 2.2\text{ Hz}$, OH), 2.09 (s, 3H), 1.57 (s, 3H), 1.43 (s, 3H), 1.36 (s, 3H), 1.33 (d, 3H, $J = 6.1\text{ Hz}$), 1.31 (s, 3H), 1.21 (s, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3): $\delta = 169.8, 112.1, 111.2, 100.9, 96.6, 85.5, 82.8, 79.7, 74.7, 74.1, 72.6, 69.6, 27.3, 26.2, 26.1, 24.7, 21.0, 17.6, 17.1$; FT-IR (neat film) 3453, 2984, 2938, 2880, 1742, 1456, 1374, 1232, 1078, 855 cm^{-1} ; HR-MS (FAB): m/z : calcd for $\text{C}_{20}\text{H}_{32}\text{O}_{10}\text{Na}$ [MNa^+] 455.1892, found 455.1893.

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- [9] Excess **8** (0.8 equiv) could be recovered in pure form.

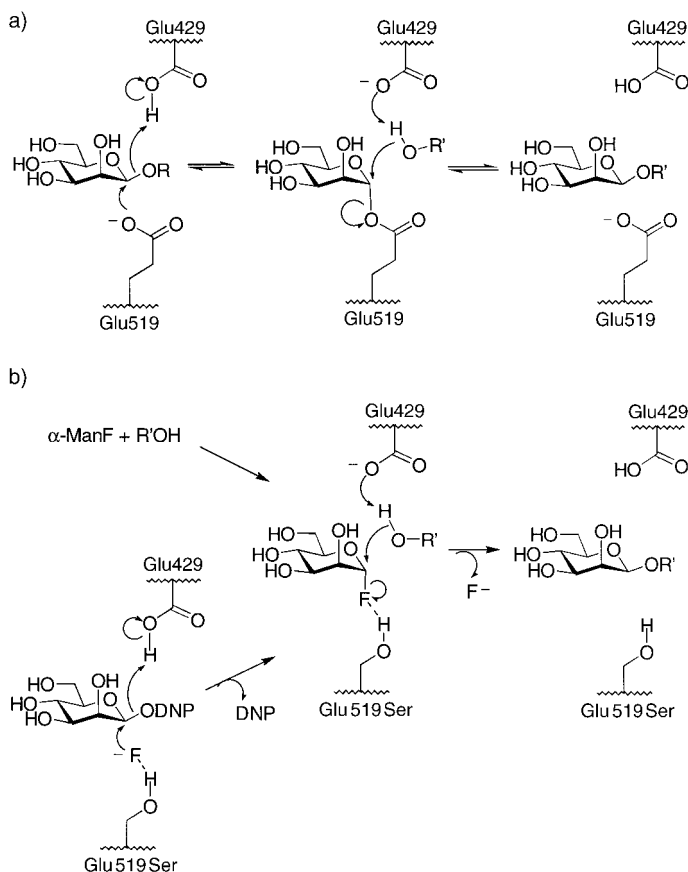
β -Mannosynthase: Synthesis of β -Mannosides with a Mutant β -Mannosidase**

Oyekanmi Nashiru, David L. Zechel, Dominik Stoll, Taraneh Mohammadzadeh, R. Antony J. Warren, and Stephen G. Withers*

The β -D-mannopyranoside linkage is found in a number of biological structures, most notably in the core trisaccharide of N-linked glycoproteins,^[1] as well as within the antigenic polysaccharides of yeasts,^[2] *Salmonella*,^[3] and glycolipids.^[4] This is arguably the most difficult glycosidic bond to synthesize chemically and has inspired numerous approaches.^[5] Despite these successes, each method requires a

number of protection and activation steps prior to glycosylation, and few methods can achieve complete anomeric stereoselectivity.^[5f,h]

Enzymatic synthesis of β -mannosides avoids both of these problems.^[6] Successful transfer of β -mannosyl residues to a variety of acceptor sugars has been achieved with retaining β -glycosidases,^[7] which function through the mechanism shown in Scheme 1a ($R' = \text{glycoside acceptor}$). However, the yields



Scheme 1. a) Hydrolysis ($R' = H$) and transglycosylation ($R' = \text{glycoside acceptor}$) mechanisms of the retaining *Cellulomonas fimi* β -mannosidase (Man2a). b) Mechanism of the Man2a Glu519Ser mutant acting as a mannosynthase (upper pathway) and catalyzing the in situ generation of α -mannosyl fluoride (α -ManF; lower pathway). $R'OH = \text{glycoside acceptor}$. DNP = 2,4-dinitrophenyl.

of these transglycosylation reactions are inherently modest as the product formed is a substrate for the glycosidase used, resulting in hydrolysis. Further, the approach requires the preparation of a β -mannoside as a glycosyl donor, thereby minimizing advantages. Substantially better yields have been obtained with recombinant yeast and *Salmonella* β -mannosyltransferases (60–90 %),^[8] but these enzymes are limited by their requirement for a complex acceptor. In contrast to the above, glycosynthases^[9] are new enzymatic catalysts for oligosaccharide synthesis that are derived by mutating the catalytic nucleophiles of retaining glycosidases.^[10] Here we report the successful construction of a mannosynthase from a retaining β -mannosidase and its use in the synthesis of β -mannosides with the readily accessible donor, α -D-mannosyl fluoride (Scheme 1b, upper pathway).

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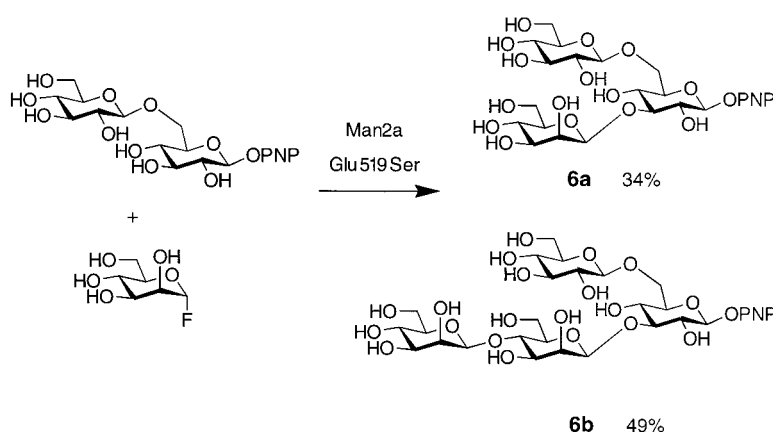
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The retaining β -mannosidase Man2a was cloned from *Cellulomonas fimi* and overexpressed in *E. coli* to yield a 95 kDa monomeric enzyme belonging to family 2 of the glycosyl hydrolases.^[11] The active site nucleophile was identified as Glu519 by trapping the covalent mannosyl–enzyme intermediate with the mechanism-based inactivator 2-deoxy-2-fluoro β -D-mannosyl fluoride, followed by proteolysis and sequencing of the labeled peptide by ESI-MS/MS.^[12, 13] Mutation of the nucleophile to alanine (Glu519Ala) produced an enzyme that was inactive as a hydrolase. However, Man2a Glu519Ala also proved to be a poor mannosynthase, from which only an 8% yield of di- and trisaccharides was obtained upon the reaction of α -D-mannosyl fluoride (α -ManF) with *para*-nitrophenyl β -D-mannopyranoside (PNP β -mannoside).

Based upon recent successes with a family 1 glycosynthase in which a much more effective catalyst was obtained by replacing the catalytic nucleophile with serine,^[9c] the Glu519Ser mutant of Man2a was made. This mutant proved to be a much more effective glycosynthase affording a 99% overall yield (determined by HPLC) of oligosaccharides from the reaction of α -ManF with PNP β -D-cellobioside (Table 1). A number of other sugars also acted as viable acceptors, with oligosaccharide yields typically in excess of 70% (Table 1). Benzyl β -D-*N*-acetylglucosaminide, PNP β -D-*N*-acetylglucosaminide, or chitobiose

would not function as an acceptors.^[14] Reaction times varied from 24 hours for disaccharide acceptors to several days for the poorer monosaccharide acceptors. HPLC analyses of the reaction mixtures and $^1\text{H}/^{13}\text{C}$ NMR spectroscopic analyses of the per-O-acetylated products indicated that the oligosaccharide products contained a mixture of β (1,3) and β (1,4) linkages (Table 1).^[15] A notable example was the mixture derived from PNP β -gentiobioside, which afforded branched tri- and tetrasaccharide products **6a** and **6b**, respectively, in which mannose residues are β (1,3) linked to the PNP-bearing glucose residues (Scheme 2).^[16]



Scheme 2. Branched oligosaccharide products derived from the reaction of PNP β -gentiobioside with α -mannosyl fluoride in the presence of Man2a Glu519Ser. PNP = *para*-nitrophenyl.

Table 1. Product yields for the reaction of α -mannosyl fluoride with various acceptors, catalyzed by Man2a Glu519Ser.

Acceptor	di	tri	Yield of oligosaccharide [%] ^[a]	penta	hexa	Total
PNP β -mannoside	21 1a β (1,4)	32 1b (5) β (1,4), β (1,4) 1c (2) β (1,4), β (1,3)	19 1d (5) all β (1,4) 1e (1) β (1,4), β (1,4), β (1,3)	2	–	74
2,4-DNP 2-deoxy-2-fluoro- β -mannoside	7	39 2a (1) β (1,4), β (1,4) 2b (1) β (1,4), β (1,3)	15	8	1	70
PNP β -glucoside	22 3a β (1,3)	36 3b (1) β (1,4), β (1,4) 3c (15) β (1,4), β (1,3)	13 3d β (1,4), β (1,4), β (1,3)	–	–	71
PNP β -xylobioside	8 4a (1) β (1,4) 4b (1) β (1,3)	64 4c (1) β (1,4), β (1,4) 4d (2) β (1,4), β (1,3)	19 4e (1) all β (1,4) 4f (1) β (1,4), β (1,4), β (1,3)	3	–	94
PNP β -cellobioside	–	27 5a (8) β (1,3) 5b (5) β (1,4)	56 5c (4) β (1,4), β (1,4) 5d (1) β (1,4), β (1,3)	5 5e all β (1,4)	1	99
PNP β -gentiobioside	–	34 6a β (1,3)	49 6b β (1,4), β (1,3)	8	0.5	91

[a] Yields were determined by HPLC and are based on remaining acceptor. The relative ratios of products are indicated in parentheses. The sequence of linkages formed in each product is indicated. Spectroscopic data are provided in the Supporting Information.

Kinetic parameters for transglycosylation by the Man2a Glu519Ala and Ser mutants were determined by use of a fluoride electrode to monitor fluoride release during the coupling of α -ManF with PNP β -cellobioside. The reaction was first studied in the presence of a fixed concentration of acceptor. In this way apparent k_{cat} values of 12 min^{-1} (at 29 mM PNP β -cellobioside) and 0.33 min^{-1} (at 20 mM PNP β -cellobioside) were obtained for the Glu519Ser and Glu519Ala mutants, respectively. The apparent K_{m} values for α -ManF determined under the same conditions were very similar: 0.70 mM for Glu519Ser and 0.57 mM for Glu519Ala. The reaction was then studied in the presence of a fixed, saturating concentration of α -ManF (50 mM), but saturation with PNP β -cellobioside could not be obtained with either mutant. Thus, the apparent $k_{\text{cat}}/K_{\text{m}}$ values of $0.35 \text{ min}^{-1} \text{ mM}^{-1}$ and $0.013 \text{ min}^{-1} \text{ mM}^{-1}$ for Glu519Ser and Glu519Ala, respectively, were determined from the slope of the plot of rate versus PNP β -cellobioside concentration. This corresponds to a 27-fold transglycosylation rate enhancement for the Glu519Ser mutant relative to the Ala mutant and is remarkably similar to the 24-fold increase obtained previously with the family 1 glycosynthase, Abg Glu358Ser.^[9c] The mechanistic origins of this rate increase are uncertain, but may arise from a stabilizing interaction between the departing fluoride ion and the serine side-chain hydroxyl in the transglycosylation transition state (Scheme 1b). Transglycosylation rates were also studied as a function of pH, and the Man2a Glu519Ser mutant was found to be most active between pH 5 and 6 (data not shown). This is fortunate because α -ManF undergoes rapid spontaneous hydrolysis above pH 7, presumably through the base-catalyzed formation of a 1,2 epoxide.^[17]

A characteristic feature of nucleophile mutants of retaining glycosidases is their ability to recover glycosidic bond cleaving activity when provided with anionic nucleophiles such as acetate, formate, and azide.^[18] To our surprise, fluoride ions (2 M KF) also rescued significant bond-cleaving activity when 2',4'-dinitrophenyl β -D-mannopyranoside (2,4-DNPM) was used as a substrate for both the Man2a Glu519Ala ($k_{\text{cat}} = 21 \text{ min}^{-1}$, $K_{\text{m}} = 0.13 \text{ mM}$) and Glu519Ser ($k_{\text{cat}} = 14 \text{ min}^{-1}$, $K_{\text{m}} = 0.036 \text{ mM}$) mutants. Despite the poor nucleophilicity of fluoride ions in aqueous solution, this chemical rescue corresponds to at least a 10^4 -fold increase in rate, since the nucleophile mutants are essentially inactive in the absence of fluoride ions.^[19] This appears to be an exceedingly rare form of chemical rescue and to our knowledge is the first example of the fluoride ion acting as a substitute nucleophile in a mutant enzyme system.^[20] The reaction of a fluoride ion with 2,4-DNPM will result in the in situ generation of α -ManF, which may then be used as a mannosyl donor to a second molecule of 2,4-DNPM acting as an acceptor (Scheme 1b, lower pathway).^[21] Accordingly, thin layer chromatographic and ^1H NMR spectroscopic analyses of a preparative rescue reaction carried out with Man2a Glu519Ser confirmed the formation of the donor, α -ManF.

The existing glycosynthase methodology has been successfully extended to include the enzymatic synthesis of β -mannoside linkages. In what may be a general feature of these catalysts,^[9c] the serine nucleophile mutant of Man2a

proved to be a dramatically better glycosynthase than the corresponding alanine mutant. Finally, we report here the first instance of the fluoride ion acting as a nucleophile in the chemical rescue of mutant-enzyme activity.

Experimental Section

Mutagenesis, expression, and purification of Man2a Glu519Ser: The plasmid pETMan2aGlu519Ser carrying the Glu519Ser mutation was introduced by modification of a "megaprimer" procedure (details provided in the Supporting Information).^[22] Recombinant Man2a Glu519Ser was purified from isopropyl- β -D-thiogalactopyranoside (IPTG)-induced cultures of *E. coli* BL21 (DE3) electrocompetent cells carrying the plasmid pETMan2aGlu519Ser. Harvested cells were twice passed through a French press at 4 °C, then centrifuged at 15 000 g for 30 min. Man2a Glu519Ser was isolated from the supernatant by Ni²⁺-chelation chromatography (His-bind resin, Novagen). The yield of Man2a Glu519Ser was 350 mg L^{-1} culture.

Rescue and transglycosylation kinetics: Mutant Man2a concentrations were determined by absorbance at 280 nm using the extinction coefficient $E_{280}^{0.1\%} = 2.2 \text{ cm}^{-1}$, estimated from the corresponding amino acid sequences.^[23] Rescue kinetics with the substrate 2,4-DNPM^[24] were performed at 25 °C in 100 mM citrate (pH 6.0) supplemented with bovine serum albumin (BSA; 1 mg mL^{-1}) and 2 M potassium fluoride (750 μL total volume). Reactions were initiated with the addition of Man2a Glu519Ser or Glu519Ala (5–10 μL , 0.1–0.4 μM final concentrations) and the resulting liberation of 2,4-dinitrophenol was monitored spectrometrically at 400 nm ($\Delta\epsilon = 10900 \text{ M}^{-1} \text{ cm}^{-1}$). Observed rates were corrected for the spontaneous hydrolysis of 2,4-DNPM. Transglycosylation kinetics were performed at 25 °C in 100 mM citrate and 150 mM NaCl (pH 6.0; 400 μL total volume) using α -ManF as a donor and PNP β -cellobioside as an acceptor. Transglycosylation was initiated with the addition of Man2a Glu519Ser or Glu519Ala (20–50 μL , 5.5 to 70 μM final concentrations). The reactions were then stirred while monitoring fluoride release (until 5–20% donor had been consumed) using an Orion fluoride electrode (model 96–09BN) interfaced with Logger-Pro software.^[25] For pH studies, transglycosylation rates were measured using 5.5 μM Man2a Glu519Ser, 6 mM α -ManF, 5 mM PNP β -cellobioside, and 1 mg mL^{-1} of BSA in the following buffers: 100 mM citrate/150 mM NaCl (pH 5.0–6.5), 100 mM NaPi/150 mM NaCl (pH 6.5–8.0), and 100 mM 2-hydroxy-3-[(2-hydroxy-1,1-dimethylethyl)amino]1-propanesulfonic acid (AMPs0)/150 mM NaCl (pH 8.0–9.0). Kinetic parameters for rescue and transglycosylation kinetics were calculated from the initial rates using GraFit.^[26]

Oligosaccharide synthesis, purification, and characterization: In a typical reaction, acceptor glycoside (20–40 mg) was dissolved in 150 mM citrate buffer (2 to 3 mL, pH 6.0) to afford a 30–50 mM solution. α -ManF (1.5–3 equiv) was added as a concentrated solution, followed by Man2a Glu519Ser (1–2 mg mL^{-1}). The reaction mixture was maintained at room temperature and monitored by thin layer chromatography (Kieselgel 60 F₂₅₄ (Merck), ethyl acetate/methanol/water (7/2/1)). Chromatographic plates were visualized under UV light and by exposure to 10% ammonium molybdate in 2 M H₂SO₄, followed by charring. Reaction times ranged from one to five days. Upon completion of the reaction the products were purified by preparative HPLC with UV detection.^[9c] Masses of product fractions were confirmed by ESI-MS. Product fractions were evaporated, dried, and acetylated with acetic anhydride/pyridine (1/2), then purified by flash chromatography on silica gel (230–400 mesh) prior to NMR spectroscopic analysis.

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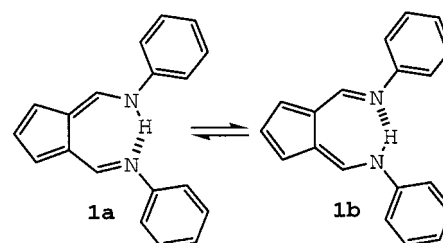
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6-Aminofulvene-1-alimine: A Model Molecule for the Study of Intramolecular Hydrogen Bonds**

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The search for new systems that sustain phenomena such as intramolecular hydrogen bonds (IMHB),^[1,2] proton transfer along hydrogen bonds,^[3,4] and coupling constants through hydrogen bonds,^[5,6] led us to select 6-aminofulvene-1-alimines. These compounds were reported in the 1970s by Müller-Westerhoff and Ammon, who determined the X-ray structure of **1** and its NMR spectroscopic properties in solution.^[8,9]



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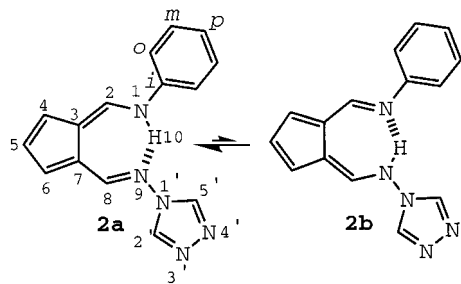
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It is clear from these studies and from others by Jackman et al.,^[10] that **1** is very suitable for advancing the knowledge of the problems that we have summarized above. It is an analogue of the enol of a double imine (the β -enamino-imines),^[11] but with a pseudo seven-membered instead of pseudo six-membered ring. The X-ray structure shows that **1** has an asymmetric hydrogen bond in the solid state while in solution it behaves like a symmetric compound, that is, as if **1a** and **1b** were in very rapid equilibrium. These observations can be rationalized with the hypothesis that **1** is a case of low barrier hydrogen bonding (LBHB) with a double-well potential.

The "symmetric" character of **1** makes it difficult to study its NMR properties in solution. Therefore, we decided to synthesize a highly asymmetric 6-aminofulvene-1-alimine. We chose to replace one of the phenyl groups in **1** with a triazole, which results in compound **2**. For the NMR studies, labeling of the nitrogen atoms of the hydrogen bond, N1 and N9, was required. Since the four nitrogen atoms of aminotriazole (N9, N1', N3', and N4') come from hydrazine, it is easy to prepare the fully labeled compound [¹⁵N₅]-**2**. Compounds **2** and [¹⁵N₅]-**2** were prepared, in two steps, from 6-*N,N*-dimethylaminofulvene-1-*N,N*-dimethylaldimmonium perchlorate (**3**; not shown).^[12] First, reaction of **3** with one mole of 4-amino-1,2,4-triazole afforded the intermediate *N*-[5-[(dimethylamino)methylene]-1,3-cyclopentadien-1-yl]methylene-4-amino-1,2,4-triazole (**4**; not shown), which after isolation was treated with one mole of aniline. The corresponding [¹⁵N₅]-labeled derivative was prepared in the same way but with [¹⁵N]-aniline (commercial) and [¹⁵N₄]-4-amino-1,2,4-triazole (see Experimental Section).



The crystal structure analysis of **2** (Figure 1 a) shows^[13] that pattern of the bond lengths and angles does not display the C_{2v} symmetry previously observed in compound **1**.^[9] This fact is consistent with the presence of a maximum close to the N1 atom and with the lack of electron density near N9 in a difference synthesis computed at the end of the refinement. The C8–N9 and C2–N1 distances are close to the values of 1.279(8) and 1.339(16) Å reported for caryl–C=N–C and C=C–NH–C fragments.^[17] In addition, the value of the angle at N1, to which the H atom is bonded, is significantly greater

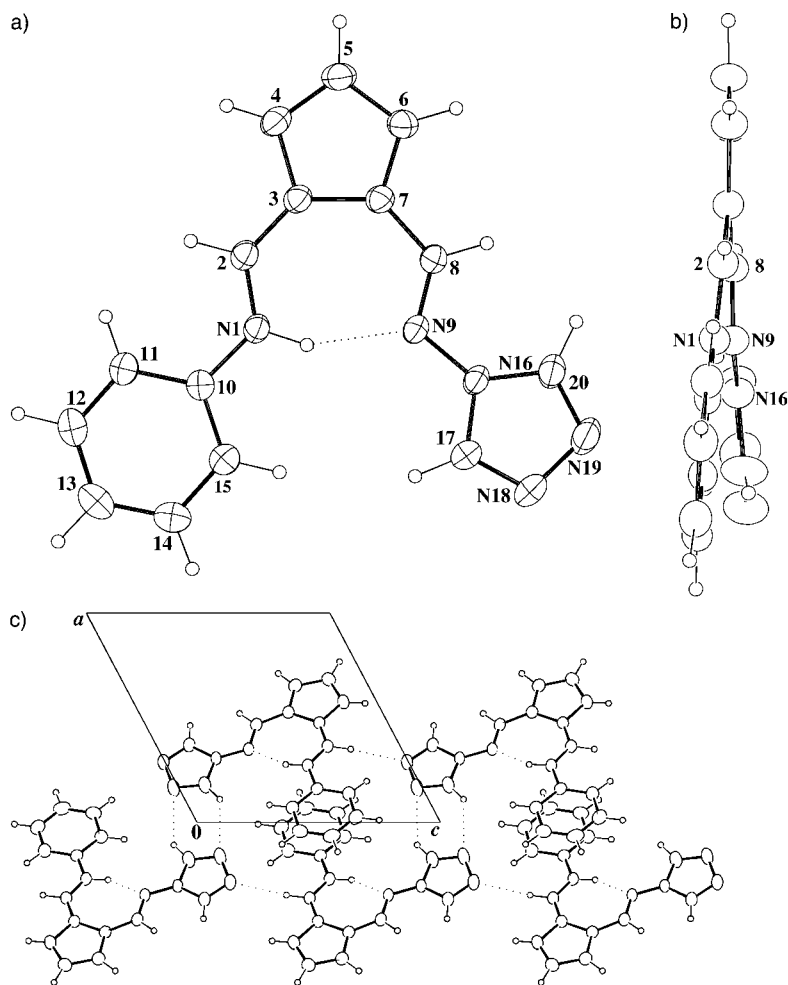


Figure 1. Compound **2** in the solid state. a) Molecular structure which shows the numbering system. Selected bond lengths [Å] and angles [°]: N1–C2 1.321(2), C2–C3 1.377(2), C7–C8 1.423(2), C8–C9 1.285(2); C2–N1–C10 126.1(1), C8–N9–N16 116.0(1). b) A perpendicular view to that of a) which shows the conformation of the molecule. Selected angles [°]: C2–C3–C7–C8 – 8.3(3), C3–C7–C8–N9 3.4(3), C7–C8–N9–N16 – 179.1(2), C8–N9–N16–C20 – 7.0(3), C7–C3–C2–N1 – 1.6(3), C3–C2–N1–C10 – 178.6(2), C2–N1–C10–C11 1.6(3). c) Partial packing diagram along the *b* axis to illustrate the one strand formed by two centrosymmetric hydrogen-bonding chains. Hydrogen-bonding interactions (given as D–H...A (symmetry operation), D...A and H...A distances [Å], D–H...A angle [°]): N1–H1...N9 (*x,y,z*), 2.837(2) and 1.97(2), 153(1); C17–H17...N18 (*–x,1–y,–z*), 3.349(3) and 2.55(3), 138(2); C2–H2...N19 (*x,y,1+z*), 3.470(3) and 2.64(3), 141(2).

than the corresponding one at N9. The phenyl and the triazole rings are almost coplanar in **2** (Figure 1 b), the greatest torsion angle is the C2–C3–C7–C8 angle, and the C2 and C8 atoms are located on opposite sides of the five-membered plane—0.094(2) and 0.076(2) Å, respectively. The presence of the N1–H1...N9 intramolecular hydrogen bond may be responsible for the planarity of this system, together with some degree of charge delocalization, which is mainly observed in the C7–C3–C2–N1 fragment. Figure 1c illustrates the arrangement of molecules in centrosymmetric dimers through C17–H17...N18 contacts between triazoles. Besides this, weaker C2–H2...N19 contacts form a chain of dimers giving rise to a ribbon-like network and allowing a partial overlap of the phenyl rings. These strands, related by 2_1 -screw axis/glide plane, pack in a herringbone fashion. In summary, the structure of **2** determined by X-ray crystal analysis is that of tautomer **2a**, a result that is in agreement with the higher

acidity of the N-triazole group relative to the N-phenyl moiety.

Table 1 summarizes the most relevant data related to the IMHB of compound **2** in solution. Of importance are: 1) the negative primary isotope shift, $^p\Delta = -0.13$, which corresponds to an asymmetric double well potential, according to Hibbert and Emsley, between medium and weak hydrogen bonds;^[18]

Table 1. Summary of the most relevant NMR spectroscopy data^[a] of compound **[¹⁵N₅]-2** and its derivative [¹⁵N₅,²H₁]-**2** (monodeuterated at position 10).

	[¹⁵ N, ¹ H]- 2	[¹⁵ N, ² H]- 2
$\delta^1\text{H}$	12.77	–
$\delta^2\text{H}$	–	12.65
$^p\Delta$ ^[b]	–0.13	
$\delta^{15}\text{N1}$	–238.1	–239.3
$\delta^{15}\text{N9}$	–121.0	–120.9
$^1J(\text{N1,H})$ ^[c]	88.6	–
$^1J(\text{N1,D})$ ^[c]	–	13.2
$^1J(\text{N1,H})/^1J(\text{N1,D})$ ^[d]		6.7
$^1\text{H}(\text{N9,H})$ ^[c]	4.4	–
$^1\text{D}J(\text{N9,D})$ ^[c]	–	not observed
$^1J(\text{N9,H})/^1J(\text{N9,D})$ ^[d]		< 1
$^2\text{H}J(\text{N1} \cdots \text{H} \cdots \text{N9})$ ^[c]	8.6	–
$^2\text{D}J(\text{N1} \cdots \text{D} \cdots \text{N9})$ ^[c]	–	8.5

[a] Solvent = CDCl₃. [b] $\delta^2\text{H} - \delta^1\text{H}$. [c] Values in Hz. [d] Theoretical value = 6.5.

2) the coupling constants involving the N–H $\cdots$ N system and in particular the scalar one, $^2\text{H}J(\text{N1–H} \cdots \text{N9})$, of 8.6 Hz. Note that the ratio of $^1J(^{15}\text{N},^1\text{H})$ to $^1J(^{15}\text{N},^2\text{H})$ is close to the theoretical value of 6.5, while there was no significant effect on the coupling constant $^2\text{D}J(\text{N–H(D)} \cdots \text{N})$ when deuterium replaced protium. Moreover, we have prepared the N-methyl derivative of [¹⁵N₅]-**2** (replacement of H10 by a methyl group) and in this case the $^2\text{H}J(^{15}\text{N}_1,^{15}\text{N}_9)$ disappears.

We have carried out HF/6-31G** and HF/6-311G** ab initio calculations on tautomers **2a** and **2b**, and on a model compound **5** (where the phenyl rings of **1** have been replaced by hydrogen atoms). In the case of compound **2**, the HF/6-31G** calculations yield the following values: **2a**: energy = –847.75472 hartrees, $\mu = 7.25$ D, ($r_{\text{NN}} = 2.893$ Å); **2b**: energy = –847.74843 hartrees, $\mu = 5.59$ D, ($r_{\text{NN}} = 2.833$ Å). Therefore, an extra stabilization of 16.5 kJ mol^{–1} is found for tautomer **2a**; this result corresponds to the experimental findings both in the solid state and in solution.

Three series of calculations were carried out on model compound **5**, HF/6-31G**, HF/6-311G**, and B3LYP/6-31G*. The calculated barriers to proton transfer are 47.8, 49.4, and 18.8 kJ mol^{–1}, respectively. As expected, the inclusion of electronic correlation, through the density functional approach, considerably improves the results.^[19] When the zero-point energy correction is included, the last barrier lowers to 7.3 kJ mol^{–1}. Therefore, **5**, and probably **1** and **2** as well, are LBHB although the hydrogen bonds are not necessarily very strong.

Since we have established without doubt that a $^2\text{H}J(^{15}\text{N},^{15}\text{N})$ is evident for compound **2** (see Table 1), then the coupling constant of 4.4 Hz could have been assigned to either a $^1J(^{15}\text{N9},^1\text{H10})$ for **2a** or a classical $^1J(^{15}\text{N9},^1\text{H10})$ for a small

amount of tautomer **2b**. We do not think that the latter explanation is true because both $^1J(^{15}\text{N1},^1\text{H10})$ of 88.6 Hz and the $^1\text{H}J(^{15}\text{N9},^1\text{H10})$ of 4.4 Hz are independent of temperature and solvent (the same values were obtained in THF and DMF). Even if ΔS could be zero, it is highly improbable that the equilibrium **2a/2b** would be solvent independent when the difference in dipole moments is taken into account (see above). Therefore, we assume that the large value of $^1\text{H}J(^{15}\text{N9},^1\text{H10})$ is associated with the special properties of the hydrogen bond in **2**.

A novel, asymmetric ¹⁵N-labeled seven-membered hydrogen chelate exhibiting a strong intramolecular asymmetric hydrogen bond has been synthesized, and its structure studied by X-ray crystallography, NMR spectroscopy, and ab initio calculations. The compound does not only exhibit a substantial ¹⁵N $\cdots$ ¹⁵N coupling constant but also an unusually large H $\cdots$ ¹⁵N coupling across the hydrogen bond. Evidence is provided that this coupling is not the result of a tautomerism. These results open up a new field of hydrogen-bond research by NMR spectroscopy. This work has increased the understanding of the behavior of 6-aminofulvene-1-aldimines, but ¹³C and ¹⁵N NMR studies in the solid state are necessary and ¹⁵N-labeled **1** should be prepared in order to determine the values of $^2\text{H}J(^{15}\text{N},^{15}\text{N})$ and $^1\text{H}J(^{15}\text{N},^1\text{H})$ in the case of a “symmetrical” compound by indirect NMR methods in solution.

Experimental Section

General: Melting points were determined by differential scanning calorimetry on a SEIKO DSC 220C connected to a Model SSC5200H Disk Station. Thermograms (sample size 3–10 mg) were recorded at the scanning rate of 2.0 °C min^{–1}. Column chromatography was performed on silica gel (Merck 60; 70–230 mesh) and the *R_f* values were measured by thin layer chromatography on aluminum sheets of silicagel (60 F254; thickness 0.2 mm) using the appropriate eluent. FAB mass spectrometry of **2** has already been described.^[20] Hartree–Fock ab initio calculations were carried out with the Spartan 5.0 package running on a Silicon Graphics O2 workstation. NMR spectra were recorded on a Bruker DRX 400 spectrometer (9.4 Tesla, 400.13 MHz for ¹H, 61.42 MHz for ²H, 100.62 MHz for ¹³C, and 40.56 MHz for ¹⁵N). Chemical shifts (δ) are given based on internal CDCl₃ (7.26 (¹H), 7.25 (²H), and 77.0 ppm (¹³C)) and external nitromethane for ¹⁵N. Coupling constants (*J*) are accurate to ± 0.2 Hz for ¹H and ± 0.6 Hz for ¹³C and ¹⁵N.

Compound [¹⁵N₄]-**4**: A solution of 6-*N,N*-dimethylaminofulvene-1-*N,N*-dimethylaldimmonium perchlorate (**3**)^[21] (1 g, 3.21 mmol) in EtOH (20 mL) was refluxed with [¹⁵N₄]-4-amino-1,2,4-triazole^[21] (0.57 g, 6.48 mmol) for 21 h. The solvent was removed by evaporation and the crude product was purified by column chromatography with EtOH/chloroform (1/3) to afford [¹⁵N₄]-**4** (0.42 g, 60%). mp 201.6 °C (decomp up to 207.4 °C); ¹H NMR (CDCl₃): δ = 8.81 (br. s, H2), 8.47 (ddd, $^2J_{\text{H8,N9}} = 2.2$, $^3J_{\text{H8,N1}} = 8.1$, $^3J_{\text{H8,H4}} = 0.6$ Hz; H8), 8.42 (m; H2' and H5'), 6.97 (dd; H4), 6.86 (dd, $^4J_{\text{H6,H4}} = 1.6$ Hz; H6), 6.52 (ddd, $^3J_{\text{H5,H6}} = 3.2$, $^3J_{\text{H5,H4}} = 4.6$, $^5J_{\text{H5,H2}} = 0.9$ Hz; H5), 3.46 (s, CH₃), 3.36 (s, CH₃); ¹³C NMR (CDCl₃): δ = 157.5 ($^1J = 156.5$, $^3J_{\text{C,H}} = 3.4$ Hz; C8), 152.9 ($^1J = 170.1$, $^4J_{\text{C,N}} = 3.8$ Hz; C2), 138.3 ($^1J = 211.7$, $^3J_{\text{C,H}} = 4.0$, $^1J_{\text{C,N}} = 13.5$ Hz; C2' and C5'), 134.2 ($^1J = 165.2$, $^3J_{\text{C,N}} = 3.9$ Hz; C6), 125.0 ($^1J = 166.2$ Hz; C4), 124.7 ($^2J_{\text{C,N}} = 5.2$, $^3J_{\text{C,N}} = 6.9$ Hz; C7), 123.0 ($^1J = 167.0$, $^2J_{\text{C,H}} = ^2J_{\text{C,H}} = 3.6$ Hz; C5), 113.1 (C3), 48.2 ($^1J = 140.3$ Hz; CH₃), 41.0 ($^1J = 140.5$ Hz; CH₃); ¹⁵N NMR (CDCl₃): δ = –268.2 (N1), –162.6 ($^1J_{\text{N9,N1}} = 13.8$ Hz; N1'), –103.6 ($^1J_{\text{N9,N1}} = 13.8$ Hz; N9), –66.5 (N3' and N4'); elemental analysis calcd for unlabeled C₁₁H₁₃N₅: C 61.38, H 6.09, N 32.54; found: C 61.59, H 6.18, N 32.42.

Compound [¹⁵N₅]-**2**: A solution of [¹⁵N₄]-**4** (0.35 g, 1.60 mmol) in EtOH (18 mL) was refluxed with ¹⁵N-labeled aniline (0.19 g, 2.00 mmol) for 7 h. The solvent was removed by evaporation and the crude product was purified by column chromatography with the following eluents: with

AcOEt/hexane (5/1) [$^{15}\text{N}_2$]-**1** (R_f 0.88 in $\text{CHCl}_3/\text{EtOH}$ (10/1)) was eluted first, followed by unreacted aniline (R_f 0.67 in $\text{CHCl}_3/\text{EtOH}$ (10:1)); with AcOEt [$^{15}\text{N}_2$]-**2** was eluted (R_f 0.46 in $\text{CHCl}_3/\text{EtOH}$ (10:1)); finally, with $\text{CHCl}_3/\text{EtOH}$ (10/1), the starting material [$^{15}\text{N}_2$]-**4** was recovered (R_f 0.24 in $\text{CHCl}_3/\text{EtOH}$ (10:1)). Product: [$^{15}\text{N}_2$]-**2** (0.21 g, 49%); mp 213.9 °C (decomp); $^1\text{H NMR}$ (CDCl_3): δ = 12.77 (ddd, $^1J_{\text{N}_1\text{H}_{10}}$ = 88.6, $^3J_{\text{H}_{10}\text{H}_2}$ = 13.9, $^4J_{\text{N}_9\text{H}_{10}}$ = 4.4 Hz; H₁₀), 8.54 (ddd, $^2J_{\text{H}_8\text{N}_9}$ = 2.4, $^3J_{\text{H}_8\text{N}_1}$ = 7.3 Hz; H₈), 8.51 (m; H_{2'} and H_{5'}), 8.06 (td, $^4J_{\text{H}_2\text{N}_9}$ = $^5J_{\text{H}_2\text{H}_6}$ = 0.9 Hz; H₂), 7.44 (t; ArH(*m*)), 7.26 (ddd; H₆), 7.24 (m; ArH(*o*)), 7.20 (m; ArH(*p*)), 7.08 (ddd, $^4J_{\text{H}_6\text{H}_4}$ = 1.9, $^5J_{\text{H}_4\text{H}_8}$ = 0.7 Hz; H₄), 6.53 (dd, $^3J_{\text{H}_5\text{H}_6}$ = 3.2, $^3J_{\text{H}_5\text{H}_4}$ = 4.3 Hz; H₅); $^{13}\text{C NMR}$ (CDCl_3): δ = 157.9 (^1J = 159.4, $^3J_{\text{C}_\text{H}}$ = 4.0, $^1J_{\text{C}_\text{N}}$ = 4.8 Hz; C₈), 143.9 (^1J = 166.7, $^1J_{\text{C}_\text{N}}$ = 15.9 Hz; C₂), 141.4 (^1J = 159.4, $^3J_{\text{C}_\text{N}}$ = 4.8 Hz; C₆), 139.0 ($^1J_{\text{C}_\text{N}}$ = 14.8 Hz; ArC(*i*)), 138.4 (^1J = 211.1, $^1J_{\text{C}_\text{N}}$ = 12.3 Hz; C_{2'} and C_{5'}), 135.9 (^1J = 166.4, $^3J_{\text{C}_\text{N}}$ = 3.5 Hz; C₄), 130.2 (^1J = 162.1, $^3J_{\text{C}_\text{N}}$ = 1.9 Hz; ArC(*m*)), 125.8 (^1J = 163.8 Hz; ArC(*p*)), 122.3 (^1J = 168.7 Hz; C₅), 120.0 ($^2J_{\text{C}_\text{N}}$ = 5.2, $^3J_{\text{C}_\text{N}}$ = 8.5 Hz; C₇), 117.4 (^1J = 155.3 Hz; ArC(*o*)), 116.9 (C₃); $^{15}\text{N NMR}$ (CDCl_3): δ = -238.1 ($^{2h}J_{\text{N}_1\text{H}_{10}\text{N}_9}$ = 8.6 Hz; N₁), -167.7 ($^1J_{\text{N}_9\text{N}_1}$ = 11.8 Hz; N_{1'}), -121.0 ($^{2h}J_{\text{N}_1\text{H}_{10}\text{N}_9}$ = 8.6, $^1J_{\text{N}_9\text{N}_1}$ = 11.8 Hz; N₉), -64.4 (N_{3'} and N_{4'}); $^{15}\text{N NMR}$ ($\text{CDCl}_3 + \text{D}_2\text{O}$): δ = -239.3 ($^1J_{\text{N}_1\text{D}}$ = 13.2, $^{2h}J_{\text{N}_1\text{D}\text{N}_9}$ = 8.5 Hz; N₁), -167.3 ($^1J_{\text{N}_9\text{N}_1}$ = 12.0 Hz; N_{1'}), -120.9 ($^1J_{\text{N}_9\text{N}_1}$ = 11.9, $^{2h}J_{\text{N}_1\text{D}\text{N}_9}$ = 8.5 Hz; N₉), -66.8 (N_{3'} and N_{4'}); elemental analysis calcd for unlabeled $\text{C}_{15}\text{H}_{13}\text{N}_5$: C 68.42, H 4.98, N 26.60; found: C 68.60, H 4.96, N 26.52.

The N-methyl derivative of [$^{15}\text{N}_2$]-**2** in $[\text{D}_8]\text{THF}$ presents the following $^{15}\text{N NMR}$ signals: δ = -254.2 (N₁), -163.6 (N_{1'}), -100.2 (N₉) and -63.5 (N_{3'} and N_{4'}).

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Fourier maps. The weighting scheme was established in an empirical way so as to give no trends in $\langle\omega\Delta^2F\rangle$ versus $\langle F_o\rangle$ or $\langle\sin\theta/\lambda\rangle$ ($\omega = K/(a + bF_o)^2[c + d\sin\theta/\lambda]$; the *a*, *b*, *c*, and *d* parameters were adjusted to flatten the initial trends.^[15] Most calculations have been performed with the Xtal system.^[16] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-144230. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Identification and Isolation of a Receptor for N-Methyl Alkylammonium Salts: Molecular Amplification in a Pseudo-peptide Dynamic Combinatorial Library**

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Dynamic combinatorial chemistry^[1] (DCC) offers a new strategy for the identification of new host and guest compounds with the potential for catalysis and drug activity.^[1, 2] It combines the merits of combinatorial chemistry^[3] with molecular evolution, whereby a combinatorial library of candidate molecules is generated by the assembly of building blocks through reversible bonds. As a consequence, all the library members are interconverting through exchange processes to give a product distribution which is under thermody-

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namic control and which may be influenced by template effects. Candidate molecules which bind strongly to templates will become amplified in concentration, while those that exhibit poor binding to the template will decrease in concentration by virtue of the Le Chatelier principle (Figure 1). Here

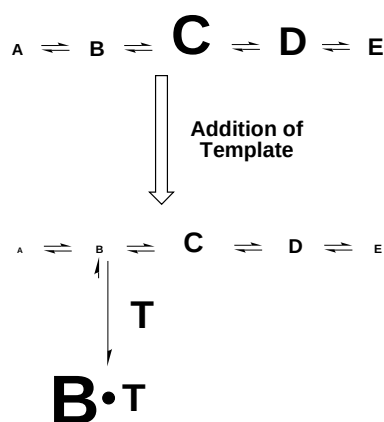
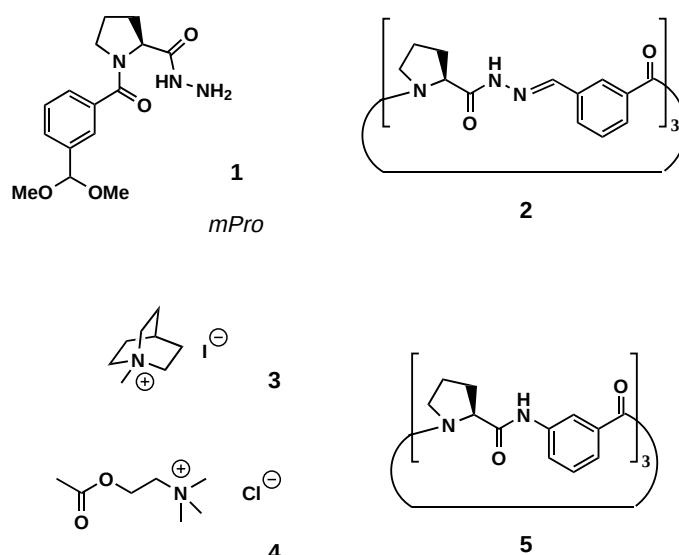


Figure 1. Schematic representation of the interconversion of library members by equilibrium processes and the subsequent product distribution change exerted by a template (T). Letter sizes are representative of product concentration.

we report molecular amplification from a dynamic combinatorial library (DCL) of pseudo-peptides of a macrocyclic receptor that binds selectively to acetylcholine and *N*-methyl quinuclidinium salts. The shifts in product distribution we report are to our knowledge the largest yet observed for covalent dynamic combinatorial systems, and serve as proof of the concept that dynamic combinatorial chemistry (DCC) may be used to identify and isolate new molecules from large pools of candidates through noncovalent template effects.

DCLs have been generated noncovalently through metal–ligand exchange^[4] and hydrogen-bonding networks,^[5] and covalently deploying a range of reversible reactions^[1] such as transesterification,^[6] disulfide exchange,^[7] allylpalladium chemistry,^[8] and transimination.^[9] However, reported examples of successful templating of covalent DCLs are so far very limited. We have generated libraries of hydrazone-based pseudo-peptides which interconvert by transimination at the hydrazone bond,^[10] and have recently reported significant molecular amplification in such a library by complexation of [18]crown-6 to the monomer hydrazinium cation.^[11] This effect is general for hydrazinium cations, but we now report specific molecular amplification of a macrocycle in a dynamic combinatorial mixture of hydrazone-based pseudo-peptides.

The DCL formed from building block *mPro* **1** was designed to contain a cyclic structure that would emulate cation binding observed with Kubik's cyclic peptides.^[12] Kubik's cyclic peptide **5** binds acetylcholine (ACh) iodide and *N*-methyl quinuclidinium (NMQ) iodide in chloroform with stability constants of 11 000 M^{−1} and 42 200 M^{−1}, respectively.^[12a] Comparison of the *mPro* trimer **2** with receptor **5** reveals very similar structures, with the exception of six additional bonds in our receptor. The expectation was that ACh and NMQ would bind the *mPro* cyclic trimer **2** strongly enough to template its formation leading to molecular amplification.



L-Proline was therefore equipped with the requisite hydrazone and aldehyde groups to form oligomeric pseudo-peptide cyclic hydrazones, with a view to biasing the thermodynamic product distribution to favor a complex between the cyclic trimer and the cation. Treatment of the *mPro* monomer **1** at a concentration of 5 mM in chloroform with one equivalent of trifluoroacetic acid (TFA) affords the complete range of cyclic oligomers from cyclic dimer to cyclic 15mer as kinetic products, the dominant kinetic product being cyclic trimer, according to HPLC and ESI-MS. Hydrazone exchange is catalyzed by TFA such that the reaction mixture, over a period of two days, reaches thermodynamic equilibrium. In the case of the *mPro* homooligomeric library proof-reading^[13] and editing led to a thermodynamic mixture, as recorded by HPLC, which comprises mainly cyclic dimer (88 %) and cyclic trimer (11 %) (Figure 2b). This is an example of thermody-

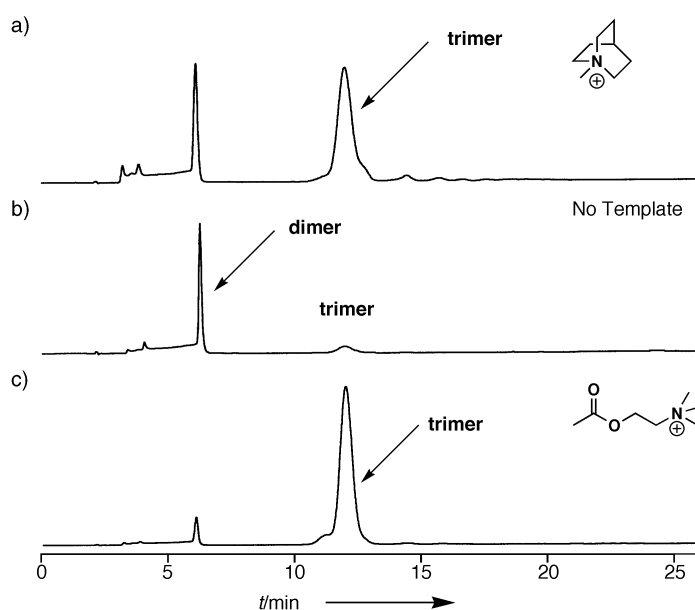
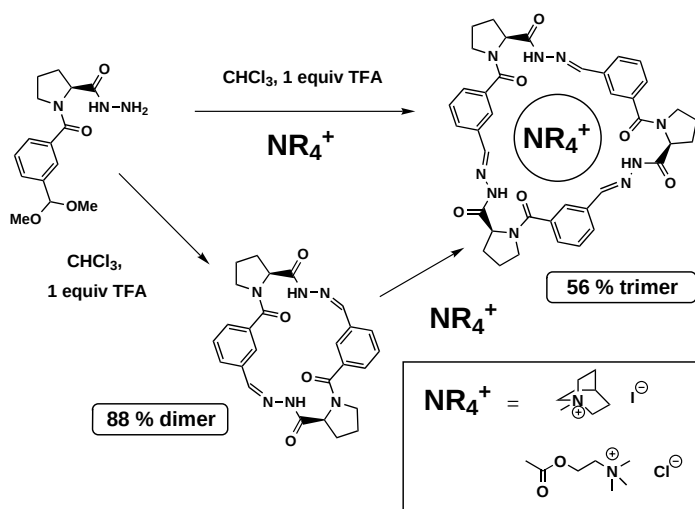


Figure 2. a) HPLC trace for **1** cyclized in the presence of two equivalents of *N*-methyl quinuclidinium iodide after two days. b) Compound **1** cyclized in the absence of template under the same conditions. c) Cyclization in the presence of two equivalents of acetylcholine.

namic control over product distribution in a DCL, whereby a diverse library of kinetic products—more diverse than the 14 cyclic species observed by mass spectrometry because of *cis/trans* isomers, conformers, and low-level linear species—thermodynamically evolves to form the more energetically favorable dimer. ^1H NOESY analysis of the cyclic dimer in CDCl_3 and inspection of models led us to believe that $\pi-\pi$ stacking^[14] between the aromatic units of the two monomers may contribute to dimer stability.

Cyclization of **1** in chloroform at 5 mM in the presence of two equivalents of NMQ iodide with one equivalent of TFA reveals a dramatically different library composition strongly biased towards cyclic trimer—cyclic dimer (41 %) and cyclic trimer (56 %)—with traces of higher oligomers (Figure 2a). This product distribution is attained irrespective of whether introduction of the template occurs before addition of TFA or to the equilibrating mixture containing predominantly dimer (Scheme 1). This confirms that the distribution observed is



Scheme 1. The two routes possible for templating of the product distribution towards cyclic trimer, included intermediate thermodynamic synthesis of cyclic dimer.

representative of a thermodynamically controlled process rather than kinetic trapping of cyclic trimer. Acetylcholine (ACh) chloride exerts an even greater influence on the product distribution, giving under the same conditions 86 % trimer, 13 % dimer, and insignificant quantities of higher oligomers (Figure 2c). The change in product distribution represents more than 50-fold amplification of cyclic trimer relative to cyclic dimer. As expected, increasing the concentration of template increases the bias towards trimer.

Our first evidence that these observations are the result of specific template effects is mass spectrometry. Electrospray mass spectrometry is a powerful technique for identifying supramolecular complexes,^[15] and under some conditions can give estimates of relative stability constants for such adducts.^[16] Analysis of the cyclization reactions templated with NMQ and ACh revealed the dimeric ($[M+\text{H}]^+ = 487.3$) and trimeric ($[M+\text{H}]^+ = 730.4$) cyclic oligomers with traces of the higher oligomers. Significantly, adducts of NMQ and ACh are observed for the trimer only; no such adducts are observed with the dimer (Figure 3).

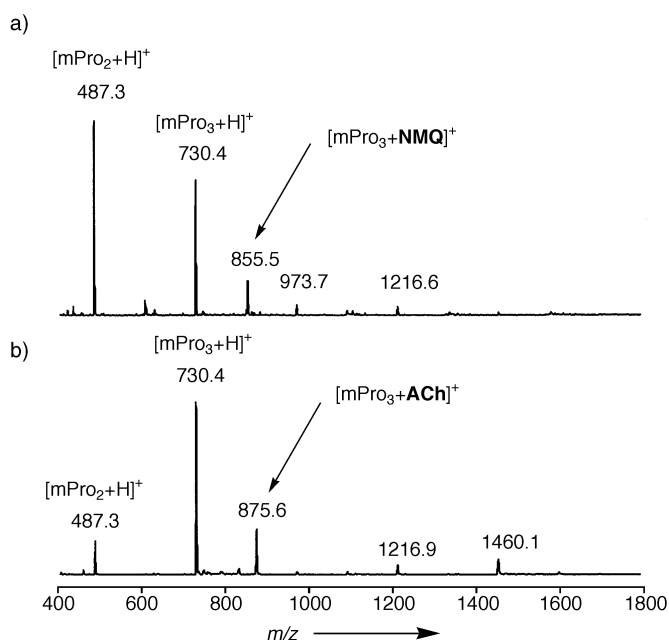


Figure 3. a) Electrospray mass spectrum of the cyclization mixture of **1** in the presence of *N*-methyl quinuclidinium iodide, depicting the trimer–quinuclidinium adduct. b) The mass spectrum for the analogous experiment with acetylcholine.

Pure trimer was readily isolated on a hundred milligram scale by silica gel chromatography of a reaction mixture templated by NMQ. The reaction was washed with water to remove much of the TFA and NMQ template and then evaporated under reduced pressure for purification by chromatography; under the conditions, template and receptor are sufficiently dissociated to allow separation.

The ^1H NMR spectrum of template-free trimer in a 95:5 chloroform/methanol mixture—to ensure complete solubility—is complicated by the presence of *cis/trans* and conformational isomers of the trimer (Figure 4b). Inspection of the α -proton region of the spectrum reveals one major conformer ($\delta = 4.74$) and a range of α -proton signals between $\delta = 4.5$ and 6.0. That all of these conformers for the trimer are interconverting is clear from the NOESY spectrum which shows exchange peaks between all the α -proton signals. The α -proton signals at $\delta = 5.63$ and 5.74 have shifts comparable to that observed for the dimer, suggesting that some of the trimer conformers may be folded by $\pi-\pi$ stacking in a similar way to cyclic dimer.

The addition of a template to cyclic trimer dramatically changes the ^1H NMR spectrum of each component: adding one equivalent of NMQ or ACh generates a simpler trimer spectrum dominated by a single conformer (Figure 4),^[17] accompanied by downfield shifts for the *N*-methyl protons by 0.15 ppm and 0.27 ppm for ACh and NMQ, respectively. The chirality of the receptor induces significant changes in the ^1H NMR signals for the CH_2 groups α to the ammonium center: the two protons are now nonequivalent (Figure 4). In the case of ACh the appearance of the signals for $-\text{CH}_2\text{a}-$ and $-\text{CH}_2\text{b}-$ and the observed *gem*, *cis*, and *trans* coupling constants for $-\text{CH}_2\text{b}-$ ($J = 15.7$, 2.9, and 7.5 Hz, respectively, Figure 5) led to the interpretation that acetylcholine is bound

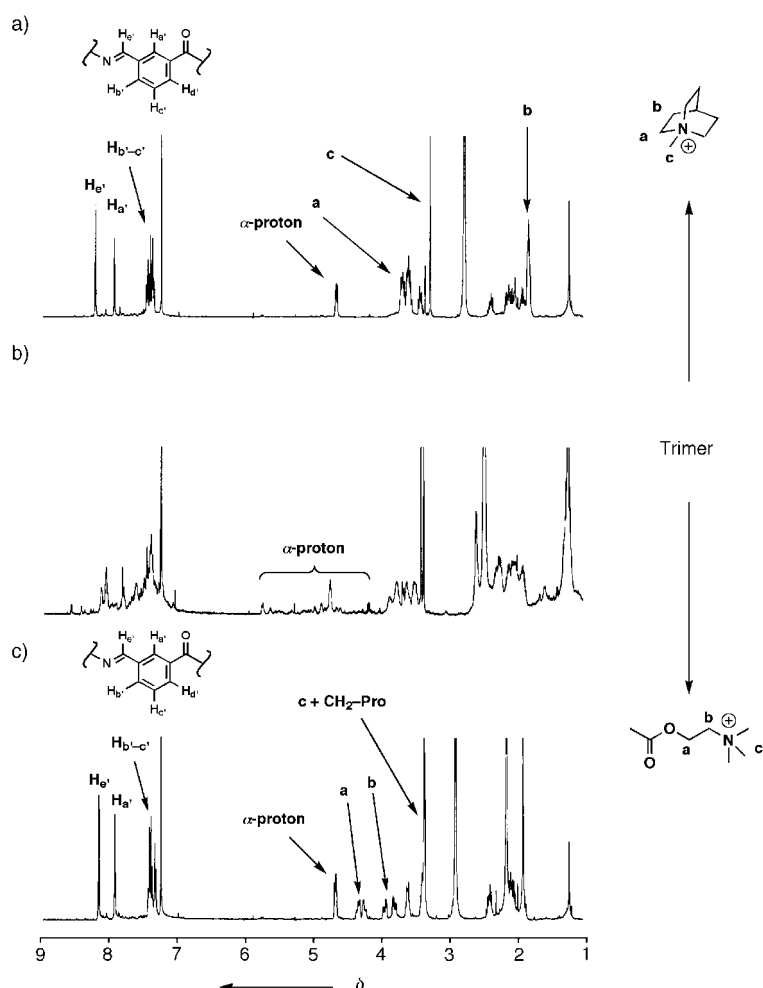


Figure 4. a) Partial 400 MHz ¹H NMR spectrum for cyclic trimer with one equivalent of *N*-methyl quinuclidinium salt, showing assignments for the trimer aromatic signals, trimer α-proton, and selected template protons. b) Partial ¹H NMR spectrum for cyclic trimer of **5**, highlighting the complex array of α-proton signals arising from multiple conformers. c) The ¹H NMR spectrum for cyclic trimer in the presence of one equivalent of acetylcholine, including some selected assignments for the template and host.

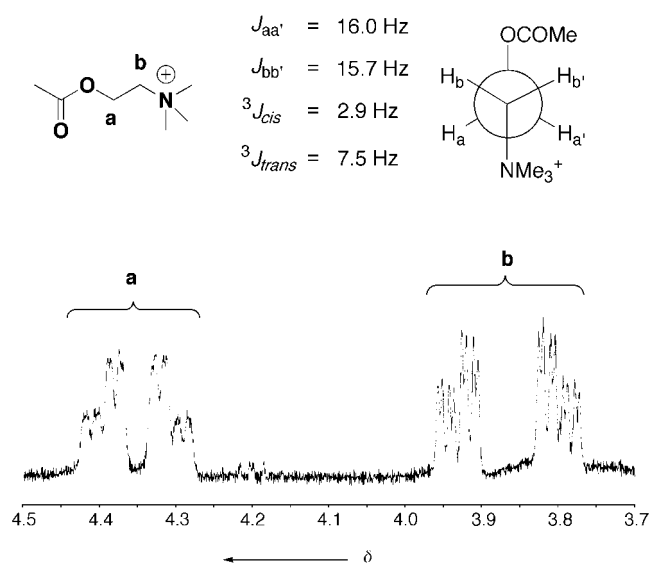


Figure 5. Acetylcholine CH₂aCH₂b resonances in the 500 MHz ¹H NMR spectrum of the acetylcholine-cyclic trimer adduct, with derived binding conformation of the guest. Stereospecific assignments of H_a versus H_{a'} and H_b versus H_{b'} are unknown.

in the *trans* conformation.^[18] Control experiments of 1:1 mixtures of templates with cyclic dimer afforded ¹H NMR spectra which show none of the changes in chemical shifts or splitting of CH₂ signals observed with cyclic trimer. In conjunction with an absence of a dimer·template adduct in the mass spectra, this represents good evidence that only the cyclic trimer binds to the ammonium salt templates. Significant binding to higher oligomers is excluded by the observation that they are not amplified by the addition of templates.

Binding constants for the two templates to the cyclic trimer in a CDCl₃/CD₃OD mixture (95:5) were estimated as 230 M⁻¹ and 150 M⁻¹ for ACh and NMQ, respectively, by monitoring the changes in chemical shift for the *N*-methyl groups during ¹H NMR titrations. Good fits with uncertainties of less than 5% were obtained on the basis of simple 1:1 equilibria. These relative binding constants match the templating response, the shift towards cyclic trimer being 1.5-fold greater for ACh than for NMQ. However, the conditions under which titrations were performed do not entirely reflect those of the cyclization reaction (100% chloroform with 1 equiv TFA). It is reasonable to believe that the presence of 5% methanol could give weaker binding than would be operating under the reaction conditions. Kubik's cyclic peptide **5** has a reversed preference for the acetylcholine and *N*-methyl quinuclidinium salts; it happens that our receptor is more selective for acetylcholine.

The most direct evidence for supramolecular complexation between cyclic *mPro* trimer **2** and NMQ comes from ¹H NOESY analysis of a 1:1 mixture in CDCl₃/CD₃OD (95:5) at 40 °C. Despite elevated temperatures the binding between the trimer and NMQ guest is strong enough for NOEs to be observed between the *N*-methyl, CH₂a and CH₂b protons of NMQ with Ar-H_a of the cyclic trimer. The strongest NOE signals are for the CH₂a and *N*-methyl groups suggesting that the ammonium center is directed at the cavity of the trimer. The NOESY spectrum acquired of a 1:1 mixture of ACh and cyclic trimer under the same conditions as for quinuclidinium also exhibits a small NOE between the acetylcholine NMe₃ protons and cyclic trimer.

The NOESY spectra for the trimer in the presence of template are dominated by exchange peaks between the dominant trimer conformer and the minor conformers that are present in very low concentrations; this has prevented elucidation of a binding conformation for the trimer. Identification of the noncovalent interactions responsible for the binding observed is therefore speculative. In the trimer·template complexes the *N*-methyl groups and α-CH₂ protons of ACh and NMQ experience downfield shifts which are characteristic of hydrogen bonding, whereas cation-π complexation of cations in cavities lined with aromatic subunits generally causes an upfield shift of the guest protons. The positive charge of alkylammonium cations is somewhat dispersed rather than resident as a point charge on the

ammonium center,^[19] so methylene protons adjacent to ammonium centers are slightly acidic, giving rise to hydrogen bonding capabilities. We believe that C–H···O hydrogen bonding^[20] is likely to occur between the CH₂ groups of the ammonium salts and the amide C=O oxygen atoms, and is a driving force for templating and molecular amplification in our system. This binding rationale contrasts with that applied to other synthetic acetylcholine receptors where cation– π interactions are invoked.

In conclusion, we have reported proof-reading to form cyclic dimer from a diverse kinetic combinatorial library of hydrazone-based cyclic pseudo-peptide oligomers. Using *N*-methylammonium salts acetylcholine chloride and quinuclidinium iodide we have been able to thermodynamically bias the product distribution of the dynamic combinatorial library towards a cyclic trimer. Binding between the cations and cyclic trimer has been unequivocally proven by mass spectrometry and ¹H NMR spectroscopy. To date this is the most significant example of templating in a covalent dynamic combinatorial library, facilitating the identification and isolation of a specific receptor. Extension of this approach to more diverse dynamic combinatorial libraries may afford highly effective receptors for acetylcholine and quaternary ammonium compounds as mimics for a wide range of biological binding sites. The concept of thermodynamic control of product distributions in DCLs by template effects has been proven and sets the scene for the identification of new, more efficient and selective receptors and enzyme mimics.

Experimental Section^[21]

mPro 1: 1) L-Proline methyl ester hydrochloride (0.59 g, 3.56 mmol) and 3-carboxybenzaldehyde dimethoxyacetal (0.70 g, 3.57 mmol) were dissolved in dry CH₂Cl₂ (20 mL) with dry Et₃N (1.0 mL, 7.17 mmol) under Ar (g) and the solution was cooled to 0 °C on an ice bath. To this solution were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (0.68 g, 3.57 mmol) and 4-dimethylaminopyridine (DMAP) (25 mg, 0.20 mmol) and the solution stirred at 0 °C for 1 h before being allowed to warm to room temperature and stirred overnight. The work-up involved the addition of CH₂Cl₂ (120 mL) and washing with 3 × 100 mL portions of H₂O. The organic portion was dried (MgSO₄) and the solvent removed in vacuo to afford a yellow oil. This oil was subjected to silica gel chromatography (EtOAc/hexane (8/2)) to afford the target compound as a colorless oil (0.76 g, 69%); *R*_f = 0.46 (EtOAc/hexane (8/2)); UV, I₂. 2) This oil (0.74 g, 2.41 mmol) was dissolved in MeOH (25 mL) and treated with hydrazine monohydrate (1.2 mL, 24.7 mmol) at room temperature for 20 h. Evaporation of the solvent under reduced pressure afforded a yellow oil which after silica gel column chromatography (CH₂Cl₂/MeOH (90/10)) yielded the target monomer **5** as a white foamy oil (0.57 g, 77%); *R*_f = 0.48 (CH₂Cl₂/MeOH (90/10)); UV, I₂; ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS): δ = 8.31 (s, 1H; NH), 7.62 (s, 1H; Ar-H), 7.53–7.48 (m, 2H; Ar-H), 7.40 (t, ³J(H,H) = 7.6 Hz, 1H; Ar-H), 5.39 (s, 1H; CH(OMe)₂), 4.67 (m, 1H; α -H), 3.94 (s, 2H; NHNH₂), 3.58 (m, 1H; Pro-CH_aH_b), 3.47 (m, 1H; Pro-CH_aCH_b), 3.31 (s, 6H; CH(OMe)₂), 2.37 (m, 1H; Pro-CH₂), 2.07 (m, 2H; Pro-CH₂), 1.83 (m, 1H; Pro-CH₂); ¹³C NMR (100 MHz, CDCl₃, 25 °C): δ = 172.0, 170.7, 138.5, 135.9, 128.7, 128.3, 127.3, 125.6, 102.4, 58.6, 52.7, 50.4, 27.8, 25.5; ESI: *m/z*: 308.4 [M+H]⁺, 276.3 [M-OMe]⁺, 244.4 [M-2OMe]⁺; HRMS: C₁₅H₂₁N₃O₄ [M+Na]⁺ requires 330.1430, found 330.1446.

Cyclization reactions were carried out in freshly distilled CHCl₃ at 5 mm with one equivalent of TFA with respect to monomer. Cyclizations and templated reactions were analyzed by ESI-MS and HPLC. Electrospray mass spectra were recorded on a Micromass Quattro-LC triple quadrupole apparatus fitted with a z-spray source. The electrospray source was heated to 100 °C and the sampling cone voltage (*V*_c) was 30 V. Samples were

introduced into the mass spectrometer source without work-up with an LC pump (Shimadzu LC-9A) at a rate of 4 μ L min⁻¹ of MeCN/H₂O (1/1). Calibration was performed by using protonated horse myoglobin. Scanning was performed from *m/z* 200 to 2200 in 6 s and several scans were summed to obtain the final spectrum which was processed using MassLynx V3.0 software.

HPLC analysis was performed on a Hewlett-Packard 1050 instrument using reversed phase conditions of H₂O:MeCN gradients with a 15 cm × 4.6 mm i.d. 3 μ m particle size, Supelco ABZ⁺plus C16 alkylamide column. Data were analyzed by using HP ChemStation. All NMR spectroscopy was performed on Bruker DRX 400 or DPX 500 instruments and chemical shifts are quoted in parts per million with respect to TMS.

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Synthesis of a Conjugated Macromolecular Initiator for Nitroxide-Mediated Free Radical Polymerization**

Ulf Stalmach, Bert de Boer, Alice D. Post,
Paul F. van Hutten, and Georges Hadziioannou*

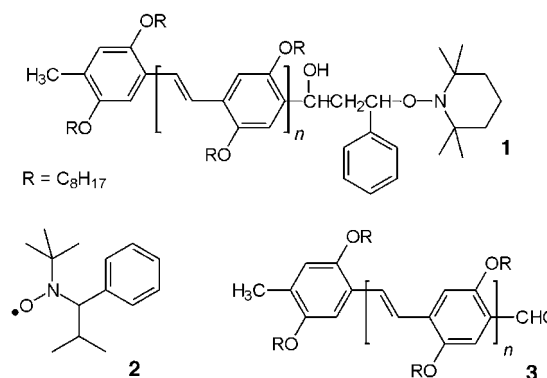
Recent years have seen the increased use of organic materials for opto–electronic applications, such as light-emitting diodes (LEDs) and photovoltaic cells. Such applications require a combination of material properties, for example, good conductivities for holes as well as for electrons, or both electron-donating and electron-accepting capabilities. Since this combination is not likely to be found in a single component, a range of multicomponent systems have been evaluated for use in devices and some have clearly shown beneficial effects.^[1] However, simple mixtures containing a polymer component may exhibit macrophase separation. Macrophase separation occurs on a length scale of micrometers (or coarser), which is too large for optimum performance. This is especially true when essential processes rely on the diffusion of excited species to the interface between the components. The diffusion length of a neutral exciton, for example, is of the order of a few nanometers.^[2] Hence, in a simple blend, most of the excitons will be lost to some decay channel before having a chance to interact with the second component.

When it comes to the combination of desirable properties in a single chemical compound, block copolymers may be the materials of choice. They might show the phenomenon of microphase separation (if the product of molecular weight (*N*) and interaction parameter (χ) is large enough) into various

ordered structures on a nanometer scale, while the blocks of one macromolecule can have different functionalities.^[3] These properties comply well with the requirements for performance enhancements of optoelectronic devices, and our research therefore focuses on the preparation and evaluation of appropriately functionalized block copolymers.

Our goal is to obtain block copolymers suitable for photonic applications such as LEDs or photovoltaic cells. We chose one of the blocks as poly(2,5-dioctyloxy-1,4-phenylene vinylene) (PPV), a polymer frequently used in opto–electronic applications serving as the hole-transporting and luminescent material in an LED or as the light absorber and electron donor in a photovoltaic cell.^[1] The second block should contain the complementary functionality required for the specific application: an electron-conducting material to achieve balanced charge transport in LEDs (e.g. an oxadiazole) or an electron acceptor (e.g. C₆₀) for photovoltaic cells. To achieve microphase separation, the second block should also be incompatible (high value of the interaction parameter) with the PPV block.

Recently, we published our approach to synthesizing this kind of molecule, which involves the attachment of an alkoxyamine to the PPV block.^[4] This yields a macroinitiator **1**, which is suitable for nitroxide-mediated free radical



polymerization (NMRP), one of several controlled radical polymerization techniques.^[5] The nitroxide we used was the commercially available 2,2,6,6-tetramethylpiperidin-1-yl-N-oxyl (TEMPO). While a number of publications on conjugated rod–coil block copolymers have appeared in the literature,^[6] only a few deal with the use of controlled radical polymerization techniques to construct the coil block.^[7] These rather new methods allow the synthesis of block copolymers and tolerate a wide range of substituents.

The aim of our work, controlling optoelectronic properties by synthesizing appropriate block copolymers, can be achieved by varying two parameters: the length of the blocks (degree of polymerization *N*) or their degree of incompatibility (described by the χ -parameter).^[8] The control over the block length is achieved by using a “living” polymerization method (the NMRP method), in which the block length increases linearly with polymerization time. One of the major drawbacks of the use of TEMPO in this controlled radical polymerization is that control can only be established for

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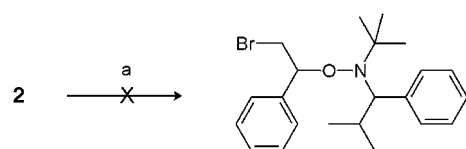
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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

styrene and some of its derivatives. To achieve microphase separated systems, it might be desirable to use chemically different monomers for the coil block, such as (meth)acrylates. These would have the additional advantage of being easily derivatized through esterification.

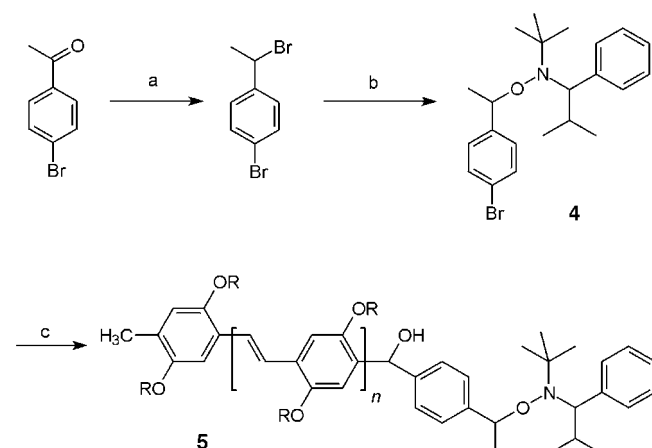
Recently, Benoit et al.^[9] synthesized a whole library of alkoxyamines and investigated their usefulness in the NMRP of styrene as well as other monomers, such as acrylates, and acrylonitrile^[9] or 1,3-dienes.^[10] They found that acyclic nitroxides such as **2**, yield polymers with very low polydispersities for a wide variety of monomers. Hence, we decided to pick up this strategy for our synthesis of rod-coil block copolymers containing a rodlike PPV block. Herein we describe the synthesis of a new macroinitiator for this strategy.

After synthesizing nitroxide **2** (TIPNO) according to reference [9], we first tried to utilize the reaction sequence that we had used successfully for the TEMPO-containing macroinitiator **1**. However, it turned out that the method of Kobatake et al.^[11] could not be employed for the synthesis of a brominated alkoxyamine by a route analogous to that used for TEMPO (Scheme 1). Most probably, the intermediate salt of bromine and the nitroxide is formed readily (the reaction mixture became cloudy), but does not add styrene in the following step.



Scheme 1. Reagents: a) 1) Br₂, CCl₄, RT; 2) styrene, 50 °C.

Consequently, a different strategy had to be devised for the synthesis of an alkoxyamine, from **2** (TIPNO), that is substituted with a halogen atom for the subsequent coupling of the initiator to the conjugated polymer. This approach is illustrated in (Scheme 2) for the synthesis of the macroinitiator **5**. The first step is the reduction of 4-bromoacetophenone with LiAlH₄ and its subsequent conversion to the



Scheme 2. Reagents: a) 1) LiAlH₄, diethyl ether, RT, 3 h; 2) PBr₃, toluene, pyridine, RT, 12 h; b) **2**, CuBr, Cu, bipy, toluene, 75 °C, 12 h; c) 1) *n*-BuLi, diethyl ether, −40 °C → RT; 2) **3**, THF, 60 °C, 2 h. Full details in the Supporting Information. RT = room temperature, bipy = 2,2'-bipyridine.

bromide by treatment with PBr₃. The alkoxyamine **4** was synthesized by the procedure of Matyjaszewski et al.^[12] from 1-(4-bromophenyl)ethylbromide and nitroxide **2**. The coupling to the PPV-aldehyde **3**, obtained by Siegrist polycondensation as described by Kretzschmann and Meier,^[13] is accomplished by first lithiating the alkoxyamine with equimolar amounts of *n*-butyllithium, followed by addition to a solution of **3** in THF.

As a first test we polymerized *n*-butylacrylate (BA) from the new macroinitiator to form PPV-*b*-PBA. Samples were withdrawn after 4 and 7 hours and precipitated into methanol (see Supporting Information).

As a control experiment, BA was polymerized with alkoxyamine **4** under the same conditions as for the block copolymers. The resulting polymer was still soluble in methanol. Therefore, the presence of *n*-butylacrylate homopolymer in the block copolymer samples can be excluded.

The molecular weights of the two block copolymers are shown in Table 1. The weight fractions were obtained from NMR spectroscopic data by comparing the resonance signals in the aromatic part (PPV) with those centered at $\delta = 4.1$ (OCH₂ of PPV and BA). The length of the PPV block was

Table 1. Molecular weights of PPV-*b*-PBA determined from ¹H NMR spectroscopy after polymerization for 4 and 7 hours (with the PPV-block taken as 3.9×10^3 g mol^{−1}).

Sample	<i>w</i> _{PPV} ^[a]	<i>M</i> _n [10 ³ g mol ^{−1}]
PPV-TIPNO	1.00	3.9
PPV- <i>b</i> -PBA 4 h	0.61	6.4
PPV- <i>b</i> -PBA 7 h	0.40	9.7

[a] Weight fraction of PPV block as calculated from ¹H NMR spectroscopy.

estimated through UV/Vis absorption spectroscopy by comparing the absorption maximum with those of monodisperse alkoxy-substituted oligo(*p*-phenylene vinylene)s.^[14] The λ_{max} value of 477 nm obtained for the macroinitiator **5** (PPV-TIPNO) would correspond to an oligomer with nine repeating units. Therefore, the average molecular weight of the PPV block was taken as 3.9×10^3 g mol^{−1}; based on this number, the number average total molecular weights were calculated from the NMR spectroscopic data (Table 1). To verify the values, we also measured the absorption spectra of **5** and of the two block copolymers, and normalized the signals on weight (Figure 1). Taking **5** as a reference, the absorption of the two block copolymers is reduced to 68 % and 48 %, respectively. These values are somewhat higher than the values calculated from NMR spectroscopy, but show the same trend.

Values obtained from gel permeation chromatography (GPC) measurements in THF are at least one order of magnitude higher than the values from NMR spectroscopy. Aggregation might be the reason for the overestimated molecular weights determined by GPC. That compounds **3** and **5** are also strongly overestimated in GPC measurements, indicates that the rodlike structure of the PPV is responsible for this overestimation. Nevertheless, these measurements show the increase of molecular weight with polymerization time, indicating the formation of block copolymers in a “living” manner. The ratios between the molecular weight

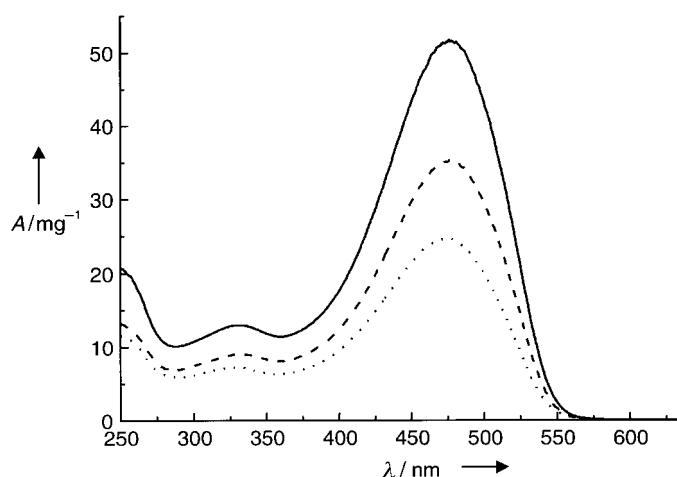


Figure 1. Mass-normalized UV/Vis absorption spectra in CHCl_3 of macro-initiator **5** (—) and block copolymers PPV-*b*-PBA after polymerization for 4 h (---) and PPV-*b*-PBA after polymerization for 7 h (····).

data obtained from NMR spectroscopy and GPC are roughly the same for **3**, **5**, and the block copolymers, providing evidence for similar aggregation numbers for all samples.

The glass transition temperature (T_g) of the PBA block in the block copolymer PPV-*b*-PBA (7 h polymerization) is -43°C and the melting temperature of the PPV block is 180°C as determined by differential scanning calorimetry (DSC). The corresponding homopolymers of PBA and (dioctyloxy)PPV show a T_g of -61°C and a melting temperature of 185°C , respectively. Thermogravimetric analysis (TGA) shows a decomposition temperature of the block copolymer of 340°C (5 % weight loss).

Transmission electron microscopy (TEM) studies on a drop-cast film revealed elongated domains of a fairly uniform thickness of approximately 10 nm (Figure 2). This size is

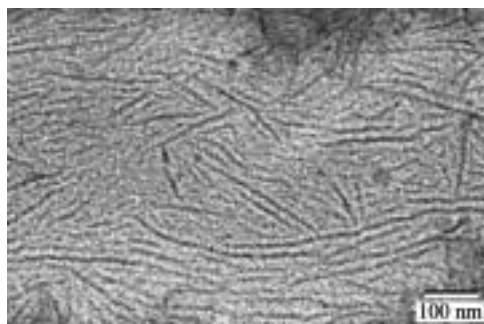


Figure 2. Bright field electron micrograph of PPV-*b*-PBA (polymerization for 7 h) revealing the microphase separated morphology.

compatible with a double-layer of the PPV blocks. The bright field electron micrograph does not resemble traditional images of highly ordered phase-separated coil-coil block copolymers. Firstly, this is probably because of the rodlike character of the PPV block. Rod-coil polymers have been found to exhibit morphologies quite different from coil-coil polymers.^[15] Secondly, because of the low molecular weight of our block copolymers, the system may be in the weak segregation regime of the phase diagram. The presence of

PPV block in the material between the domains is very well supported by the increase of T_g .

To conclude, we have synthesized a new PPV-containing macroinitiator suitable for nitroxide-mediated free radical polymerization (NMRP) and have used it successfully to obtain rod-coil block copolymers comprising a PPV (rod) and an *n*-butylacrylate (coil) block. The block length increased with polymerization time, as indicated by UV/Vis absorption and NMR spectroscopy. Transmission electron microscopy studies revealed a microphase separated morphology. As acrylates can easily be functionalized, this method offers a promising way to synthesize block copolymers for optoelectronic applications.

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X-Ray Photoelectron Spectroscopy of Porphycenes: Charge Asymmetry Across Low-Barrier Hydrogen Bonds**

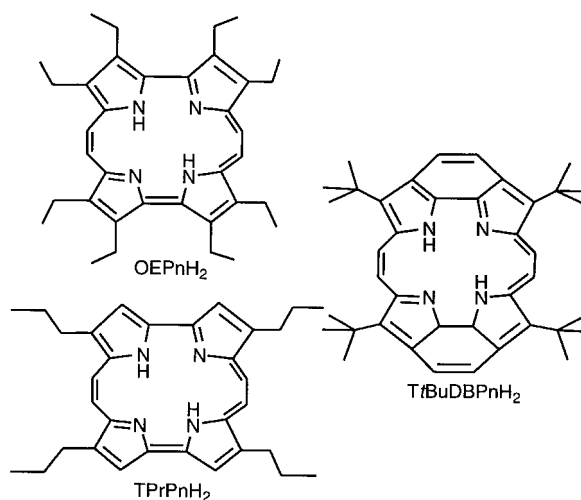
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Low-barrier hydrogen bonds (LBHBs), also known as short, strong hydrogen bonds (SSHBs), appear to be ubiquitous in both organic chemistry and biology.^[1] They are found in many common organic compounds such as carboxylate–carboxylic acid complexes^[2] and β -diketones.^[3] Gerlt and Gassman^[4] have invoked LBHBs to rationalize the stabilization of various enol intermediates in enzymatic hydrogen abstraction from carboxylic acids. They proposed a bonding scenario in which the hydrogen atom resides midway between the enolic oxygen atom and the conjugate base of the active site catalyst. Cleland and Kreevoy^[5] extended the same argument to cover enolate-type intermediates in enzyme-catalyzed reactions. They noted that these enzymes all exhibit unusually short heteroatom–heteroatom distances, which is a diagnostic feature of LBHBs. They further suggested that the bonding energy associated with the formation of an LBHB may be as high as 40–85 kJ mol^{−1} and that LBHBs are essentially covalent. Frey et al.^[6] found evidence, in the form of a strongly deshielded proton in ¹H NMR spectra, of an aspartate–histidinium LBHB in the catalytic triad of serine proteases. Other researches have doubted^[2] or disputed^[7] the importance of LBHBs in enzyme catalysis, with the result that a lively debate has surrounded this topic.^[8]

On the basis of our involvement with porphyrin chemistry^[9, 10] and X-ray photoelectron spectroscopy (XPS),^[11] it occurred to us that XPS^[12] may furnish unique insights into the LBHBs found in porphyrin analogues, such as porphyrin isomers, corroles, and related macrocycles. The activation energy for NH tautomerism in free-base porphyrins is about 12 kcal mol^{−1}^[13] and the central protons appear delocalized in the ¹H NMR spectra at room temperature. The maximally symmetric free-base porphyrin tetraphenylporphyrin (TPPH₂) reveals the presence of a single *trans* tautomer on cooling the NMR sample.^[14] In contrast, XPS, which gives a

practically instantaneous picture of the molecules, reveals two well-resolved ionization potentials (IPs), separated by 2.0–2.1 eV, of the nitrogen core when measured from above room temperature down to liquid-nitrogen temperature. The higher IPs are those of the protonated nitrogen atoms.^[11c] An interesting feature of this result is that this difference in IPs (ΔI_{N-1s}), which may be regarded as a difference of about 200 kJ mol^{−1} (of electronic charge) in the electrostatic potential between the protonated and unprotonated nitrogen atoms, is about 3–4 times the activation energy for proton transfer. Thus, there is a substantial asymmetry in the charge distribution between the donor and acceptor atoms even for moderately low-barrier hydrogen bonds. This result provided the motivation for an XPS study of the exceptionally low-barrier hydrogen bonds found in various porphyrin-type molecules.

The porphycenes (Scheme 1) are of interest in this regard. The N–H...N hydrogen bonds in porphycene are exceptionally strong^[15] and the barrier to tautomerism is so low that ¹H and ¹³C NMR spectra remain unchanged down to 165 K.^[16–18] A density functional theoretical (DFT) study^[19] at the B3LYP/TZDP level provided strong evidence that the ground state of unsubstituted porphycene corresponds to the *trans* tautomer. At this level of theory the optimized N–H and NH...N distances for the *trans* tautomer are 1.041 and 1.703 Å, which corresponds to a geometrical asymmetry of 0.662 Å for the N–H...N unit. The *trans* → *cis* activation barrier, corrected for zero-point energy effects, was predicted to be only 2.1 kcal mol^{−1}, which is consistent with the lack of change in the NMR spectra down to 165 K. In contrast, the N...H distances involving each hydrogen-bonded proton in the optimized geometry of dibenzoporphycene^[20] are nearly identical, namely, 1.23 and 1.26 Å, which corresponds to a geometrical asymmetry of 0.03 Å. This minute geometrical asymmetry is at, or beyond, the limit of what can be reliably predicted with DFT, which raises the intriguing prospect that the dibenzoporphycenes may provide a rare, if not unique, example of a symmetrical N...H...N hydrogen bond. XPS provides a convenient means for examining this issue and here we report an XPS^[21] study of 2,3,6,7,12,13,16,17-octaethylporphycene (OEPnH₂),^[22] 2,7,12,17-tetra-*n*-propylporphycene



Scheme 1. Free-base porphycenes studied in this work.

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(TPrPnH₂),^[23] and 2,7,12,17-tetra-(*tert*-butyl)-3,6-13,16-dibenzo[cde;mno]porphycene (TtBuDBPnH₂; Scheme 1).^[24]

Table 1 lists the N 1s and C 1s peak maxima obtained by XPS and Figure 1 shows the N 1s XPS spectra. The energy splitting between the different ionization potentials of the

Table 1. XPS peak maxima [eV] of different compounds studied.

Compound	N 1s	ΔI_{N-1s}	C 1s
TPPH ₂	397.4, 399.5	2.1	284.6
OEPnH ₂	397.9, 399.65	1.75	285.0
TPrPnH ₂	397.8, 399.2	1.4	284.9
TtBuDBPnH ₂	397.95, 398.9	0.95	284.6

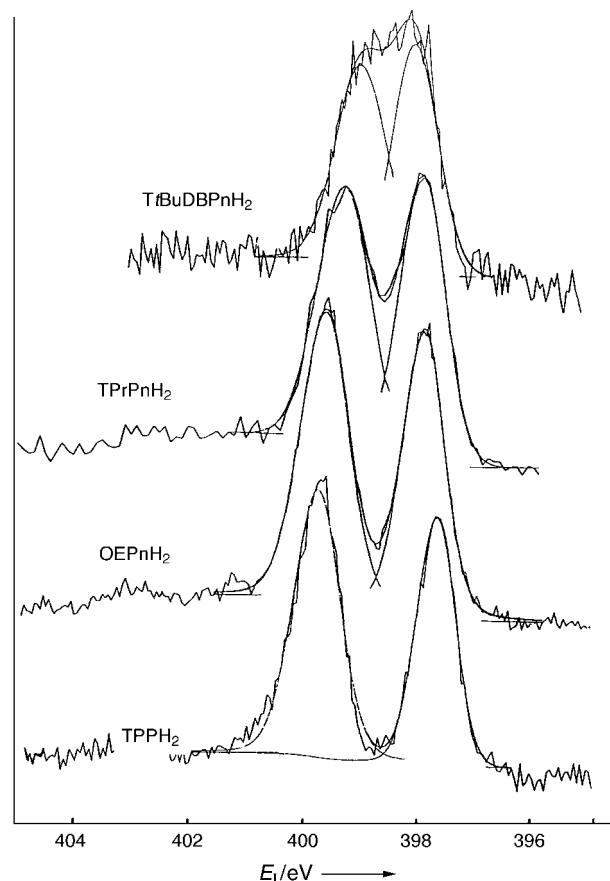


Figure 1. Nitrogen 1s maxima of the various compounds studied by XPS. The x axis gives IPs or binding energies in eV. The spectral intensities along the y axis are in arbitrary units. The lower signal-to-noise ratio in the case of the spectrum of TtBuDBPnH₂ is a consequence of the extra high instrument resolution used relative to the other samples.

nitrogen core (ΔI_{N-1s}) decreases along the series TPPH₂ (2.1 eV), OEPnH₂ (1.75 eV), TPrPnH₂ (1.4 eV), and TtBuDBPnH₂ (0.95 eV). The two types of nitrogen atoms appear as well-resolved peaks in all cases except for TtBuDBPnH₂ where the splitting of 0.95 eV approaches the limit of the instrument resolution. The results afford a number of interesting conclusions as well as provoke some significant unanswered questions, as discussed below.

All the compounds studied have localized, albeit rapidly tautomerizing, central protons. The assignment of the spectra

are straightforward, based on previous XPS studies^[11] as well as ab initio Hartree–Fock^[11] and DFT equivalent-core^[25] calculations: for each molecule, the higher IP of the nitrogen core corresponds to the protonated nitrogen atoms.^[11c]

The core IPs of the “unprotonated” nitrogen atoms increases along the series of compounds TPPH₂, OEPnH₂, TPrPnH₂, and TtBuDBPnH₂, while the core IPs of the “protonated” nitrogen atoms decreases.^[26] However, although the difference in the electronic character between the protonated and unprotonated nitrogen atoms narrows across this series of compounds, the two types of nitrogen atoms do not quite equalize. Remarkably, even for TtBuDBPnH₂, whose hydrogen bonds are almost perfectly symmetrical in a geometrical sense,^[20] a significant charge asymmetry persists across the N...H...N units.

The decrease in the ΔI_{N-1s} value, or the increase in the hydrogen-bond strength, along the series TPPH₂, OEPnH₂, TPrPnH₂, and TtBuDBPnH₂, correlates with a decrease in the N...N separations in the N...H...N hydrogen-bonded units in these compounds, with the N...N distances being 2.93,^[27] 2.79–2.80,^[22] 2.61–2.62,^[23] and 2.51 Å,^[24c] respectively, for the four compounds (Figure 2). This correlation also

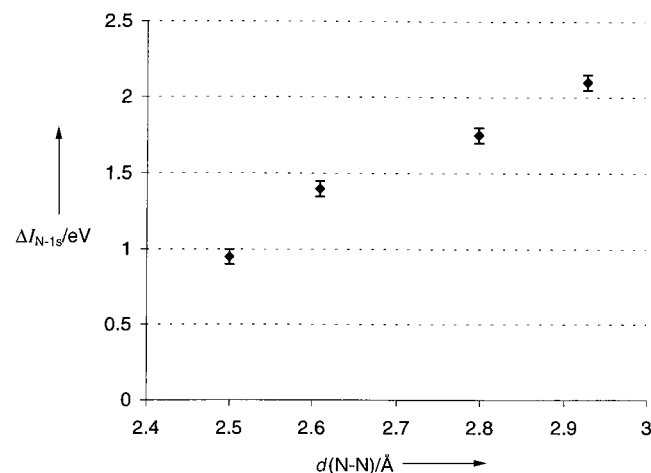


Figure 2. Variation of the ΔI_{N-1s} [eV] values with N...N separation [$d(N-N)$, Å]. From left to right: the data points are for TtBuDBPnH₂, TPrPnH₂, OEPnH₂, and TPPH₂.

explains a somewhat puzzling aspect of the data shown in Table 1: the ΔI_{N-1s} value of TPrPnH₂ (1.4 eV) is significantly smaller than that of OEPnH₂ (1.75 eV). On the basis of the foregoing argument it appears that this anomaly results from differences in the skeletal geometry between the two compounds. Indeed, there appears to be a monotonic relationship between the ΔI_{N-1s} values and the N...N separations that also extends to other tetrapyrroles, such as different porphyrin and corrole isomers.^[9, 28] We shall report XPS results, along with DFT equivalent-core simulations, on these substances in a forthcoming paper.^[29]

Can we understand or rationalize these large charge asymmetries, as measured by ΔI_{N-1s} , across exceedingly low-barrier hydrogen bonds in terms of a simple physical picture? Simple electrostatics provides part of the answer. Consider a proton P placed in a vacuum approximately halfway between

two points A and B so that the distances $P \cdots A$ and $P \cdots B$ are 1.23 and 1.26 Å, respectively (these being the NH distances in an optimized structure of dibenzoporphycene as mentioned above). A simple calculation shows that the geometrical asymmetry of 0.03 Å with respect to the proton results in a fairly significant difference in the electrostatic potential (about 0.3 V) between points A and B. For $P \cdots A = 1.21$ Å and $P \cdots B = 1.27$ Å, the difference in the electrostatic potential between points A and B is about 0.6 V. These simple-minded “proton-in-vacuum” calculations help somewhat in demystifying how geometrical asymmetries of less than 0.1 Å may engender electrostatic potential differences of several tenths of an eV (as measured by ΔI_{N-1s} in this study) across the termini of a low-barrier hydrogen bond. Clearly, obtaining a proper understanding the charge distribution of LBHBs involves much more than these crude considerations and we hope to present a theoretical analysis of the experimental results reported here in the not too distant future.

A brief comment may be in order on the question of whether perfectly symmetrical hydrogen bonds (that is, with single-well potential energy minima) exist. The bifluoride ion HF_2^- is believed to provide the prototypical example of such bonding. Another well-studied example of an LBHB system with at least near-perfect geometrical asymmetry is provided by the $[(CO)_5Cr-CN \cdots H \cdots NC-Cr(CO)_5]^-$ ion.^[30] However, in light of the present results, these as well as other LBHB systems are well worth reexamining by XPS.

Finally, how might the present results relate to current research on the role of LBHBs in enzyme catalysis? How similar are the LBHBs in porphycenes and those found in biological systems? Although these questions remain unanswered at this point, we felt obliged to articulate them here because, eventually, the large and diverse body of results on LBHBs, including the present findings, must come together in a coherent picture.

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Cyano-Bridged 4f–3d Coordination Polymers with a Unique Two-Dimensional Topological Architecture and Unusual Magnetic Behavior**

Bao-Qing Ma, Song Gao,* Gang Su, and Guang-Xian Xu

Cyano-bridged dimetallic hybrid Prussian Blue one- to three-dimensional (1D–3D) coordination polymers based on $[M(CN)_6]^{3-}$ ($M = Fe, Cr, Mn$) have attracted great attention because of their rich and interesting structures and magnetic behavior.^[1] These studies were mainly focused on transition metals. In principle, it would be possible to enhance the coercive field by the introduction of paramagnetic lanthanide ions because these possess rather large and anisotropic magnetic moments. However, the magnetism, rarely investigated, for known cyano-bridged lanthanide / transition metal complexes such as ion pairs, dinuclear, trinuclear, tetranuclear, and one-dimensional chains,^[2] does not seem exciting, since the couplings between the lanthanide and transition metals are very weak, because of the effective shielding of the 4f electrons by the outer-shell electrons. However, the 3D polymer $[SmFe(CN)_6] \cdot 4H_2O$, with strong anisotropic coercive field, exhibits a long-range ferrimagnetic ordering below 3.5 K, and that $[TbCr(CN)_6] \cdot 4H_2O$ has the highest known Curie temperature ($T_C = 11.7$ K) for 4f–3d molecule-based magnets.^[3] This implies that increasing the number of dimensions may enhance and improve bulk magnetic properties. Our strategy for the rational synthesis of a high-dimen-

sional network is to use a suitable combination of cyanide groups and other bridging ligands. Here, 2,2'-bipyrimidine (bpym) was selected, in preference to 4,4'-bipyridine and pyrazine, because it is more capable of transmitting magnetic interactions^[4] and its bis(chelating) coordination modes facilitate connection between lanthanide ions. Unexpectedly, two novel coordination polymers $[NdM(bpym)(H_2O)_4(CN)_6] \cdot 3H_2O$ ($M = Fe$ (**1**), Co (**2**)) were obtained, which have a unique 2D topological architecture, and exhibit unusual magnetic behavior.

Compounds **1** or **2** were obtained by the slow diffusion of $K_3[Fe(CN)_6]$ or $K_3[Co(CN)_6]$ and bpym with $Nd(NO_3)_3$ in a 1:1:1 molar ratio in aqueous solution (30 mL); X-ray diffraction analysis reveals that the compounds are isomorphous.^[5] The structure of **1** (Figure 1) consists of a 2D net with

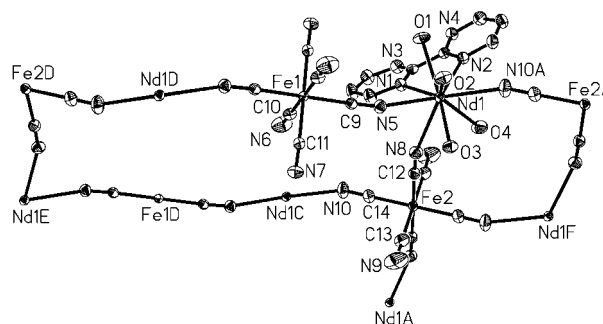


Figure 1. ORTEP plot of **1**. Selected bond lengths [Å]: Nd1–O1 2.4235(10), Nd1–O2 2.4524(11), Nd1–O3 2.4739(11), Nd1–N5 2.5105(10), Nd1–O4 2.5326(10), Nd1–N10A 2.5972(15), Nd1–N8 2.6399(13), Nd1–N1 2.6875(13), Nd1–N2 2.7293(10) (Symmetry codes: A: $x + 1, y, z$).

alternating fused rows of rhombuslike $Fe_2Nd_2(CN)_4$ rings and six-sided $Fe_4Nd_4(CN)_8$ rings. Each Nd^{3+} ion is nine coordinate being bound by two N atoms from one chelating bpym molecule (the mean length of $Nd-N = 2.7084$ Å), four O atoms from water molecules (the mean length of $Nd-O = 2.4706$ Å) and three N atoms from three bridging CN^- groups (the mean length of $Nd-N = 2.5825$ Å), yielding a monocapped square anti-prism. The top and bottom planes are defined by O1, O2, N2, N10A and O3, O4, N1, N5, respectively, and N8 occupies the cap position. The bpym ligand coordinates to the Nd ions in a chelating fashion, and the remaining two N atoms form the hydrogen bonds with the coordinated water molecules of neighboring Nd^{3+} ion (not shown: $O3 \cdots N3A$ 2.929 Å, $O3-H5 \cdots N3A$ 155.80°; $O2 \cdots N4A$ 2.850 Å, $O2-H3 \cdots N4A$ 160.08°; symmetry: A: $x, y + 1, z$). Although on chelation bpym and 2,2'-bipyridine (bipy) ligands have similar steric effects, they give different structures with $K_3[Fe(CN)_6]$ and $Nd(NO_3)_3$. For the latter, an ion pair compound $[FeNd_2(CN)_6(bipy)_4(H_2O)_8][Fe(CN)_6] \cdot 8H_2O$ is formed.^[2f] The difference is tentatively attributed to the different affinity of both ligands.

In the structure of **1** there are two crystallographically unequal Fe atoms per asymmetric unit; they are located at inversion centers. The Fe2 center employs four CN^- groups in the same plane to connect the Nd^{3+} ions, giving rise to a double strand chain as found in $[Cu(dien)_2Cr(CN)_6]_n$ – $[Cu(dien)(H_2O)Cr(CN)_6]_n \cdot 4nH_2O$ (dien = diethylenetri-

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amine).^[6] Thus, a 12-membered rhombus subunit $\text{Fe}_2\text{Nd}_2(\text{CN})_4$ is generated with the distances between the cyanide-bridged metal centers $\text{Nd1} \cdots \text{Fe2}$ and $\text{Nd1} \cdots \text{Fe2a}$ being 5.616 and 5.606 Å, respectively, similar to those observed in $[\text{Fe}_2(\text{CN})_4(\text{phen})_4\text{Yb}_2\text{Cl}_6(\text{H}_2\text{O})_2] \cdot 2\text{H}_2\text{O} \cdot 2\text{CH}_3\text{OH}$.^[21] Fe1 uses two *trans* CN^- groups to link neighboring chains ($\text{Nd1} \cdots \text{Fe1}$ 5.381 Å), leading to an unusual 2D sheet structure (Figure 2a and schematically represented in Figure 2b; a discussion of

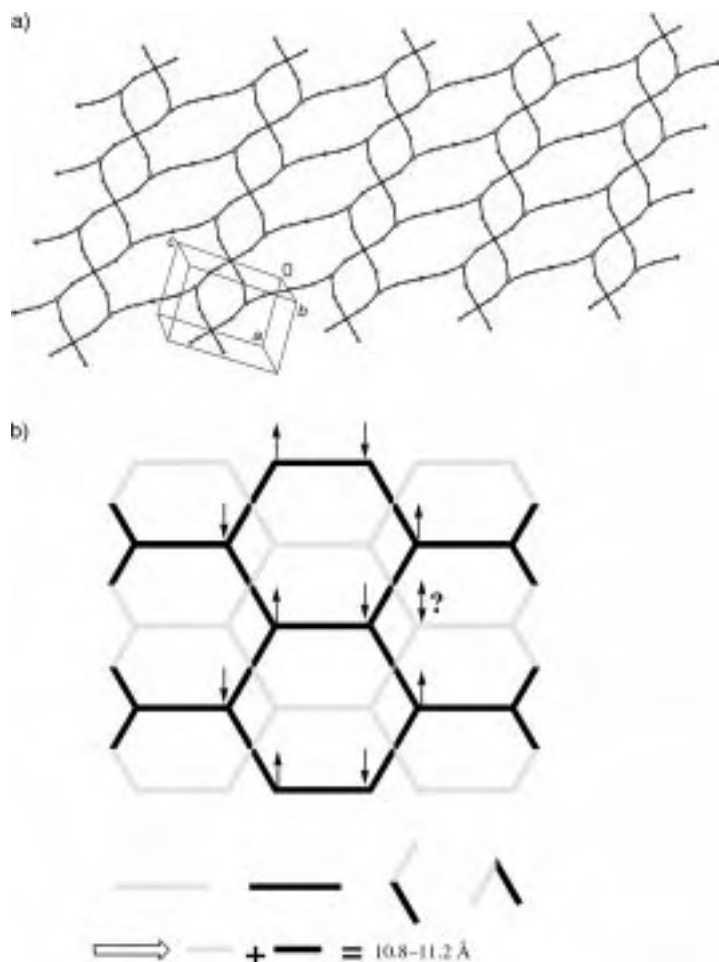


Figure 2. a) Layer structure of **1**, exhibiting a unique topological architecture. For clarity, only the cyanide groups and metal centers are shown. b) The 2D connection of the Nd^{3+} ions can be viewed as two sets of equivalent honeycombs (black and gray). The rods (either black or gray) and the two different modes of joining black and gray rods represent the three different kind of link between the Nd^{3+} ions in the 2D structure. This arrangement leads to spin frustration in compound **2** (see text for details).

spin frustration in compound **2** is given below). The shortest interlayer $\text{Nd} \cdots \text{Fe}$, $\text{Nd} \cdots \text{Nd}$, and $\text{Fe} \cdots \text{Fe}$ distances are 9.390, 8.897, and 9.197 Å, respectively. The $\text{Fe}-\text{C}$ distances are in the range of 1.9171–1.9450 Å and $\text{Fe}-\text{C}\equiv\text{N}$ bond angles are nearly linear. The bridging cyanide ligands link the Nd^{3+} ions in a bent fashion with the $\text{Nd}-\text{N}\equiv\text{C}$ bond angles ranging from $158.52(9)^\circ$ to $166.11(11)^\circ$. The lattice water molecules reside between layers and link the 2D sheets into a 3D network through extensive hydrogen bonding.

The previously reported cyanide-bridged 4f–3d complexes with mixed ligands have an isolated 0D or 1D structure. The

compounds **1** and **2** reported herein are the first two-dimensional cyanide-bridged compounds containing both lanthanide and transition metal ions. More interestingly, they have a 2D topological architecture type that is very different from the known 2D cyanide-bridged structures: square,^[7] honeycomb,^[8] brick wall,^[9] partial cubane structures,^[10] and also of other 2D coordination polymers (grid, kagome, herring bone, triangular).^[11]

The temperature dependences of the $\chi_{\text{M}}T$ for crystalline samples **1** and **2** confined in parafilm, measured at 10 kOe and 500 Oe fields, are shown in Figure 3 and in the inset

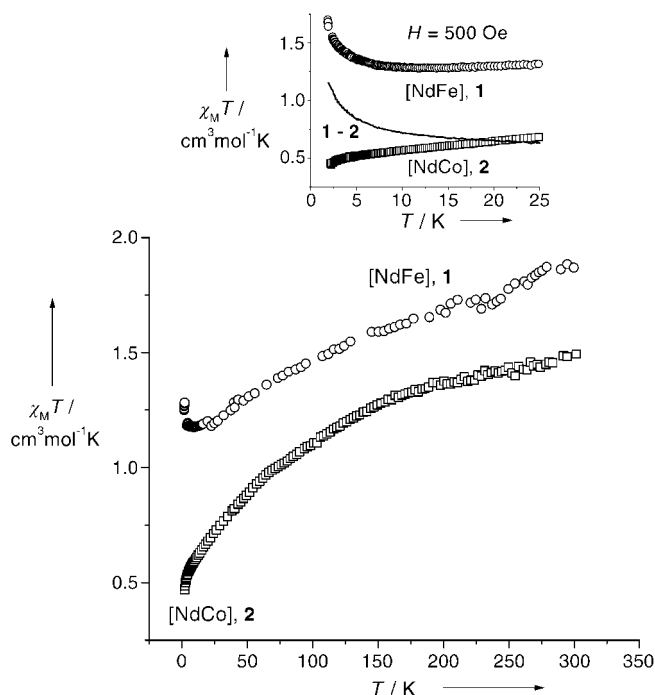


Figure 3. Temperature dependence of $\chi_{\text{M}}T$ for [NdFe] **1** (○) and [NdCo] **2** (□) at 10 kOe. Inset is the curves of $\chi_{\text{M}}T$ versus T at 500 Oe. More magnetic measurements can be found in the Supporting Information.

respectively. The observed $\chi_{\text{M}}T$ values for **1** and **2** at 300 K are 1.87 and $1.49\text{ cm}^3\text{mol}^{-1}\text{K}$, respectively, slightly smaller than the calculated values of 2.00 and $1.64\text{ cm}^3\text{mol}^{-1}\text{K}$ for non-interacting free ions per NdFe and NdCo unit, respectively (the Co^{3+} ion is diamagnetic in the present strong-field case). Upon cooling, the $\chi_{\text{M}}T$ of **2** decreases continuously from 300 to 2 K, while the $\chi_{\text{M}}T$ of **1** is roughly parallel with that of **2** above 80 K. The difference varies little, it is approximately $0.38\text{ cm}^3\text{mol}^{-1}\text{K}$ which is the value for an isolated iron(III) ion. These observations suggest that the decrease of $\chi_{\text{M}}T$ with decreasing temperature must be considered as an intrinsic characteristic of the Nd ion, which may be attributed to the depopulation of its Stark levels.^[12a] With further cooling, the $\chi_{\text{M}}T$ of **1** reaches a minimum at approximately 10 K, then increases rapidly. To exclude the contribution of spin-orbital coupling of the Nd^{3+} ion, the $\chi_{\text{M}}T$ of **2** was subtracted from that of **1**. It is found that the difference (solid line in the inset of Figure 3) increases steadily with cooling, indicative of ferromagnetic interactions between the Nd^{3+} and Fe^{3+} ions. No long-range ordering was observed down to 2 K based on

measurements of the field-dependent magnetization and the zero-field alternating current (AC) susceptibility, however. The field dependence of magnetization (M) for **1** and **2** was measured at 1.8 K. The magnetization values at 50 kOe are 2.06 and 1.05 N β , respectively, close to saturation. For the Nd³⁺ ions in **2**, the crystalline field resolves the 10-fold degenerate ⁴I_{9/2} ground states into five doublets, only one of which is populated at 20 K or below.^[12b] If the saturation magnetization value of **2** is taken as 1.09 N β (60 kOe), the effective spin in the ground state for one Nd³⁺ ion is 1/2, and g' is 2.18, consistent with the above argument. The difference M for **1** and **2** yields 1.01 N β for the Fe³⁺ ions, in reasonable accord with the theoretical value 1 N β .

Compound **2** containing only one type of paramagnetic Nd³⁺ ion was magnetically investigated in some detail. The zero field AC susceptibility was measured in the 3–8 K range at different frequencies (111–1111 Hz), and shown in the upper panel of Figure 4. Normal paramagnetic behavior of the

with very similar linear five-atom N-C-Co-C-N bridges close to 11 Å in length. If just one set of honeycombs, for example, the black one, is considered, the antiferromagnetic (AF) coupling between neighboring Nd³⁺ ions should not give rise to frustration. However, since the pathways between the two sets of honeycombs are also through N-C-Co-C-N five-atom bridges, the magnetic interaction between the neighboring spins on different honeycombs might be comparable with that in each honeycomb, so that the magnetic moments located in Nd³⁺ will be frustrated.

Experimentally, at zero field no frustration was observed for **2** because of very weak AF interactions between the Nd³⁺ ions, whereas the introduction of a DC field might enhance the AF correlation, which gives rise to the unusual field-dependent magnetic relaxation.

Experimental Section

bpym was purchased from Aldrich and used without further purification. K₃[Co(CN)₆] was prepared by the literature method.^[14] Compound **1** was prepared by mixing K₃[Fe(CN)₆] (1 mmol) and bpym (1 mmol) in aqueous solution (20 mL), followed by the slow addition of an aqueous solution of Nd(NO₃)₃ (1 mmol; 10 mL) without stirring. The resulting solution was allowed to slowly diffuse and evaporate at room temperature in the dark. After two weeks, bright yellow single crystals were obtained, which were collected by filtration, washed with small amounts of water and ethanol, and dried in air (41% yield). Elemental analysis calcd for C₁₄H₂₀FeNdN₁₀O₇ (%): C 26.23, H 3.12, N 21.86; found: C 26.86, H 2.78, N 22.26. Compound **2** was synthesized following the same procedure as **1**, but K₃[Fe(CN)₆] was replaced by K₃[Co(CN)₆] (43% yield). Elemental analysis calcd for C₁₄H₂₀CoNdN₁₀O₇ (%): C 26.09, H 3.11, N 21.77; found: C 26.43, H 2.83, N 22.16.

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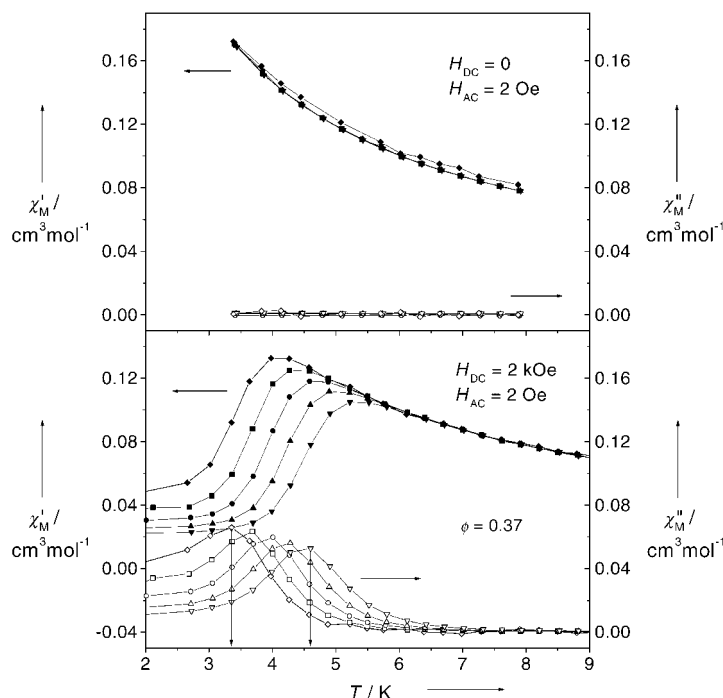


Figure 4. Frequency dependence of AC susceptibility at zero and 2 kOe DC bias field for compound **2**. $\diamond$ = 111 Hz, $\square$ = 199 Hz, $\circ$ = 355 Hz, $\triangle$ = 633 Hz, ∇ = 1111 Hz. The filled symbols are for the in-phase component χ'_M , the open symbols are for the out-of-phase component χ''_M .

in-phase component χ'_M and negligible small signal of the out-of-phase component χ''_M , indicate the absence of long-range ordering and any spin-glasslike behavior. However, under an intermediate direct current DC bias field (2 kOe), two peaks (T_P) appear for both χ'_M and χ''_M , respectively, as shown in the lower panel of Figure 4. Moreover, χ'_M and χ''_M are strongly frequency dependent with a considerably larger ϕ value 0.37 ($\phi = \Delta T_P / (T_P \Delta(\log f))$) than that for normal spin glass (< 0.1),^[13] suggesting the unusual glasslike behavior, which may be attributed to the geometrically frustration of Nd³⁺ ions as shown in Figure 2b. The 2D connection of the Nd³⁺ ions can be viewed as two sets of honeycombs (gray and black)

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- [5] Crystal data. Compound **1**: $C_{14}H_{20}FeNdN_{10}O_7$, $M_r = 640.49$, triclinic, $P\bar{1}$, $a = 8.9399(5)$, $b = 9.1967(3)$, $c = 15.4335(7)$ Å, $\alpha = 76.054(3)$, $\beta = 89.359(3)$, $\gamma = 67.756(3)^\circ$, $V = 1135.31(9)$ Å³, $Z = 2$, $\rho = 1.874$ Mg m⁻³, $\mu(Mo_{K\alpha}) = 2.957$ mm⁻¹, $F(000) = 632$, $GoF = 1.055$. A total of 18535 reflections were collected and 5364 are unique ($R_{int} = 0.0507$). The final $R1$ and $wR2$ are 0.0310 and 0.0758, respectively, for 345 parameters and 4889 reflections ($I > 2\sigma(I)$). Compound **2**: $C_{14}H_{20}CoNdN_{10}O_7$, $M_r = 643.57$, triclinic, $P\bar{1}$, $a = 8.7801(5)$, $b = 9.2011(5)$, $c = 15.4319(10)$ Å, $\alpha = 76.337(4)$, $\beta = 88.982(4)$, $\gamma = 67.542(4)^\circ$, $V = 1115.89(11)$ Å³, $Z = 2$, $\rho = 1.915$ Mg m⁻³, $\mu(Mo_{K\alpha}) = 3.102$ mm⁻¹, $F(000) = 634$, $GoF = 1.029$. A total of 14884 reflections were collected and 5118 are unique ($R_{int} = 0.1088$). The final $R1$ and $wR2$ are 0.0638 and 0.1483, respectively, for 345 parameters and 3829 reflections ($I > 2\sigma(I)$). The data of both compounds were collected on a Nonius Kappa CCD with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) at 293 K. The structures were solved by direction method and refined by a full matrix least-squares technique based on F^2 using SHELXL 97 program. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-147180 (**1**) and CCDC-147181 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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Immobilization of Homogeneous Palladium(II) Complex Catalysts on Novel Polysiloxanes with Controllable Solubility: Important Implications for the Study of Heterogeneous Catalysis on Silica Surfaces**

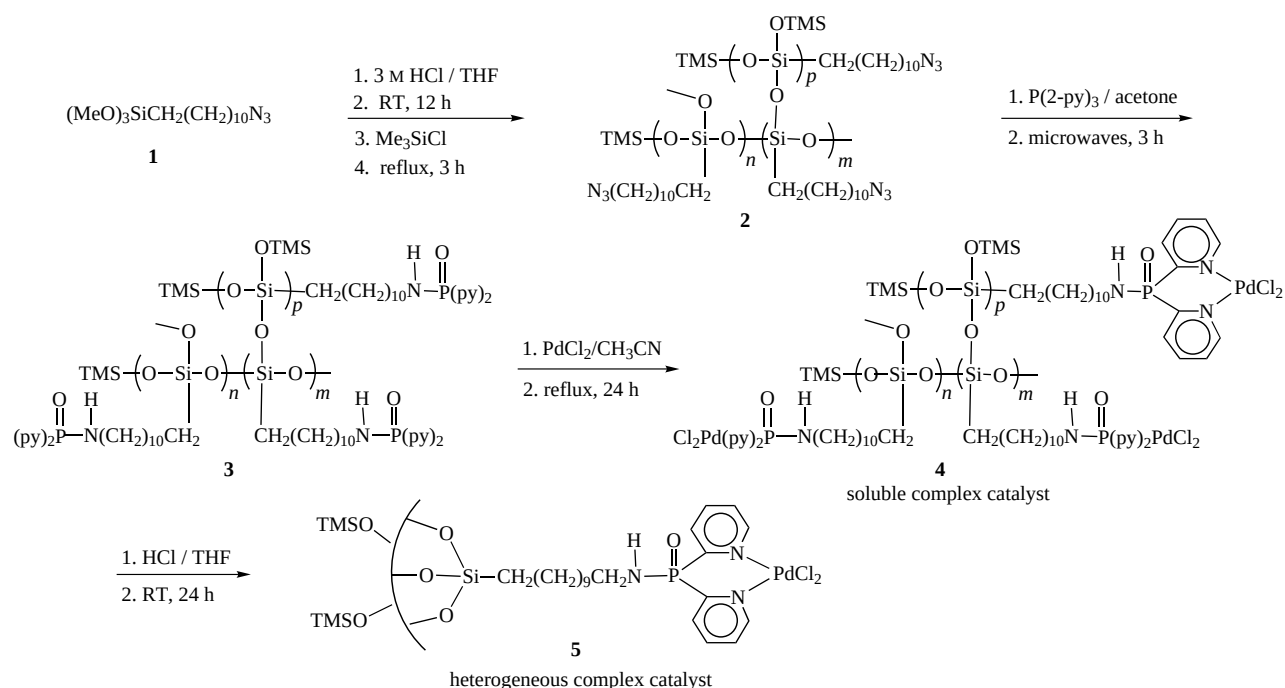
Yaw-Shyan Fu and Shuchun J. Yu*

Immobilization of homogeneous transition metal complex catalysts by tethering them to silica supports has been intensively studied during the past few decades.^[1] These supported homogeneous transition metal complex catalysts should in principle combine the advantages of both heterogeneous and homogeneous systems. However, the problems of significant metal leaching^[2] and low catalyst selectivity^[1b, 3] are major drawbacks that prevent their potential use. Due to the insoluble nature of these supported catalysts, it has been difficult to obtain detailed information about the exact chemical structures of the catalyst systems and to estimate any loss of activity resulting from heterogenization. Therefore, a major development in this field would be the development of a method that would allow silica-supported homogeneous transition metal complexes and their reactions to be investigated by NMR spectroscopy with the resolution typically attained for soluble systems.^[4] Here we describe the preparation and characterization of homogeneous Pd^{II} complex catalysts tethered to a range of polysiloxanes. These materials were designed to mimic the surface of silica gel but with properties that are more readily controlled than those of silica gel. The molecular weight and degree of cross-linking can be systematically varied to provide catalyst systems ranging from soluble, homogeneous model compounds to heterogeneous three-dimensional networks. The structures and reaction chemistry of the soluble system were studied by NMR spectroscopy in solution, while the reactivity and regioselectivity were investigated in the catalytic [2+2+2] cyclotrimerization of alkynes.

The incomplete acid-catalyzed hydrolysis^[5] of (MeO)₃-Si(CH₂)₁₁N₃ (**1**) in THF generated silica fragments small enough to be soluble in conventional organic solvents. Subsequent silylation with trimethylsilyl chloride (TMSCl) was performed to end-cap the remaining Si-bound hydroxy groups to prevent further self-condensation of polysiloxanes (Scheme 1). The resulting polysiloxane **2** can then be readily derivatized with P(2-py)₃ (2-py = 2-pyridyl) in situ or after isolation to afford polysiloxane **3** with NHP(O)(2-py)₂ functionality.^[6] Polysiloxanes **2** and **3** with molecular weights around 5500 and polydispersity indexes of about 1.5 were thus obtained.^[7] As expected, these polymers exhibited excellent

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Scheme 1. Immobilization of homogeneous Pd^{II} complex catalysts on polysiloxanes with controllable solubility.

solubility and gave clear ^1H and ^{29}Si NMR spectra (Figure 1), which allowed us to determine to good accuracy the weight percent of functionalized alkyl side chains and the degree of branching.^[8] Furthermore, the molecular weight and degree of branching can be controlled by varying the acid concentration and reaction time, and the TMS-end-capped polysiloxanes were highly resistant to further self-condensation, even after exposure to moist air for months.

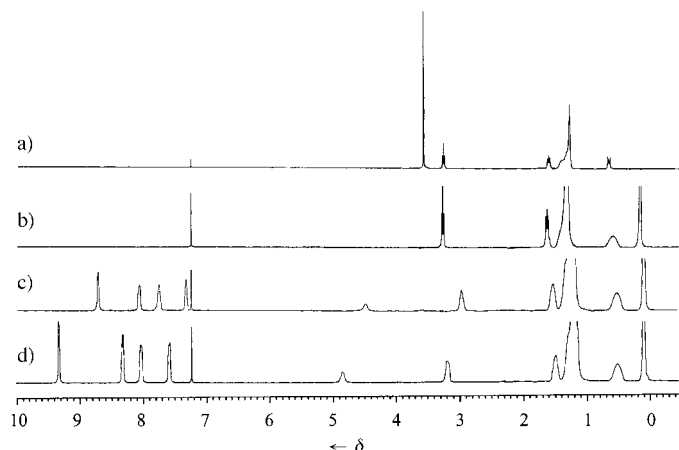


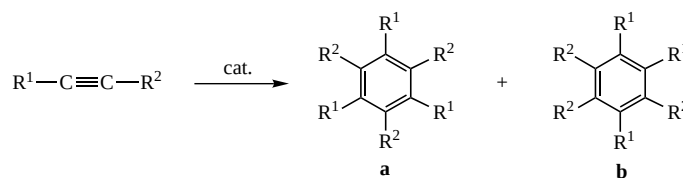
Figure 1. 400 MHz ^1H NMR spectra of a) **1**, b) **2**, c) **3**, and d) **4**.

The commonly used phosphane-based tethering ligands possess excellent properties for binding transition metal complexes onto silica surfaces. However, they are easily transformed into the corresponding phosphane oxides.^[9] This can cause significant metal leaching and has restricted their industrial application. Hence, we designed and synthesized the aza-based ligand $\text{SiCH}_{11}\text{NHP}(\text{O})(2\text{-py})_2$, with bidentate

bis-pyridyl functionality (py-P-py 105.5°),^[10] which could exhibit a large py-M-py bite angle when coordinated to metal centers and has the potential for greater catalyst stability and regioselectivity.^[1b, 11] As anticipated, homogeneous Pd^{II} complexes were covalently immobilized by the ligating bis-pyridyl groups to afford the soluble, polysiloxane-supported Pd^{II} complex **4** (Scheme 1) with small specific surface areas ($\approx 25 \text{ m}^2 \text{ g}^{-1}$ (BET(N_2))). Progressive heterogenization was conducted by further treatment of **4** with HCl to yield the insoluble counterpart **5** with larger specific surface areas ($\approx 190 \text{ m}^2 \text{ g}^{-1}$ (BET(N_2))).

Although various Pd complexes are known to promote alkyne cyclotrimerization,^[12] the problems of low chemo- and regioselectivity greatly hamper the utilization of the reaction. In the present study, both **4** and **5** were found to be excellent catalysts for various alkyne cyclotrimerization reactions (Table 1). With a catalyst loading of 4 mol %, the homogeneous reactions with **4** can be performed under milder conditions to afford polysubstituted benzenes in about 90 % yields of isolated products. Conversely, reactions catalyzed by **5** had to be conducted at higher temperature since the system is heterogeneous.

A series of **4**-catalyzed cyclotrimerization reactions was also carried out in a 400 MHz solution-phase ^1H NMR probe to monitor the course of catalysis. Catalyst **4** was demonstrated to be robustly stable against decomposition and Pd leaching at 27 and 62 °C, and this made it an attractive candidate for heterogenization. In a comparative study, control experiments were performed under similar conditions with $[(\text{PhCN})_2\text{PdCl}_2]$ as catalyst. This resulted in a suspension of $(\text{LPdCl} \cdot \text{PdCl}_2)_n$ ($\text{L} = \text{PhCN}$ or alkyne) and a color change from yellow to dark red.^[13] In contrast, neither color change nor precipitation was observed during the course of **5**-catalyzed reactions under similar conditions. Also, the lack

Table 1. [2+2+2] alkyne cyclotrimerization reactions promoted by three Pd^{II} catalyst systems.

Entry	Alkyne ^[a]		Catalyst ^[b]	T [°C]	t [h] ^[c] (RT/62 °C)	Yield [%] ^[d] (RT/62 °C)	Product ratio ^[f] a:b (RT/62 °C)
	R ¹	R ²					
1	Me	Me	[(PhCN) ₂ PdCl ₂]	RT	24	85	
2	Me	Me	4	RT/62	24/12	88/94	
3	Me	Me	5	62	12	94	
4	Me	<i>n</i> Pr	[(PhCN) ₂ PdCl ₂]	RT	36	78	63:37
5	Me	<i>n</i> Pr	4	RT/62	36/16	83/96	94:6/91:9
6	Me	<i>n</i> Pr	5	62	16	86	90:10
7	Et	Et	[(PhCN) ₂ PdCl ₂]	RT	36	83	
8	Et	Et	4	RT/62	36/16	88/91	
9	Et	Et	5	62	16	94	
10	<i>n</i> Pr	<i>n</i> Pr	[(PhCN) ₂ PdCl ₂]	RT	36	81	
11	<i>n</i> Pr	<i>n</i> Pr	4	RT/62	36/16	90/93 (>99 %, cycles 1–6) ^[e]	
12	<i>n</i> Pr	<i>n</i> Pr	5	62	16	95 (>99 %, cycles 1–6) ^[e]	
13	Ph	H	[(PhCN) ₂ PdCl ₂]	RT	36	85	52:48
14	Ph	H	4	RT/62	36/16	91/94	82:18/81:19
15	Ph	H	5	62	16	92	79:21
16	Ph	Ph	[(PhCN) ₂ PdCl ₂]	RT	36	86	
17	Ph	Ph	4	RT/62	36/16	89/95	
18	Ph	Ph	5	62	16	90	

[a] Alkyne (0.56 mmol) in CHCl₃ (3 mL). [b] Catalyst loading = 4 mol %. [c] Time for >90 % alkyne conversion at room temperature (RT) and 62 °C for catalyses by **4** and **5**. [d] Products were purified and isolated by flash chromatography on SiO₂ with hexane/ethyl acetate (10/1) as eluent. [e] >99 % conversion was determined by NMR spectroscopy for each of the six catalytic cycles (16 h per cycle) at 62 °C. [f] Products were identified by NMR spectroscopy, and isomer ratios were determined by HPLC.

of any Pd species detectable by atomic adsorption spectroscopy in the filtrate of the reaction solution further verified that catalyst **5** was able to resist Pd leaching under catalytic conditions. In the case of asymmetric alkynes such as 2-hexyne and phenylacetylene, both **4** and **5** were more regioselective than [(PhCN)₂PdCl₂], and this was presumably due to the formation of palladacycles. In addition, catalyst-recycling experiments were performed in CHCl₃ at reflux by using **4** and **5** as catalysts for the cyclic cyclotrimerization of 4-octyne to study the relative degree of catalyst deactivation (Table 1, entries 11 and 12). Both **4** and **5** exhibited excellent stability with greater than 99 % 4-octyne conversion through six cycles. Also, the ¹H NMR spectrum in the pyridyl region of the **4**-containing solution from the last cycle showed negligible difference from that of freshly prepared **4**. This suggested that both **4** and **5** have sufficiently long catalyst lifetime to be effectively recycled.

In summary, we have demonstrated that the homogeneous palladium(II) complex catalysts were successfully immobilized on a range of polysiloxane materials with controllable solubility and degree of cross-linking. Catalysts **4** and **5** prepared in this way were found to be very active and regioselective in various alkyne cyclotrimerization reactions. Further studies of regio- and chemoselective coupling are in progress. The current system shows that a given metal catalyst can be studied and characterized progressively as its support was systematically varied from the homogeneous to the heterogeneous phase. Accordingly, these results may provide important insights into the field of heterogeneous catalysis on silica surfaces.

Experimental Section

1: (MeO)₃Si(CH₂)₁₁Br (2.0 g, 5.63 mmol) was added to a solution of NaN₃ (0.493 g, 6.75 mmol) in DMF (20 mL). The mixture was stirred for 6 h. NaBr was filtered off, and the filtrate was extracted with hexane (6 × 10 mL). The extract was dried to give **1**. Yield: 1.60 g (90 %). ¹H NMR (400 MHz, CDCl₃, 27 °C): δ = 0.63 (t, ≡SiCH₂), 1.20–1.40 (brs, ≡SiCH₂(CH₂)₈), 1.58 (m, ≡Si(CH₂)₉CH₂), 3.25 (t, ≡Si(CH₂)₁₀CH₂N₃), 3.55 (s, (OMe)₃Si).

4: PdCl₂ (94 mg, 0.525 mmol) was added to a solution of **3** (200 mg, 0.966 mmol of py) in CH₃CN (15 mL). The mixture was stirred at reflux for 24 h. All volatile substances were removed, and the residue was extracted with CHCl₃ (2 × 10 mL). The extract was dried to give **4** as a yellow solid. Yield: 260 mg (91 % based on py). ¹H NMR (400 MHz, CDCl₃, 27 °C): δ = 0.63 (brs, ≡SiCH₂), 1.20–1.40 (brs, ≡SiCH₂(CH₂)₈), 1.53 (brs, ≡Si(CH₂)₉CH₂), 3.27 (brs, ≡Si(CH₂)₁₀CH₂NH), 4.91 (brs, ≡Si(CH₂)₁₁NHP(O)), 7.64 (brs, py), 8.07 (brs, py), 8.34 (brs, py), 9.35 (brs, py); ³¹P NMR (160 MHz, CDCl₃, 27 °C): δ = 16.1.

5: HCl (3 M, 1 mL) was added to a solution of **4** (100 mg) in THF (20 mL). The solution was stirred for 24 h. The mixture was filtered and dried under vacuum to give **5** as a yellow solid.

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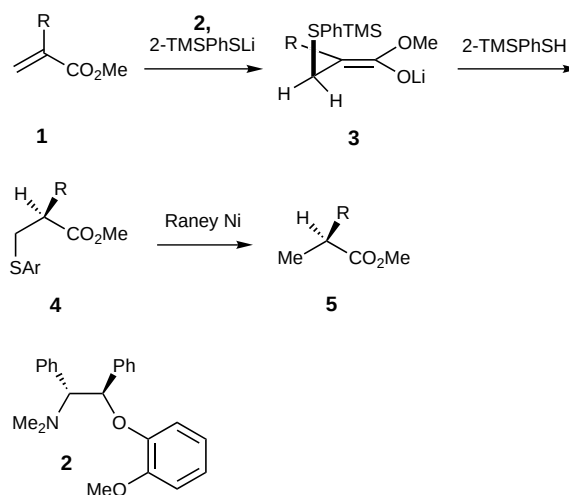
Catalytic Enantioselective Protonation of Lithium Ester Enolates Generated by Conjugate Addition of Arylthiolate to Enoates**

Katsumi Nishimura, Masashi Ono, Yasuo Nagaoka, and Kiyoshi Tomioka*

Enantioselective protonation of prochiral enolates represents a most useful advance in recent synthetic chemistry.^[1, 2] In particular, catalytic enantioselective protonation has been a challenging target.^[3] Generally, such reactions rely on a

combination of an excess achiral proton source and a substoichiometric chiral proton source such as imides,^[4] phenols,^[5] alcohols,^[6] amino alcohols,^[7] and amines.^[8] Prochiral substrates are often metal enolates, generated by the reaction of silyl enol ethers or enol acetates with an excess of an organometallic species. In spite of the recent impressive progress in this field, there have been few approaches that use a catalytic amount of a metal cation for the generation of metal enolates.^[9]

We present here the chiral ligand catalyzed enantioselective protonation of a transient lithium ester enolate **3**—generated by a conjugate addition of lithium arylthiolate to propenoates **1** in the presence of the chiral amino diether **2**—to give the 3-arylsulfanyl 2-substituted propanoates **4** with high *ee* values (Scheme 1).^[10] Reductive desulfurization of **4**, bearing a chiral



Scheme 1. Catalytic asymmetric addition–protonation and desulfurization. TMS = trimethylsilyl.

center at the C2 position, with Raney nickel completes the catalytic enantioselective protonation to afford the corresponding chiral propanoates **5** in high yield without racemization. The two-step procedure is characterized by an asymmetric protonation of a lithium enolate generated by a catalytic amount of a lithium cation.

The strategy for the catalytic asymmetric protonation is based on our previously developed asymmetric addition of 2-trimethylsilylbenzenethiol (2-TMSPhSH) to enoates, which is controlled by a chiral ligand.^[11] The addition of a thiolate to an enoate and protonation of the resulting enolate by a thiol are highly stereoselective procedures and provide the *anti*-protonation product.^[12] Furthermore, the attack of the thiolate on the 2-enoate is the rate-determining step of the addition–protonation reaction,^[13] and hence protonation of the resulting enolate by thiol is rapid. Consequently, if the protonation of enolate **3** takes place before this species undergoes a conformational change, it probably proceeds in an *anti* manner to the C–S bond to afford **4** with high *ee* values.

The asymmetric addition–protonation is exemplified by the reaction of methyl 2-phenylpropenoate (**1c**, R = Ph) with 1.2 equivalents of 2-trimethylsilylbenzenethiol. The reaction

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was catalyzed by a combination of lithium 2-trimethylsilylbenzenethiolate (1 mol %) and (1*R*,2*R*)-1-dimethylamino-2-(2-methoxyphenoxy)-1,2-diphenylethane (**2**, 1.2 mol %)^[14] in toluene/hexane (1/1) at -78°C for 0.5 h to give methyl 3-(2-trimethylsilylphenylsulfanyl)-2-phenylpropanoate (**4c**, Ar = 2-TMSPh, R = Ph), bearing a chiral center at C2, in quantitative yield (Scheme 1). The enantioselectivity was determined to be 92 % by chiral stationary phase HPLC (Daicel Chiralcel AS) of the protodesilylated phenylsulfanyl ester (Ar = R = Ph), which was obtained quantitatively by treatment of **4c** with trifluoromethanesulfonic acid in toluene at room temperature for 10 min.^[15] The absolute configuration of **4c** was determined to be *S* by measurement of the specific rotation of desulfurized methyl 2-phenylpropanoate (**5c**, R = Ph).^[16] Desulfurization of **4c** with Raney nickel W-4 in THF/methanol in the presence of acetate buffer at room temperature for 0.5 h gave **5c** in 97 % yield without racemization. The other propenates **1a**, **b**, **d–f** having methyl, benzyl, 1-naphthyl, 2-naphthyl, and 6-methoxy-2-naphthyl groups at C2 were successfully converted into the corresponding chiral propenates **4a**, **b**, **d–f** with good to high *ee* values (Table 1). The absolute configuration of **4a** was determined by protodesilylation and subsequent LiAlH_4 reduction to the *S* alcohol.^[17] For the other products the absolute configurations were determined by measurement of the specific rotations of **5b**,^[18] **5d**,^[19] **5e**,^[19] and **5f**.^[20]

Table 1. Asymmetric addition–protonation of methyl 2-substituted propenates **1** and subsequent desulfurization of **4** to provide **5** (Scheme 1).

Entry	Propenoate	<i>T</i> [$^{\circ}\text{C}$]	<i>t</i> [h]	4 ^[a]		5 ^[b]	
				yield [%]	<i>ee</i> [%]	yield [%]	<i>ee</i> [%]
1	1a (R = Me)	-60	16	99	75 ^[c]		
2	1b (R = PhCH ₂)	-60	16	99	60 ^[c]	94	59
3	1c (R = Ph)	-78	0.5	99	92	97	92
4	1d (R = 1-naphthyl)	-78	0.5	99	88	95	87
5	1e (R = 2-naphthyl)	-78	0.5	93	91	96	90
6	1f (R = 6-MeO-2-naphthyl)	-78	0.5	99	90 ^[c]	99	99 ^[d]

[a] The reaction was carried out with 2-TMSPhSH (1.2 equiv), 2-TMSPhSLi (1 mol %), **2** (1.2 mol %), and **1** (1 mmol) in toluene/hexane (3 mL, 1/1) unless otherwise noted. The *ee* values of **4a**, **b**, **d–f** were determined by chiral stationary phase HPLC using Daicel Chiralcel AD. [b] The absolute configuration and the *ee* values were determined from the specific rotation of **5**. [c] The reaction was carried out using 2-TMSPhSLi (8 mol %) and **2** (10 mol %). [d] Enantiomerically enriched **4f** (Ar = Ph), obtained by protodesilylation and recrystallization in 82 % yield and with 99 % *ee*, was desulfurized to **5f**.

The synthesis of a pharmaceutical agent demonstrates the utility of the present asymmetric protonation reaction. Compound **5f**, an intermediate on the way to the antiinflammatory agent naproxen, was successfully synthesized in 80 % overall yield and with 99 % *ee* from **1f** through enantioenrichment by recrystallization of **4f** (Ar = Ph, 91 % *ee*), which was obtained quantitatively by protodesilylation (Table 1, entry 6).

The reactions of **1c–f** bearing aryl substituents at C2 proceeded to completion within 0.5 h at -78°C , while those of **1a** and **1b** bearing alkyl groups required higher temperatures and longer reaction times. The aryl substituents proved

to be more advantageous than alkyl substituents in terms of enantioselectivity as well.

The sense of the asymmetric protonation was the same in all reactions examined, regardless of whether an α -alkyl or aryl substituent was present. The absolute configurations are those expected based on enantiofacial differentiating attack of arylthiolate with **1** to give **3**, controlled by the chiral ligand **2**, and subsequent *anti* protonation.

The asymmetric protonation was highly dependent on the substituent of the benzenethiol. In the presence of 8 mol % of lithium benzenethiolate and 10 mol % of **2** in toluene, the reaction of three equivalents of benzenethiol with **1a** (R = Me) at -60°C was quite sluggish. In contrast, at -20°C the reaction was completed within 3 h to give the corresponding product (*S*)-**4a** (Ar = Ph) with 37 % *ee* and in 94 % yield.

The amount of 2-TMS-benzenethiol had little effect on the selectivity. The reaction of **1c** (R = Ph) with 1.2, 3, and 9 equivalents of the thiol in the presence of 2-TMSPhSLi (8 mol %) and **2** (10 mol %) at -78°C for 0.5 h afforded **4c** in quantitative yield and with 92–93 % *ee*. The dose-independent effects on both enantioselectivity and reactivity imply that the present enantioselective protonation is quite fast, probably due to rapid electrophilic trapping of the transient lithium enolate **3**.^[21]

The characteristic features of the present asymmetric protonation are the use of a catalytic amount of a lithium cation as well as a chiral ligand, and the absence of any chiral proton source. The chiral ligand **2** can be recovered quantitatively for reuse.

Experimental Section

Typical procedure (Table 1, entry 3): To a solution of 2-trimethylsilylbenzenethiol (2.18 g, 12 mmol) in toluene/hexane (1/1, 26 mL) was added BuLi (0.063 mL, 0.1 mmol, hexane) followed by a solution of **2** (42 mg, 0.12 mmol) in toluene/hexane (1/1, 1 mL) at 0°C . After the mixture had been stirred for 0.5 h at room temperature, a solution of **1c** (R = Ph, 1.62 g, 10 mmol) in toluene/hexane (1/1, 3 mL) was added at -78°C . The mixture was stirred for 0.5 h at -78°C , and quenched with water. The aqueous layer was extracted with toluene. The combined organic layers were washed with 10 % aq KOH and brine, and then dried over Na_2SO_4 . Concentration followed by column chromatography on silica gel (benzene, then benzene/acetone (2/1)) gave (*S*)-**4c** (Ar = 2-TMSPh, R = Ph; 3.44 g, 99 %) as colorless cubes and recovered **2** (42 mg, 99 %).

(*S*)-**4c**: M.p. $82–83^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{25} = +49.2$ (*c* = 1.17, CHCl_3); ^1H NMR (CDCl_3 , 270 MHz): δ = 0.32 (s, 9H), 3.24 (dd, *J* = 5.3, 13.2 Hz, 1H), 3.62 (dd, *J* = 9.9, 13.2 Hz, 1H), 3.68 (s, 3H), 3.87 (dd, *J* = 5.3, 9.9 Hz, 1H), 7.16–7.41 (m, 8H), 7.45 (dd, *J* = 1.7, 7.2 Hz, 1H); ^{13}C NMR (CDCl_3 , 67.8 MHz): δ = -0.05 , 38.2, 51.2, 52.1, 125.8, 127.6, 127.8, 128.8, 129.7, 135.0, 137.7, 142.0, 172.8; IR (nujol): $\tilde{\nu}$ = 1735 cm^{-1} ; MS: *m/z*: 344 [*M*⁺]; elemental analysis calcd for $\text{C}_{19}\text{H}_{24}\text{O}_2\text{SSi}$: C 66.23, H 7.02; found: C 66.16, H 7.09.

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Synthesis of Nanophase Iron Oxide in Lumazine Synthase Capsids**

Wayne Shenton, Stephen Mann,* Helmut Cölfen, Adelbert Bacher,* and Markus Fischer

The ability to control the crystallization of inorganic materials at the nanometer length scale has prompted the use of self-assembled “nanoreactors” such as surfactant^[1] and block copolymer^[2] micelles, liquid crystalline mesophases,^[3] and porous two-dimensional protein crystals.^[4] In general, these systems consist of spatially confined environments that are topologically distinct and comprise nucleation sites which direct the growth of the inorganic phase. A biological archetype of this strategy is the protein ferritin, in which iron oxide nanoparticles are synthesized within an 8-nm-diameter hollow polypeptide cage.^[5] It has previously been shown that this bio-nanoreactor can be used to produce a number of dispersed protein–inorganic nanocomposites^[6–8] that have potential applications in medical imaging^[9] and neutron capture therapy.^[10] The utilization of other biomolecular systems analogous to ferritin could have important implications for the development of a general class of self-assembled bioinorganic materials with designed functionality and biocompatibility. For example, viral capsids have been recently used to synthesize inorganic-based nanoparticles.^[11] Herein we describe a new type of bio-nanoreactor based on the enzyme lumazine synthase which can be utilized for the biomimetic synthesis of iron oxide nanoparticles, even though there is no evidence for such a function in vivo.

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Lumazine synthase is a hollow 1 MDa bacterial enzyme complex of 60 subunits that is involved in the synthesis of lumazine, a precursor to riboflavin. The structure of lumazine synthase from *Bacillus subtilis* has recently been elucidated and the X-ray structure analysis confirms it has a hollow porous shell with icosahedral ($T=1$) morphology and inner and outer diameters of 7.8 nm and 14.7 nm, respectively (Figure 1).^[12] The intersubunit contacts of the capsid consist of

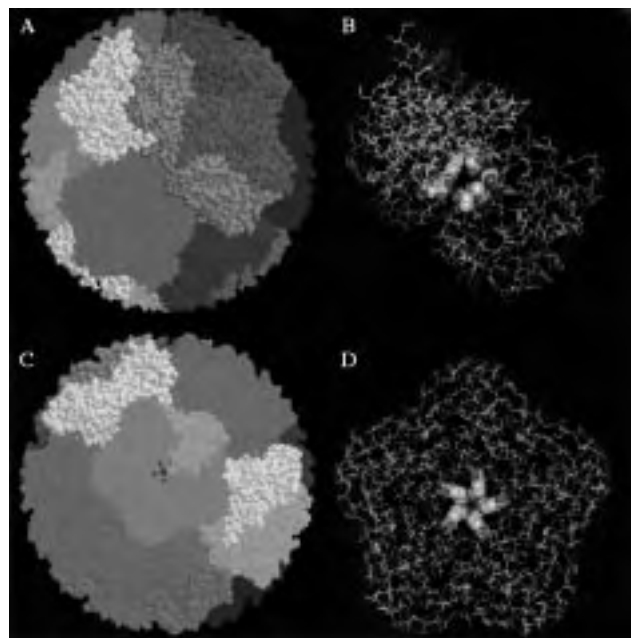


Figure 1. Computer-generated images of lumazine synthase. A) View down the threefold channel of the enzyme. B) View highlighting the glutamic acids lining the threefold channel. C) View down the fivefold channel. D) View highlighting the lysine residues lining the fivefold channel.

dimers, trimers, and pentamers. The trimer contacts are formed by several segments at the inner capsid wall (residues 21–29, 81–85, 120–143) that produce a contact region consisting of a cluster of three glutamic acid residues.^[13] As there are no compensating ligands, a large negative charge density exists on the inner wall of the capsid. Interestingly, similar domains of negative charge are present in ferritin and may act as nucleation sites for iron oxide deposition.^[5] The interior of the lumazine synthase capsid is accessed through hydrophilic funnel-shaped channels lined with glutamic acid residues, and located at the ten threefold axes. Channels are also formed along the six fivefold pentamer axes,^[12] and consist of symmetrically arranged α -helices, reminiscent of membrane channel proteins. The inner surface of these pores is dominated by polar residues, which have been implicated in substrate import and product export from the catalytic centers of the enzyme.^[14] The compact nature of the capsid structure implies the channels have a significant role in substrate exchange.^[15]

Previous work^[13] has shown that the lumazine synthase capsid possesses 60 substrate binding sites at the pentamer interfaces. These binding sites are located on the inner wall and consequently the stability of the capsid is dependent upon

the presence of the substrate (5-nitro-6-ribitylamino-2,4(1*H*,3*H*)-pyrimidinedione) or substrate analogues. The 15-nm-diameter capsid is highly stable at pH 7 in the presence of phosphate buffer and substrate analogues (Figure 2A). In the absence of these ligands, however, the structure can dynamically rearrange into larger forms, notably a $T=3$ icosahedron containing 240 subunits, but depends on the buffer composition and pH.^[16]

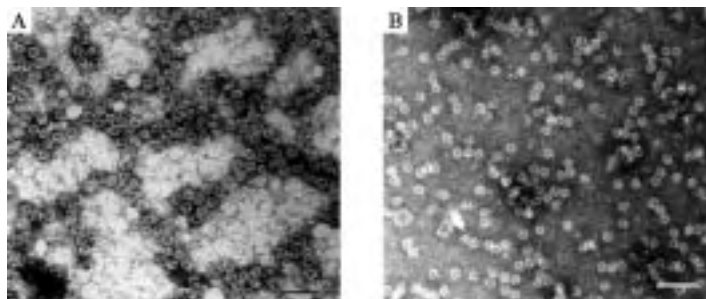


Figure 2. TEM images of negatively stained lumazine synthase showing hollow spherical 15-nm-diameter capsids infiltrated with uranyl acetate: A) in phosphate buffer, scale bar 50 nm, and B) 24 h after addition to MES buffer at pH 6.5 showing the presence of a few larger capsids with diameters of 30 nm (arrow). Scale bar 50 nm.

To investigate the potential of lumazine synthase as a nanoreactor for iron oxide mineralization we prepared protein solutions in 4-morpholine-ethanesulfonic acid (MES) buffer at pH=6.5 in the absence of substrate molecules. Transmission electron microscopy (TEM) images of samples stained with uranyl acetate indicated that the 15-nm-diameter capsids were stable under these conditions, although some larger structures (about 5 % of the population) with external and internal diameters of about 30 and 20 nm, respectively were occasionally observed (Figure 2B). The synthesis of iron oxide in these solutions was undertaken by adding aliquots of a 1 mM de-aerated solution of aqueous Fe^{II} ions stepwise in air to a de-aerated enzyme solution (0.1 mg mL^{-1} , MES buffer, pH 6.5). Typically, aliquots of approximately 1.7 Fe^{II} ions per subunit (100 Fe^{II} ions per capsid) were added every 15 minutes to give final theoretical loadings of 5, 17, 25, and 33 Fe ions per subunit (300, 1000, 1500, and 2000 Fe atoms per 15-nm diameter capsid). Control experiments with identical concentrations of Fe^{II} ions but without the enzyme were also undertaken. Significantly, whereas the control solutions turned red-brown and produced a bulk precipitate as a result of slow aerial oxidative hydrolysis and condensation of Fe^{II} ions to Fe^{III} oxide, the protein solutions remained transparent and free from sediment. The corresponding UV/Vis spectra (Figure 3) recorded 24–48 h after the addition of the final aliquot of Fe^{II} ions showed a single broad absorption band extending to 550 nm for the control solutions, but a distinct absorption edge at 400 nm as well as an absorption at 270 nm corresponding to an aromatic amino acid side chain for the lumazine synthase solutions. The red-brown colour of the control samples is characteristic of extended arrays of polynuclear oxo- and hydroxo-bridged Fe^{III} centers such as is observed for the fully formed ferrihydrite cores of ferritin. In contrast, the strong

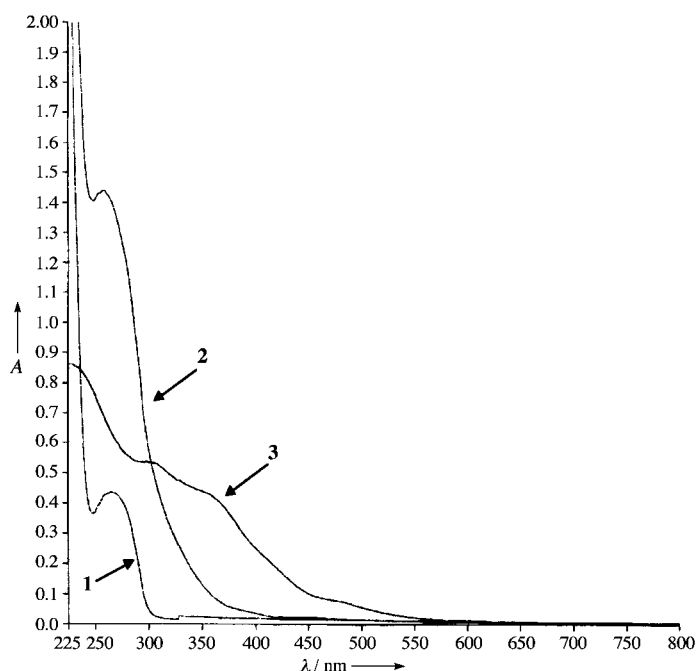


Figure 3. UV/Vis spectra of lumazine synthase: 1) in MES buffer prior to the addition of Fe^{II} ions showing an absorbance at 270 nm from the aromatic side chains; 2) 24 h after the addition of a total of 5 Fe atoms per subunit (300 Fe atoms per capsid); and 3) control sample, which corresponds to the experimental conditions of (2), but without protein.

absorption in the UV region observed for the iron-containing lumazine synthase solutions is indicative of relatively low molecular weight Fe^{III} -containing clusters with incomplete bridging ligands which are possibly associated with protein side chains.^[17]

TEM images and corresponding energy dispersive X-ray (EDX) analysis of unstained samples of Fe-loaded lumazine synthase solutions showed the presence of iron-containing electron-dense nanoparticles. At a loading of five Fe atoms per subunit the particles were diffuse, low in contrast, and heterogeneous in shape and size (Figure 4A). Most particles were less than 30 nm in dimension. Selected area electron diffraction (SAED) patterns showed weak and broad concentric rings with d spacings of 0.32, 0.19, and 0.17 nm corresponding to the (021), (002), and (151) reflections of the iron(III) oxide mineral lepidocrocite ($\gamma\text{-FeOOH}$). Similar results were obtained at a higher loading of 17 Fe atoms per subunit except that the $\gamma\text{-FeOOH}$ nanoparticles were more electron dense and crystalline (d spacings, 0.32, 0.19, 0.17, and 0.152 nm; Figure 4C). The particles were between 10 and 15 nm in size (mean = 13.4 nm, σ = 2.0 nm). In contrast, no nanoparticles were observed in samples prepared in the absence of lumazine synthase. Instead, the TEM analysis showed micrometre-sized plate-shaped particles of lepidocrocite (data not shown).

The presence of lumazine synthase capsids in the Fe-loaded samples was confirmed by staining the air-dried samples with uranyl acetate (Figures 4B, D). Particle size measurements on samples prepared with a loading of 17 Fe atoms per subunit showed a broad distribution of capsid diameters centred around values of 15 and 30 nm, which corresponds to about 30 and 70 % of the population, respectively. The results suggest

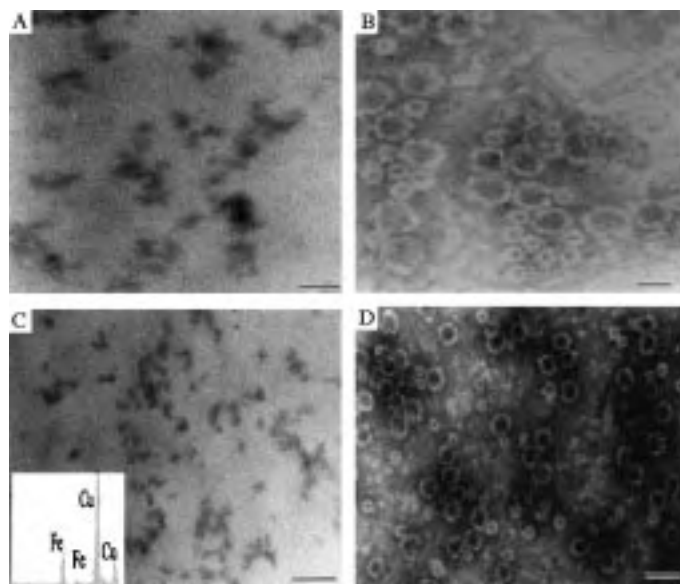


Figure 4. TEM images of iron oxide mineralized lumazine synthase samples, approximately 48 h after the addition of the final aliquot of Fe^{II} ions to the protein solutions. A) and C) Unstained samples prepared with a loading of 5 and 17 Fe atoms, respectively, per subunit showing the presence of iron oxide nanoparticles; scale bars = 30 nm and 50 nm, respectively. The inset in C) shows the corresponding EDX, which confirms the presence of Fe ions (the Cu comes from the TEM grid). B) and D) Negatively stained images of the samples shown in A) and C), respectively, showing the presence of a mixed population of capsids with diameters centred around 30 and 15 nm; scale bars = 30 and 50 nm, respectively.

that the 15-nm-diameter native form of the lumazine synthase capsids is to some extent destabilized in the presence of Fe^{III} ions and replaced by intact capsids with larger diameters. The latter have diameters around 30 nm, which is comparable to those previously measured for a $T=3$ icosahedral form of lumazine synthase.^[16]

Analytical ultracentrifugation (AUC) analysis of a solution of lumazine synthase in MES buffer showed a single species with a well-defined sedimentation coefficient ($s_{20,w}$) of 23.0 S (Figure 5), which was slightly lower than the published value

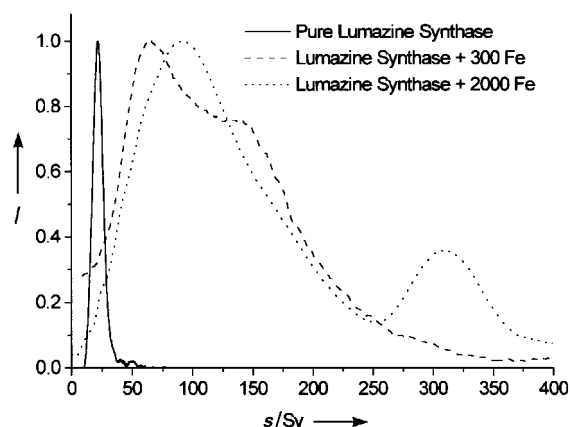


Figure 5. Apparent sedimentation coefficient distributions for lumazine synthase solutions prepared with a loading of 5 Fe or 33 Fe atoms per subunit (300 or 2000 Fe atoms per capsid, respectively) at 25 °C in MES buffer. The samples were analyzed several days after the addition of the final aliquot of Fe^{II} ions to the protein solution. I = Intensity.

of 26 S,^[17] probably because of the concentration dependence of sedimentation. Only a very small peak was observed at $s_{20,w} = 48$ S, which confirmed that the 15-nm capsid was stable in MES buffer. In contrast, the Fe-loaded lumazine synthase solutions showed the presence of a broadened spread of sedimentation coefficients at significantly higher S values, which suggests that there were significant heterogeneities in the extent of iron loading or structure of the higher aggregates, or both (Figure 5). At a loading of five Fe atoms per subunit the sedimentation coefficient distribution showed no distinct peak corresponding to the native 15-nm capsid; instead, a broad distribution with a major peak at $s_{20,w} = 67$ S and a shoulder at 138 S were observed (Figure 5). The former is close to the 70 S species previously observed for lumazine synthase under conditions of capsid reorganization,^[18] which suggests that this component corresponds to higher order capsids that are iron-free or associated with only low levels of iron oxide. The shoulder at 138 S, on the other hand, probably represents a wide distribution of the same structures with significant iron oxide cores. Similar broad density distributions were observed for higher iron loadings with a concomitant shift in the S value for the peak maxima (Figure 5).

The results indicate that the bulk precipitation of Fe^{III} oxide is strongly inhibited in the presence of lumazine synthase because the mineral phase is specifically encapsulated within the internal cavity of the capsid. Interactions between the enzyme and iron appear to destabilize the native capsid, which then transforms into a higher order structure in association with discrete nanoparticles of iron oxide. The nature of this rearrangement remains unclear, but previous results^[18] have suggested that the formation of 30-nm diameter capsids involves the assembly of 240 subunits. In general, iron atoms could permeate the porous shell of the capsids by diffusion through the threefold channel lined with glutamic acid residues. Ion binding at the anionic domains on the inner wall would then increase the rate of nucleation specifically within the internal cavity by lowering the interfacial energy of the critical nucleus formed from oxidative hydrolysis. Growth of the nucleus is likely to be autocatalytic because the iron oxide phase promotes further oxidation of Fe^{II} ions directly on the surface of the developing nanoparticle. This explains the "all or nothing" distribution of nanoparticles in which a subset of molecules contain a high iron loading whilst other capsids remain effectively empty.

In conclusion, this work has shown for the first time that lumazine synthase, a hollow enzyme found in bacteria and fungi, can serve as a mineralization template in the fabrication of nanocrystalline iron oxide. The presence of positive and negatively charged channels in the capsid shell suggests that it might be possible to simultaneously sequester both cationic and anionic reactants for the synthesis of other types of inorganic nanoparticles besides iron oxides for potential uses in electronic, optical, or magnetic devices.

Experimental Section

Droplets (5 μ L) of lumazine synthase solutions (10 and 0.1 mg mL⁻¹) in phosphate (pH 7) or MES (Aldrich) buffer adjusted to pH 6.5 by addition of 0.1M NaOH were blotted dry onto formvar-covered carbon-coated copper TEM grids and imaged in a JEOL 2000FX analytical TEM. Some

grids were stained with a 2% aqueous uranyl acetate solution for 1 min and washed several times with distilled water. Similar methods were used with concentrated iron-containing lumazine synthase solutions prepared in a centrifugal filtration device (10 kDa cut off, Millipore Ltd).

The iron oxide mineralization protocol was as follows: A 1 mM solution of (NH₄)₂SO₄·FeSO₄·6H₂O was prepared and de-aerated under N₂ for 30 min prior to the start of the mineralization experiment. The aqueous stock solution of Fe^{II} ions was kept under N₂ for the duration of the experiment. A 0.1 mg mL⁻¹ solution of lumazine synthase in MES was de-aerated for 15 mins under N₂, after which the gas was removed and aliquots of the Fe^{II} solution added with slow stirring. Phosphate buffers were not used since they strongly complex aqueous Fe^{II} ions. Typically, aliquots of 100 Fe^{II} ions per native capsid were added in air every 15 min with a microsyringe to give final theoretical loadings of 5, 17, 25, and 33 Fe atoms per subunit (300, 1000, 1500, and 2000 Fe atoms per capsid). The addition of each volume of Fe^{II} ions was undertaken slowly over a period of 10 s to ensure slow aerial oxidation. After the final addition, the protein solutions were stirred at room temperature for 24 h. Typically, samples were analysed by TEM approximately 48 h after the addition of the final aliquot of Fe^{II} ions to the protein solutions. Control experiments with identical concentrations of Fe^{II} ions but without the enzyme were undertaken.

UV/Vis spectra were recorded using a Perkin Elmer UV/Vis spectrophotometer and spectra displayed using the Lambda 11 software package. Samples were analyzed at regular intervals (every 2 h) by transfer of 3-mL aliquots from the reaction vessel to quartz cuvettes. Samples were returned to their respective reaction vessels before further aliquots of Fe^{II} ions were added. Spectra were also recorded 24–48 h after the addition of the final aliquot of Fe^{II} ions to the protein solution.

Samples were analyzed by analytical ultracentrifugation several days after the addition of the final aliquot of Fe^{II} ions to the protein solution using a Beckman Optima XL-I (Beckman-Coulter, Palo Alto, CA) with UV/Vis absorption optics at 280 nm. The solutions were investigated in 12-mm self-made double-sector titanium centrepieces at 25 °C and 20000 RPM (pure protein, and protein + 5 Fe atoms per subunit) and 10000 RPM (protein + 33 Fe atoms per subunit). Apparent sedimentation coefficient distributions were recorded using the time derivative method.^[19] The sedimentation coefficients were not corrected to infinite dilution.

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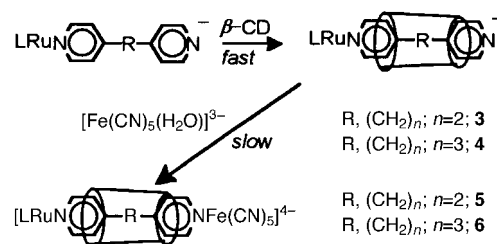
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β -Cyclodextrin-Assisted Intervalence Charge Transfer in Mixed-Valent [2]Rotaxane Complexes Having Metal Centers Linked by an Interrupted π -Electron System**

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The study of intramolecular electron transfer in redox active dinuclear transition metal complexes, where redox active metal centers are linked by a hydrocarbon bridge is of fundamental importance and an area of contemporary research.^[1] Though there are many reports on the role of the bridging ligand (BL) in tuning metal–metal interactions in di/polynuclear metal complexes,^[2] to date very little is known about the role of the BL when it is trapped in hydrophobic cyclodextrin (CD) cavity.^[3] Spectroscopic and kinetic studies on supramolecular self assembly of [2]rotaxanes with symmetric/asymmetric threads, that is, hydrocarbon chains with identical bulky metal units as stoppers or cationic species as electric traps have been reported.^[4] These studies exploit the phenomenon of non-covalent bonding interaction between α - or β -CD and hydrocarbon spacers. However, no such supramolecular assembly using metal units in different oxidation states as stoppers has been reported. This approach can enable us to investigate the effect that inclusion of BLs in the CD cavity has and thus the effect of nonbonding interactions on intervalence charge transfer (IVCT) and metal–metal interactions. We report herein the syntheses of [2]rotaxane complexes having transition metal units with different oxidation states as stoppers, β -CD as a cyclic molecular head, and 4,4-bipyridyl derivatives as the BL. Also, the effect of the inclusion of the BL in the hydrophobic CD cavity is discussed.

The complexes $[\text{RuL}(\text{H}_2\text{O})]$ (L is Hedta^{3-} ; H_4edta is ethylenediaminetetraacetic acid) and $\text{Na}_3[\text{Fe}(\text{CN})_5(\text{H}_2\text{O})]$ produced by the rapid aquation of $\text{K}[\text{RuCl}]\cdot 2\text{H}_2\text{O}$ and $\text{Na}_3[\text{Fe}(\text{CN})_5(\text{NH}_3)]\cdot 3\text{H}_2\text{O}$, respectively, react with N-donor heterocycles through a facile aqua-substitution pathway on the stopped-flow time scale to form the corresponding metal complex in near quantitative yield.^[4–6] We have taken advantage of the aqua-substitution reaction of these two complexes, along with the great tendency of β -CD to bind 1,2-bis(4-pyridyl)ethane (bpe) and 1,3-bis(4-pyridyl)propane (bpp),^[6] to synthesize [2]rotaxane complexes, **5** and **6**, respectively by treating the semirotaxane complexes **3** and **4** with $[\text{Fe}(\text{CN})_5(\text{H}_2\text{O})]^{3-}$ (Scheme 1). In the UV/Vis spectra



Scheme 1.

complexes **5** and **6** show a characteristic broad absorbance at ≈ 1000 nm both in aqueous solution and the solid state, this absorbance is not seen for the complexes **1–4**. Proposed formulations for the isolated inclusion complexes **3–6** match nicely with the analytical data.^[7] The formation in solution of semirotaxane complexes of bpe and bpp with β -CD, **3**, and **4**, can also be demonstrated in the ^1H NMR spectra by inspection of the complexation-induced shift of the resonance signals for the guest molecule (Figure 1). The [2]rotaxane

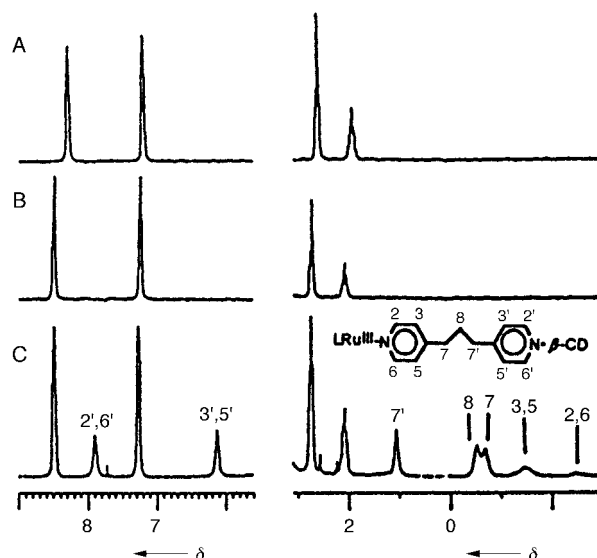
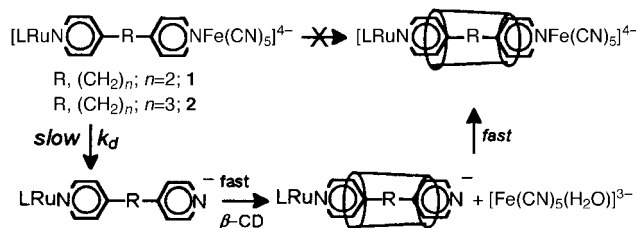


Figure 1. ^1H NMR spectra (200 MHz) of A) bpp in D_2O ; B) $(\text{bpp} \cdot \beta\text{-CD})$ and excess $\beta\text{-CD}$ in D_2O ; C) $(\text{LRubpp} \cdot \beta\text{-CD}, \text{bpp} \cdot \beta\text{-CD})$ and excess $\beta\text{-CD}$ in D_2O . $[\text{bpp}] = 2.0 \times 10^{-3} \text{ M}$, $[\beta\text{-CD}] = 1.6 \times 10^{-2} \text{ M}$, and $[\text{RuL}(\text{H}_2\text{O})] = 6.66 \times 10^{-4} \text{ M}$. Spectral features arising from $\beta\text{-CD}$ protons are excluded for clarity. The pH of the resulting mixture was maintained at ≈ 5.0 using Na_2HPO_4 .

species **5** and **6** also form in solution by self-assembly through the reverse aquation reaction of the pre-synthesized dinuclear complexes **1** and **2** (Scheme 2), respectively, in the presence of excess β -CD (Figure 2). On addition of excess DMSO^[8] to aqueous solutions of complexes **5** and **6** a decrease in the



Scheme 2.

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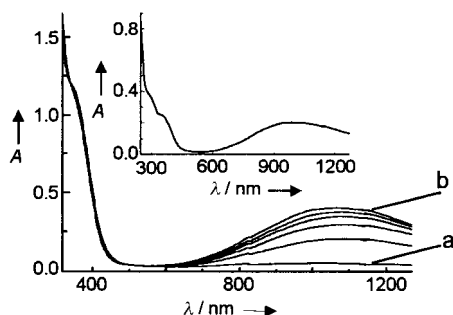
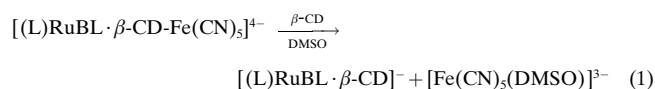


Figure 2. UV/Vis/NIR absorption spectra of aqueous solutions of: [(edta)Ru(bpp)] (1 mL; 3.5×10^{-3} M), $[\text{Fe}(\text{CN})_5(\text{H}_2\text{O})]^{3-}$ (0.1 mL; 3.5×10^{-4} M, $\mu = 0.1$ M (KCl)) which were kept in dark of 15 min after mixing at pH 5.0. To this solution β -CD (1.2 mL; 1.6×10^{-2} M) was added and electronic spectra were recorded at different time intervals, keeping reaction temperature at 35°C . The time interval between the initial (a) and final (b) spectra was 90 min; inset: absorption spectra of isolated complex **6** (1.5×10^{-4} M) in water.

absorbance at ≈ 1000 nm was registered with time. DMSO reacts with the $[\text{Fe}(\text{CN})_5(\text{H}_2\text{O})]^{3-}$ species, produced by dissociation of complex **5** or **6**, to form an inert complex $[\text{Fe}(\text{CN})_5(\text{DMSO})]^{3-}$ and thereby prevents further dinuclear complex formation [Eq. (1)]. This result also confirms that the synthesis of [2]rotaxane complexes, **5** and **6** is through a self-assembly route. Further, almost identical spectral features are observed for the complexes **5** and **6** in both the solid state and in freshly prepared aqueous solutions, which suggests that these complexes remain unchanged in solution.



The UV/Vis/NIR spectra of aqueous solutions of complexes **5** and **6** show a broad absorption band centered around 1000 nm in addition to the bands expected for LMCT (ligand to metal charge transfer) transitions (310 nm) for the (edta)-Ru-py chromophore (py = pyridine) and the MLCT (metal to ligand charge transfer) band (360 nm) for the $(\text{CN})_5\text{Fe}^{\text{II}}$ -py chromophore.^[7] The band at 1000 nm disappears when the Ru^{III} center of complex **5** or **6** is reduced by bulk electrolysis (at -0.3 V, vs. SCE). This observation indicates that the band around 1000 nm arises from an optical electron transfer from Fe^{II} to Ru^{III} .^[5,9] No such IVCT band is either expected or observed for complex **1** or **2**, where the Fe^{II} and Ru^{III} centers are separated by the interrupted π -electron system of the BL.^[9,10] The inclusion into the CD cavity also prevents folding of the bpe or bpp units as well as a closed conformation for **5** and **6**, as was proposed for $[(\text{CN})_5\text{Fe}(\text{bpe})\text{Co}(\text{NH}_3)_5]^{11}$. This excludes any probability of electron transfer “through space” because in the absence of folding the two metal centers cannot come closer than 11 Å which is too large a distance for direct electron transfer through space. Moreover, cyclodextrin is made of carbohydrates and is not expected to mediate electron transfer.

Upon inclusion of the coordinated N-heterocyclic ligand into the β -CD cavity the MLCT band ($d_{\text{Fe}} \rightarrow \pi_{\text{py}}^*$; 380 nm for complex **5** and 378 nm for complex **6**) for the $(\text{CN})_5\text{Fe}$ -py center shows a red shift of about 22 nm—indicating a lowering

of the LUMO energy of the BL as a result of inclusion—while a small blue shift (≈ 10 nm) is observed for the LMCT band ($d_{\text{Ru}} \leftarrow \pi_{\text{py}}$) at 300 nm for the (edta)Ru-py center. Careful analysis of the results of cyclic and differential pulse voltammetric experiments for **5** and **6** show that the $E_{1/2}$ for the $\text{Fe}^{\text{II/III}}$ couple in both complexes has shifted to the anodic side (< 20 mV) on the inclusion of the BL into the β -CD cavity, while $E_{1/2}$ for the $\text{Ru}^{\text{II/III}}$ couple remains almost unchanged. The ΔE ($E_{1/2}(\text{Ru}^{\text{III/II}}/\text{Ru}^{\text{II}}) - E_{1/2}(\text{Fe}^{\text{III/II}}/\text{Fe}^{\text{II}})$) value decreases by only ~ 15 mV on the inclusion of the BL in the β -CD cavity. Thus, there is no appreciable change in the potential energy barrier for electron transfer even after the inclusion of the BL in the β -CD cavity. Other noticeable changes in the cyclic voltammogram include an appreciable decrease in the current intensity and broadening of the redox waves ($E_p - E_a \geq 180$ mV for both $\text{Fe}^{\text{II/III}}$ and $\text{Ru}^{\text{II/III}}$ couples) for complexes **3–6**. This is expected considering the anticipated decrease in the values for the diffusion coefficient of the respective complexes compared to the non-inclusion complexes at the same concentration. These results reveal that inclusion of the BL in the β -CD cavity does not alter the ground state energy of the metal centers. Thus it is reasonable to presume that hydrogen bonding and other non-covalent interactions, which account for the stability of the inclusion complex of the bpe or bpp groups in the β -CD cavity,^[3,12] play a role in lowering the energy of the LUMO of the BL without affecting the energy of the d-orbitals of the Fe^{II} and Ru^{III} centers. Thus, it seems plausible that for **5** and **6**, inclusion of the BL in the β -CD cavity lowers the energy of the LUMO so that the energy of the respective metal orbital and the LUMO of the BL are similar, which allows the electron transfer to occur. A similar explanation was also offered for a series of donor–acceptor type molecules containing rigid saturated hydrocarbon bridges (dimethoxy naphthyl donor and dicyanovinyl acceptor separated by norbornyl group or $\text{Ru}^{\text{II}}(\text{NH}_3)$ and $\text{Ru}^{\text{III}}(\text{NH}_3)$ separated by dithiospiro rings).^[13] It was proposed that for the dithiospiro spacer group, electron transfer between the ends was possible because of the energetic proximity of the donor and acceptor centers and the LUMO of the BL. Further, the apolar interior of β -CD requires less reorganization to accompany the optical electron transfer in **5** and **6**, than the solvent water surrounding a non-inclusion complex (**1** and **2**) would.^[14] Although small, this may have some contribution in lowering the energy of activation for optical electron transfer. Following the Hush theory for weakly interacting mixed-valence species, ground state electronic delocalisation^[15] (α^2 ; 1.6×10^{-3} for **5** and 1.06×10^{-3} for **6**) and the extent of ground state electronic coupling arising for orbital mixing (H_{AB} , 400 for **5** and 330 for **6**) reveal that metal–metal coupling is much weaker than in the related mixed valence complex separated by a conjugated spacer.^[9] Electron transfer through space between donor and acceptor sites linked by a proline oligomer was explained by the participation of solvent water molecules bound to the helical bridging peptide which connect different peptide residues in the helicate through nonbonding interactions and short circuit the long “through bond” electron-transfer pathway across the peptide covalent bonds.^[16] A similar possibility for electron transfer in the present system involving

the OH functionality and the high electron density inside the β -CD cavity also cannot be ruled out. However, the absence of charge transfer between aromatic donors and acceptors,^[17] separated by a saturated hydrocarbon bridge in the β -CD inclusion complex does not favor this proposition. Further, Kaim and co-workers have demonstrated^[18] that a low lying π^* LUMO of BLs with higher molecular orbital (MO) coefficient at the coordinating center is crucial in effecting stronger metal–metal coupling in dinuclear complexes.

In conclusion, we have synthesized two mixed valent [2]rotaxane complexes with Ru^{III} and Fe^{II} units as the two molecular heads. Inclusion of a saturated bridging ligand (bpe or bpp for complex **5** and **6**, respectively) into the β -CD cavity has initiated optical electron transfer from the Fe^{II} to the Ru^{III} center, which is not observed in the absence of inclusion.

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- [7] Formation of 1:1 inclusion complex, as proposed for complexes **3–6** was ascertained by FAB and ES mass spectrometry and analytical data. Complex **3**: FAB m/z : 1710 [M^+]; elemental analysis: calcd with 2H₂O (%): C 44.9, H 5.55, N 3.28; found: C 44.1, H 5.7, N 3.2; UV/Vis (H₂O): 269 nm (sh); Complex **4**: FAB m/z : 1722 [M^+]; elemental analysis: calcd with 2H₂O (%): C 44.7, H 5.6, N 3.28; found: C 43.6, H 5.6, N 3.2; UV/Vis (H₂O): 270 nm (sh); Complex **5**: ES-MS m/z : 1963 [M^+], elemental analysis: calcd with 2H₂O (%): C 41.7, H 4.8, N 6.34; found: C 41.0, H 4.9, N 6.2; UV/Vis/NIR (ϵ , H₂O): 296 (7.3×10^3), 352 (5.3×10^3), 998 nm (1.46×10^3); diffused reflectance spectra (BaSO₄ matrix): 376, 1042 nm (br); Complex **6**: ES-MS m/z : 1977 [M^+], elemental analysis: calcd with 0.07 β -CD and 2H₂O (%): C 42.0, H 4.85, N 6.3 (0.07 mole β -CD, in addition to the included one, is trapped with Complex **6**); found: C 41.6, H 4.9, N 6.2; UV/Vis/NIR (ϵ , H₂O): 300 (2.4×10^3), 356 (1.6×10^3), 985 nm (1.36×10^3), diffused reflectance spectra (BaSO₄ matrix): 380, 1050 nm (br) (for detailed synthetic procedure see the Supporting Information).
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Synthesis and Self-Assembly of Monodisperse Indium Nanoparticles Prepared from the Organometallic Precursor [In(η^5 -C₅H₅)]**

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The current interest in studying elements of nanometer size^[1] stems from the structural changes that can arise from size reduction, from the physical properties which can be modified (melting point, band gap of semiconductors, magnetism), from the expected enhanced chemical properties, and from the possibility to use organized nanoparticles for various applications, for example, in microelectronic devices.^[2] Hence, much attention has been devoted during the past few years to precise spatial arrangement in two- and three-dimensional superlattice structures^[3] of metals (Au, Ag, Cu, Pt, Pd, Co),^[4] semiconductors (CdSe, CdS, CdTe),^[5] sulfides (Ag₂S)^[6] and oxides (CoO, Fe₂O₃, BaCrO₄).^[7] However, ordering and exploitation of the nanomaterials necessitates the synthesis of monodisperse individual particles, for which no general method is presently available. Low-temperature decomposition of organometallic precursors produces monodisperse nanoparticles of noble or magnetic metals.^[8] This method was recently extended to the synthesis of alloys and of semiconducting oxides for gas sensors.^[8b, 9]

To prove the generality of the method and its potential use for preparing particles that can be organized in superlattices, we considered indium, for which to our knowledge no organized nanoparticles have been reported. Indium, a low-melting metal, is a likely candidate for such studies; it adopts a tetragonal structure which may or may not be affected by size reduction^[10] and can be of various practical interests. It is easily alloyed and converted, for example, to InP^[11] and InAs,^[12] which are III–V semiconductors that display interesting optoelectronic properties. Indium is easily oxidized to In₂O₃, a transparent semiconducting material (band gap: 3.6 eV), which forms with SnO₂ the mixed indium tin oxide (ITO), a conducting glass.^[13] However, studies on indium nanoparticles are very rare. Indium particles 8–15 nm in size were prepared by metal vapor deposition.^[10] In addition, indium nanoparticles were prepared, among other colloidal metals, by evaporation of metal into a polymerizable monomer in order to study the thermal stability of the resulting composite material.^[14] Indium particles displaying an oxidized surface were synthesized by reduction of InCl₃ by alkalides or

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electrides.^[15] The literature concerning nanoparticles of indium compounds (InP, InAs) is more extensive, for example recent reports on the formation of semiconducting nanofibers.^[16] In contrast, the literature concerning In_2O_3 remains limited, although applications in optoelectronic devices are expected; for example, nanoparticles of this oxide embedded in mesoporous silica display photoluminescence.^[17] Here we describe the synthesis of monodisperse indium nanoparticles by an organometallic route and their arrangement in two- and three-dimensional networks.

The precursor chosen was $[\text{In}(\eta^5\text{-C}_5\text{H}_5)]$ ([InCp]). This indium(I) complex is easily prepared from InCl and LiCp in diethyl ether at room temperature,^[18] and its decomposition is expected to be facile. In fact, [InCp] decomposes spontaneously at room temperature in dry anisole containing polyvinylpyrrolidone (PVP) as stabilizer. The weight ratio of indium to PVP was fixed at 33%, in which case the reaction produces nanoparticles with size centered near 5 ± 3 nm and a broad size distribution (colloid **1**; Figure 1 a). However, in the

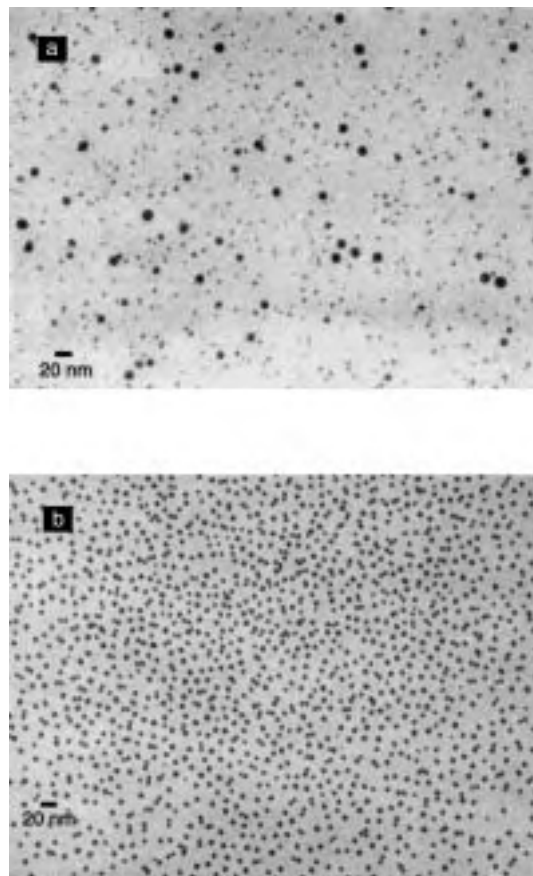


Figure 1. Transmission electron micrographs of indium particles in PVP. a) In the absence of water (colloid **1**). b) In the presence of traces of water (colloid **2**).

presence of a small quantity of water (e.g., 225 ppm, as determined by the Karl Fischer technique; $[\text{In}]:[\text{H}_2\text{O}] \approx 4$) the reaction proceeds under the same conditions to yield monodisperse particles with a mean diameter of 6 ± 0.7 nm (colloid **2**; Figure 1 b). The size of the particles is independent of the In:PVP ratio (5 or 33 wt%), but the presence of PVP is

necessary, since in its absence, even under the same conditions, agglomerated large particles are produced. The particles in colloid **2** consist essentially of indium metal, as demonstrated by X-ray diffraction (XRD) and wide-angle X-ray scattering (WAXS) studies, yet peaks attributable to In_2O_3 can also be observed by XRD. They presumably result from oxidation during preparation of the XRD sample. A high-resolution electron microscopy (HREM) study showed particles of uniform size, most of which did not present any fringe pattern and therefore appear amorphous (Figure 2),

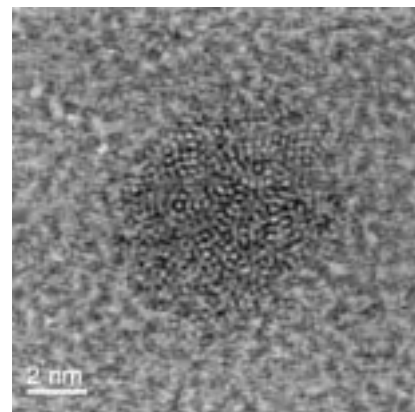


Figure 2. High-resolution electron micrograph of one particle of colloid **2** showing the amorphous (or disordered) structure.

but did not provide evidence for the presence of an oxide shell. A few crystalline particles were visible and were identified as In_2O_3 , the presence of which presumably results again from exposure of the sample to air prior to introduction into the microscope; further exposure to air increases the number of oxidized particles. The WAXS studies do not indicate the occurrence of any oxidation but clearly demonstrate the presence of indium metal. The radial distribution function (RDF) shows the presence of an amorphous phase, structurally related to the expected bct phase of bulk indium, in agreement with HREM observations. The presence of this amorphous phase may account for the large discrepancy between the coherence length obtained from WAXS studies (ca. 3.5 nm) and the size (6 nm) found by transmission electron microscopy (TEM). The lack of evidence for an oxide shell by any physical method, even if the presence of water clearly controls the growth of the particles, suggests the presence of a thin oxide surface layer which prevents further growth of the particles.

Having demonstrated the possibility of synthesizing particles of regular size embedded in a polymer, it was of interest to undertake a similar study in the absence of a polymer to test the suitability of these particles for use in electronic devices. For this study, we chose trioctylphosphane oxide (TOPO), since this ligand was previously used for stabilization and organization of nanoparticles.^[19] The reaction between [InCp] and TOPO (0.25 or 0.5 equiv) at room temperature or 50 °C in toluene containing about 50 ppm H_2O in the absence of light produced a stable brown solution (colloid **3**). This solution consists of well-separated, monodisperse indium particles of 5.2 ± 0.5 nm mean size. The

WAXS studies provide evidence for the presence of amorphous In with a similar structure to that observed in PVP for colloid **2**. The same conclusions regarding the structure can be deduced from HREM studies as for colloid **2**. Upon exposing the samples to air, we observed both a modification of the WAXS spectrum and of the HREM micrographs, which display crystalline features associated with the presence of In_2O_3 . The solution can easily be deposited as monolayers or multilayers on a carbon grid, as evidenced by TEM and HREM studies (Figure 3). It is apparent that the particles

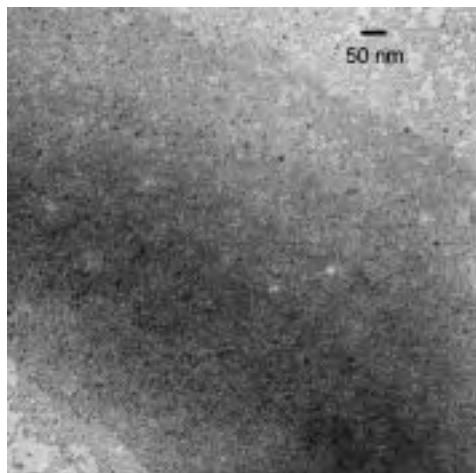


Figure 3. Mono- and multilayers of colloid **3** showing TOPO-protected In particles of narrow size dispersity.

tend to assemble to form regular networks. When more of the colloidal solution was deposited on the carbon grid, spontaneous self-organization of the particles into a monolayer displaying an hexagonal arrangement was observed, in which the distance between the particles from center to center is only 8.4 ± 0.7 nm. When at least four layers are present, crystallization of the particles into a compact structure (Figure 4) is observed. Given the recent increase in interest in nanoparticle self-assembly, the ease of these synthesis and assembly procedures make this system an attractive candidate for testing electrical properties. It is also noteworthy that when these particles are left in air in the solid state for several days, no change occurs in their self-organization, but HREM

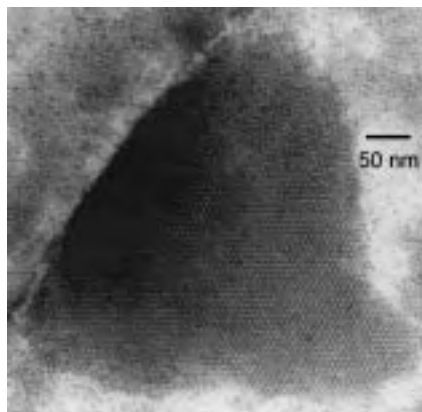


Figure 4. Ordered arrays of colloid **3**.

analysis clearly shows the presence of the cubic lattice of In_2O_3 and hence demonstrates the oxidation of the particles.

In conclusion, we have achieved the first synthesis of indium nanoparticles under mild conditions using the organometallic precursor [InCp]. The particles can be stabilized by a polymer or by ligands and, whatever the synthesis and stabilization method, the particles generally have a uniform size. They also adopt an amorphous (or disordered) structure derived from the bct structure of bulk indium. The particles prepared in wet anisole in the presence of PVP or in toluene in the presence of TOPO are monodisperse, and this clearly suggests the generality of the synthesis mode involving decomposition of organometallic precursors under mild conditions. The low size dispersity of the TOPO-stabilized particles allow their crystallization in a compact superlattice. These particles can be oxidized easily in air into cubic In_2O_3 , a semiconducting oxide, without changing their organization. This is therefore a material of interest for applications involving electron transfer and electroluminescence.

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Induction of a Preferred Twist in a Biphenyl Core by Stereogenic Centers: A Novel Approach to the Absolute Configuration of 1,2- and 1,3-Diols**

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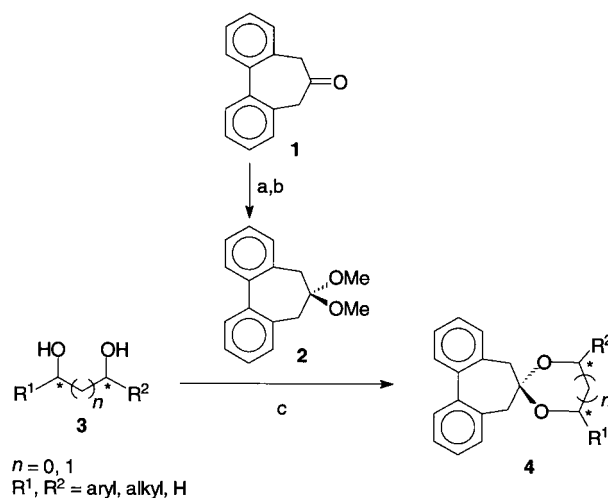
2,2',6,6'-Tetrasubstituted biphenyls and 2,2'-disubstituted-1,1'-binaphthyls are the paradigms of atropisomeric^[1] chiral substances because the steric hindrance to rotation around the C_{Ar}–C_{Ar} bond means that they can exist as a stable pair of enantiomers *P* and *M*.^[1,2] These configurationally stable biaryls have enjoyed a lot of attention in natural products chemistry,^[3] asymmetric synthesis,^[4] materials science,^[5] and molecular recognition,^[6] while only very recently nonatropisomerically stable, flexible biaryl compounds have also been used in asymmetric catalysis^[7] and molecular recognition.^[8] These latter compounds are usually present as racemic (*P,M*) mixtures because the free rotation around the C_{Ar}–C_{Ar} bond does not allow the isolation of a single enantiomer. A preferred enantiomeric conformation can be, however, stabi-

lized through interaction with chiral metal complexes^[7a] and/or substitution with chiral auxiliaries.^[7b–c]

We present herein a novel application of flexible biphenyl compounds for the nonempirical determination of the absolute configuration of 1,2- and 1,3-diols by CD spectroscopy. This is a task of great importance considering the wide use of such diols as chiral building blocks^[9] and chiral controllers in asymmetric processes.^[4a, 10] Although CD spectroscopy has been already employed for this purpose, such as in the dibenzoate-^[11] and in the metal-induced CD methods,^[12] the former nonempirical approach often involves difficult conformational assignments, while the latter, being an empirical method, does not allow an immediate and completely reliable correlation between the CD spectrum and configuration. For these reasons we recently developed alternative nonempirical CD approaches to the assignment of the absolute configuration of 1,2-diarylethane-^[13] and 1-arylethane-1,2-diols,^[14] in which the problem of the conformational determination is overcome by transforming the original flexible diols into their 2,2-dimethyl-1,3-dioxolanes or 4-biphenylboronates, respectively (that is, cyclic, conformationally defined derivatives).

We were looking for a more general method that would also be suitable for nonchromophoric alkyl-substituted diols, and have developed the approach described herein which is based on the formation of conformationally defined derivatives between a diol and a pro-atropisomeric^[7a] flexible biphenyl moiety. In order to determine the absolute configuration of aliphatic (and hence UV transparent) diols by CD analysis it is necessary to introduce suitable chromophores which are sensitive to the chirality of the diol and give rise to Cotton effects in the CD spectrum. Moreover, the mechanism by which the diol stereogenic centers induce optical activity in the chromophore must be known in order to obtain a nonempirical correlation between the CD spectrum and the absolute configuration of the diol.

Following our previous approaches,^[13, 14] we thought that the dioxolanes **4** (Scheme 1), derived from chiral diols **3** and the dimethylacetal **2** (which in turn is obtained from the 2,2'-bridged biphenyl ketone **1**)^[15] would constitute suitable



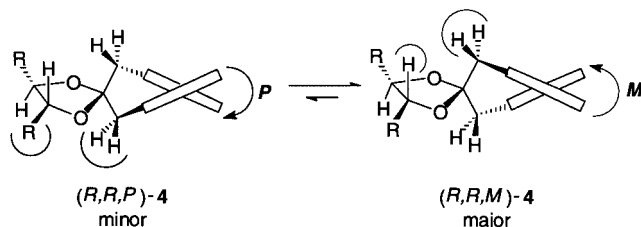
Scheme 1. Synthesis of biphenyldioxolanes **4**. a) CH(OCH₃)₃, *p*TsOH, MeOH, RT; b) NH₃ 2 M in EtOH; c) CHCl₃, 4-Å MS, RT. Ts = toluene-4-sulfonyl; MS = molecular sieve.

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[+] Crystal structure analysis

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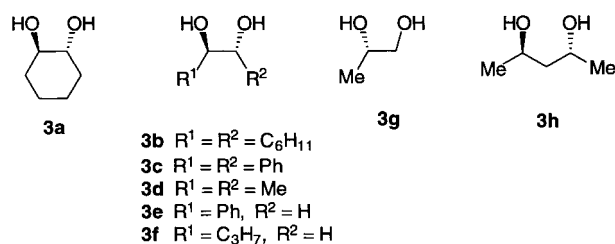
derivatives for our purposes. Several authors reported^[16] that in seven-membered 2,2'-bridged biphenyl derivatives such as **4** the inversion barrier is about 14 kcal mol⁻¹ and that a conformational equilibrium resulting from rotation around the C_{Ar}-C_{Ar} bond occurs at room temperature. This fact ensures that if we obtain a pair of dioxolanes (*R,R,P*)-**4** and (*R,R,M*)-**4** (Scheme 2) from nonracemic 1,2-diols (*R,R*)-**3** (R¹, R² = alkyl, aryl; *n* = 0; Scheme 1) their diastereoisomeric ratio is determined only by their thermodynamic stability and is independent of their mechanism of formation.



Scheme 2. Conformations of the dioxolanes **4** as derived from molecular mechanics calculations. In the isomer (*R,R,P*)-**4** the benzyl protons are close to a R residue, while in (*R,R,M*)-**4** they face a smaller hydrogen atom.

Molecular mechanics calculations^[17] revealed that in dioxolanes **4** derived from chiral *threo*-(*R,R*)-1,2- or -1,3-diols,^[18] the most stable diastereoisomer, independent of the diol structure, is the one having an *M* torsion of the biphenyl moiety. From the structures in Scheme 2 it can be clearly seen that in (*R,R,P*)-**4** both the benzylic CH₂ moieties face a bulky R substituent, while in (*R,R,M*)-**4** the benzylic residues are opposite hydrogen atoms and only minor steric interactions then result. In this system an efficient transfer of chirality from the diol (central chirality) to the twisted biphenyl (axial chirality) should occur^[7d] and then the absolute configuration of the diols can be determined simply by recognizing the prevailing sense of twist of the biphenyl moiety. The relationship between the sense and angle of torsion of a biphenyl moiety and its CD spectrum is clearly and reliably established,^[16c, 19, 20] so the use of such a system as a probe allows the chirality of the diol to be directly related to the features in the CD spectrum.

The ketone **1** was prepared in high yield according to two different literature procedures,^[21] starting from commercially available 2,2'-biphenyldicarboxylic acid, and transformed in its dimethyl acetal **2** by treatment with trimethyl orthoformate in the presence of *p*TsOH, followed by neutralization with ethanolic ammonia (Scheme 1).^[22] Solutions of crude **2** in CHCl₃ were treated directly with the diols **3a–h**^[23] in the presence of traces of *p*TsOH and 4-Å molecular sieves.^[24]



After filtration, evaporation of the solvent, and column chromatography the dioxolanes **4a–h** were isolated and their CD and UV spectra recorded (THF) between 200–330 nm.

The absorption spectrum of **4a** (Figure 1) shows the typical bands of a biphenyl chromophore: the A band at 250 nm ($\epsilon \sim 15000$) and a more intense absorption at 215 nm ($\epsilon \sim 30000$) which is referred to the C band.^[25] It is known^[19, 20]

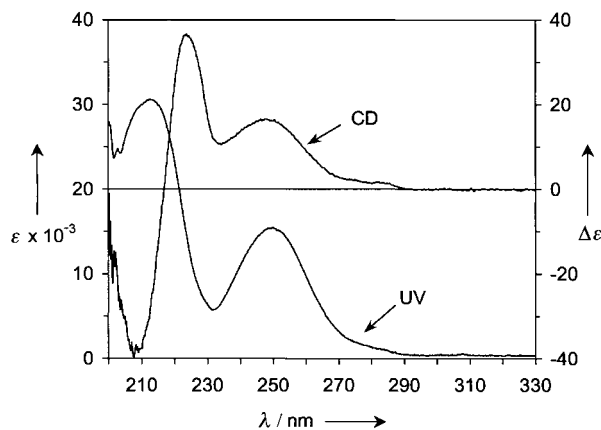


Figure 1. UV and CD spectra (THF) of dioxolane **4a**.

that the A band is very sensitive to the biphenyl torsion angle θ and Suzuki has calculated^[25] θ values of 44–47° for its present wavelength position. This value of θ is in agreement with our molecular mechanics calculations and with the values determined by Sandström and co-workers for similar seven-membered 2,2'-bridged biphenyls.^[16c, 20] A positive Cotton effect ($\Delta\epsilon = 15$) occurs in the CD spectrum at 250 nm (that is, corresponding to the A band), followed by a positive couplet-like feature centered at 220 nm. As shown by Mislow and co-workers^[19] and Sandström and co-workers,^[16c, 20] a positive Cotton effect arising from the A band is related to an *M* torsion of the C_{Ar}-C_{Ar} bond. Thus the CD spectrum of **4a** experimentally confirms that the (*R,R*)-diol really induces *M* torsion in the biphenyl chromophore.

In order to confirm and extend this correlation to more flexible acyclic diols and to determine the effect of the bulkiness of the diol substituents on the diastereoisomeric ratio we tested our approach with 1,2-disubstituted diols **3b–d** (with decreasing size of substituents) with the less sterically hindered monosubstituted 1,2-diols **3e–g** and with the 1,3-diol **3h**, which gives rise to a more-flexible six-membered ring dioxolane. The absorption and CD spectra of the dioxolanes **4a–f, h** show the same sequence in wavelength, sign, and shape of bands while **4g**, which is derived from an *S*-configured diol, gives rise to a mirror image CD spectrum. The CD spectra of compounds **4** only differ in the intensities of the Cotton effects. These results confirm that in all the derivatives tested we have the same expected correlation of *R,R*-diol and *M* torsion of the biphenyl. In addition, almost the same angle of twist of the biphenyl occurs as evidenced by the A band always occurring at 250 nm. These results show that this induction model is not limited to *threo*-dialkyl- or -diaryl-1,2-disubstituted diols **3a–d**, but works very well also with the 1,3-diol **3h** and even with the less

sterically demanding monoaryl diol **3e** and monoalkyl diols **3f, g**. It is important to point out the sensitivity of this method: a small group, such as the methyl in **4g**, is sufficient to induce enough population difference between the diastereoisomers to give rise to an intense and clearly interpretable CD spectrum. This method is also of general validity because it can be applied to all those systems having negligible absorption at 250 nm (for example, **3c** and **3e**).

The crystal structure analysis of **4c** (Figure 2) confirms the stereochemical correlation between the absolute configuration of the carbon stereocenter of the diol and the sense of

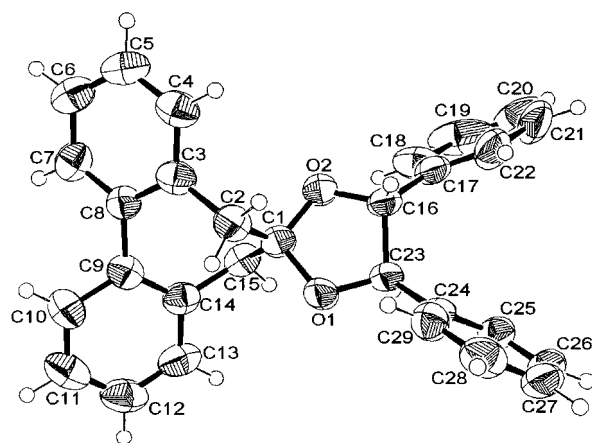


Figure 2. Crystal structure of *(R,R,M)*-**4c**; torsion angle C3-C8-C9-C14: 46.2°.

twist of the biphenyl moiety.^[26] In fact, the *R,R* absolute configuration of the two stereocenters gives a negative (*M*) torsion of the biphenyl moiety and the absolute value of the torsion angle C₃-C₈-C₉-C₁₄ is 46.2°, which is in excellent agreement with the values proposed by the Suzuki analysis^[27] and with literature values for similar biphenyl derivatives.^[16c, 28]

In order to confirm the presence of a thermodynamic equilibrium between the two stereoisomers *(R,R,P)*-**4** and *(R,R,M)*-**4**, the rotational process about the pivotal axis of the biphenyl moiety for the representative dioxolanes **4a, c, e, g, h** was monitored by dynamic NMR spectroscopy (DNMR; Table 1), and by freezing the exchange process at low temperature the diastereoisomeric ratio was measured. Changes in the line shape with the temperature for both the

Table 1. Diastereoisomeric ratios d.r., coalescence temperatures, rate constants, and free energies of activation involved in the *(R,R,M)*-**4** to *(R,R,P)*-**4** interconversion.^[a]

Compound	<i>R,R,M</i> : <i>R,R,P</i>	<i>T</i> [K]	<i>k</i> [s ⁻¹]	$\Delta\nu$ ^[b] [Hz]	$\Delta G^\ddagger$ [kcal mol ⁻¹]
4a	92:8	278	14	34	14.8
4c	90:10	268	8	30	14.5
4e	78:22	273	18	37	14.4
4g	74:26	258	7	12	14.0
4h	90:10	265	4	32	14.7

[a] All the activation parameters of the dioxolanes were measured from the ¹H NMR spectra recorded in CD₂Cl₂. [b] Signal separation in ¹H NMR spectra.

benzylic and the dioxolane ring protons were observed in the ¹H NMR experiments.^[29] In derivative **4e**, for instance, the diastereomerization process was easily monitored by lowering the temperature and observing the decoalescence of the OCH signals belonging to the dioxolane ring at 3.83, 4.40 (Figure 3), and 5.2 ppm. Indeed the sharp multiplets detected at +45 °C broadened upon cooling, decoalesced at about 0 °C, and at

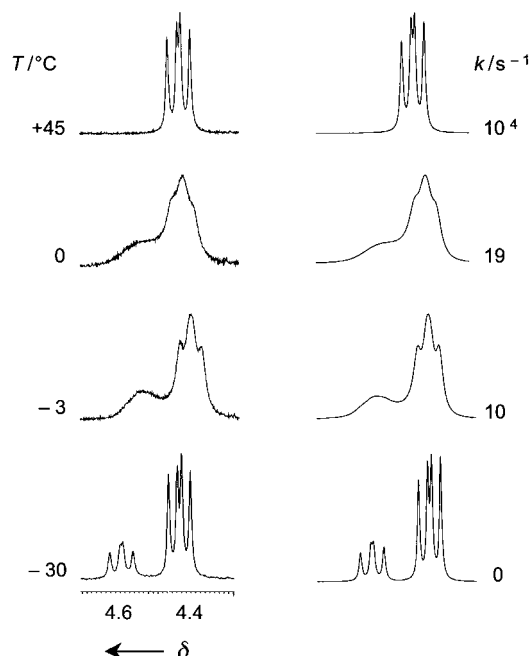


Figure 3. ¹H NMR spectra at 300 MHz in CD₂Cl₂ for the signal of the OCH group of dioxolane **4e**. On the left are shown the experimental traces, and on the right the computer simulated ones.

−30 °C appeared clearly split into a set of signals having an approximate 75:25 ratio. An analysis of the kinetic process for the transformation of the more- into the less-stable stereoisomer afforded a first-order rate constant and a $\Delta G^\ddagger$ value of 14.4(±0.15) kcal mol⁻¹. Similar values of $\Delta G^\ddagger$ were found for the other ketals examined (Table 1) and ranged from 14.0 to 14.8 kcal mol⁻¹, while d.r. values ranging from 74:26 to 92:8 were determined.^[30] These measurements, which confirm the presence of a low activation barrier for the atropisomeric interconversion of the dioxolanes **4**, demonstrate with certainty that the diastereoisomer ratio is only determined by their thermodynamic stability and that the structure of the major diastereoisomer is nonempirically predictable.

In summary, we have described a novel CD method for determining the absolute configuration of 1,2- and 1,3-diols based on a chirality transfer from the diol to a biphenyl chromophore. According to our protocol, to determine the absolute configuration of a diol it is simply necessary to prepare its biphenyldioxolane derivative **4**, to measure the CD spectrum, and to look at the sign of the A band (at 250 nm): A positive A band corresponds to an *M* torsion of the biphenyl and to a *R* or *R,R* configuration of the diol and vice versa. This method is quite simple, straightforward, and general, being applicable to many classes of 1,2- and 1,3-diols: cyclic, acyclic, mono- and disubstituted.

Experimental Section

Compounds **4a–h** show analytical and spectral (^1H , ^{13}C NMR, MS) data in agreement with the assigned structures. Absorption and CD spectra were recorded on a JASCO J600 spectropolarimeter at RT in THF ($c \sim 6 \times 10^{-3} \text{ M}$) in 0.1 and 1.0-mm cells. During the measurement the instrument was thoroughly purged with N_2 . Low temperature ^1H and ^{13}C NMR spectra were recorded in solution at 300 and 75.5 MHz, respectively. The cooling of the samples was achieved by means of a precooled flow of dry nitrogen in a standard NMR-VT device. The accuracy of the real temperature in the NMR probe was checked before the VT experiments with a calibrated thermocouple. The computer simulations of the line shapes were performed by a computer program based on the Bloch equations, and the best fit was visually checked by direct superimposition of the simulated and experimental traces.

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Fullerene Anions: Unusual Charge Distribution in C_{70}^{6-} **

Tamar Sternfeld, Roy E. Hoffman, Ivan Aprahamian, and Mordecai Rabinovitz*

C_{70} , the second most abundant fullerene,^[1] has an ellipsoid structure with symmetry of D_{5h} .^[2] Its ^{13}C NMR spectrum, consisting of five lines with intensities in the ratio of 1:2:1:2:1 provides very strong evidence for its structure and symmetry (Figure 1).^[3]

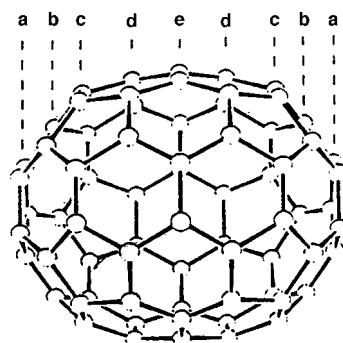


Figure 1. Schematic diagram of C_{70} depicting the different carbon sites a–e (reprinted from ref. [3]; copyright 1990 The Royal Society of Chemistry).

Reduction of C_{70} with lithium yields its hexaanion^[4] where the ^{13}C NMR spectrum has the same pattern as the neutral compound, and a slight overall deshielding ($\Delta\delta = 0.9$ per carbon).^[5] Although the reduction does not change the symmetry of C_{70} , it significantly changes the magnetic and electronic properties of the fullerene. The bulk and internal properties of charged C_{70} (that is C_{70}^{6-}) were previously investigated by the measurement of the ^3He NMR chemical shifts in the endohedral $\text{He}@C_{70}^{6-}$.^[6] These experiments, as well as magnetic susceptibility calculations,^[7] indicate a decrease in the aromaticity of C_{70}^{6-} . Studying the local properties of fullerenes can provide a deeper understanding of their aromatic character. The fullerenes consist of five- and six-membered rings (5-MRs and 6-MRs, respectively) that have different magnetic properties which define the overall character of the system.^[8] Calculations indicate that the paramagnetic ring current of the 5-MRs disappears in C_{70}^{6-} . Moreover there is a decrease in the diamagnetic ring current of the 6-MRs, that results in an overall decrease of the C_{70} -fullerene diamagnetism.^[9] We have previously studied the external and local magnetic properties by measuring the ^1H NMR chemical shifts of the fullerenoids $C_{71}\text{H}_2$.^[10] We concluded that the added electrons in C_{70}^{6-} are mainly located at the 5-MRs, thus converting them from paramagnetic into

diamagnetic rings. The diamagnetism of the 5-MRs at the poles is much stronger than that of the 5-MRs far from the poles and also than that of the 6-MRs.

According to the above mentioned studies^[9, 10] and because of the D_{5h} symmetry of C_{70} , it seems that the extra electrons of C_{70}^{6-} are not distributed evenly over the fullerene skeleton. Studying the carbon NMR chemical shifts can shed light on the magnetic properties of the fullerene surface, and help towards completing the C_{70}^{6-} puzzle. Therefore, a full assignment of the ^{13}C NMR spectrum is required, to determine the changes in the charge density on each set of carbons and the changes in the magnetic susceptibility.

To determine conclusively the chemical shift of each carbon type in C_{70}^{6-} , a 2D INADEQUATE (incredible natural abundance double quantum transfer experiment) NMR experiment was performed. This experiment correlates the ^{13}C NMR resonance of a carbon to that of its bonded neighbor.^[11]

A sample of 4 mg of ^{13}C -enriched C_{70} ($\sim 13\%$)^[12] was prepared by using $[\text{D}_8]\text{THF}$ as solvent and in the presence of corannulene (1 mg), which acts as an “electron shuttle”,^[6] in a 5 mm NMR tube equipped with a top reduction chamber containing excess lithium metal.

The 2D INADEQUATE spectrum (Figure 2) of the sample shows, as expected, four interactions that make the assignment of the carbon connectivity possible.^[13] The interaction

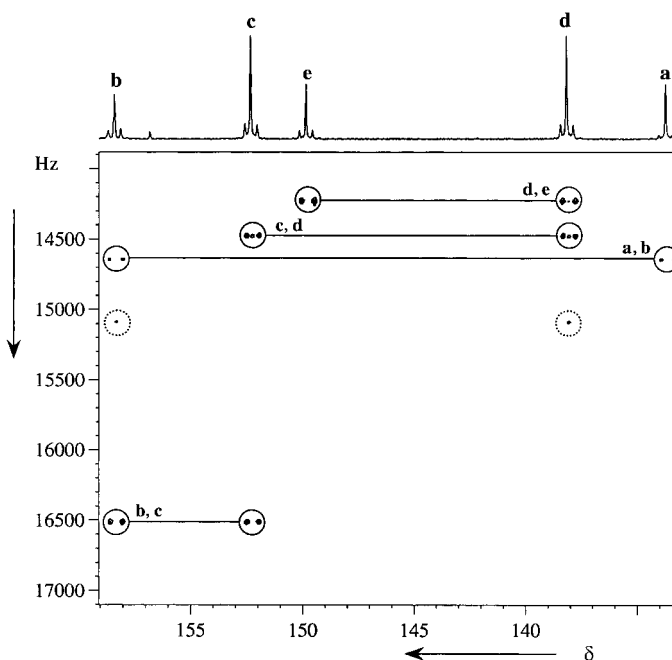


Figure 2. 2D NMR INADEQUATE spectrum of C_{70}^{6-} , short-range interactions: solid circles, long-range interactions: dashed circles.

between the signal that appears at $\delta = 133.6$ and the signal at $\delta = 158.3$, where both represent 10 carbon atoms, leads to the following assignment (Figure 1): carbons **a**: $\delta = 133.6$; carbons **b**: $\delta = 158.3$; carbons **c**: $\delta = 152.3$; carbons **d**: $\delta = 138.1$; carbons **e**: $\delta = 149.8$.

To understand the changes that occur as a result of the addition of electrons to C_{70} a comparison with the neutral molecule^[14] is necessary (Table 1). Chemical shift changes,

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Table 1. ^{13}C NMR chemical shifts (δ) and coupling constant (J_{cc} [Hz]) for the carbon atoms of C_{70} ^[a] and C_{70}^{6-} .

Carbon	C_{70}	C_{70}^{6-}
a	150.1 ($J_{\text{ab}} = 68$)	133.6 ($J_{\text{ab}} = 60.9$)
b	146.8 ($J_{\text{bc}} = 55$)	158.3 ($J_{\text{bc}} = 53.8$)
c	147.5 ($J_{\text{cd}} = 55$)	152.3 ($J_{\text{cd}} = 56.4$)
d	144.8 ($J_{\text{de}} = 62$)	138.1 ($J_{\text{de}} = 58.4$)
e	130.3	149.8

[a] Taken from ref. [14].

caused by the addition of electrons to the molecule, originate from the changes of the electron density, as well as changes of induced ring currents in the molecule.^[15] Although in many polycyclic aromatic hydrocarbons the carbon atoms are not sensitive to anisotropic effects, in C_{70}^{6-} it is obvious that there is such an influence, as there is an overall deshielding. The anisotropic effect is also expressed by the K_{c} value (-0.15 ppm per electron) that was calculated by Equation (1).

$$\delta_{\text{c}} = \delta_{\text{N}} - K_{\text{c}} \Delta q_{\pi} \quad (1)$$

δ_{c} and δ_{N} are the chemical shifts of a carbon in the charged and the neutral species, respectively, K_{c} is a proportionality factor and q_{π} is the extent of π charge.^[16] In C_{60} , the reduction to the hexaanion leads to a $\Delta\delta = 14$ deshielding of the ^{13}C NMR spectrum,^[5] which results from increasing diamagnetism, as shown by calculation^[7] and the ^3He NMR spectrum.^[6]

As mentioned above, the local aromaticity or antiaromaticity of fullerenes is studied by examining the ring current of each ring. Each carbon is not only in the nodal plane of a π -ring system, where theory predicts small ring current effects, but is also adjacent to other rings, where the ring current effect may be significant. Therefore, it is difficult to distinguish between the different contributions to the chemical shifts.

Comparison between the chemical shifts in the ^{13}C NMR spectra of the neutral C_{70} ^[14] and the hexaanion (Table 1) shows a large change for the signals of carbon atoms **a** and **e**, which are located at the pole and the "equator" of the fullerene, respectively. The signal of carbon atoms **a** have a strong up field shift ($\Delta\delta = -17$). This shift is rationalized by the concentration of the negative charge on the polar 5-MRs, as was previously shown for charged C_{71}H_2 .^[10] Therefore, **a** type carbon atoms carry the highest negative charge. On the other hand, the signal of the **e** type carbon atoms have a strong low field shift ($\Delta\delta = 19$). Such a shift may originate from a decrease in the charge distribution^[17] on the carbons at the equator of the C_{70}^{6-} surface as well as from global ring currents. Calculations by Haddon and co-workers^[9a] show that in neutral C_{70} the **e** type carbons are the most affected by the ring current. The change in chemical shift of the signal of this carbon atom follows the same trend of that of the shifts in the ^3He NMR spectra of He@C_{70} ^[18] and He@C_{70}^{6-} ,^[6] which might indicate similar ring current influences on the endohedral atom and the atoms at the equator. The chemical shifts of the signals of carbon atoms **b–d** show smaller changes. These shifts could result from the local effects of the magnetic ring

currents of neighboring rings.^[19] The low field shift of the signals of carbon atoms **b** and **c** can be explained by the diamagnetism of the 5-MRs in C_{70}^{6-} , since, the carbon atoms **b** and **c** are connected through one bond to the 5-MRs periphery, they are thus affected by the diamagnetic ring current of the 5-MRs. Moreover, each carbon of type **b** is near a polar 5-MR, so it is much more affected by the ring current, and thus shows a lower field chemical shift than **c** type carbon atoms.^[10]

The high field of the signal of the **d** carbons can be explained in terms of a reduction of the diamagnetic ring current of some of the 6-MRs, since the **d** carbons are connected by one bond to those rings. This tendency was calculated by Bühl^[9b] and by Haddon and co-workers,^[9a] who independently showed a small aromatic character of 6-MRs in C_{70}^{6-} .

The J_{cc} for each interaction was also measured and was compared to the equivalent value in the neutral C_{70} ^[14] (Table 1). The most significant change of coupling constants is for J_{ab} that is reduced by 7 Hz. This result confirms that the location of the charge is at the poles, leading to increased bond lengths between the carbons of the 5-MRs at the poles(**a**) and their radially attached neighbors (**b**).

In addition to a full assignment of the ^{13}C NMR spectrum of C_{70}^{6-} , we have added another dimension to the study of the aromaticity of charged fullerenes and especially of C_{70}^{6-} . As has been shown,^[6, 7, 9] the global aromaticity of C_{70}^{6-} is significantly weaker than that of C_{70} . Therefore, understanding the origin of the global magnetic properties requires an insight into the local characteristics of the anion. It can be concluded that the low aromatic character of C_{70}^{6-} results from the following causes; first, the charge distribution of the added electrons on the C_{70}^{6-} skeleton is not symmetrical and charge concentrates at the poles of the fullerene. The effect of the ring current is not equal over the entire fullerene, or the fullerene surface. Second, the addition of the electrons to the 5-MRs renders them diamagnetic. The global decrease in the aromaticity of C_{70}^{6-} could be accounted for by a reduced aromaticity in some of the 6-MRs.

Finally, this study represents a substantial addition to the understanding of the behavior of C_{70}^{6-} . Having studied the molecule from the inside^[6] and the outside^[10] we have now looked at it from the surface thus observing the molecule from every perspective.

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At the same time, construction of artificial ion channels by using simple molecular systems may provide important information with regard to understanding natural ion channels and to establishing structure–function relationships.

Several approaches to artificial ion channels have been reported by us^[3] and others.^[4] We have already obtained several nonpeptidic ion channels by two approaches: supramolecular and molecular half channels. Two important results were: 1) A macrocyclic resorcin[4]arene with four alkyl chains **1** (Figure 1) gave a single ion channel having only

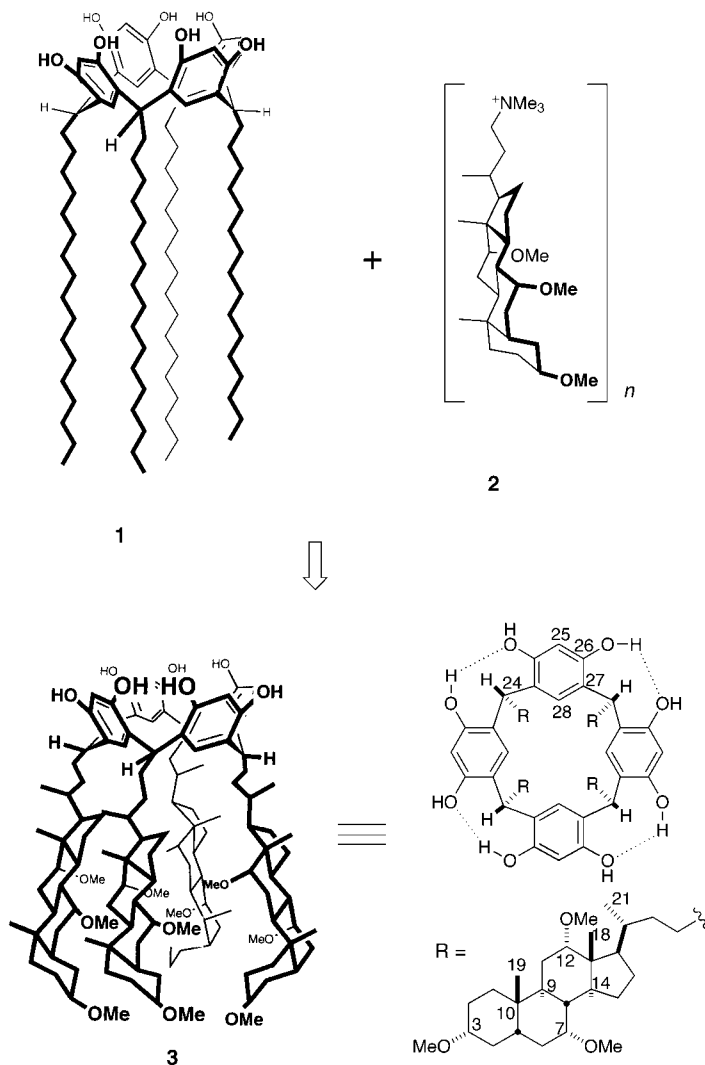


Figure 1. Structures of compounds **1**–**3**.

one conductance level.^[3d] 2) A supramolecular ion channel obtained by using the rigid methyl cholate **2** with amphiphilic nature showed a long-lasting open state.^[3e] We have now combined these two functions by synthesizing a macrocyclic resorcin[4]arene having four amphiphilic methyl cholate groups (**3**) in the hope of obtaining a fundamental molecular channel unit with a single conductance level and a stable open state. Then, refined design of the ion-transporting path by modifying the rigid molecular plane of the cholic acid residues is expected to modify the conductance and ion selectivities so that structure–function relationships can be established.

An Artificial Ion Channel Formed by a Macrocyclic Resorcin[4]arene with Amphiphilic Cholic Acid Ether Groups**

Naomi Yoshino, Akiharu Satake, and Yoshiaki Kobuke*

Ion channels are naturally occurring molecular devices in the brains and nerve systems of all animals that generate large ionic fluxes with on–off gate control. An ion channel with a typical conductance of 10 pS allows the passage of 5×10^6 ions per second through a single molecular pore. Even at such high ionic fluxes, ion channels generally discriminate different ionic species, for example, cation/anion and Na^+/K^+ .^[1] These functions are of potential use as the basis for molecular ionic devices^[2] that can transfer information across a thin membrane. If these functions are properly attributed to artificial ion channels, they should show great advantages with regard to handling, stability, and availability over large natural proteins, which are hardly expected to meet these demands.

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[**] The authors thank Prof. Masahiro Sokabe for helpful discussions.

Macrocyclic resorcin[4]arene **3** was synthesized by one-pot condensation of 3,7,12-trimethylcholanal with resorcinol under acidic conditions. Crude **3** was obtained by simple filtration from the reaction mixture. Purification by column chromatography (SiO_2) afforded **3** in 32 % yield. A FAB mass spectrum of **3** directly showed the existence of resorcin tetramer (m/z 2106.47 [$M+H^+$]). Proton and ^{13}C NMR spectra of **3** in $[\text{D}_6]\text{DMSO}$ at 90°C gave only one set of signals for aromatic and steroidal components: sharp signals for one set each of methine protons α to methoxy groups (H^3 , H^7 , and H^{12}), methine protons α to two phenylene groups (H^{24}), and aromatic protons (H^{25} and H^{28}). Furthermore, all ^{13}C signals of the aromatic and steroidal components were observed separately. These results indicated that **3** has a C_{4v} -symmetrical structure. The four steroidal units are located at axial positions in a bowl-shaped conformation by intramolecular hydrogen bonding of adjacent resorcin units,^[5] as shown in Figure 1. As resorcin[4]arene **3** has hydrophilic head groups and amphiphilic steroidal parts, a tail-to-tail coupled pair of molecules of **3** are expected to assemble in a bilayer membrane to afford a transmembrane channel (Figure 2). The hydrophilic molecular sides of the steroidal groups are expected to be aligned to form a hydrophilic pore near the central axis, while the hydrophobic sides are directed to the surrounding lipid alkyl groups.

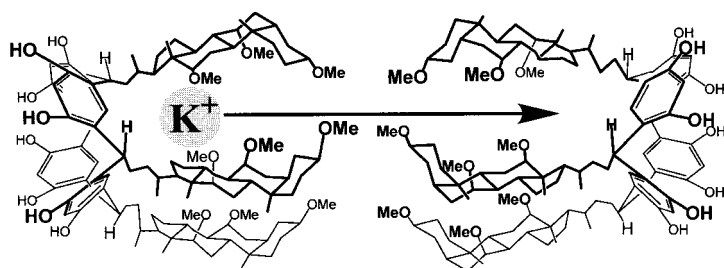


Figure 2. Tail-to-tail assembly of two molecules of **3** to give a bilayer membrane with an intramembrane channel.

The properties of single ion channels were examined according to established methods.^[3b–g] A premixed solution of soybean lecithin and **3** in $\text{CHCl}_3/n\text{-decane}$ (1/5) was applied to a hole in a partition separating two aqueous chambers to form a planar bilayer. Incorporation of 0.2 wt % of **3** in the lipid gave stable single-channel currents at various applied voltages. Figure 3a shows a typical record of single-channel currents at 70 mV with symmetrical 500 mM KCl at pH 7.2

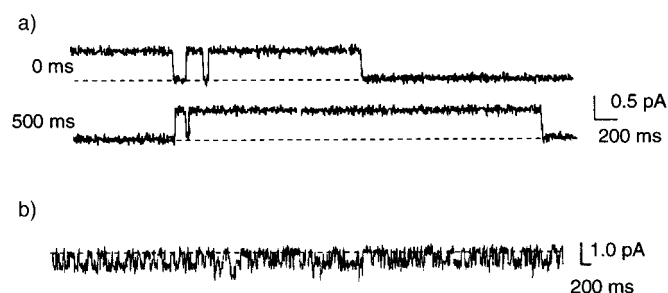


Figure 3. Time profiles for single-channel currents. a) **3**, 500 mM KCl, pH 7.2, 70 mV. b) **1**, 500 mM KCl, pH 7.2, -74.4 mV.

(tris-hepes buffer). As shown in this example, ion channels formed from **3** usually showed long-lasting and stable open states. The ratio of open to closed states was about 95 to 5, and the average open times determined by histogram analysis of open durations were in the range of 2.5–4.5 s. In the case of the alkyl resorcin channel **1**,^[3d] very rapid open–closed transitions were observed (Figure 3b) and their analysis gave an average open time of 35 ± 10 ms. Comparison of the two systems suggests that the rapid transitions in **1** are based on molecular motion of flexible alkyl side chains. In **3** with rigid steroidal anchors in the membrane, these rapid open–closed transitions are almost quenched. In the gramicidin A channel, intermolecular hydrogen bonding in a β -helical conformation results in stable pore formation across the bilayer membrane, and its open lifetime of 0.56 ± 0.06 s^[6] has been ascribed to a head-to-head dimer. Interestingly, the average open time of **3** exceeds even this value. Therefore, fairly strong interactions are suggested to exist in the channel formed by two molecules of **3**. The higher stability of ion channels of **3** not only results from the rigid steroid framework, but also from the polar methoxy groups, which are absent from **1** and should hold the tails of **3** that face each other together by polar interactions and/or by cation complexation.

The conductance values in KCl and NaCl under symmetrical conditions were obtained from the linear relationship between voltages and current for several experimental runs (Figure 4). In each case, only one conductance value, 9.9 ± 0.1 and 5.3 ± 0.1 pS, was obtained in 500 mM solutions of KCl and

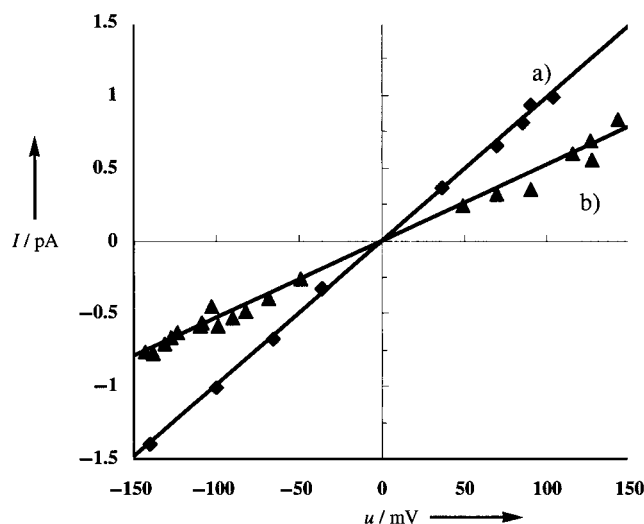


Figure 4. Current–voltage plots of single ion channel **3**. a) Symmetrical 500 mM KCl, pH 7.2; b) symmetrical 500 mM NaCl, pH 7.2.

NaCl, respectively. The value in KCl solution (9.9 pS) was higher than that of the alkyl resorcin channel **1** (6.1 pS in 500 mM KCl). Cation/anion selectivity was examined with asymmetrical salt concentrations: *cis*, 100 mM KCl; *trans*, 500 mM KCl. Reversal potential values E_{rev} from several experimental runs converged at 27.9 ± 1.8 mV (Figure 5). The permeability ratio $P_{\text{K}}/P_{\text{Cl}} = 8.2 \pm 1.6$ was then determined from the Goldman–Hodgkin–Katz equation.^[1] The value was significantly lower than that of **1** ($P_{\text{K}}/P_{\text{Cl}} = 20$). Compar-

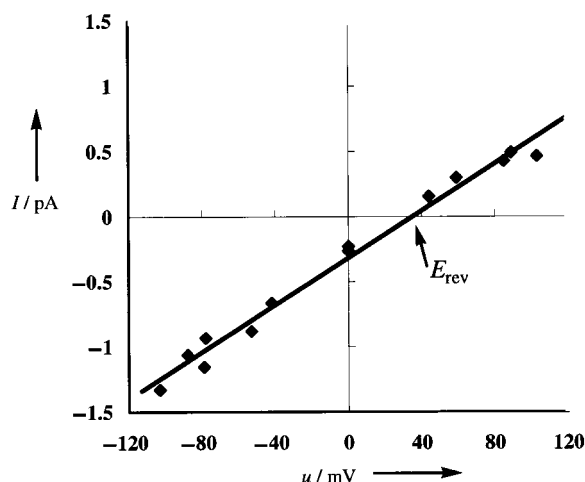


Figure 5. Current–voltage plot of single ion channel **3** under asymmetric salt concentrations: *cis* 100 mM KCl and *trans* 500 mM KCl, pH 7.2.

ison of conductance values and cation/anion selectivities between resorcin channels **1** and **3** showed clearly the effect of the steroidal units, which resulted in the formation of a more hydrophilic environment at the central pore. The conductance value increased by 60 % but was accompanied by a 60 % loss of cation/anion selectivity.

Finally, K^+/Na^+ selectivity was examined under asymmetric salt concentration conditions: *trans* 450 mM NaCl+50 mM KCl; *cis* 450 mM KCl+50 mM NaCl. The permeability ratio P_K/P_{Na} was determined as 2.8 ± 0.6 , which was similar to that of **1** ($P_K/P_{Na}=3$). Therefore, steroidal units have negligible influence on the K^+/Na^+ selectivity. The result confirms the previous conclusion that the resorcin[4]arene macroring may provide the selectivity filter of the channel. The aromatic moiety provides only a weak electric field, which can desolvate the K^+ ion ($r=1.33 \text{ \AA}$) with its lower dehydration energy (355 kJ mol^{-1}) but only partly desolvate the Na^+ ion ($r=0.95 \text{ \AA}$; 438 kJ mol^{-1}), which therefore finds it hard to pass through the bottleneck of the resorcin[4]arene. On the other hand, the Rb^+ ion ($r=1.48 \text{ \AA}$), with its smaller dehydration energy of 330 kJ mol^{-1} , but with a slightly larger ionic radius stops K^+ currents by atomic blockage.

Resorcin[4]arene channels have potential utilities for establishing the structure–function relationship in ion channels because of their single conductance level and facile variation of the tail unit. The steroidal tails introduced here have the advantages of a long-lasting open state and modification of the hydrophilic pore without changing the overall structural features, as evidenced here by conductance and selectivity values of cation/anion and metal-ion species. We are now investigating modification of the cholic acid tails of resorcin[4]arene channels.

Experimental Section

3: Concentrated HCl (0.185 mL) was added to a mixture of resorcinol (127 mg, 1.15 mmol) and 3,7,12-trimethylcholanal (500 mg, 1.15 mmol) in

ethanol (1.15 mL) at 0°C . The mixture was heated at 70°C for 10 h. The resulting mixture was cooled to room temperature, and precipitates were filtered off. Water was added to the filtrate and the resulting precipitate was collected by filtration. The combined solids were washed with hot water (80°C , $3 \times 10 \text{ mL}$), and dried under reduced pressure. The crude solid was subjected to column chromatography (SiO_2 , EtOAc/MeOH = 19/1) to give **3** (196 mg, 32 %). $^1\text{H NMR}$ (600 MHz, $[\text{D}_6]\text{DMSO}$, 90°C , TMS): δ = 8.69 (br, 8H; OH), 7.18 (s, 4H; H^{28}), 6.18 (s, 4H; H^{25}), 4.21 (t, J = 7.3 Hz, 4H; H^{24}), 3.35–3.33 (m, 4H; $\text{HC}(\text{OMe})$), 3.22 (s, 24H; 2 MeO), 3.17 (s, 12H; MeO), 3.13–3.11 (m, 4H; $\text{HC}(\text{OMe})$), 2.96–2.93 (m, 4H; $\text{HC}(\text{OMe})$), 2.03–1.90 (m, 16H), 1.85–1.55 (m, 36H), 1.48–1.23 (m, 20H), 1.21–0.85 (m, 24H), 0.96 (d, J = 6.6 Hz, 12H; H^{21}), 0.86 (s, 12H; Me), 0.63 (s, 12H; Me); $^{13}\text{C NMR}$ (150 MHz, $[\text{D}_6]\text{DMSO}$, 90°C , TMS): δ = 152.25 (C(Ar), 2C), 124.90 (CH(Ar)), 124.22 (C(Ar)), 124.05 (C(Ar), 103.36 (CH(Ar)), 82.26 (CH, CH(OMe)), 80.42 (CH, CH(OMe)), 77.49 (CH, CH(OMe)), 55.95 (CH₃, MeO), 55.68 (CH₃, MeO), 55.18 (CH₃, MeO), 47.51 (CH), 46.52 (C), 42.84 (CH), 41.97 (CH), 39.85 (CH), 35.58 (CH), 35.41 (CH₂), 35.02 (C), 34.93 (CH₂), 34.72 (CH₂), 33.80 (CH, CH(Ar)₂), 32.09 (CH₂), 28.29 (CH₂), 28.19 (CH), 27.41 (CH₂), 27.19 (CH₂), 23.27 (CH₂), 23.04 (CH₃), 22.43 (CH₂), 18.66 (CH₃, C²¹), 12.82 (CH₃). FAB-MS (NBA matrix) calcd for $\text{C}_{132}\text{H}_{200}\text{O}_{20}$: 2105.46; found (intensity): 2104.43 (23), 2105.44 (72, $[\text{M}]^+$), 2106.47 (100, $[\text{M}+\text{H}]^+$), 2107.54 (80), 2108.55 (46), 2109.56 (23), 2128.44 (17, $[\text{M}+\text{Na}]^+$); analysis calcd for $\text{C}_{132}\text{H}_{200}\text{O}_{20} \cdot 4\text{H}_2\text{O}$: C 72.76, H 9.62; found: C 72.45, H 9.61.

Received: August 9, 2000 [Z15606]

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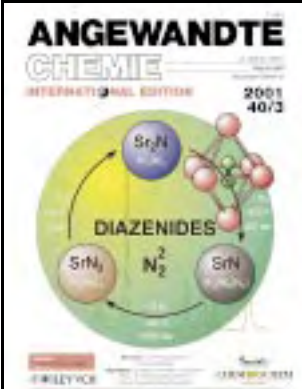
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Pages 469–634



**ANGEWANDTE
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DIAZENIDES

Sr_2N
 SrN_2
 N_2
 SrN

WILEY-VCH

*ChemBioChem 2/2001 is bound
in this issue of Angewandte Chemie.*



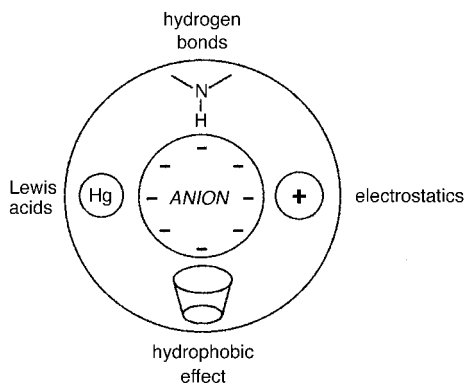
CHEMBIOCHEM
A JOURNAL OF BIOLOGICAL CHEMISTRY
2/2001
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COVER PICTURE

The cover picture shows schematically the conditions for preparation and decomposition of strontium diazenides. The crystal structures of the diazenides, which were obtained as single-phase products under high N_2 pressure (up to 5500 bar), were determined by neutron diffraction. The background is provided by a section of the powder diffraction pattern of SrN_2 , and the coordination of the diazenide ions is shown top right. The N–N bond length in the diazenide ions is 122 pm in both compounds. Details of the preparation and characterization of the Sr diazenides are reported by G. Auffermann, Y. Prots, and R. Kniep on p. 547 ff.



Since the birth of anion coordination chemistry in the late 1960s, anion recognition is today an established area of supramolecular chemistry. This review gives an overview of the state of the art of inorganic and organic anion receptors which can selectively bind and detect relevant anionic guest molecules by a variety of interactions (see picture). The most recent developments are in the areas of self-organization by anionic templates, ion-pair recognition, and the function of anions in supramolecular catalysis. Clearly this shows that the chemistry of anion recognition at the start of the new millennium is exciting, surprisingly rich, and a continually growing interdisciplinary field of coordination chemistry.



Angew. Chem. **2001**, *113*, 502–532

P. D. Beer,* P. A. Gale* 486–516

Anion Recognition and Sensing:
The State of the Art and Future
Perspectives

Keywords: anions • molecular
recognition • self-assembly • sensors •
supramolecular chemistry

CO₂, the solvent of choice! Whether it is compressed as a liquid or as a supercritical fluid the properties of CO₂ are, in principle, ideal to make it the solvent of the future. One of the main problems, the low solubility in CO₂ of many industrially important compounds, can be overcome by the development of CO₂ soluble surfactants. The broad application spectrum of this new technology is presented with examples of dispersion polymerization, polycarbonate synthesis, stone protection, and spin coating for microelectronics.

Angew. Chem. **2001**, *113*, 534–544

S. L. Wells, J. DeSimone* 518–527

CO₂ Technology Platform: An Important
Tool for Environmental Problem Solving

Keywords: carbon dioxide • micelles •
polymers • supercritical fluids •
surfactants

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.com>

Synthesis and Structure of a Ga₈₄R₂₀^{4−} Cluster—A Link between Metalloid Clusters and Fullerenes?

A. Schnepf, H. Schnöckel* ◆

From Oligomers to Conducting Polymers of the Metal–Dinitrogen Functionality

E. Solari, J. Hesschenbrouck,
R. Scopelliti, C. Floriani,* N. Re

Heterogeneous Dinuclear Rhodium(II) Hydroformylation Catalysts—Performance Evaluation and Silsesquioxane-Based Chemical Modeling

M. Nowotny,* T. Maschmeyer,
B. F. G. Johnson, P. Lahuerta,
J. M. Thomas, J. E. Davies

Formation of Super Wires of Clusters by Self-Assembly of Transition Metal Cluster Anions with Metal Cations

T. Nakajima, A. Ishiguro,
Y. Wakatsuki*

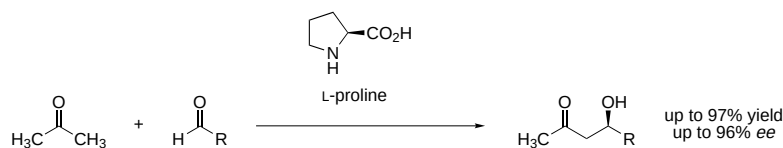
Synthesis of Conformationally Locked Carbohydrates: A Skew-Boat Conformation of L-Iduronic Acid Governs the Antithrombotic Activity of Heparin

S. K. Das, J.-M. Mallet,
J. Esnault, P.-A. Driguez,
P. Duchaussoy, P. Sizun,
J.-P. Hèrault, J.-M. Herbert,
M. Petitou,* P. Sinaÿ*

Highly Efficient and Ultrafast Phototriggers for cAMP and cGMP by Using Long-Wavelength UV/Vis Activation

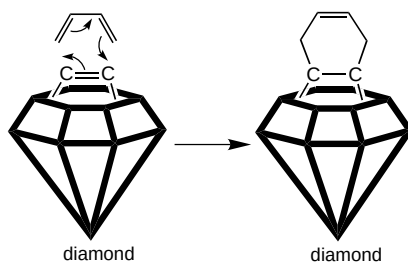
V. Hagen,* J. Bendig, S. Frings,
T. Eckardt, S. Helm, D. Reuter,
U. B. Kaupp

Can a simple amino acid act like an enzyme? This question is reviewed and discussed herein. In addition, new contributions in which simple organic molecules are used as efficient chiral catalysts in asymmetric synthesis (see scheme) are highlighted.



Angew. Chem. **2001**, *113*, 545–548

Does a diamond surface react like a large organic molecule or does the underlying bulk material affect its behavior? Fascinating work by the groups of Bent and Hamers suggests that the (100) diamond surface has a very strong organic character (a model Diels–Alder reaction is depicted), which is less affected by the underlying material than silicon or germanium.



Angew. Chem. **2001**, *113*, 548–550

Functional group tolerance and accessibility of unique microstructures are attractive features of olefin polymerization by late transition metal catalysts. Recent discovery of several new classes of highly active catalysts provide access to a range of new materials.

Angew. Chem. **2001**, *113*, 550–557

H. Gröger,* J. Wilken 529–532

The Application of L-Proline as an Enzyme Mimic and Further New Asymmetric Syntheses Using Small Organic Molecules as Chiral Catalysts

Keywords: aldol reactions • amino acids • asymmetric catalysis • enzyme mimics • homogeneous catalysis

J. M. Buriak * 532–534

Diamond Surfaces: Just Big Organic Molecules?

Keywords: cycloaddition • diamond • germanium • silicon • surface chemistry

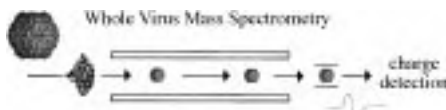
S. Mecking * 534–540

Olefin Polymerization by Late Transition Metal Complexes—A Root of Ziegler Catalysis Gains New Ground

Keywords: homogeneous catalysis • polymerization • polymers • transition metals

COMMUNICATIONS

The simultaneous measurement of the time-of-flight and the number of charges on each electrosprayed ion provides a new way to determine the mass of a whole intact virus. The weights of an icosahedral virus (rice yellow mottle virus) consisting of a single-stranded RNA surrounded by a homogeneous protein shell with a mass of 6.5×10^6 Da, and a rod-shaped RNA virus (tobacco mosaic virus) with a mass of 40.5×10^6 Da were measured with this technique.



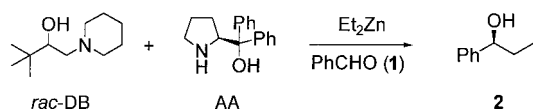
Angew. Chem. **2001**, *113*, 560–562

S. D. Fuerstenau, W. H. Benner,*
J. J. Thomas, C. Brugidou, B. Bothner,
G. Siuzdak * 541–544

Mass Spectrometry of an Intact Virus

Keywords: mass spectrometry • noncovalent interactions • RNA structures • viruses

Correct additions make a difference: Asymmetric deactivation and asymmetric amplification concepts coupled with a high-throughput screening technique provided a successful strategy for designing a highly enantioselective catalytic system by simple combination of a racemic amino alcohol (*rac*-DB) and a nonracemic additive (AA). The example in the scheme shows the conversion of **1** into **2** with up to 92.7% ee.



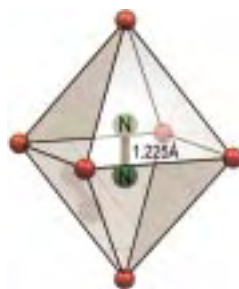
Angew. Chem. **2001**, *113*, 562–565

J. Long, K. Ding * 544–547

Engineering Catalysts for Enantioselective Addition of Diethylzinc to Aldehydes with Racemic Amino Alcohols: Nonlinear Effects in Asymmetric Deactivation of Racemic Catalysts

Keywords: asymmetric catalysis • asymmetric deactivation • high-throughput screening • nonlinear effects • zinc

Nitride and/or diazenide ions in the octahedral holes of nearly close-packed arrangements of Sr^{2+} ions (see picture) characterize the new compounds described herein. They were obtained as single-phase products by oxidation of Sr_2N with molecular nitrogen under high pressure.



G. Auffermann, Y. Prots,
R. Kniep* 547–549

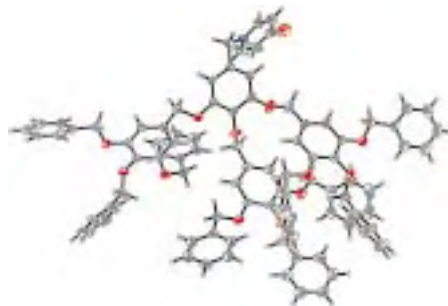
SrN and SrN_2 : Diazenides by Synthesis under High N_2 -Pressure

Keywords: diazenides •
high-pressure chemistry •
neutron diffraction • nitrides •
redox chemistry

Angew. Chem. **2001**, *113*, 565–567



Passivation of the metal surface by dendrons bearing a focal 4-pyridone functionality (the second-generation dendron is shown; C: gray, N: blue, O: red) allows controlled nucleation and growth of gold nanoclusters. The particle size is a direct function of the generation number of the dendritic ligands, with higher generation dendron producing larger particles.



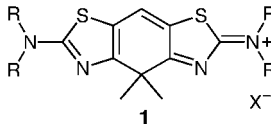
R. Wang, J. Yang, Z. Zheng,*
M. D. Carducci, J. Jiao,
S. Seraphin 549–552

Dendron-Controlled Nucleation and Growth of Gold Nanoparticles

Keywords: dendrimers •
electron microscopy • gold •
nanostructures • steric hindrance

Angew. Chem. **2001**, *113*, 567–570

The fluorescence-enhancing effect of the oxygen bridge in pyronine and rhodamine di- or triphenylmethane dyes, is connected to a significant hypsochrome shift of the absorption bands. This shift is absent when the bridge is an alkylene unit. While the preparation of such compounds is difficult, that of the heterocyclic analogues **1** is relatively simple and gives rise to intensely fluorescent dyes with absorptions at long wavelength.



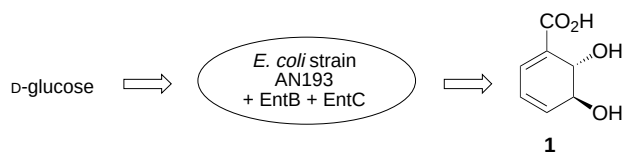
H. Hartmann,* A. Noack 552–554

Alkylene-bridged N,N,N',N' -Tetrasubstituted Bis(2-amino-5-thiazolyl)methinium Salts—A New Class of Strongly Fluorescent Dyes

Keywords: chromophores •
fluorescence • heterocycles •
methine dyes • thiazoles

Angew. Chem. **2001**, *113*, 597–599

As valuable chiral building blocks for the syntheses of natural products and pharmacologically active substances, especially of carbohydrate mimetics, functionalized cyclohexadiene-*trans*-diols such as (2*S*,3*S*)-dihydroxy-2,3-dihydrobenzoic acid (**1**) can be prepared easily in 17% yield starting from glucose by using metabolically deregulated, recombinant microorganisms such as the *Escherichia coli* strain AN193 (see scheme).



D. Franke, G. A. Sprenger,
M. Müller* 555–557

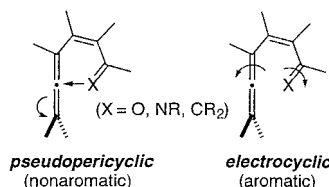
Synthesis of Functionalized Cyclohexadiene-*trans*-Diols with Recombinant Cells of *Escherichia coli*

Keywords: asymmetric synthesis •
bioorganic chemistry •
biotransformations • shikimic acid

Angew. Chem. **2001**, *113*, 578–581



Pericyclic or pseudopericyclic? Although both mechanisms lead to the same product, they are deeply different in nature. The ring-current model proves to be a useful tool to define different kinds of aromaticity and to distinguish between pericyclic and pseudopericyclic reactions (see scheme).



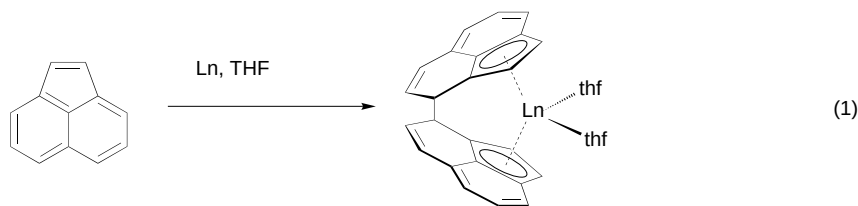
A. R. de Lera,* R. Alvarez, B. Lecea,
A. Torrado, F. P. Cossío* 557–561

On the Aromatic Character of Electrocyclic and Pseudopericyclic Reactions: Thermal Cyclization of (2*Z*)-Hexa-2,4,5-trienals and Their Schiff Bases

Keywords: ab initio calculations •
allenes • aromaticity •
electrocyclic reactions • heterocycles

Angew. Chem. **2001**, *113*, 570–574

A fulvene-type coupling results from the reduction of acenaphthylene by activated samarium or ytterbium in THF. This leads exclusively to the formation of the respective C_2 -symmetric *trans-rac*-ansa-lanthanocene complexes $[(\eta^5-C_{12}H_8)_2Ln(thf)_2]$ [Eq. (1); $Ln = Sm, Yb$].



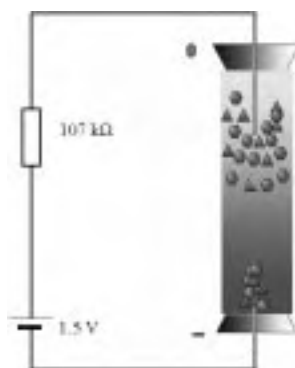
Angew. Chem. **2001**, *113*, 584–586

I. L. Fedushkin,* S. Dechert,
H. Schumann * 561–563

Stereoselective Formation of C_2 -Symmetric ansa-Lanthanocenes by Reductive Coupling of Acenaphthylene with Activated Ytterbium or Samarium

Keywords: ansa compounds • C–C coupling • lanthanides • metallocenes • polycycles

Areas of 80–3500 μm^2 are displayed by gold single-crystal ultramicroelectrodes, which were fabricated from gold single crystals grown electrolytically in silicate gels. According to their cyclic voltammograms in 0.01M HCl, these ultramicroelectrodes behave similarly to electrodes of more normal dimensions with the same crystallographic orientation of the surface.



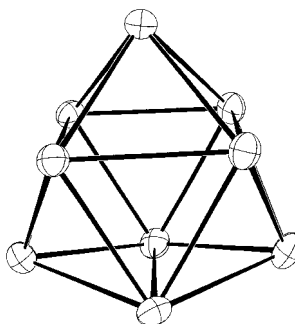
V. Komanicky, W. R. Fawcett * 563–566

Fabrication and Properties of Gold Single-Crystal Ultramicroelectrodes

Keywords: electrochemistry • electrodes • gold • single-crystal electrodes • ultramicroelectrodes

Angew. Chem. **2001**, *113*, 594–596

A simple preparative method has been employed for the synthesis of the novel cluster compound $Ga_9(CMe_3)_9$, which contains a tricapped trigonal prism of monovalent gallium atoms. Electron transfer processes were observed similar to those of polyboranes, leading to the reversible formation of the corresponding radical anion.



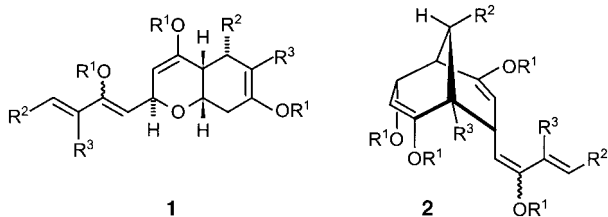
W. Uhl,* L. Cuypers, K. Harms, W. Kaim,
M. Wanner, R. Winter, R. Koch,
W. Saak 566–568

$Ga_9(CMe_3)_9$, an Important New Building Block in the Structural Chemistry of the Alkyl-element(i) Compounds E_nR_n ($E = B - In$)

Keywords: cluster compounds • electron deficiency • gallium

Angew. Chem. **2001**, *113*, 589–591

Six at a time! Up to six stereogenic centers can be diastereoselectively formed in one step in three-component domino reactions of 4-silyloxyppyrylium triflates with 2-silyloxybuta-1,3-dienes. Annulated or bridged ring systems such as **1** and **2**, respectively, can be formed with high selectivity. R^1 = silyl group; R^2, R^3 = organyl group.



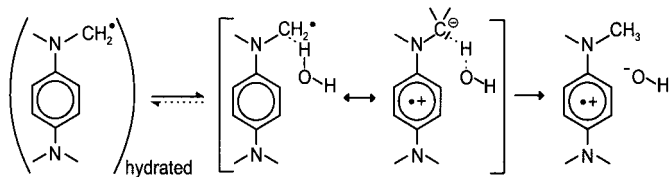
Angew. Chem. **2001**, *113*, 591–594

U. Beifuss,* K. Goldenstein, F. Döring,
C. Lehmann, M. Noltemeyer .. 568–570

Stereoselective Multiple Functionalization of Pyylium Salts by Domino Reactions with 2-Silyloxybuta-1,3-dienes

Keywords: annulation • domino reactions • heterocycles • polycycles • rearrangement

In aqueous solution, the neutral radical formed by H-abstraction by $\cdot\text{OH}$ from one of the side-chain methyl groups of *N,N,N',N'*-tetramethyl-*p*-phenylenediamine (TMPD) is protonated by water to give the aromatic radical cation, $\text{TMPD}^{\bullet+}$ (see scheme). This reaction involves an intramolecular electron transfer from the ring to the side chain and is the reverse of the classical side-chain deprotonation reaction of radical cations.



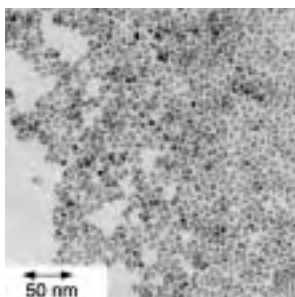
Angew. Chem. **2001**, *113*, 581–583

S. Steenken,* A. J. S. C. Vieira 571–573

Water-Assisted Intramolecular Electron Transfer from the Ring to the Side Chain in *N,N,N',N'*-Tetraalkyl-*para*-phenylenediamine Radicals—The Reverse of Side Chain Deprotonation of Radical Cations

Keywords: acidity • protonations • pulse radiolysis • radical cations • radical reactions

Nanoparticles with high photoluminescence quantum yield have been recently considered as possible biolabels and as emitters in optoelectronic devices. Now gram amounts of nontoxic, chemically stable $\text{LaPO}_4\text{:Ce,Tb}$ nanocrystals (see picture) have been obtained in a coordinating solvent. These nanoparticles can be easily redispersed in polar solvents to give scatter-free colloids that exhibit quantum yields of up to 61 %.



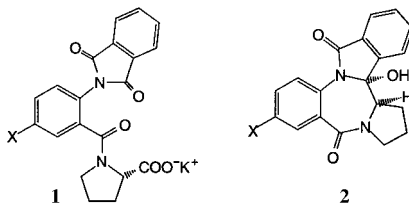
Angew. Chem. **2001**, *113*, 574–578

K. Riwotzki, H. Meyssamy, H. Schnablegger, A. Kornowski, M. Haase* 573–576

Liquid-Phase Synthesis of Colloids and Redispersible Powders of Strongly Luminescing $\text{LaPO}_4\text{:Ce,Tb}$ Nanocrystals

Keywords: colloids • luminescence • nanostructures • rare-earth compounds

Memory of chirality in triplet 1,7-diradicals was detected for the first time and to a remarkably high degree in the decarboxylative photocyclization of the proline derivative of *N*-phthaloyl anthranilic acid **1** into **2** (X = H: 45 % yield, 86 % *ee*; X = Cl: 50 % yield, 79 % *ee*).



Angew. Chem. **2001**, *113*, 586–589

A. G. Griesbeck,* W. Kramer, J. Lex 577–579

Diastereo- and Enantioselective Synthesis of Pyrrolo[1,4]benzodiazepines through Decarboxylative Photocyclization

Keywords: atropisomerism • circular dichroism • diradicals • memory of chirality • photochemistry

The intermolecular exchange coupling $2J$ for the light-induced radical pair in a crystal of 2,2'-di(*ortho*-chlorophenyl)-4,4',5,5'-tetraphenylbiimidazole (*o*-Cl-HABI) was measured for the first time on the basis of Curie analyses of the EPR spectral intensities. The coupling constant evaluated from density functional theory calculations compares well with the experimental value. The picture shows the distribution of spin density for the radical pair.



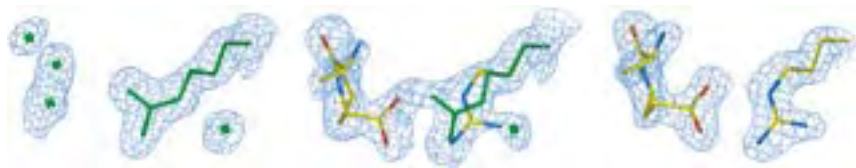
Angew. Chem. **2001**, *113*, 600–602

J. Abe,* T. Sano, M. Kawano, Y. Ohashi, M. M. Matsushita, T. Iyoda 580–582

EPR and Density Functional Studies of Light-Induced Radical Pairs in a Single Crystal of a Hexaarylbiimidazolyl Derivative

Keywords: density functional calculations • EPR spectroscopy • photochromism • radicals • through-space interactions

Crystallographic snapshots of protein–ligand complexes have been determined by soaking protein crystals in solutions of different ligand concentrations. The crystallographic refinement of ligand occupancy allows the calculation of the ligand binding constant in the crystal. The picture shows three different stages along the binding pathway: from free protein (left) to ligand-bound protein (right).



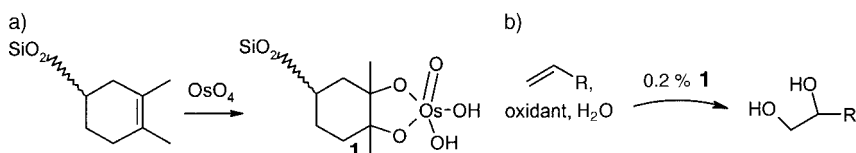
Angew. Chem. **2001**, *113*, 602–606

S.-y. Wu, J. Dornan, G. Kontopidis,
P. Taylor, M. D. Walkinshaw* . 582–586

The First Direct Determination of a
Ligand Binding Constant in Protein
Crystals

Keywords: kinetics •
noncovalent interactions • protein
structures • structure elucidation

Involatile OsO_4 ! A tetrasubstituted olefin is immobilized on SiO_2 and reacts with OsO_4 to form a stable osmate(IV) ester (see scheme), which is a leak-proof heterogeneous catalyst for the *cis*-dihydroxylation of olefins.



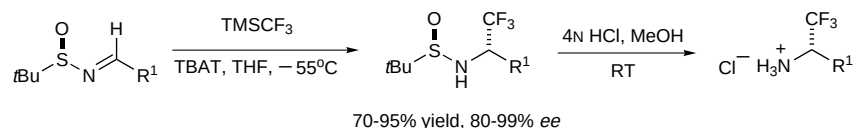
Angew. Chem. **2001**, *113*, 606–609

A. Severeys, D. E. De Vos, L. Fiermans,
F. Verpoort, P. J. Grobet,
P. A. Jacobs* 586–589

A Heterogeneous *cis*-Dihydroxylation
Catalyst with Stable, Site-Isolated
Osmium–Diolate Reaction Centers

Keywords: dihydroxylation •
heterogeneous catalysis •
immobilization • osmium • oxidations

 **A very general reaction is presented** to achieve the nucleophilic transfer of “ CF_3 ” to chiral *N*-(*tert*-butylsulfinyl)imines in high yield and high stereoselectivity (see reaction scheme). Tetrabutylammonium difluorotriphenylsilicate (TBAT) functions as a fluoride source, and aromatic, heterocyclic, and aliphatic sulfinylimines react smoothly. The high stereoselectivity suggests that the reaction proceeds through an open transition state. TMS = trimethylsilyl.



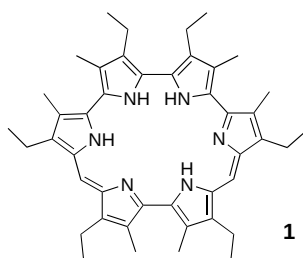
Angew. Chem. **2001**, *113*, 609–610

G. K. S. Prakash,* M. Mandal,
G. A. Olah* 589–590

Stereoselective Nucleophilic
Trifluoromethylation of *N*-(*tert*-
Butylsulfinyl)imines by Using
Trimethyl(trifluoromethyl)silane

Keywords: amines •
asymmetric synthesis • imines •
nucleophilic addition • sulfinamides

Applications of actinide chemistry, whether for energy or defense purposes, have left a legacy of potential waste hazards. The new expanded porphyrin ligand **1** forms stable complexes with both uranyl (UO_2^{2+}) and neptunyl (NpO_2^{2+}) ions and presents a potential new avenue for waste remediation.



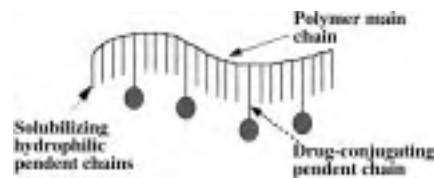
Angew. Chem. **2001**, *113*, 611–614

J. L. Sessler,* D. Seidel, A. E. Vivian,
V. Lynch, B. L. Scott,
D. W. Keogh* 591–594

Hexaphyrin(1.0.1.0.0.0): An Expanded
Porphyrin Ligand for the Actinide
Cations Uranyl (UO_2^{2+}) and Neptunyl
(NpO_2^{2+})

Keywords: actinides •
coordination chemistry •
macrocyclic ligands • porphyrinoids •
transuranium elements

Atom transfer polymerization has been used to prepare a narrow molecular weight distribution (MWD), active ester homopolymer that acted as a precursor to prepare families of narrow MWD polymer–drug conjugates during preclinical studies (see schematic representation).



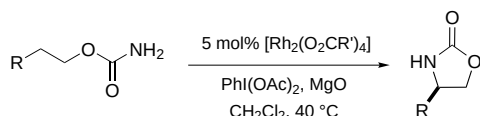
A. Godwin, M. Hartenstein,
A. H. E. Müller,* S. Brocchini* 594–597

Narrow Molecular Weight Distribution
Precursors for Polymer–Drug Conjugates

Keywords: drug research •
polymerization • polymers

Angew. Chem. **2001**, *113*, 614–617

Selective intramolecular alkane oxidations: an Rh^{II} carboxylate catalyzed C–H amination reaction facilitates the preparation of 1,2-amino alcohols from primary carbamates. The reaction is stereospecific, providing access to chiral α -branched amines from optically pure starting materials with no loss in enantiomeric excess (see scheme).



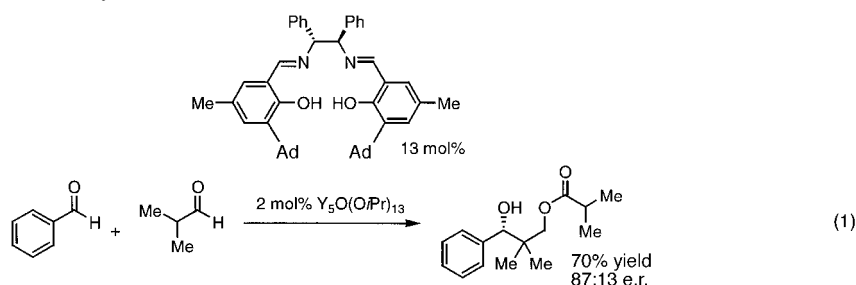
Angew. Chem. **2001**, *113*, 618–620

C. G. Espino, J. Du Bois* 598–600

A Rh-Catalyzed C–H Insertion Reaction
for the Oxidative Conversion of
Carbamates to Oxazolidinones

Keywords: amino alcohols •
C–H insertion • cyclization •
homogeneous catalysis • rhodium

Unmodified carbonyl compounds are converted in an enantioselective aldol-Tishchenko reaction directly into the chiral adduct by using catalytic amounts of a chiral base prepared in situ [Eq. (1)]. The catalyst was developed through the combination of arrayed catalyst evaluation and informed ligand design. Ad = adamantyl.



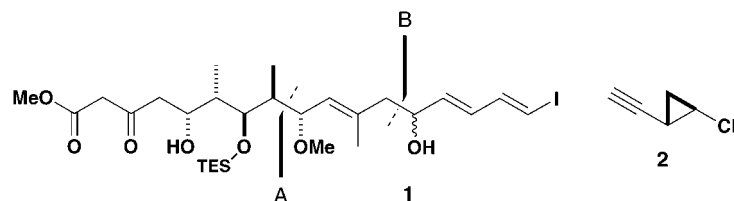
Angew. Chem. **2001**, *113*, 621–623

C. M. Mascarenhas, S. P. Miller,
P. S. White, J. P. Morken* 601–603

First Catalytic Asymmetric Aldol-
Tishchenko Reaction—Insight into the
Catalyst Structure and Reaction
Mechanism

Keywords: aldol reactions •
asymmetric catalysis • lanthanides •
reaction mechanisms • yttrium

Following macrolactonization, a Sonogashira coupling leads efficiently from **1** and **2** to the aglycon of the structurally unique cytotoxic macrolide callipeltoside A, isolated in tiny quantities from the lithistid sponge *Callipelta* sp. Key steps in the preparation of macrolide precursor **1** include a boron-mediated anti-aldol coupling (A) in tandem with Yamamoto's vinylogous aldol reaction (B). TES = triethylsilyl.



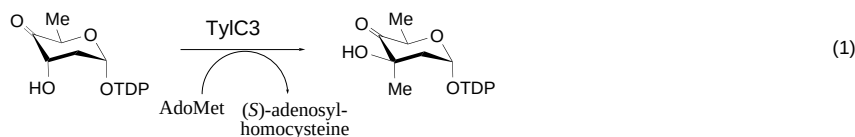
Angew. Chem. **2001**, *113*, 623–627

I. Paterson,* R. D. M. Davies,
R. Marquez 603–607

Total Synthesis of the Callipeltoside
Aglycon

Keywords: antitumor agents • boron •
macrolides • natural products •
total synthesis

A C-methyltransferase involved in methyl-branch formation in sugars has been characterized for the first time. TylC3, an (*S*)-adenosylmethionine(AdoMet)-dependent enzyme, catalyzes the attachment of a methyl branch [Eq. (1)] in the biosynthesis of L-mycarose, an unusual sugar found in tylosin and as its O-3-methyl derivative in erythromycin. The C-3 methylation proceeds with inversion of configuration and does not require the assistance of any cofactors. The turnover rate is $1.4 \pm 0.1 \text{ min}^{-1}$. TDP = thymidine-5'-dihydrogenphosphate.



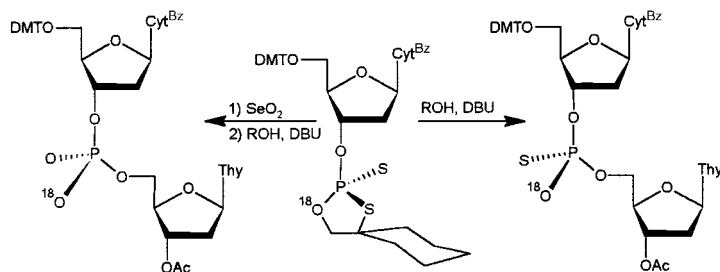
Angew. Chem. **2001**, *113*, 627–630

H. Chen, Z. Zhao, T. M. Hallis, Z. Guo, H.-w. Liu* 607–610

Insights into the Branched-Chain Formation of Mycarose: Methylation Catalyzed by an (*S*)-Adenosylmethionine-Dependent Methyltransferase

Keywords: alkylation • biosynthesis • carbohydrates • enzyme catalysis • transferases

Diastereomerically pure and isotopically labeled 5'-O-DMT-nucleoside-3'-O-(2-thio- and -oxo-4,4-"spiro"-pentamethylene-1,3,2-[^{18}O]oxathiaphospholane)s were used for stereocontrolled synthesis of P-chiral, isotopically labeled oligonucleotide phosphorothioates and phosphates, as well as "chimeric" $\text{PS}^{18}\text{O}/\text{P}^{18}\text{O}$ oligomers (see scheme) without loss of isotope enrichment. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMT = 4,4'-dimethoxytrityl, ROH = 3'-O-acetylthymidine, Bz = benzoyl



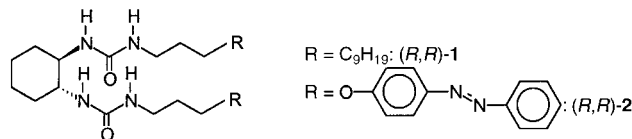
Angew. Chem. **2001**, *113*, 630–633

P. Guga, K. Domański, W. J. Stec* 610–613

Oxathiaphospholane Approach to the Synthesis of P-Chiral, Isotopomeric Deoxy(ribonucleoside phosphorothioate)s and Phosphates Labeled with an Oxygen Isotope

Keywords: oligonucleotides • phosphorothioates • isotopic labeling

Chiral recognition in organogels occurs in the coassembly of the chiral gelator **1** with the chiral guest molecule **2**. The diastereomeric aggregates formed from (*R,R*)-**2** with (*R,R*)-**1** or (*S,S*)-**1** were found to be truly different in structure and strength. Cooperativity makes a major contribution to the chiral recognition in this system.



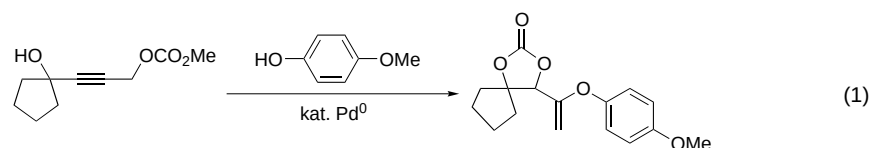
Angew. Chem. **2001**, *113*, 633–636

M. de Loos, J. van Esch,* R. M. Kellogg, B. L. Feringa* 613–616

Chiral Recognition in Bis-Urea-Based Aggregates and Organogels through Cooperative Interactions

Keywords: aggregation • chirality • cooperative effects • gels

Refixation of the CO_2 from a decarboxylation occurs in the palladium-catalyzed domino reaction of 4-methoxycarbonyloxy-2-butyne-1-ols with phenols. The reaction enables the construction of various cyclic carbonates [Eq. (1)] by efficient reincorporation of the CO_2 molecule under mild conditions, and is thus a convenient and environmentally friendly method.



Angew. Chem. **2001**, *113*, 636–639

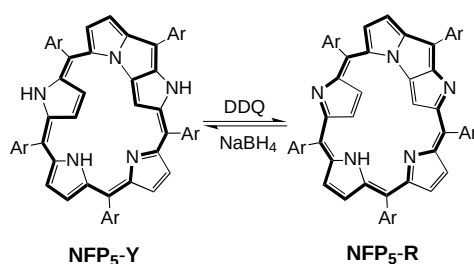
M. Yoshida, M. Ihara* 616–619

Palladium-Catalyzed Domino Reaction of 4-Methoxycarbonyloxy-2-butyne-1-ols with Phenols: A Novel Synthetic Method for Cyclic Carbonates with Recycling of CO_2

Keywords: carbon dioxide fixation • cyclization • domino reactions • palladium



From the acid-catalyzed condensation of aryl aldehyde and pyrrole a new type of fused expanded porphyrins, *N*-fused pentaphyrins **NFP₅-Y** (24 π , yellow) and **NFP₅-R** (22 π , red) were obtained in total yields of 2–19%. The two normal-type porphyrins are quantitatively interchanged through a redox reaction (see scheme). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.



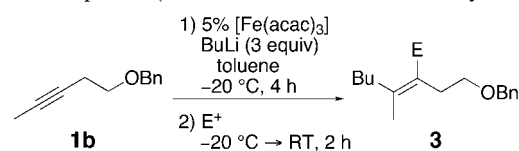
J.-Y. Shin, H. Furuta,*
A. Osuka* 619–621
N-Fused Pentaphyrin

Keywords: heterocycles • macrocycles • porphyrinoids • redox chemistry

Angew. Chem. **2001**, *113*, 639–641



Butylation problems ironed out: 3-Pentynyl ethers react with butyllithium at –20°C in toluene, upon addition of a catalytic amount of a cheap iron(III) salt, to afford (*E*)-4-methyl-3-octenyl ethers in high yields. Stereochemically defined tetrasubstituted alkenes were also obtained by the subsequent addition of electrophiles (E^+ , see scheme; acac = acetylacetonate, Bn = benzyl).



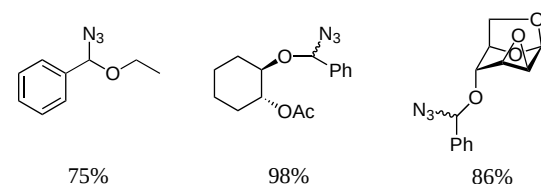
Angew. Chem. **2001**, *113*, 641–643

M. Hojo, Y. Murakami, H. Aihara,
R. Sakuragi, Y. Baba,
A. Hosomi* 621–623

Iron-Catalyzed Regio- and
Stereoselective Carbolithiation of
Alkynes

Keywords: alkenes • homogeneous catalysis • iron • lithium • nucleophilic addition

Introduction of an azido substituent at the α position of benzyl ethers can be achieved by treating them with IN_3 in refluxing acetonitrile. Some of the products obtained after 20 min–5 h are given.



Angew. Chem. **2001**, *113*, 643–645

C. Viuf, M. Bols* 623–625

Radical Azidation of Benzylic
Positions with Iodonium Azide

Keywords: azides • benzyl ethers • iodine reagents • radical reactions



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

* Author to whom correspondence should be addressed



BOOKS

Design and Analysis in Chemical Research	Roy L. Tranter	<i>H. Kubinyi</i> 627
Chemical Topology	Daniel Bonchev, D. H. Rouvray	<i>P. Fowler</i> 628
Stereoselective Biocatalysis	Ramesh N. Patel	<i>W. Klaffke</i> 628
Semiconducting Polymers	Georges Hadziioannou, P. F. van Hutten	<i>T. Fuhrmann</i> 629
Solid-Phase Synthesis	Steven A. Kates, F. Albericio	<i>W. K. Stähle</i> 630



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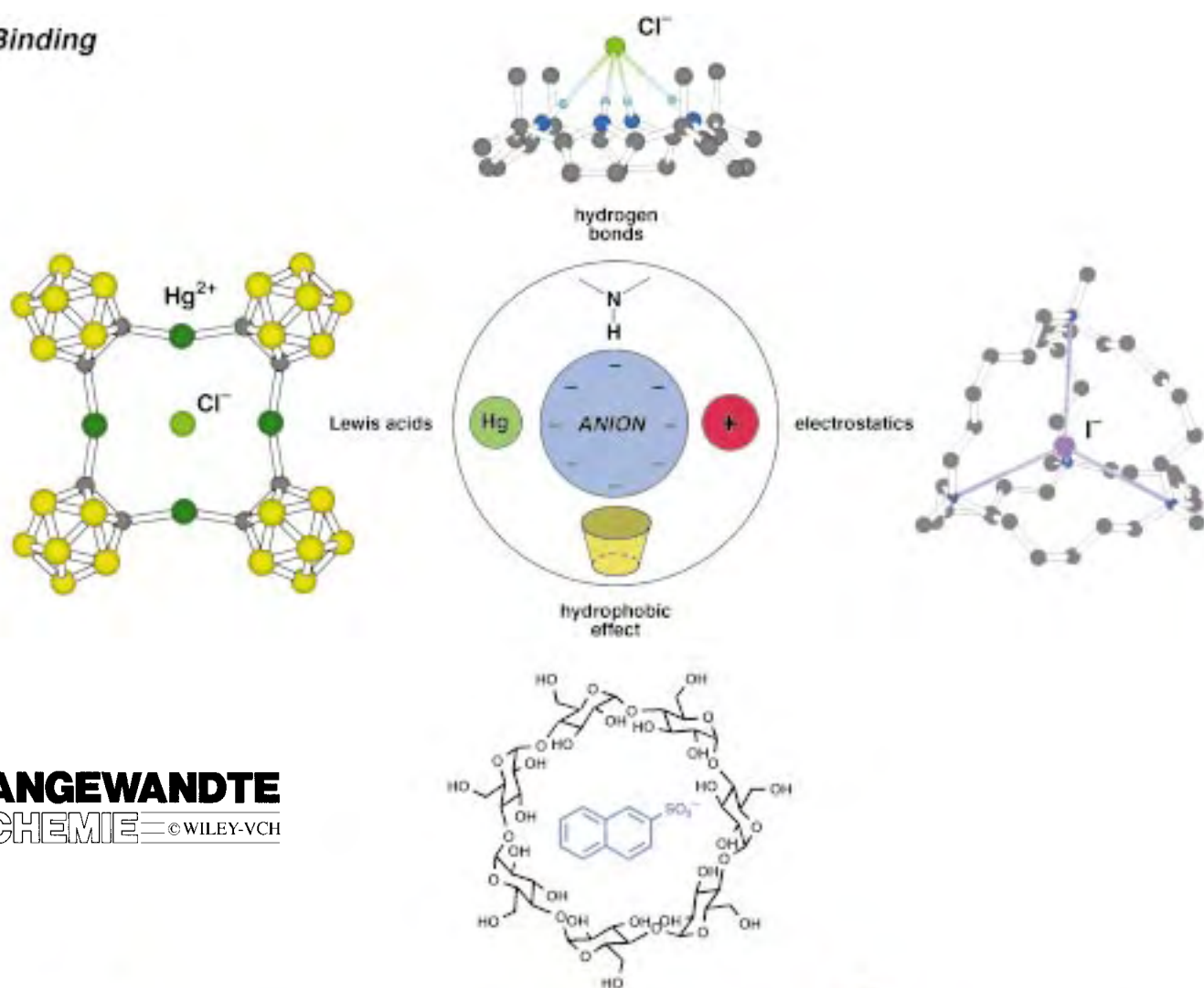
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• Sources	A13	• Authors	633
• Classified	A15	• Preview	634

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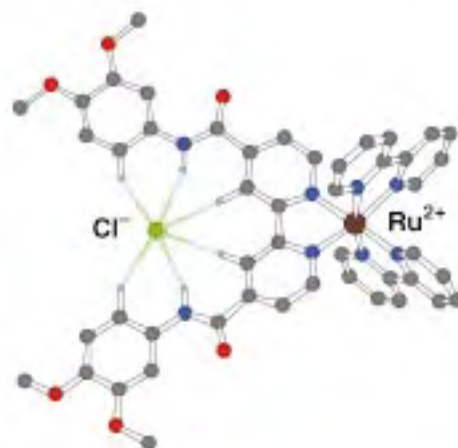
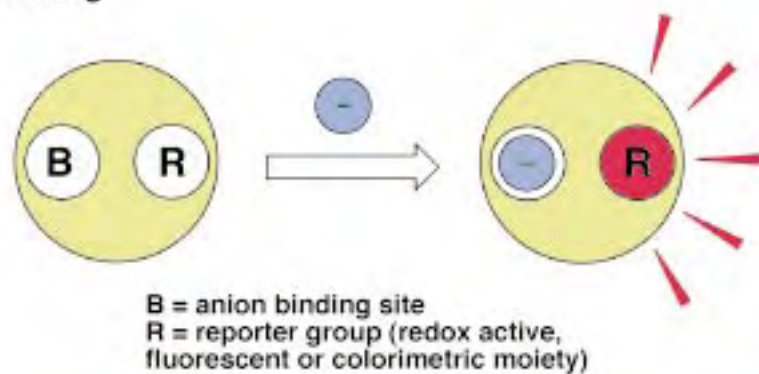
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Binding

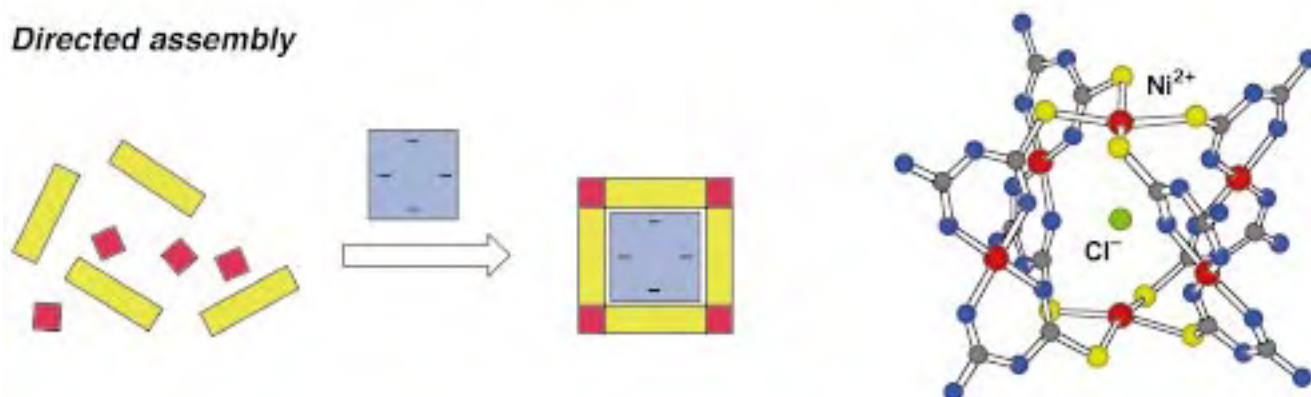


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Sensing



Directed assembly



Anion Recognition and Sensing: The State of the Art and Future Perspectives

Paul D. Beer* and Philip A. Gale*

Anion recognition chemistry has grown from its beginnings in the late 1960s with positively charged ammonium cryptand receptors for halide binding to, at the end of the millennium, a plethora of charged and neutral, cyclic and acyclic, inorganic and organic supramolecular host systems

for the selective complexation, detection, and separation of anionic guest species. Solvation effects and pH values have been shown to play crucial roles in the overall anion recognition process. More recent developments include exciting advances in anion-templated syntheses and directed self-

assembly, ion-pair recognition, and the function of anions in supramolecular catalysis.

Keywords: anions • macrocycles • molecular recognition • self-assembly • sensors • supramolecular chemistry

1. Introduction

Anion recognition chemistry has its roots in work conducted in the late 1960s around the same time that Pedersen reported the synthesis and coordination chemistry of crown ethers and Lehn published the first accounts of cation coordination chemistry by cryptands. In the 1970s, the coordination chemistry of group 1 and 2 metal and ammonium cations attracted most interest and consequently cation recognition is now a well-developed and mature area of supramolecular chemistry. By contrast, the coordination chemistry of anions received little attention (with a few notable exceptions) and it has only been in the last twenty years that sustained effort has been applied to the problems inherent in binding anions.^[1] There are a number of reasons for this sudden growth in this new area of coordination chemistry. Anions are ubiquitous throughout biological systems. They carry genetic information (DNA is a polyanion) and the majority of enzyme substrates and co-factors are anionic. A well known example is carboxypeptidase A,^[2] an enzyme that coordinates to the C-terminal carboxylate group

of polypeptides by the formation of an arginine–aspartate salt bridge, and catalyzes the hydrolysis of this residue. The salt-bridge binding motif is also observed in zinc finger/DNA complexes^[3] and RNA stem loop–protein interactions.^[4] Anions also play roles in the areas of medicine and catalysis, whilst pollutant anions have been linked to eutrophication of rivers (from the over use of phosphate-containing fertilizers)^[5] and carcinogenesis (metabolites of nitrate).^[6] The production of pertechnetate during the reprocessing of nuclear fuel (and its subsequent discharge into the seas and oceans) is also a matter of environmental concern.

The design of anion receptors is particularly challenging. There are a number of reasons for this. Anions are larger than isoelectronic cations (Table 1)^[7] and therefore have a lower charge to radius ratio. This means that electrostatic binding interactions are less effective than they would be for the smaller cation. Additionally anions may be sensitive to pH values (becoming protonated at low pH and so losing their negative charge), thus receptors must function within the pH window of their target anion. Anionic species have a wide range of geometries (Figure 1) and therefore a higher degree of design may be required to make receptors complementary to their anionic guest.

Solvent effects also play a crucial role in controlling anion binding strength and selectivity. Electrostatic interactions

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Table 1. A comparison of the radii r of isoelectronic cations and anions in octahedral environments.^[7]

Cation	r [Å]	Anion	r [Å]
Na ⁺	1.16	F [−]	1.19
K ⁺	1.52	Cl [−]	1.67
Rb ⁺	1.66	Br [−]	1.82
Cs ⁺	1.81	I [−]	2.06

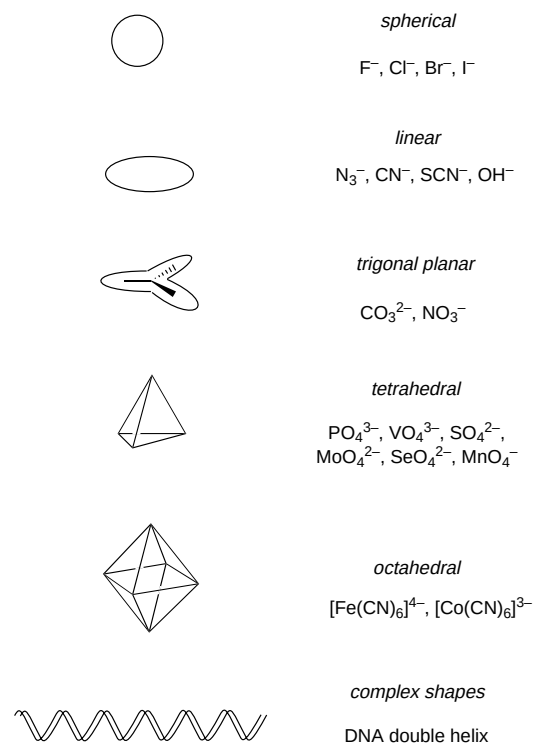


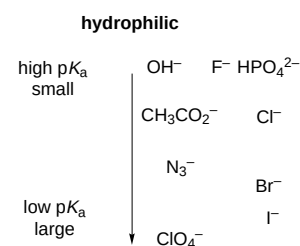
Figure 1. The structural variety of anions.

generally dominate in anion solvation, and hydroxylic solvents in particular can form strong hydrogen bonds with anions. A potential anion receptor must therefore effectively

compete with the solvent environment in which the anion-recognition event takes place. For example, a neutral receptor that binds anions solely through ion–dipole interactions may only complex anions in aprotic organic solvents, whereas a charged receptor has the capacity to bind highly solvated (hydrated) anions in protic solvent media. It is no coincidence that biological anion receptor systems are optimized to operate in a very specific range of environments where the source of selectivity for the biological anion is the difference in free energy lost on dehydrating the anion and that gained by the interaction of the anion with the binding site.^[8]

Hydrophobicity can also influence the selectivity of a receptor. The Hofmeister series^[9] (Scheme 1), which was first established through studies on the effect of salts on the solubility of proteins, orders anions by their hydrophobicity (and therefore degree of aqueous solvation). Hydrophobic anions are generally bound more strongly in hydrophobic binding sites.

This review article will highlight important developments in the recognition and sensing of anionic substrates and look at recent advances^[10–13] that suggest that anion coordination chemistry will have a rich future in the 21st Century.



hydrophobic
Scheme 1. Hydrophilic/hydrophobic series of anions.

Paul D. Beer was born in Totnes, Devon (UK). In 1979 he obtained a first class honours degree in chemistry from King's College London, and remained there to undertake research in the field of organophosphorus chemistry under the supervision of Dr C. D. Hall. In 1982 he received a PhD, and a Royal Society postdoctoral fellowship enabled him to conduct research in supramolecular chemistry with Professor J.-M. Lehn at the Université Louis Pasteur, Strasbourg (France). After a demonstratorship at the University of Exeter in 1983, he took up a New Blood Lectureship at the University of Birmingham in 1984. In 1990 he moved to the University of Oxford, where he is also a tutorial fellow at Wadham College. He became a professor of chemistry in 1998. He was awarded the RSC Meldola medal in 1987, the UNESCO Javed Husain prize in 1993, and the RSC Corday-Morgan medal in 1994. His research interests cover many aspects of charged and neutral guest coordination chemistry, including the synthesis and coordination properties of redox- and photo-responsive receptors designed to selectively recognize and sense biological and environmentally important guest species.



P. D. Beer



P. A. Gale

Philip A. Gale was born in Liverpool (UK) in 1969. He graduated from Wadham College, Oxford with a BA (Hons.) in Chemistry in 1992 (and an MA in 1995). In 1992, he moved to Linacre College and carried out graduate work at the Inorganic Chemistry Laboratory. He graduated in 1995 (DPhil) for work carried out with Professor Paul D. Beer on the cation coordination chemistry of calix[4]diquinones and the functionalization of calix[5]arenes. He was awarded a Fulbright post-doctoral fellowship in 1995 and joined Professor Jonathan L. Sessler's research group at the University of Texas at Austin working on the synthesis, anion coordination properties, and applications of calix[4]pyrroles (meso-octaalkylporphyrinogens). In 1997, he took up a Royal Society University Research Fellowship at the Inorganic Chemistry Laboratory, Oxford. In 1999 he moved to his present position as Royal Society University Research Fellow and Lecturer at the University of Southampton. His research interests include many aspects of supramolecular chemistry including anion receptor chemistry.

2. Anion Recognition

The design of selective hosts for anions requires that the geometry and basicity of the anion and the nature of the solvent medium be taken into account. Complementarity between the receptor and anion is clearly crucial in determining selectivities. A useful way of categorizing anion receptors is to consider the types of noncovalent interaction used to complex the anionic guest. These include electrostatic interactions, hydrogen bonding, hydrophobicity, coordination to a metal ion, and combinations of these interactions working together. The work described in this section is not a comprehensive review of the literature. It is intended to be a series of paradigms that illustrate particular elements of anion recognition.

2.1. Electrostatic Interactions

In some very elegant early work, Schmidtchen produced the macrotricyclic quaternary ammonium hosts **1** and **2**^[14, 15] and found that these receptors formed complexes with a variety of anionic guests in water.^[16] The cavity in receptor **1** has an internal diameter of 4.6 Å and forms a strong complex with an iodide ion (diameter: 4.12 Å). The crystal structure of the iodide complex (Figure 2) reveals that the anion is encapsulated within the macrotricyclic.^[17] The larger receptor **2** is able to form complexes with anions such as *p*-nitrophenolate that are too large to form complexes with receptor **1**. Receptors **1** and **2** are positively charged and are therefore associated with counterions that may compete for the anion-binding site. To overcome this, Schmidtchen produced zwitterionic receptors such as **3** and **4** that are neutral.^[18, 19] NMR experiments in water showed that receptor **4** forms stronger complexes with chloride, bromide, and iodide ions than receptor **1**.

Dipolar bonds can also be used for anion recognition.^[20, 21] The phosphine oxide–disulfoxide macrocycle **5** contains three convergently arranged dipolar bonds that define an anion binding site below the macrocyclic ring. NMR studies in CDCl₃/CD₃OD (98/2) reveal that weak complexes are obtained with chloride ($K = 65 \text{ M}^{-1}$) and other anions.

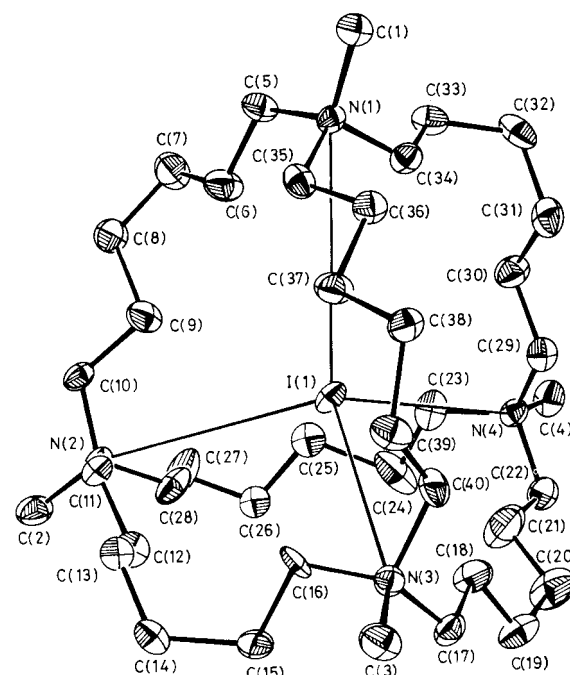
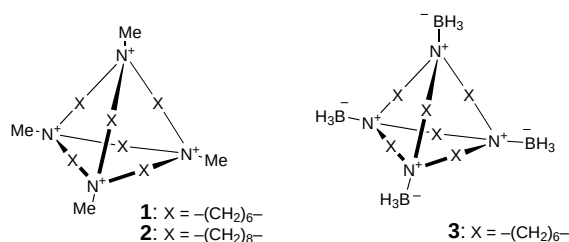
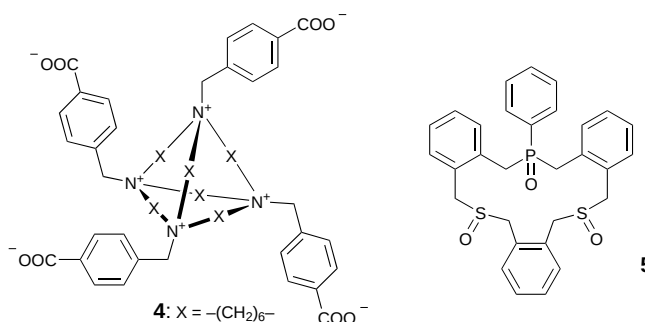
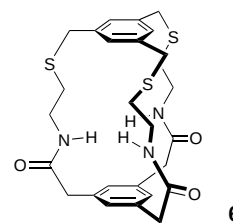


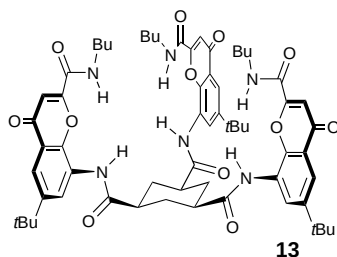
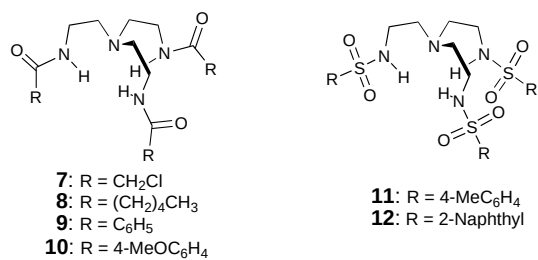
Figure 2. The X-ray crystal structure of the iodide complex of receptor **1** (hydrogen atoms are omitted). Reproduced with permission from ref. [17]. Copyright© The Royal Society of Chemistry 1984.

2.2. Hydrogen Bonds

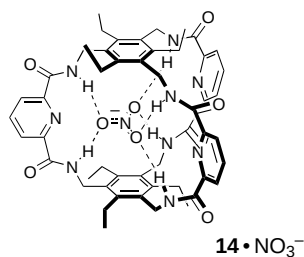
Hydrogen bonds are directional, which allows for the possibility of designing receptors with specific shapes that are capable of differentiating between anionic guests with different geometries or hydrogen-bonding requirements in non-polar solvents.

In 1986, Pascal prepared the first purely amide-based anion receptor.^[22] Receptor **6** showed evidence of binding fluoride ions in [D₆]DMSO. In 1993 Reinhoudt and co-workers produced a series of acyclic tripodal receptors containing amide groups (**7–12**)^[23] whilst Raposo et al. synthesized a preorganized amide-modified cyclohexyl ring **13**.^[24] Receptors **7–13** are all C₃ symmetric and are consequently arranged to bind tetrahedral anions.





Anslyn and co-workers have recently reported the synthesis of a trigonal box by condensation of 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene with three equivalents of 2,6-pyridinedicarbonyl dichloride in dichloromethane in the presence of triethylamine.^[25] The rigid cyclophane **14** was formed in 40 %



yield. Interestingly, because the amide NH groups in **14** are arranged in a trigonal prismatic array, they are able to coordinate to the π -electron system of planar anions such as carboxylates and nitrate. The crystal structure of the acetate complex of **14** is shown in Figure 3 and reveals that the acetate anion is bound within the cavity of the box. Anslyn et al. concluded that nitrate must also be bound within the cavity of the box because it is planar and bound very strongly (in CD₃CN/CD₂Cl₂ (3/1 (v/v)) solution it is bound only 2.6 times less strongly than acetate even though it is 10⁶ times less basic). Therefore, receptor **14** represents a significant advance in the coordination of the normally weakly coordinating nitrate ion.

Urea and thiourea are particularly good hydrogen-bond donors and are excellent receptors for Y-shaped anions such as carboxylate through the formation of two hydrogen bonds. The very simple urea-based receptor **15** shows increasingly stable complexes with more highly charged and more basic bidentate anions (Table 2).^[26]

Umezawa and co-workers have produced a series of ayclic thiourea cleft molecules including some highly preorganized systems containing a xanthene spacer.^[27] Receptors **16** and **17** bind anions very strongly with stability constants up to

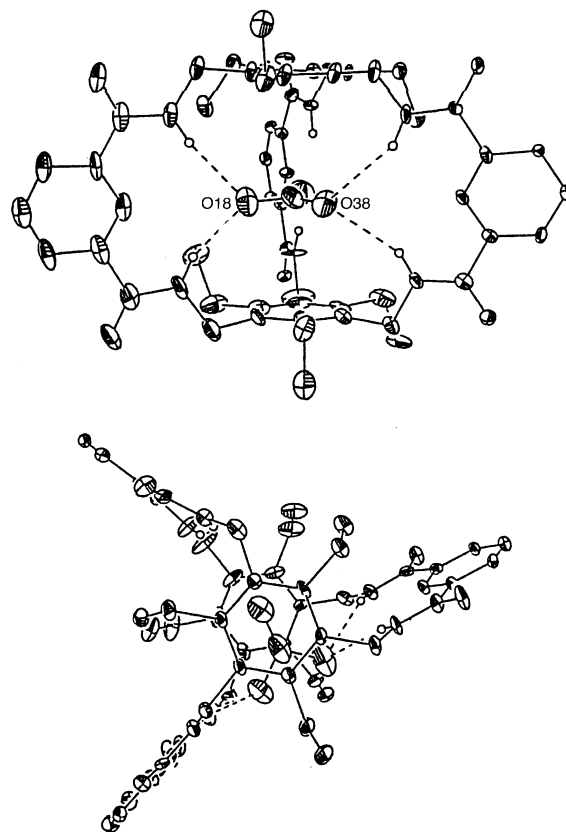


Figure 3. The X-ray crystal structure of the acetate complex of receptor **14** (hydrogen atoms are omitted). Reproduced with permission from ref. [25]. Copyright © WILEY-VCH 1997.

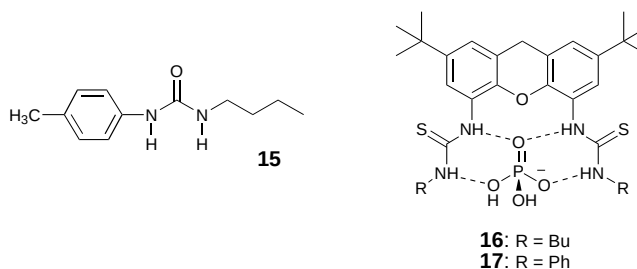
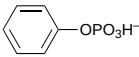
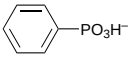
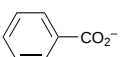
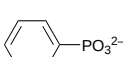
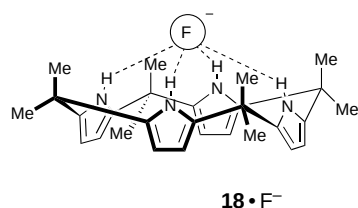


Table 2. The basicity and stability constants (in DMSO) of various bidentate anions with receptor **15**.

Guest	p <i>K</i> _b	K [M ⁻¹]
	13	30
	12	140
	10	150
	7	2500

195000 M^{-1} for receptor **17** and H_2PO_4^- ions in $[\text{D}_6]\text{DMSO}$. This is a consequence primarily of the high degree of preorganization present in these receptors. The selectivity for H_2PO_4^- ions can be attributed to the complementary hydrogen-bonding array present in these clefts that can form four hydrogen bonds to each H_2PO_4^- ion. Pyrrole NH groups may also form hydrogen bonds to anions. In 1996, Sessler and co-workers reported that calix[4]pyrroles (*meso*-octaalkylporphyrinogens), macrocycles first synthesized in the nineteenth century by Baeyer,^[28] also coordinate to anions.^[29] *meso*-Octamethylcalix[4]pyrrole **18** was shown to form complexes with fluoride, chloride, and dihydrogen phosphate with stability constants of 17200, 350, and 100 M^{-1} respectively in CD_2Cl_2 . The conformation of the macrocycle in the solid state



changes dramatically upon anion complexation. The free calixpyrrole adopts a 1,3-*alternate* conformation wherein adjacent rings are oriented in opposite directions. However the crystal structure of the chloride complex of **18** reveals that the macrocycle adopts a *cone* conformation with the four pyrrole NH groups forming hydrogen bonds to the bound chloride ion (Figure 4).

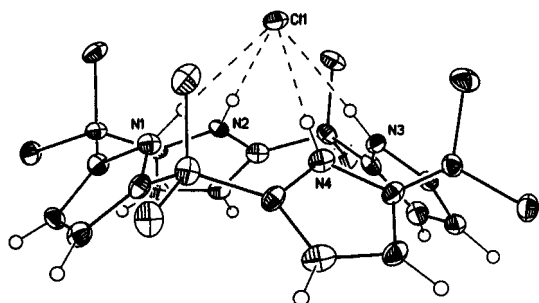


Figure 4. The X-ray crystal structure of the chloride complex of receptor **18**. Reproduced with permission from ref. [29]. Copyright© American Chemical Society 1996.

The ease of preparing calixpyrroles in high yield makes them amenable to industrial applications. Indeed, Sessler and co-workers have already produced calixpyrrole-modified solid supports (such as Gel M; Figure 5) for the separation of anions by high-performance liquid chromatography (HPLC).^[30] The separation of oligonucleotides between twelve and eighteen bases in length by Gel M is shown in Figure 5.^[31] Other uses for these macrocycles include their incorporation in ion-selective electrodes,^[32] in electrochemically active discrete molecular hosts^[33] designed to sense anionic guests, and in optical sensors for anions.^[34]

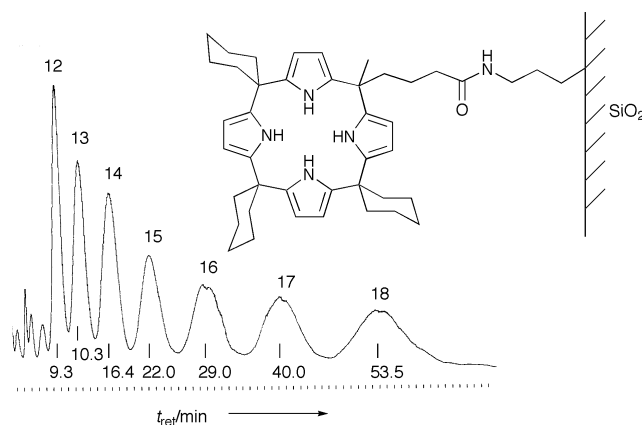
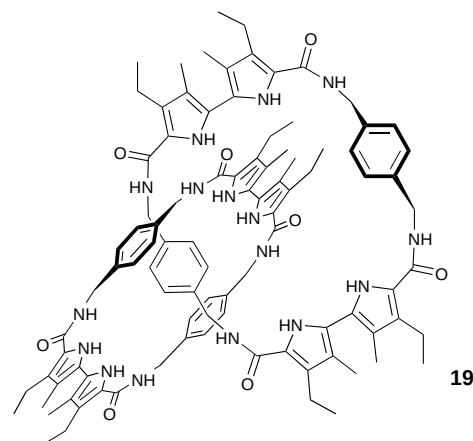


Figure 5. Separation of dT_{12} – dT_{18} on calixpyrrole-modified silica gel. Flow rate 0.4 mL min^{-1} , mobile phase $\text{MeCN}/[\text{aq NaCl (250 mM)}/\text{aq Na}_3\text{PO}_4 (50\text{ mM})]$ 1/1 (v/v; isocratic), pH 7.0, column temperature 25°C , UV detection at 265 nm. t_{ret} = retention time. Reproduced with permission from ref. [31]. Copyright© The Royal Society of Chemistry 1998.

Sessler, Vögtle and co-workers have reported the synthesis of a bipyrrrole-based [2]catenane **19** that forms extremely stable complexes with anions. NMR titration techniques



revealed that the catenane binds anions with very high stability constants (up to 10^7 M^{-1} with H_2PO_4^- in $[\text{D}_2]1,1,2,2$ -tetrachloroethane).^[35] This high stability is attributed to the formation of a tetrahedral cavity between the rings which provides an ideal coordination geometry for tetrahedral anion coordination (Figure 6).

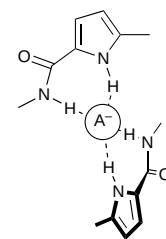


Figure 6. Catenane **19** provides an array of tetrahedral donor hydrogen bonds.

2.3. Electrostatic Interactions and Hydrogen Bonds

Hydrogen bonds and electrostatic interactions can be used together to produce very effective receptors for anions. In fact, the earliest example of a macrocyclic synthetic anion receptor, reported in 1968, bound anions by a combination of these interactions. Park and

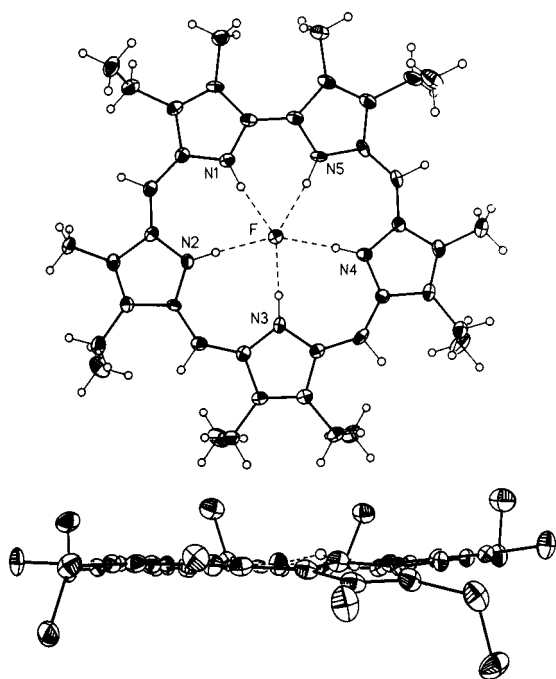
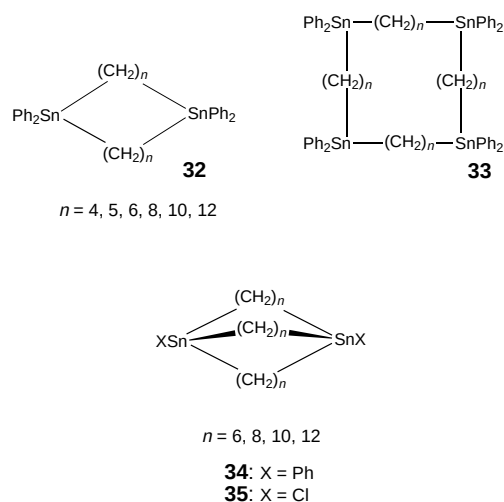


Figure 7. The crystal structure of the fluoride complex of diprotonated sapphyrin **31**. Reproduced with permission from ref. [49]. Copyright© American Chemical Society 1992.

2.4. Metal or Lewis Acid Coordination

Electron-deficient Lewis-acidic centers are able to bind to anions by an orbital overlap that causes a bonding interaction. This has led to the production of many new chelating and macrocyclic hosts for anions containing atoms such as boron, mercury, silicon, germanium, and tin.

In 1984, Azuma and Newcomb reported the synthesis of a series of tin-based macrocycles **32** and **33**.^[50] Coordination studies with **32** showed that this family of macrocycles would form 1:1 and 1:2 host:anion complexes with chloride ions in

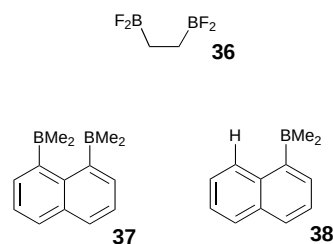


acetonitrile solution,^[51] with stability constants ranging from 400 to 850 M^{-1} .

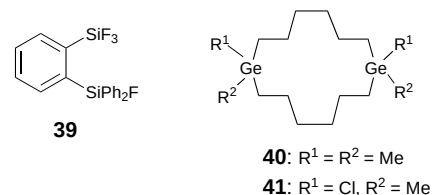
Newcomb et al. have also synthesized a series of cryptand-like tin-containing macrobicycles **34** and **35**.^[52] Anion binding

by these cage systems was found to be kinetically slower than that observed in the case of the macrocyclic receptors **32** and **33** with exclusively 1:1 complexes being observed.^[53] ^{119}Sn NMR studies showed that fluoride ions were bound five orders of magnitude more strongly than chloride ions in chloroform.^[54] Crystallographic studies later revealed that both ions were bound within the cavity. The fluoride ion was coordinated to both tin atoms ($r_{\text{Sn-F}} = 2.12/2.28 \text{ \AA}$) whereas chloride was located much closer to one tin atom than the other.^[55]

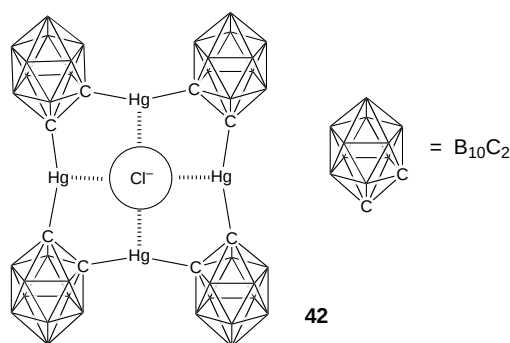
One of the earliest examples of synthetic anion coordination was reported in 1967 by Shriver and Biallas.^[56] The chelating boron-based receptor **36** was found to form stronger complexes with methoxide ions than monodentate boron trifluoride. Katz has also produced chelating boron-based receptors for anions.^[57, 58] The anion-coordinating ability of receptor **37** (with hydride, fluoride, and hydroxide) was compared with that of the monodentate analogue **38**. It was found that **37** could extract hydride or fluoride ions that were bound to compound **38**. The crystal structures of the hydride and chloride complexes of **37** show the anions are bound between the boron atoms.^[59]



A variety of silicon- and germanium-based receptors including **39**–**41** have been synthesized. Compound **39** has been shown to coordinate to fluoride ions with a stability constant of $\lg K > 9$ in $[\text{D}_6]\text{acetone}$.^[60] Germanium-based macrocycles, for example, **40** and **41** have also been prepared.^[61, 62] Receptor **40** transports chloride ions more efficiently than bromide ions across organic phases.^[63]



Mercury has been used as a Lewis-acidic center in a number of anion receptors.^[64, 65] Some of the most elegant examples of this type of receptor are the mercuracarboranes produced by Hawthorne and co-workers.^[66] These receptors consist of carborane cages linked through their carbon atoms by mercury atoms. One example containing four carborane units is receptor **42**. The X-ray crystal structure of this material



shows that a chloride ion is bound in the plane of the macrocycle equidistant (2.94 Å) from the four mercury atoms (Figure 8a). Hawthorne and co-workers have proposed that chloride ions present during the synthesis of this material act

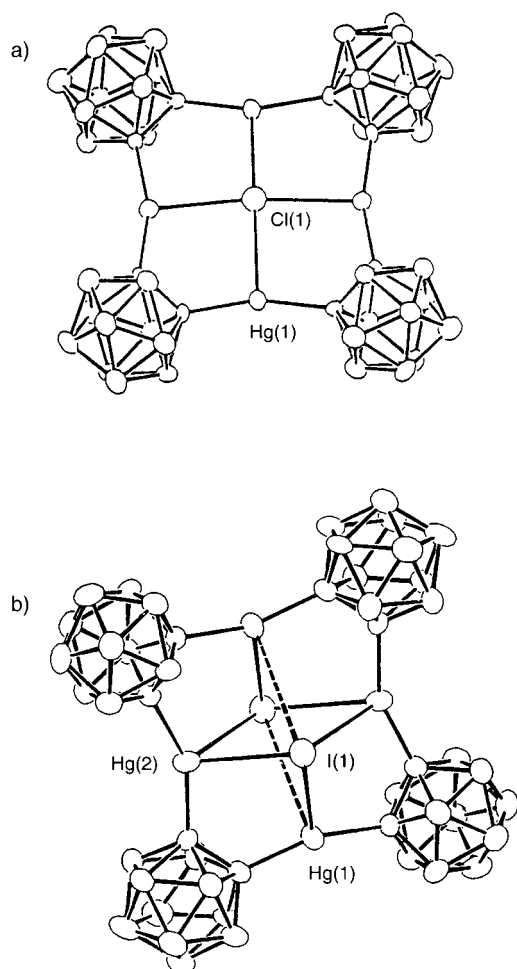
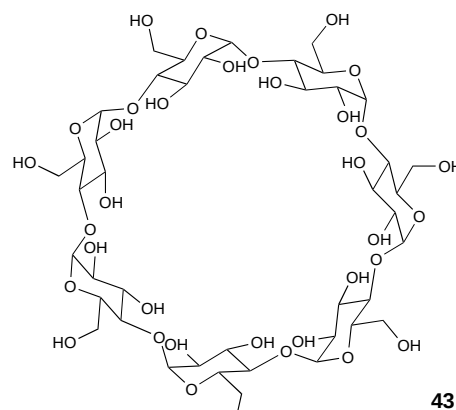


Figure 8. The X-ray crystal structures of the chloride (a) and the iodide (b) complexes of receptor **42**. a) Reproduced with permission from ref. [66]. Copyright© VCH 1991. b) Reproduced with permission from ref. [67]. Copyright© American Chemical Society 1992.

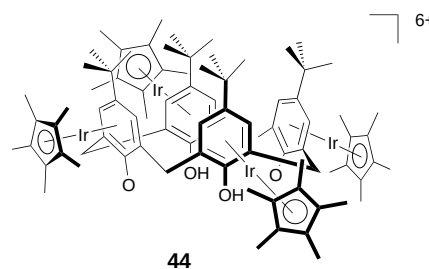
as templates around which the receptor forms. Indeed when chloride was excluded from the synthesis the yield of the product decreased. Iodide ions are too large to fit into the cavity of this receptor and instead perch over the cavity (Figure 8b).^[67] Further examples of anion-templated processes are discussed in Section 4.2.

2.5. The Hydrophobic Effect

Inoue and co-workers have studied the inclusion of a series of naphthalenesulfonates by β -cyclodextrin **43** in water.^[68] The binding interaction in these complexes is primarily a result of the hydrophobic effect, with the naphthalene residue displacing water molecules from the internal cavity of the cyclodextrin. The anionic sulfonate group remains outside the cavity in contact with the solvent, thereby controlling the orientation of the naphthalene group within the cavity.



Atwood, Steed, and co-workers have coordinated transition metals to the outside of calixarenes in order to reduce the electron density present in the “cup”, thus making the cavity more amenable to hydrophobic anionic guests.^[13, 69, 70] The crystal structures of anions bound in the calixarene cavity of a number of receptors were elucidated, including the HSO_4^- complex of **44** (Figure 9). Stability constants as high as 550 M^{-1} were observed for chloride complexation in aqueous solution.^[71]



3. Anion Sensors

With the aim of advancing chemical sensor technology, considerable recent attention has focused on the design of receptors that have the ability to selectively bind and sense the anion recognition event through a macroscopic electrochemical or optical response.^[11, 72, 73]

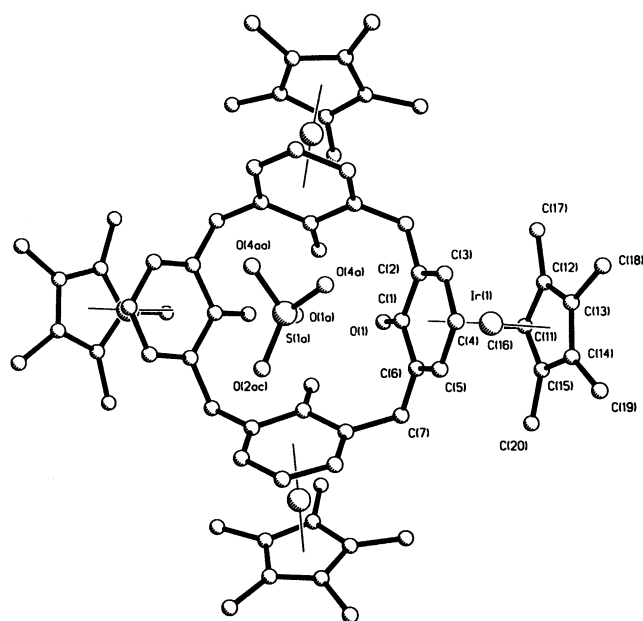
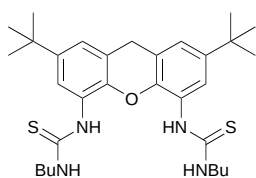


Figure 9. The X-ray crystal structure of the HSO_4^- complex of receptor **44** (hydrogen atoms are omitted). Reproduced with permission from ref. [71]. Copyright© American Chemical Society 1997.

3.1. Electrochemical Recognition of Anions

Electrochemical molecular recognition is an expanding research area at the interface of electrochemistry and supramolecular chemistry.^[74, 75] Three strategies have been applied to the electrochemical detection of the formation of receptor–anion complexes: 1) extraction of a charged guest into a membrane by a nonelectroactive host and detection of the resulting membrane potential (ion-selective electrodes (ISEs), chemically modified field-effect transistors (CHEMFETs), potentiometric sensors), 2) detection of a current/potential perturbation of the properties of a redox-active host on complex formation (voltammetric/ampereometric sensors), and 3) production of a chemically modified electrode (CME) consisting of a redox-active matrix and an anion-selective binding site.

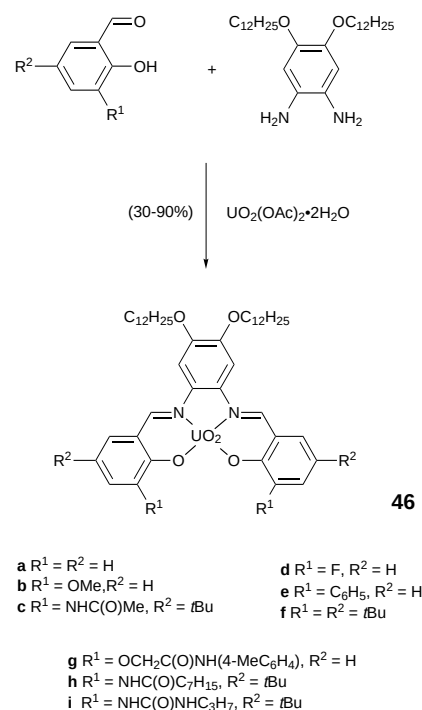
Many of the neutral lipophilic urea- and thiourea-containing receptors discussed earlier have been successfully incorporated into ion-selective electrodes (ISEs) which are capable of selective anion detection. For example, Umezawa and co-workers have recently produced chloride-selective membranes based on bis-urea systems such as **45**.^[76]



45

Reinhoudt and co-workers have incorporated an array of lipophilic uranysalophane derivatives such as **46a–i**

(Scheme 2) into chemically modified field-effect transistor (CHEMFET) membranes and shown that these devices are capable of selectively detecting a range of anions (for example, fluoride may be detected in the presence of a 150-fold excess of SCN^-), and is dependent upon the lipophilic



Scheme 2. Synthesis of uranysalophane complexes **46**.

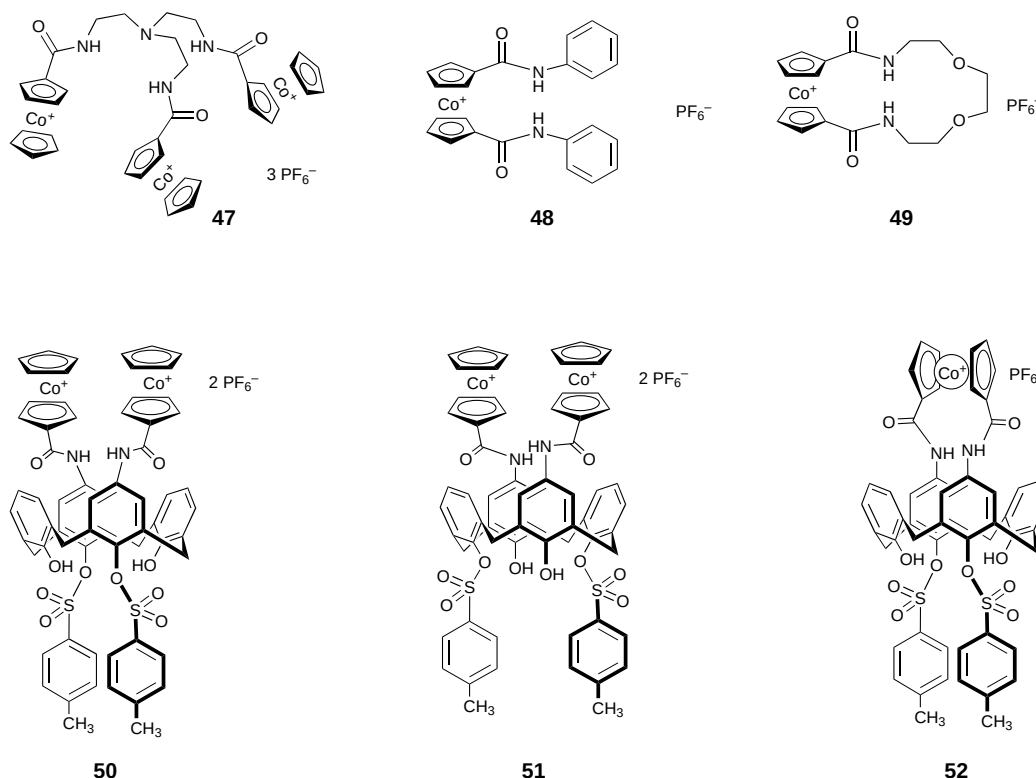
and hydrogen-bond donor/acceptor substituents near the uranyl binding site of the receptor.^[77–79]

Recently Král et al. have incorporated calixpyrrole macrocycles (for example, **18**) into ISEs and shown that the membrane is capable of acting as an anion sensor at low pH values.^[32]

A variety of organic, organometallic, and inorganic redox-active centers have been incorporated into various host frameworks and been shown to electrochemically detect charged and neutral guests.^[80, 81]

The first redox-active class of anion receptor based on the cobaltocenium moiety was reported by Beer and Keefe in 1989.^[82] Since then, a plethora of acyclic, macrocyclic, and calixarene receptors containing cobaltocenium have been prepared (for example, **47–52**^[83–87]). Cyclic voltammetric experiments demonstrated that all these receptors could electrochemically sense anions. The addition of anions to solutions of the receptors in acetonitrile resulted in significant cathodic shifts of the reversible $\text{Cp}_2\text{Co}^+/\text{Cp}_2\text{Co}$ redox couple. The complexed anionic guest effectively stabilizes the positively charged cobalt center making it more difficult to reduce. For example, complexation of chloride ions by receptors **47** and **48** induced cathodic shifts of 30 mV and 85 mV, respectively, whereas larger magnitudes of 200 mV and 240 mV were observed for the complexation of dihydrogen phosphate. The electrochemical results correlate well with stability constants determined by ^1H NMR spectroscopy, with the highest K values obtained with the H_2PO_4^- ion.

The anion-coordination properties of the cobaltocenium-bridged calix[4]arene receptors are dependent upon the degree of preorganization of the upper rim.^[88–90] Stability constant values for the isomeric receptors **50** and **51** suggests that exchanging the positions of the tosyl substituent on the



lower rim of the calix[4]arene has a dramatic influence on the anion coordination properties of the upper rim. For example, **50** binds acetate much better than H_2PO_4^- , whereas the selectivity preference is reversed with isomeric **51**. The cobaltocenium-bridged calix[4]arene **52** forms thermodynamically stronger anion complexes with carboxylate and H_2PO_4^- ions than either **50** or **51**, and with a notable selectivity for acetate. As evidenced from the crystal structure of the chloride complex of **52** (Figure 10), this selectivity preference may be rationalized by the hydrogen bond donor cavity from the upper rim bidentate amide group being of complementary topology for complexing bidentate anions such as carboxylates.

Electrochemical investigations demonstrated that each of these receptors could sense a variety of anions, with substantial cathodic perturbations of the respective $\text{Cp}_2\text{Co}^+/\text{Cp}_2\text{Co}$ redox couple by up to $\Delta E = 120$ mV for **50** and 155 mV for **52** with acetate being observed. Cathodic shifts of both the $\text{Cp}_2\text{Co}^+/\text{Cp}_2\text{Co}$ and porphyrin oxidation redox couples were noted by voltammetric methods on complexation of receptor **53** with anions.^[91]

The redox-active ferrocene moiety has also been exploited in the electrochemical sensing of anions, both in organic and aqueous media.^[80, 81] Ferrocene units appended with secondary amides have also been used for anion recognition.^[92, 93] Being neutral these receptors have no inherent electrostatic attraction for anions, which makes the stability constants, as determined by NMR spectroscopy, smaller than those of the analogous cobaltocenium systems. Electrostatic interaction can, however, be switched on by oxidation of the ferrocene group to the ferrocenium ion, and consequently these molecules exhibit interesting electrochemical anion-recognition effects. For example, **54–57** were capable of detecting H_2PO_4^- ions in acetonitrile as shown by large cathodic shifts of up to 240 mV in the presence of a tenfold excess of HSO_4^- and Cl^- ions. In contrast receptor **58** binds HSO_4^- ions selectively in the presence of H_2PO_4^- ions. The basic amine functionality of **58** is protonated by the acidic hydrogen

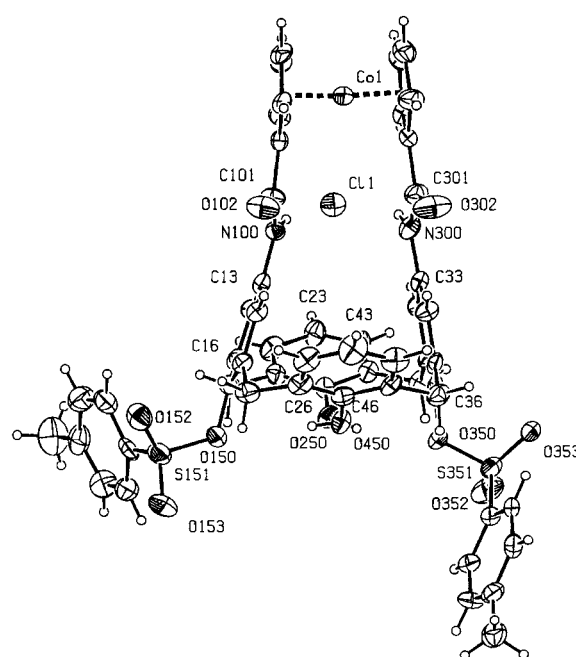
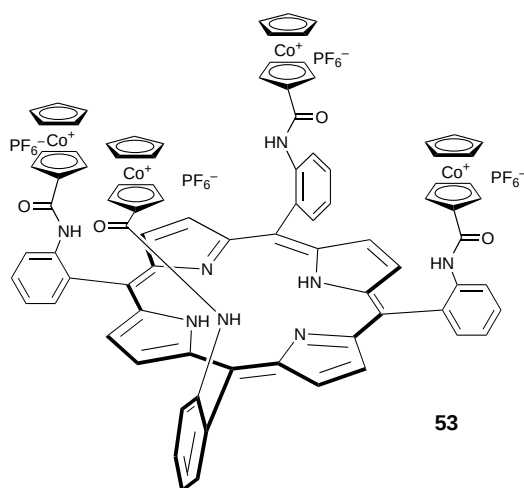
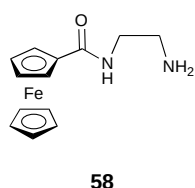
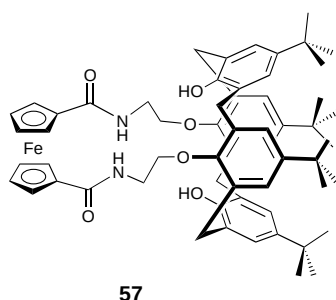
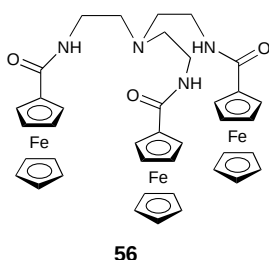
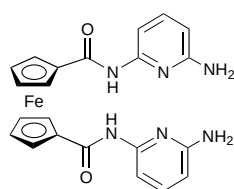
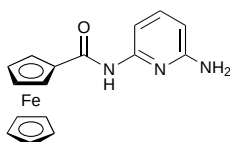


Figure 10. The X-ray crystal structure of the chloride complex of receptor **52**. Reproduced with permission from ref. [90]. Copyright© American Chemical Society 1999.

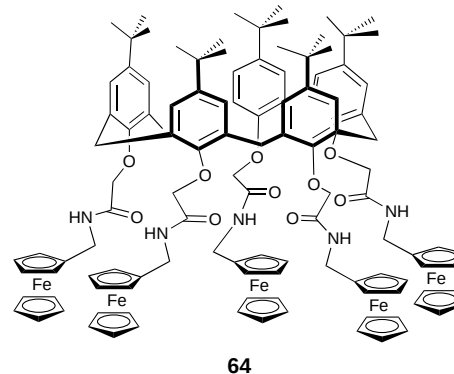
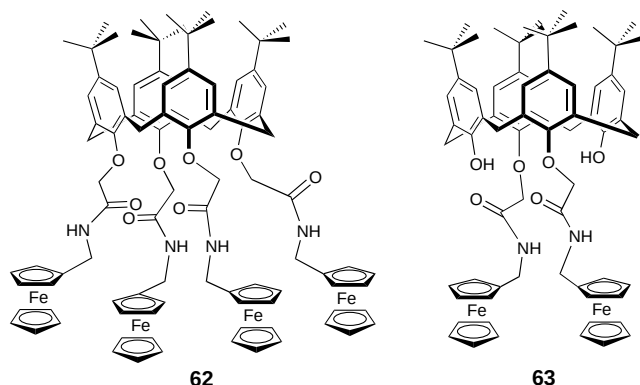


sulfate ion and the positively charged receptor strongly binds the produced SO_4^{2-} , as noted by a marked electrochemical reductive-stripping response.

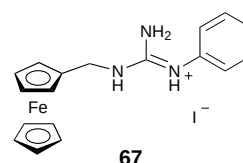
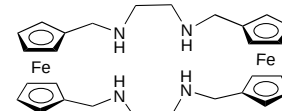
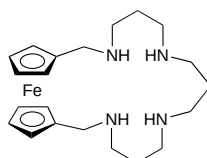


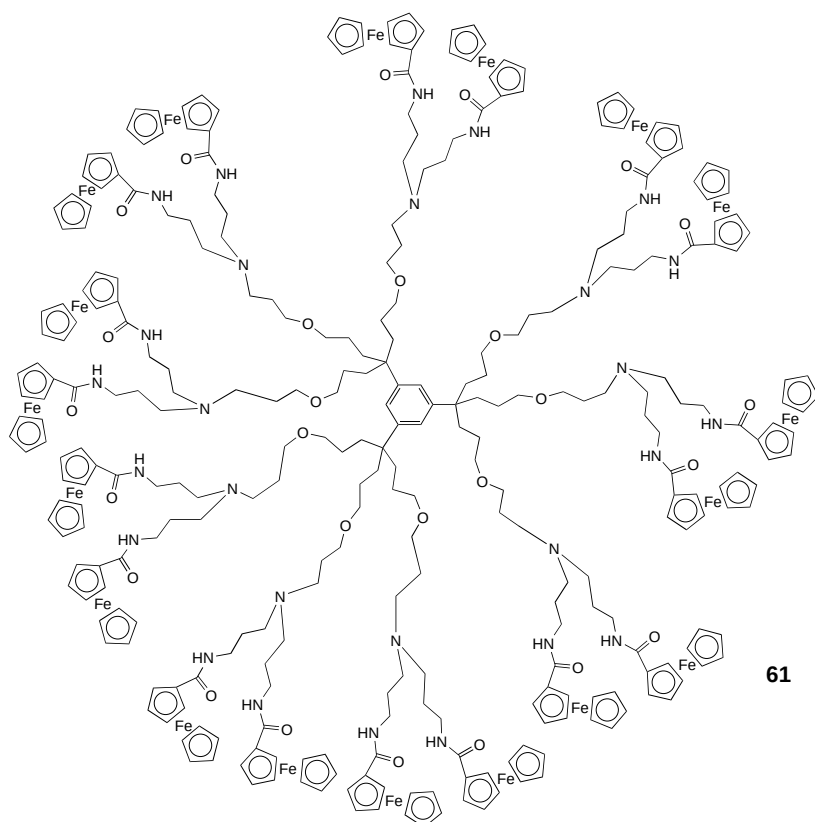
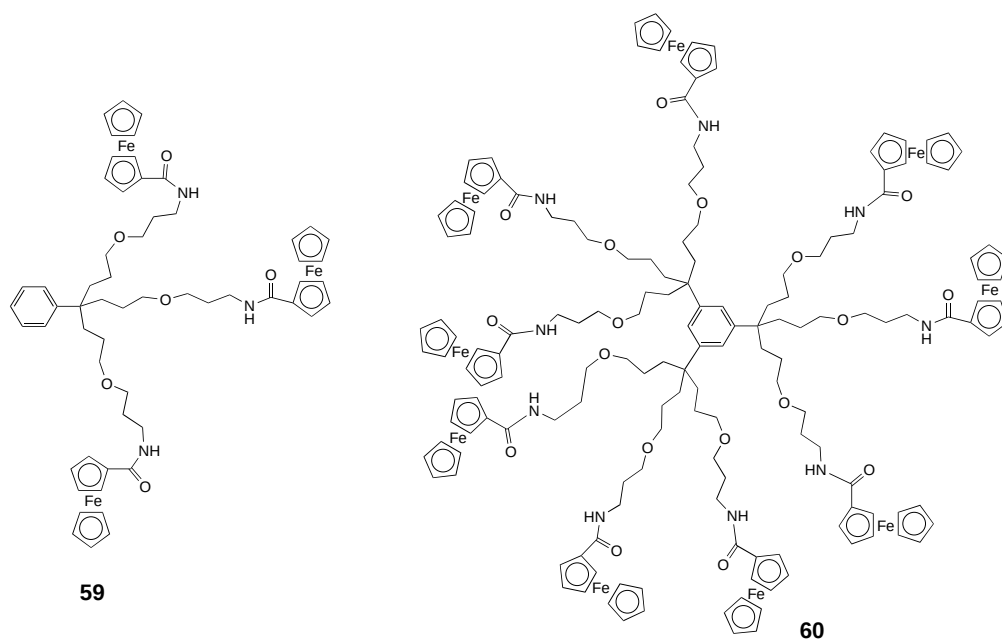
Astruc and co-workers have produced dendrimers **59–61** containing 3, 9, and 18 ferrocene units,^[94] respectively and found evidence for a dendritic effect in the anion-recognition process. The largest induced cathodic shift was observed on addition of H_2PO_4^- ions. Interestingly as the size of the dendrimer increases so does the perturbation caused by a particular anion. Recently the same research group reported that a cationic metallodendrimer with 24 $[\text{CpFe}(\eta^6\text{-}N\text{-alkylaniline})]^+$ termini is capable of recognizing chloride and

bromide ions.^[95] Lower rim polyferrocene-substituted calixarenes **62–64** have recently been shown to bind and electrochemically sense anions, with maximum cathodic perturbations of 160 mV being observed for H_2PO_4^- .^[96]



Beer et al. have synthesized a series of acyclic and macrocyclic ferroceneamine ligands (for example, **65** and **66**) that can selectively bind and electrochemically detect phosphate and sulfate (in various states of protonation) as well as nucleotide ions in water.^[97–99] For example, **65** senses phosphate ions at pH 7 as shown by a cathodic shift of 50 mV, whereas sulfate does not induce a redox response. In contrast **66** electrochemically discriminates for sulfate over phosphate at pH 4 in aqueous THF with a cathodic shift of 54 mV. Calibration curves of the change in the half-wave potential ΔE versus the $[\text{A}^-]/[\text{L}]$ ratio at a certain pH value showed that

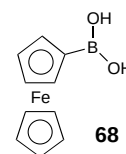




it was possible to quantitatively determine phosphate and sulfate concentrations in the presence of competing anions with **65** and **66**. This result demonstrates their potential use as prototype anion sensors.^[99] The ferrocene-appended guanidinium receptor **67** senses pyrophosphate in methanol/water mixtures and exhibits cathodic shifts of 70 mV.^[100]

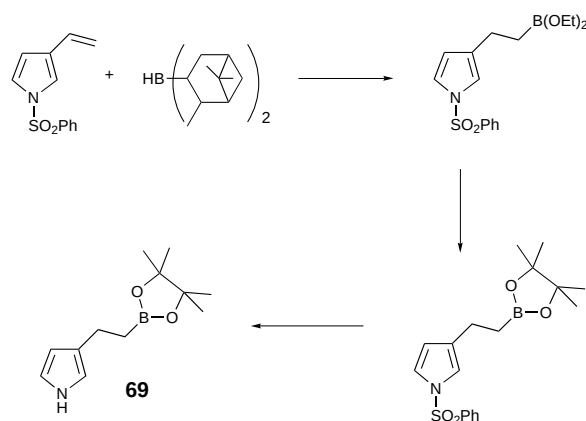
Shinkai and co-workers have reported that ferroceneboronic acid **68** is capable of acting as an electrochemical

sensor.^[101] This simple molecule has excellent selectivity for fluoride ions in the presence of other halides and ions such as SCN^- , SO_4^{2-} , and H_2PO_4^- . They found a K_{ox} value of 1000M^{-1} in $\text{MeOH}/\text{H}_2\text{O}$ (1/9) for fluoride compared to values of less than 2M^{-1} for chloride and bromide. The interaction between the boronic acid group and the fluoride ion is attributed to the hardness of



the boron atom, which strongly interacts with fluoride (a hard base). On oxidation, the ferrocene group becomes more electron-withdrawing, so decreasing the electron density of the boron atom and increasing the strength of the fluoride complex.

An alternative approach to electrochemical anion detection is to produce an electropolymerizable monomer containing an anion binding site and polymerize it onto the surface of an electrode to produce an anion-selective chemically modified electrode (CME). Fabre and co-workers have recently produced boronate-functionalized polypyrrole membranes (poly-**69**; Scheme 3) that are selective for fluoride over other putative anionic guests.^[102]

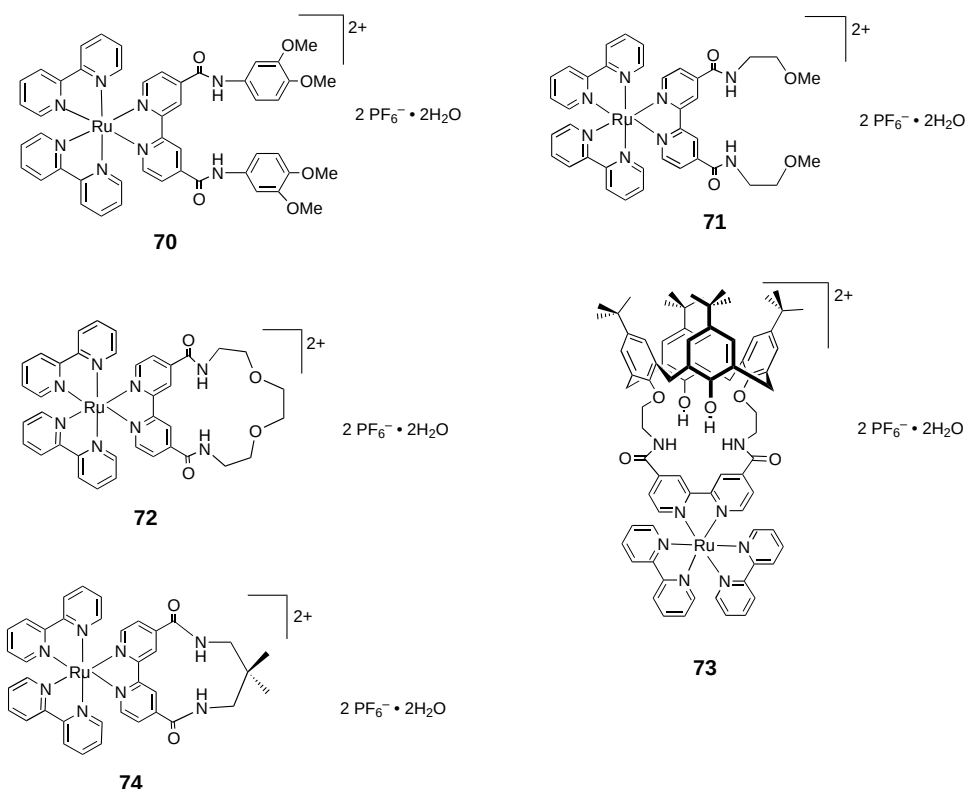


Scheme 3. Synthesis of **69**.

3.2. Optical Sensing of Anions: Luminescent Sensors

The high sensitivity of fluorescent techniques for sensing target guest species has stimulated an enormous amount of interest in the covalent attachment of organic and inorganic luminophores in proximity to charged guest-recognition sites.^[103] Examples of luminescent anion-responsive systems have combined the anthracene fluorophore with polyammonium,^[104] guanidinium,^[105] zinc(II) amine,^[106] and very recently calixpyrrole^[34] anion recognition sites. Cyclen-appended phenanthridinium europium and terbium complexes have been shown to sense halide and hydroxide ions in water.^[107, 108]

Tris(2,2'-bipyridyl)ruthenium(II) ($[\text{Ru}(\text{bpy})_3]^{2+}$) has been one of the most extensively investigated complexes as a result of its chemical stability, redox properties, excited-state reactivity, and luminescent emission.^[109, 110] Beer and co-



workers have incorporated this moiety into acyclic, macrocyclic, and calix[4]arene structural frameworks to produce a new class of anion receptor capable of optical and electrochemical sensing; examples are **70–74**.^[72, 111, 112] Single-crystal X-ray structures of the chloride complex of **70** (Figure 11) and the H_2PO_4^- complex of **73** highlight the importance of hydrogen bonding to the anion-complexation process. The determination of stability constants in DMSO demonstrated that the acyclic receptors form strong complexes with Cl^- and

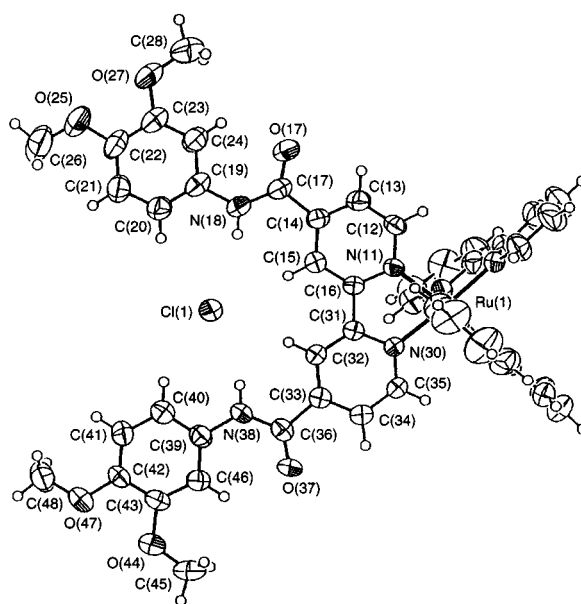
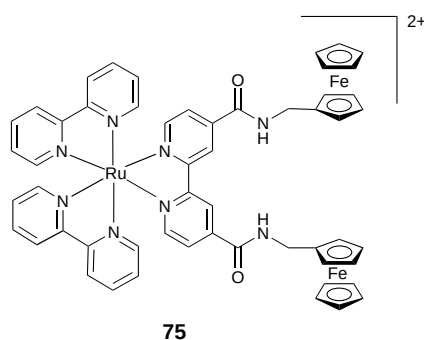


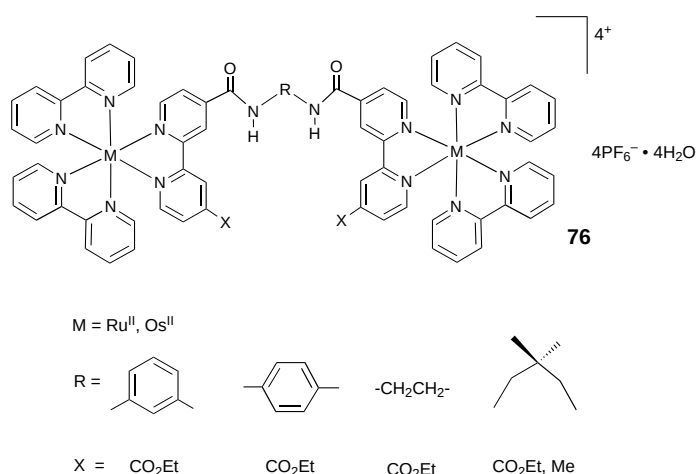
Figure 11. The X-ray crystal structure of the chloride complex of receptor **70**. Reproduced with permission from ref. [111]. Copyright© American Chemical Society 1996.

H_2PO_4^- ions. The macrocyclic and calix[4]arene receptors **72–74** form highly selective and thermodynamically stable complexes with H_2PO_4^- ions. Electrochemical anion-recognition experiments showed substantial anion-induced cathodic perturbation of the redox couple associated with the ligand-centered amide-substituted 2,2'-bipyridine reduction. These perturbations were in agreement with stability constant values, with **73** electrochemically sensing H_2PO_4^- ions in the presence of a tenfold excess of HSO_4^- and Cl^- ions. Luminescence emission measurements were also undertaken to probe the anion-binding process. All receptors exhibited significant blue shifts in the metal-ligand-charge-transfer (MLCT) emission band λ_{max} on addition of Cl^- and H_2PO_4^- ions, with **73** displaying the largest perturbation (16 nm). These shifts are not observed with unfunctionalized $[\text{Ru}(\text{bpy})_3]^{2+}$ and were accompanied by large increases in emission intensity (higher quantum yields). It was proposed that this could be a consequence of the bound anion rigidifying the receptor and inhibiting vibrational and rotational relaxation modes of nonradiative decay.

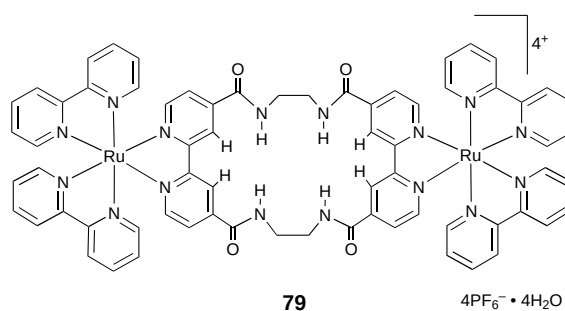
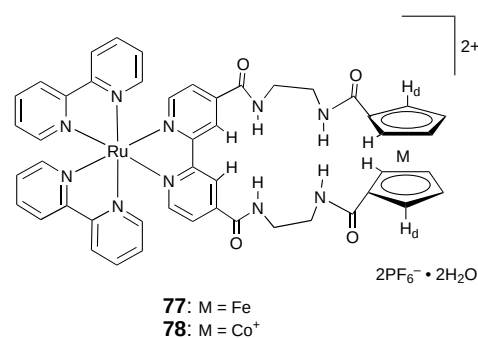
An acyclic $[\text{Ru}(\text{bpy})_3]^{2+}$ -ferrocene receptor **75** in which the emission of the ruthenium center in the free receptor is quenched by the ferrocene units has also been prepared by Beer et al.^[113] Interestingly the addition of H_2PO_4^- ions switches on the emission with a 20-fold increase. This effect was not observed with Cl^- or HSO_4^- ions. A competition experiment conducted in the presence of five equivalents of both Cl^- and HSO_4^- ions reproduced the emission increase on addition of H_2PO_4^- , thus confirming the property of **75** as a H_2PO_4^- -selective luminescent anion sensor.



Other mixed-metal receptors have included the cleft-type, in which the d^6 metals Ru^{II} , Os^{II} , and Re^{I} with various different bridging groups **76** were employed.^[114] These, like the previous examples, display selectivity for dihydrogen phosphate over chloride. The strength of binding can be tuned by the choice of the spacer/bridging moiety to quite a dramatic effect. For example, the complex with the *meta*-phenylene-bridged ligand gives a stability constant with dihydrogen phosphate of 55 M^{-1} in $[\text{D}_6]\text{DMSO}$, while that with the *para* analogue is 4320 M^{-1} . Other spacers were utilized, such as ethyl and 2,2'-dimethylpropyl. The corresponding Os^{II} receptors displayed larger anion stability constants indicating the efficient Lewis-acidic character of the $[\text{Os}(\text{bpy})_3]^{2+}$ moiety.

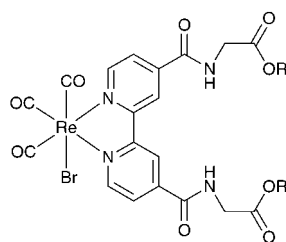


It is noteworthy that few of the receptors discussed so far exhibit specific binding and sensing of the chloride ion. Beer et al. recently prepared the macrocyclic receptors **77–79** which form extremely stable 1:1 complexes on binding chloride ions in $[\text{D}_6]\text{DMSO}$, with stability constants of up to $4 \times 10^{-4}\text{ M}^{-1}$.^[115] ^1H and ^{31}P NMR experiments on **79** showed

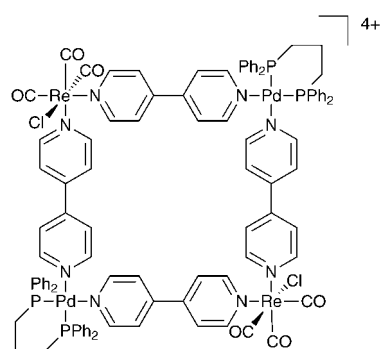


no evidence for the binding of H_2PO_4^- ions. This remarkable selectivity may be attributed to the inherently rigid structure of the macrocycle, since acyclic analogues bind H_2PO_4^- more strongly than Cl^- . The larger size and tetrahedral shape of H_2PO_4^- make this ion noncomplementary for the receptor's cavity. Luminescence studies indicated a blue-shift of the MLCT emission band with significant intensity enhancement in response to chloride ions, but no response to H_2PO_4^- ions. Interestingly increasing the size of the macrocyclic cavity by two or four methylene units dramatically reverses the trend in anion selectivity.

The neutral isoelectronic rhenium(i)–bipyridylamide receptors **80** and **81** have been prepared and shown to selectively bind and optically sense acetate ions in DMSO by MLCT enhancement.^[116] The mixed Re^I–Pd^{II} metal macrocycle **82** binds a perchlorate ion, which also results in significant MLCT enhancement in acetone.^[117]

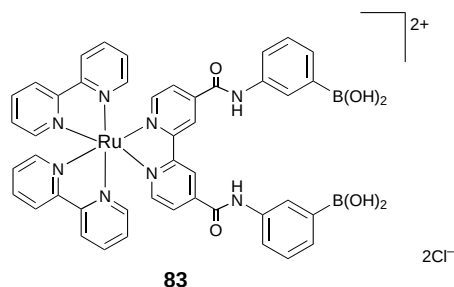


80: R = Me
81: R = CH₂Ph



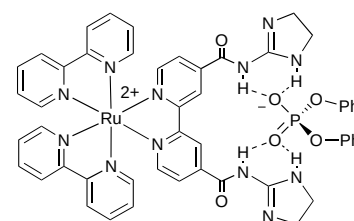
82

Deetz and Smith have synthesized an analogous compound containing saccharide-binding boronic acid groups (**83**) and shown that this material will sense the presence of phosphorylated sugars in aqueous solution through perturbations in the luminescent properties of the complex.^[118] The phosphate group of the sugar is presumably bound to the amide NH protons present in the cleft whilst the boronic acid groups coordinate to the sugar. Rhenium analogues of this material had previously been used to bind simple sugars.^[119]

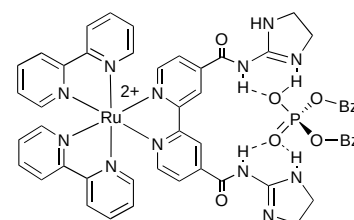


83

Watanabe et al. have produced imidazole-functionalized ruthenium–bipyridyl complexes such as **84** which recognize anionic and neutral phosphodiester with luminescent signal enhancement observed for anionic phosphodiester in acetone.^[120] The corresponding 1:1 complexes are proposed to form between **84** and tetraethylammonium diphenyl phosphate (TDPP) or dibenzylphosphate (DBHP; Bz = benzyl).

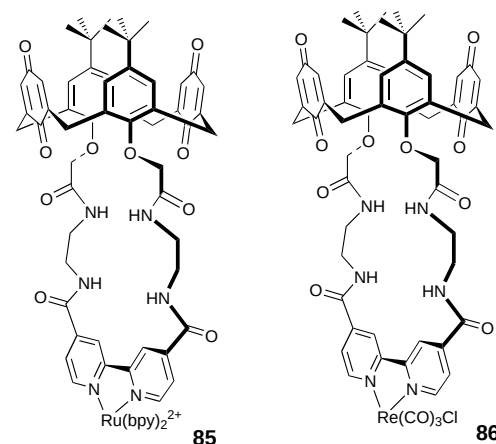


84•DPP



84•DBHP

Ruthenium(II)– and rhenium(I)–bipyridylcalix[4]diquinone receptors **85** and **86** selectively bind and sense acetate ions through remarkable retrieval effects of the luminescent emission intensity.^[121] The addition of acetate ions to solutions of **85** in acetonitrile caused a 500 % increase in the intensity of the emission, which suggests that anion binding inhibits the intramolecular oxidative electron transfer quenching mechanism between the ruthenium(II)–bipyridyl and calix[4]diquinone centers.

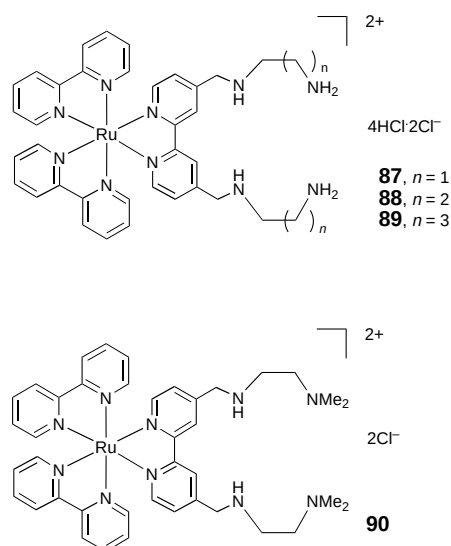


85

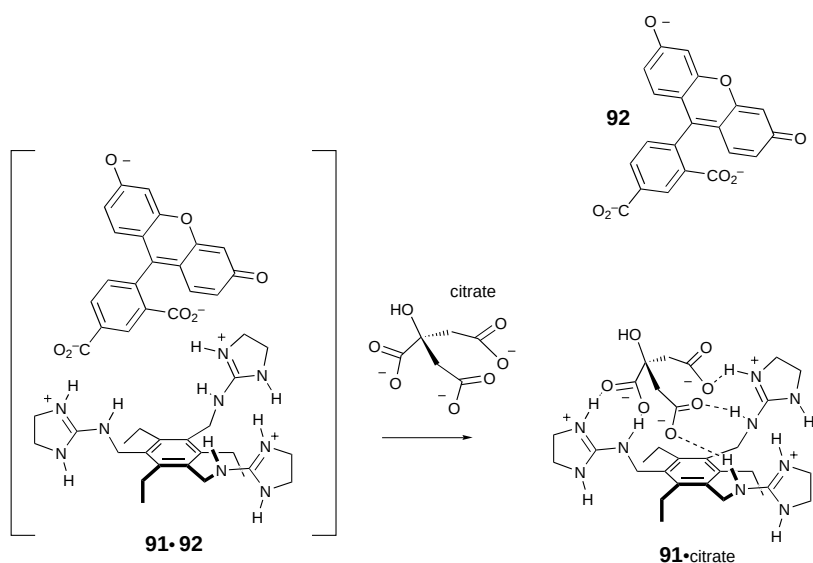
86

Water-soluble ruthenium(II)–bipyridyl–polyamine receptors such as **87**–**90** have very recently been prepared and shown to bind and detect phosphate ions in aqueous media by MLCT luminescent emission quenching.^[122]

Anslyn and co-workers have published several papers on the recognition of tricarboxylate and triphosphate polyanions by trisguanidinium receptor species such as **91** (Scheme 4).^[123] This molecule contains three guanidinium groups and is therefore complementary to guests containing three carboxylate groups. The stability constant determinations revealed that guests containing three anionic moieties, such as citrate, are bound more strongly than those with fewer anionic groups



(for example, acetate). The crystal structure of the tricarballate complex (tricarballate = 1,2,3-propanetricarboxylate) of **91** is shown in Figure 12. This receptor has been used by Anslyn and co-workers to produce a displacement-assay-type chemosensor for citrate in beverages.^[123] 5-Carboxyfluorescein (**92**) is a commercially available fluorescent probe containing two carboxylate groups. Its fluorescence is particularly sensitive to changes in pH values. The two carboxylate groups present in **92** coordinate to **91**. The $\text{p}K_{\text{a}}$ of the phenol moiety of **92** is lowered in the complex because of the positively charged microenvironment. A citrate ion displaces the carboxyfluorescein from the complex and results in a shift in the $\text{p}K_{\text{a}}$ of the phenolate group such that **92** is in a higher state of protonation when uncomplexed (Scheme 4).^[124] The fluorescence and absorbance of **92** decrease with increasing protonation. These changes could be calibrated against standard solutions of citrate to produce a quantitative sensor.



Scheme 4. Recognition of citrate ions by the trisguanidinium receptor **91**. An initially bound molecule of **92** is displaced by a citrate ion.

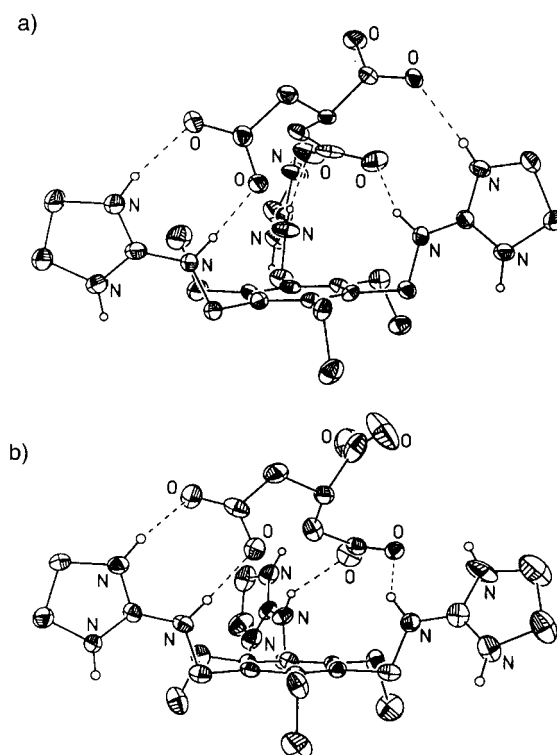


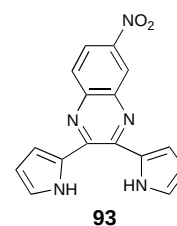
Figure 12. The X-ray crystal structure of the tricarballate complex of receptor **91** (C-bound hydrogen atoms are omitted). The unit cell contains two different host-guest complexes (a and b). Reproduced with permission from ref. [123]. Copyright © WILEY-VCH 1997.

3.3. Optical Sensing of Anions: Colorimetric Sensors

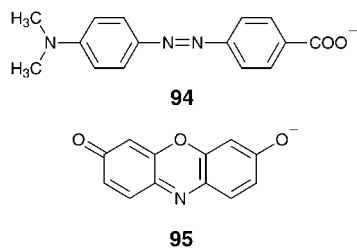
Colorimetric sensors do not require the use of a potentiostat or spectrometer to detect redox or optical perturbations (color changes are detectable by eye!) and therefore have advantages over other molecular sensors.

Sessler and co-workers reported that 2,3-dipyrrol-2'-ylquinoxalines such as **93** provide a simple, hitherto unexplored class of anion receptors that allow for the detection of fluoride ions in dichloromethane and DMSO under both visual (that is, naked eye) and fluorescence emission conditions.^[125] In fact, **93** undergoes a clear yellow to purple color change on addition of fluoride ions that is not observed on addition of other anions. The observed color changes also take place in DMSO but are reversed upon addition of water. This is presumably because water competes with the pyrrolic NH hydrogen bond donating sites for fluoride ions. Compound **93** shows a remarkable selectivity for the fluoride ion ($K_{\text{a}}(\text{F})/K_{\text{a}}(\text{Cl}) > 1800$; $K_{\text{a}}(\text{F})/K_{\text{a}}(\text{H}_2\text{PO}_4^-) > 1400$).

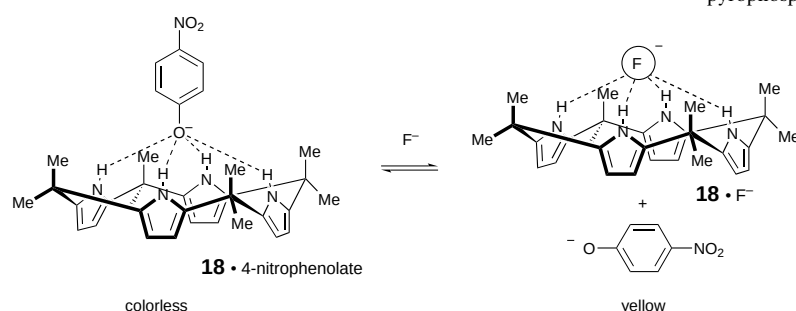
Anslyn and co-workers have extended their displacement-assay approach to include a molecular ensemble con-



sisting of the nitrate-selective trigonal amide box^[25] **14** and a variety of colorimetric dyes such as Resorufin (**94**) or Methyl Red (**95**).^[126] The resulting molecular ensembles show large changes in their absorbance upon addition of nitrate ions.



The generality of the approach of Anslyn and co-workers has been confirmed by Gale et al.^[127] The intense yellow color of the 4-nitrophenolate ion in dichloromethane or acetonitrile has been shown to dissipate upon addition of calix[4]pyrrole as a consequence of the formation of a calix[4]pyrrole–4-nitrophenolate complex. The addition of anions causes the regeneration of the bright yellow color as the added anion displaces the phenolate ion from the calix[4]pyrrole (Scheme 5). The intensity of the color is dependent upon the affinity of the calixpyrrole for the added anion and the anion concentration.



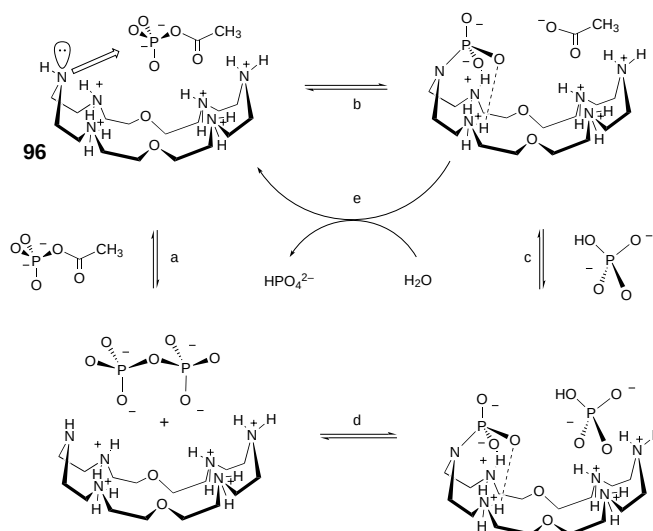
Scheme 5. F⁻-dependent equilibrium between **18 · 4-nitrophenolate** and **18 · F⁻**.

4. Into the New Millennium: Templatation, Anion-Directed Self-Assembly, Catalysis, and Ion-Pair Recognition

The previous sections have illustrated through the discussion of a range of artificial receptors the recognition and sensing of anionic guest species in organic and aqueous solvent media. The field of anion coordination chemistry is catching up with cation coordination chemistry and has recently turned its attention towards supramolecular catalysis, anion-template effects, and directed self-assembly. In addition, at the interface of anion and cation coordination chemistry, new heteroditopic multisite ligands for the simultaneous complexation of anionic and cationic guest species (ion-pair recognition) have been reported.

4.1. Catalysis

Hosseini and Lehn are pioneers in the area of supramolecular catalysis of anionic substrates. The results of their extensive work have recently been condensed into a book chapter to which the interested reader is directed for further information.^[128] One example, a proposed catalytic cycle for acetyl phosphate hydrolysis and pyrophosphate synthesis by macrocycle **96** at pH 7, is shown in Scheme 6. The mechanism

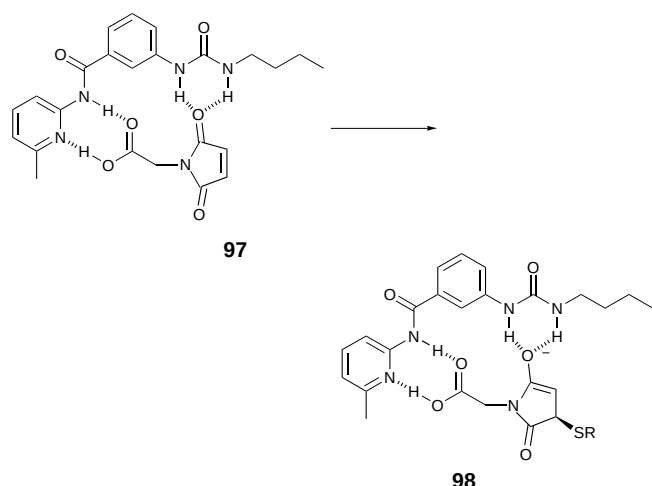


Scheme 6. Proposed catalytic cycle for acetyl phosphate hydrolysis and pyrophosphate synthesis in the presence of macrocycle **96**.

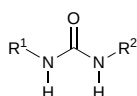
of this reaction is extremely pH sensitive with the percentage of pyrophosphate formed being a maximum at pH 7. This result arises because the mechanism of the transformation relies on the macrocycle being in the correct protonation state.

Hamilton and co-workers have used an anion-binding strategy to stabilize an oxyanion transition state and so accelerate the 1,4-addition of a thiol to a maleimide (Scheme 7).^[129] The build up of negative charge on the carbonyl oxygen atom in the enol transition state of this reaction is stabilized by hydrogen bonding from a urea group. The hydrogen bonds to the enol oxygen atom in complex **98** are stronger than those to the carbonyl oxygen atom in the starting material (**97**). Therefore the transition state is stabilized relative to the starting material and catalysis occurs.

Reinhoudt and co-workers have recently demonstrated that addition of anion-binding urea-based receptors to palladium(II)-catalyzed hydrocarbonylation reactions of cyclopentene can significantly increase hydroacylation relative to hydroformylation.^[130] The N,N'-disubstituted urea derivatives **99–103** significantly influence the performance of the [PdX₂(dppp)] catalyst (dppp = 1,3-bis(phenylphosphanyl)propane) in hydrocarbonylation reactions by coordinating to the counterions (X = OTf, TFA, OAc), which leads to a decrease in their metal-binding strength. More weakly coordinating anions X enhance the electrophilicity of the Pd^{II}

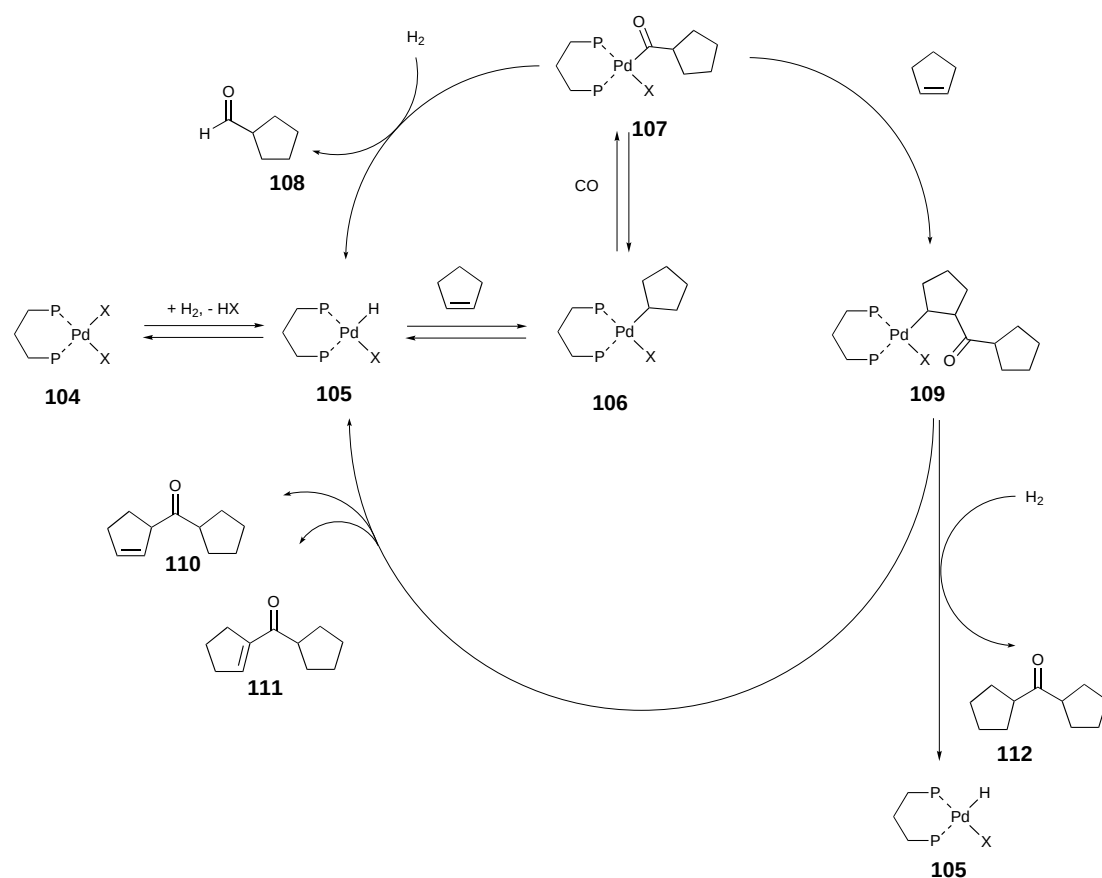


Scheme 7. Anion binding results in an accelerated 1,4-addition of thiols to a maleimide.



- 99:** $R^1 = R^2 = \text{Ph}$
100: $R^1 = p\text{-F}_3\text{CC}_6\text{H}_4$, $R^2 = \text{Ph}$
101: $R^1 = R^2 = p\text{-F}_3\text{CC}_6\text{H}_4$
102: $R^1 = n\text{Bu}$, $R^2 = \text{Ph}$
103: $R^1 = R^2 = n\text{Bu}$

metal ion and are more easily displaced from the complex, thus facilitating the formation of **107** (increased turnover) and **109** (increased selectivity for ketones; Scheme 8). The largest effect was observed on addition of compound **101**.

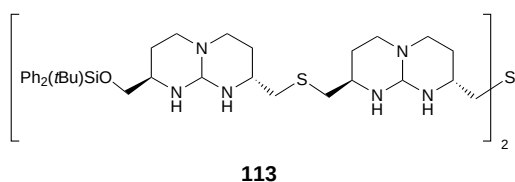


Scheme 8. Mechanism for the Pd^{II} -catalyzed hydrocarbonylation of cyclopentene.

4.2. Anion Templatation and Directed Self-Assembly

Examples of metal ions and other cationic species that act as templates for the formation of cyclic molecules or other molecular systems are widespread in the literature.^[131] Examples of anions performing the same function were, until a few years ago, difficult to find. However, this situation has now changed, and reports of the templating influence of anions are now becoming widespread. We have already discussed how anion templation assisted in the synthesis of Hawthorne's mercuracarborand receptor **42**. Other early examples of anion templation (or anion-directed self-assembly) include an interesting templation effect by nitrate in the synthesis of expanded porphyrins by Sessler et al.,^[132] the organization of organophosphate–oxovanadium clusters around chloride ions,^[133] and the construction of polyoxovanadate cages by Müller et al.^[134, 135] Recently, Müller et al. have employed H_2PO_2^- ligands in the formation of nanosized rings of formula $\text{Na}_{21}[\text{Mo}_{126}^{\text{VI}}\text{Mo}_{28}^{\text{V}}\text{O}_{462}\text{H}_{14}(\text{H}_2\text{O})_{54}(\text{H}_2\text{PO}_2)_7] \cdot x\text{H}_2\text{O}$ ($x \approx 300$).^[136]

de Mendoza and co-workers have synthesized a tetraguanidinium strand (**113**) that self-assembles around sulfate ions to form a double helix.^[137] Evidence for the anion-directed helical structure was provided by ROESY NMR spectroscopy. The complexation behavior of this and other tetraguanidinium reagents with α -helical peptides containing negatively charged aspartate residues has been reported by Hamilton, de Mendoza, and co-workers.^[138]



Lehn and co-workers have discovered a striking example of anion-directed assembly (Scheme 9).^[139, 140] The pentametallic circular helicate **115** only forms in the presence of chloride ions. It may be produced by mixing the tris(bipyridine) ligand **114** with an equimolar amount of FeCl_2 in ethylene glycol at 170°C . The chloride ion bound in the center of the helicate is locked in place and cannot be exchanged for other anions such as hexafluorophosphate or trifluoroacetate (triflate). If other iron(II) salts such as tetrafluoroborate or sulfate are used instead of chloride a hexameric complex **116** is obtained (Scheme 9). The chloride ion is therefore playing a role in the assembly of this beautiful complex (Figure 13).

Fujita et al. have used a variety of carboxylate guest ions to template the formation of metal complexes^[141] and have recently succeeded in constructing coordination nanotubes. (**118**–**120**; Scheme 10).^[142] For example, pentakis(3,5-pyridine) **117** quantitatively forms a coordination nanotube **118** with $[\text{Pd}(\text{en})(\text{NO}_3)_2]$ (en = ethylenediamine) in the presence of a linear template such as 4,4'-biphenylenedicarboxylate.

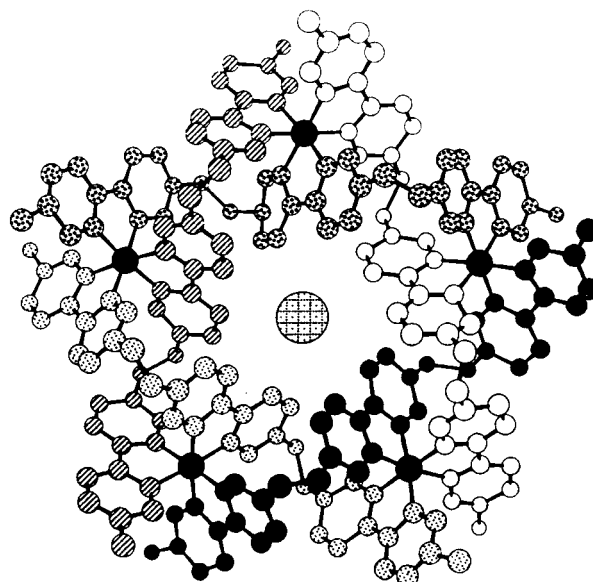
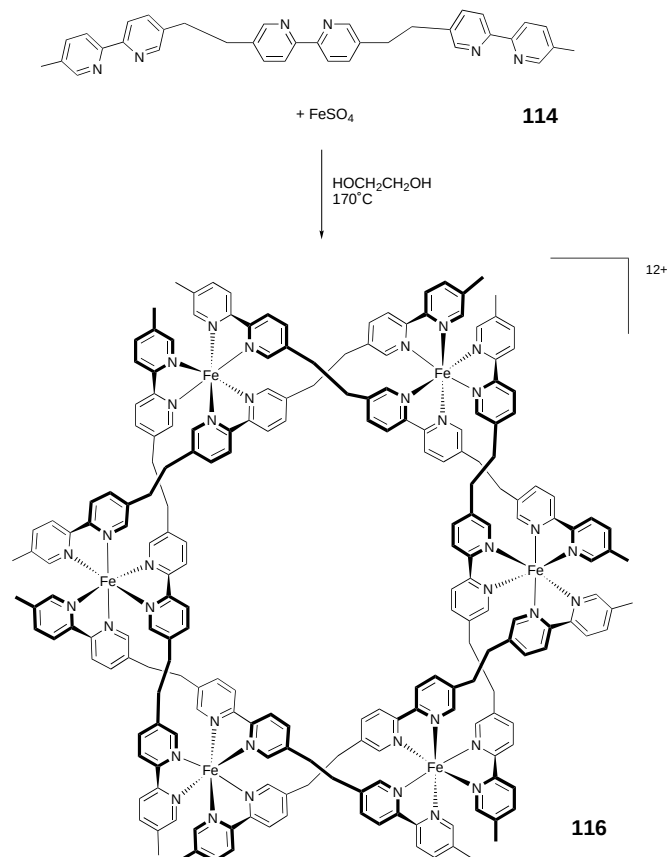
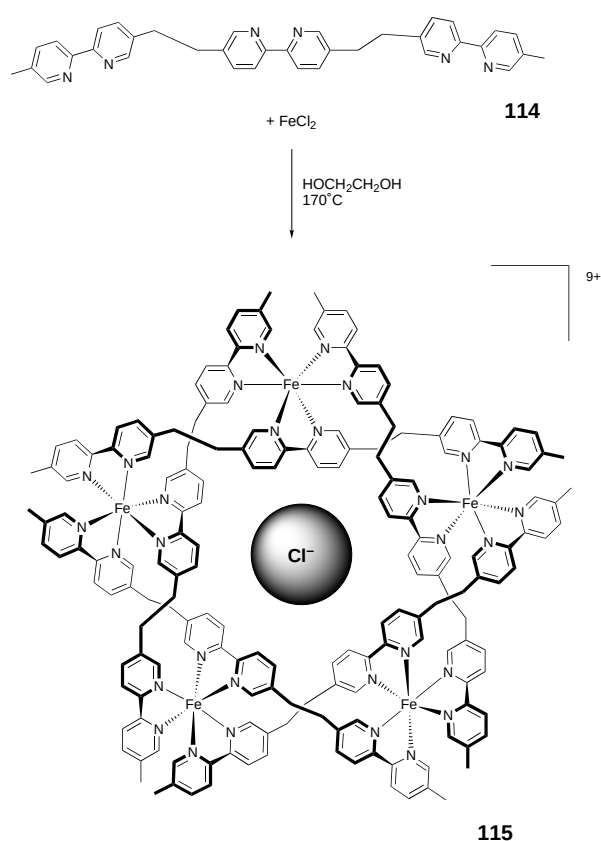
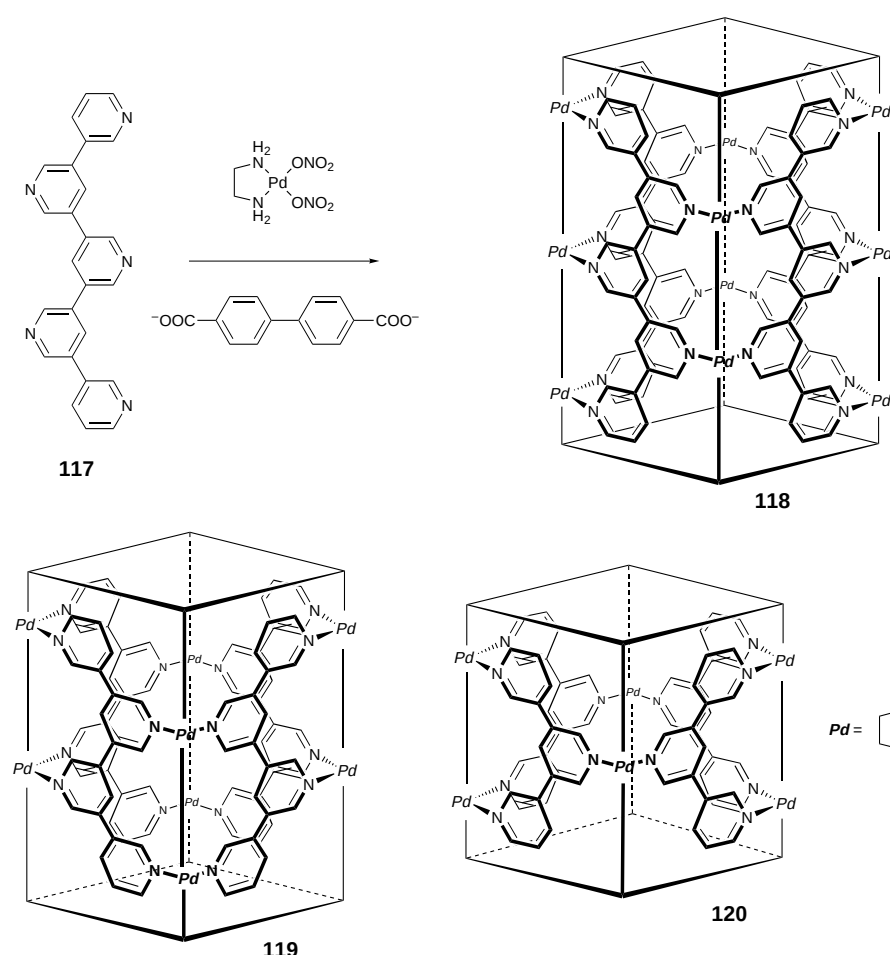


Figure 13. The X-ray crystal structure of the circular double helicate **115** (hydrogen atoms are omitted). The templating chloride ion can be clearly seen at the center of this beautiful complex. Reproduced with permission from ref. [139]. Copyright© VCH 1996.

Neutral linear templates such as biphenyl and *p*-terphenyl were also effective as templates, however, the nanotube did not form in the absence of any template. The crystal structure

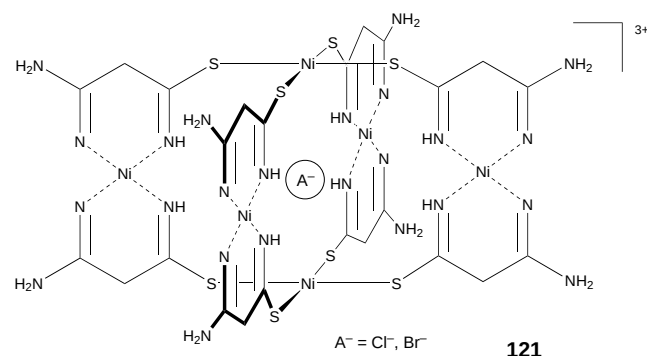


Scheme 9. Synthesis of helicates **115** and **116**.

Scheme 10. Synthesis of the coordination nanotubes **118–120**.

of $[\mathbf{120}(4,4'\text{-biphenylenedicarboxylate})_2(\text{NO}_3^-)_{10}]$ has been elucidated and reveals that the anionic template is bound within the tube by π – π and CH– π interactions.

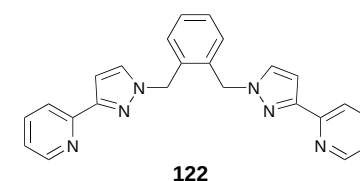
Another example of anion-directed assembly was reported by Mingos and co-workers.^[143] Reaction of NiCl_2 with amidinothiourea (atu) in methanol produces a cage complex **121**. The complex consists of eight amidinothiourea units that



coordinate six nickel ions through both nitrogen and sulfur donor atoms. A chloride ion is bound in the center of the cage by eight N–H...Cl hydrogen bonds (Figure 14). A cage complex can also be formed by replacing NiCl_2 with NiBr_2 ,

however syntheses using nickel acetate, nitrate, or perchlorate salts produce simple monomeric $[\text{Ni}(\text{atu})_2]^{2+}$ complexes. If chloride ions are subsequently added to these complexes (as KCl) the cage complex spontaneously forms around the halide ion.

McCleverty, Ward, and co-workers have shown that BF_4^- ions template the formation of tetrahedral complexes consisting of four cobalt(II) ions and six ligands **122**.^[144] The templation



process appears to be driven primarily by electrostatic interactions as the fluorine atoms are not directed towards the cobalt centers at the corners of the tetrahedron (Figure 15) but rather towards the center of the triangular faces of the tetrahedron. This is presumably a consequence of the

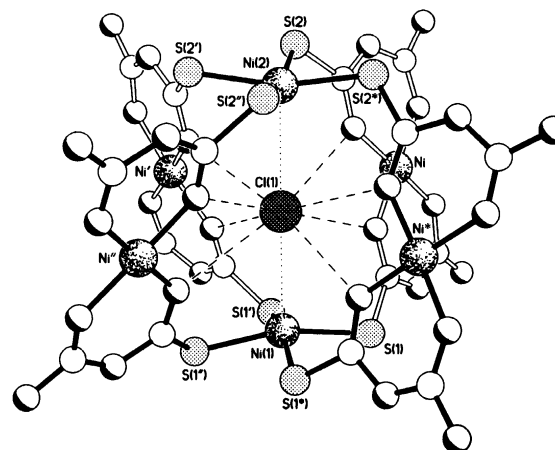


Figure 14. The X-ray crystal structure of cage complex **121** (hydrogen atoms are omitted). Reproduced with permission from ref. [143]. Copyright © WILEY-VCH 1998.

anion adopting an orientation that best fits the internal shape of the cavity. The tetrahedral complex could not be isolated without an encapsulated anion, and anion exchange between the cavity and bulk solvent was slow (at least on the NMR timescale). These facts suggest that the anion is essential in the assembly process of this complex.

Chloride ions have been used by Zheng and co-workers to direct the assembly of europium(III)–tyrosine cluster com-

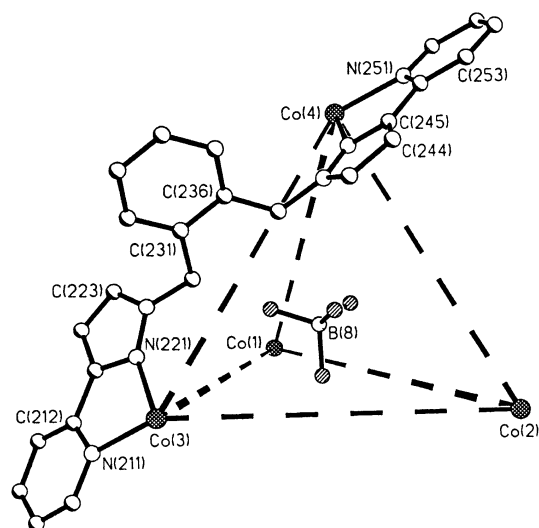


Figure 15. A partial representation of the crystal structure of the BF_4^- -templated cage complex **122** (hydrogen atoms are omitted). Reproduced with permission from ref. [144]. Copyright© WILEY-VCH 1998.

pounds^[145] such as $[\text{Eu}_{15}(\text{Cl})(\mu_3\text{-tyr})_{10}(\mu_3\text{-OH})_{20}(\mu_2\text{-H}_2\text{O})_5(\text{OH})_{12}(\text{H}_2\text{O})_8][\text{ClO}_4]_2 \cdot 56\text{H}_2\text{O}$ (**123**; Figure 16). The metal ions are assembled into three layers with each containing five metal ions. The cage is templated around a chloride ion at the center of the cluster that is coordinated to five europium atoms with an average $\text{Eu} \cdots \text{Cl}$ distance of 3.31 Å.

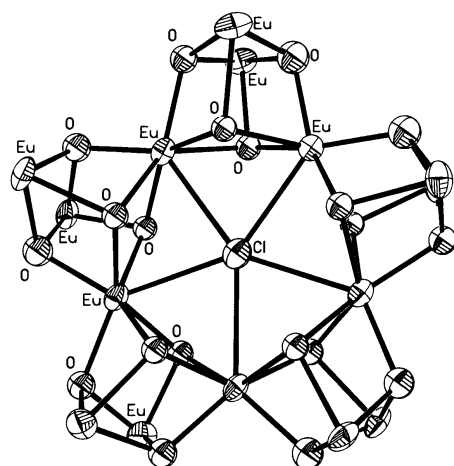


Figure 16. A plane through the X-ray crystal structure of **123** (only the Eu and O atoms are shown) showing the templating chloride ion. Reproduced with permission from ref. [145]. Copyright© 1999, WILEY-VCH.

Chen and co-workers have formed cyclic hexanuclear complexes containing quadruply bonded Mo_2 units around carbonate ions.^[146] The cyclic complex *trans*- $[\{\text{Mo}_2(\text{O}_2\text{CCF}_3)_2(\mu\text{-dppa})\}_3(\mu_6\text{-CO}_3)(\mu_3\text{-Cl})_3]\text{F}$ (**124**; Figure 17) was prepared by reaction of *trans*- $[\text{Mo}_2(\text{O}_2\text{CCF}_3)_2(\text{MeCN})_6][\text{BF}_4]_2$ and K_2CO_3 with *N,N'*-bis(diphenylphosphanyl)amine (dppa) in dichloromethane. The chloride ions present in **124** presumably originate from the solvent. The analogous reaction carried out in acetonitrile followed by the addition of ZnX_2 ($\text{X} = \text{Br}$ or I) afforded the analogous bromide or iodide complexes (**125** or **126**).

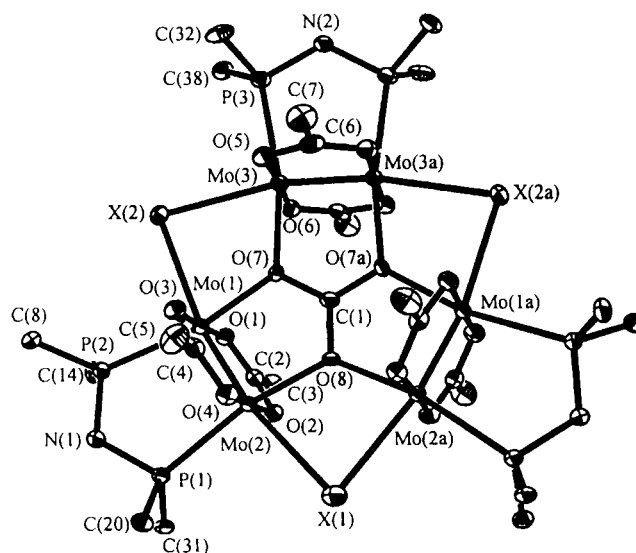
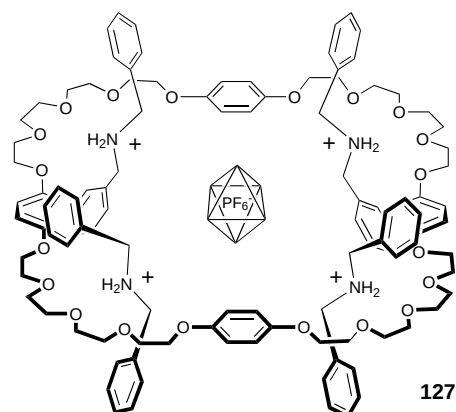


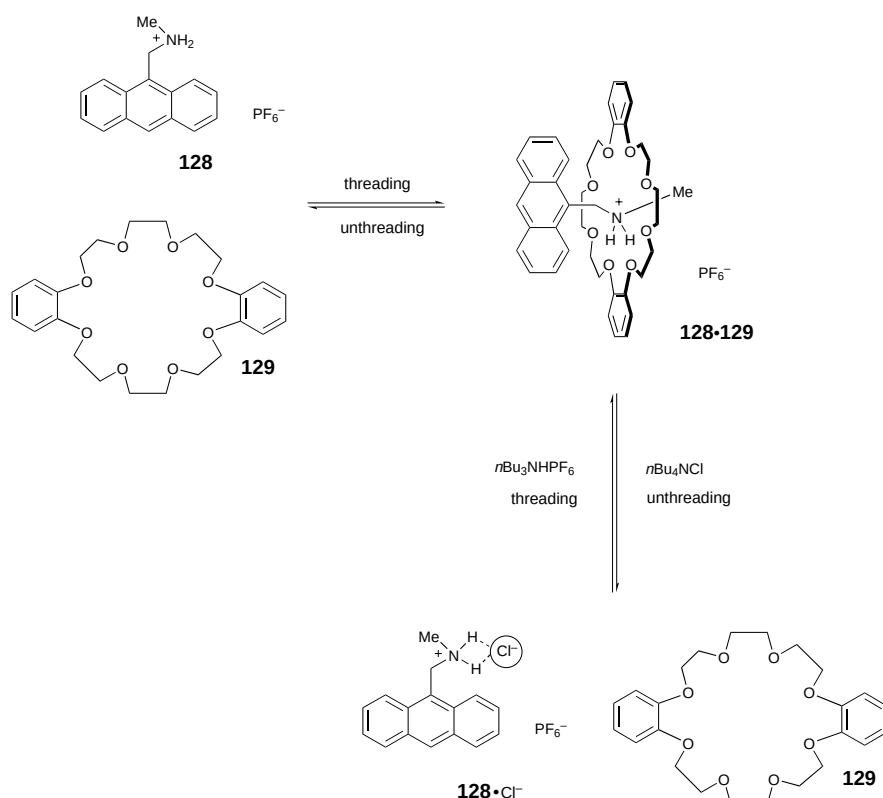
Figure 17. The crystal structure of complexes **124–126** ($\text{X} = \text{Cl}$, Br , and I , respectively; the CF_3 groups are not shown and only the *ipso* atom of the phenyl groups are shown). Reproduced with permission from ref. [146]. Copyright© The Royal Society of Chemistry 1999.

Stoddart and co-workers have also employed anions in self-assembly processes.^[147] The pseudorotaxane **127** is formed from tetrakis-*p*-phenylene[68]crown-20 and four dibenzylammonium ions. The crystal structure of this assembly shows an



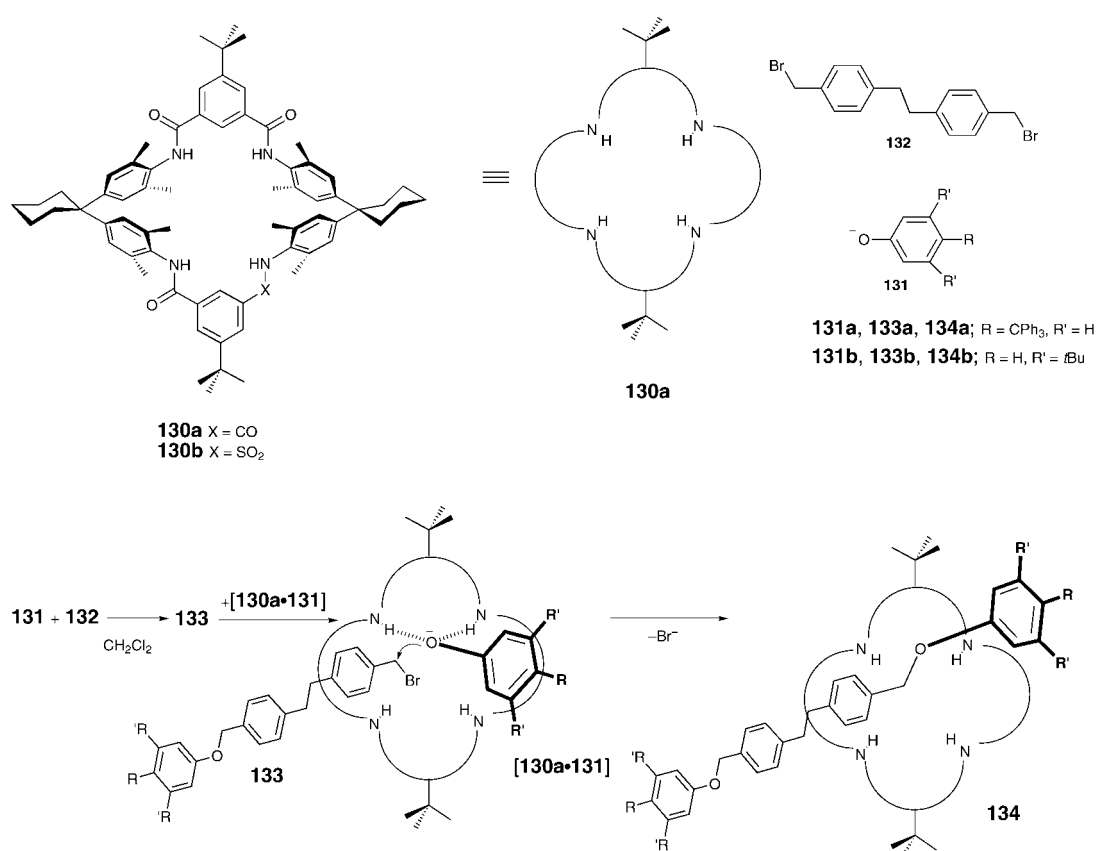
ordered PF_6^- ion bound in the center of the rotaxane. Unbound hexafluorophosphate ions are disordered in the crystal structure, that is, the octahedrally disposed fluorine atoms are not constrained to point in particular directions. However, in this case the ordering of the anion suggests the formation of $\text{C-H} \cdots \text{F}$ hydrogen bonds with the rest of the assembly, which locks the anion into a single orientation. The presence of the anion is therefore likely to reduce any electrostatic repulsion between the dibenzylammonium cations in the pseudorotaxane, thus assisting the assembly process.

Montalti and Prodi have shown that chloride ions can control the threading and unthreading of a pseudorotaxane formed between (9-anthrylmethyl)methylammonium hexafluorophosphate **128** and dibenzo-[24]crown-8 (**129**; Scheme 11).^[148] Chloride ions form a strong ion pair with


 Scheme 11. Threading and dethreading processes with **128** and **129**.

the ammonium group of **128** which prevents the threading process and effectively breaks up the pseudorotaxane ensembles present in solution. Subsequent addition of Bu_3NH^+ ions (which can compete for the chloride ions bound in the ion pairs) drives the equilibrium back in favor of the pseudorotaxane.

Vögtle and co-workers have employed anion coordination in a high-yielding rotaxane synthesis. They discovered that phenolates, thiophenolates, and sulfonamide ions are strongly bound in the tetralactam macrocycles. The bound organic anion was found to be capable of reacting as a nucleophile and therefore could be utilized in rotaxane synthesis. For example, the complex **130a**·**131** (Scheme 12) reacts with molecule **133** to form rotaxane **134** in 95% yield (probably one of the highest yields ever reported for this kind of synthesis).^[149, 150]



Scheme 12. Efficient formation of a rotaxane by precoordination of nucleophilic anions.

A synthetic solid-state anion channel has recently been produced by Lippert and co-workers.^[151] Lippert found that reaction of $[\text{Pt}(\text{en})(\text{H}_2\text{O})_2]^{2+}$ and 2,2-bipyrazine (bpz) produces the triangular complex $[\{\text{Pt}(\text{en})(2,2'\text{-bpz-}N^4,N^{4'})\}_3]^{6+}$. Subsequent reaction with additional $[\text{Pd}(\text{en})]^{2+}$ gives a hexametallic triangular complex $[\{(\text{enPd})_{2.5}(2,2'\text{-bpz})_3(\text{NH}_3)_2\text{-Pt}_3\}][\text{ClO}_4]_6[\text{NO}_3]_5 \cdot 5\text{H}_2\text{O}$ (**135**; Figure 18) with one of the corner Pd atoms having 50 % occupancy. A single perchlorate ion is bound at the center of the triangle. The triangles are

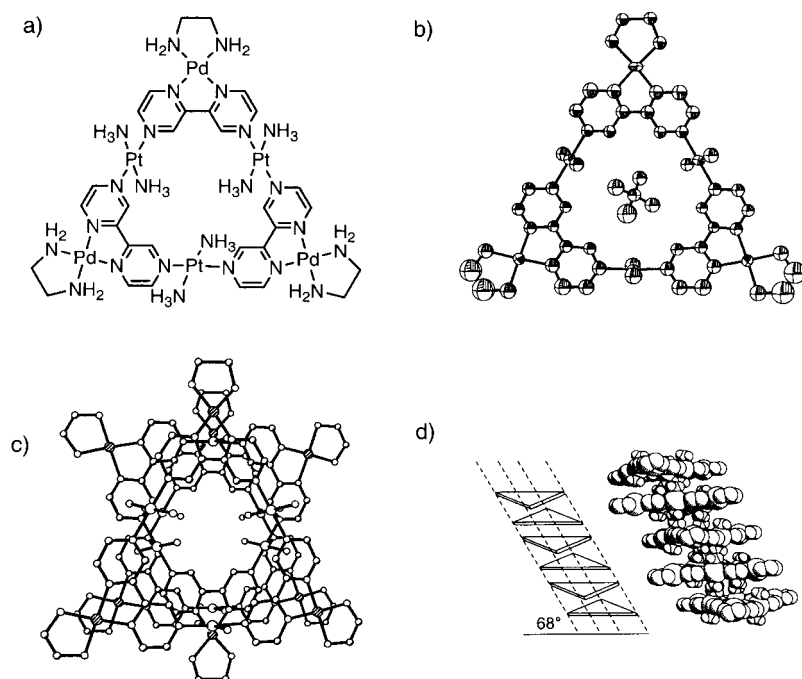


Figure 18. The cationic molecular triangle of complex **135**. a) Structure. b) X-ray crystal structure with encapsulated perchlorate ion (hydrogen atoms are omitted). c) Packing diagram showing the anion channel (perchlorate ions are omitted for clarity). d) Side view of the channel. b)–d) Reproduced with permission from ref. [151]. Copyright© The Royal Society of Chemistry 1999.

held together by bridging nitrate ions and water molecules to form channels (Figure 18c, the perchlorate ions are omitted for clarity). Therefore this structure not only contains anions but is also held together by anions. A side view is shown in Figure 18d.

4.3. Ion-Pair Recognition

Ion-pair recognition, the simultaneous complexation of cationic and anionic guest species by multisite receptors, is a new, emerging, and topical field of coordination chemistry. These heteroditopic ligands can be designed to exhibit novel co-operative and allosteric behavior, whereby the binding of one charged guest can influence, through electrostatic and conformational effects, the subsequent coordination of the pairing ion. Such systems have potential as new selective extraction and transportation reagents for ion-pair species of environmental importance and for zwitterion recognition.

For example, compound **136** is capable of coordinating to potassium and fluoride ions simultaneously. Reetz et al. showed that the potassium ion is bound by the crown ether moiety present in this receptor whilst the fluoride ion is held by a combination of orbital overlap with the Lewis-acidic boron atom and electrostatic interactions with the potassium ion.^[152, 153] The crystal structure of the potassium fluoride complex is shown in Figure 19.

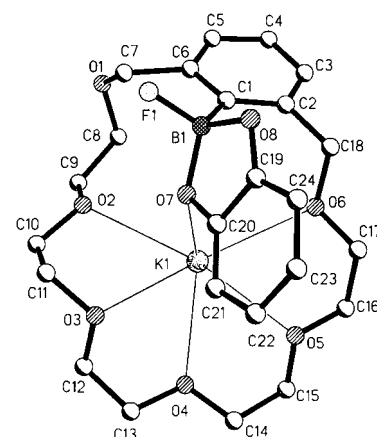
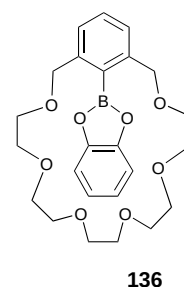
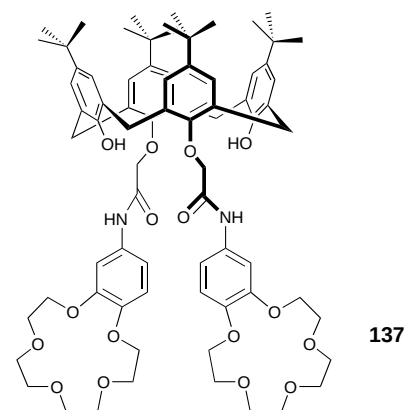


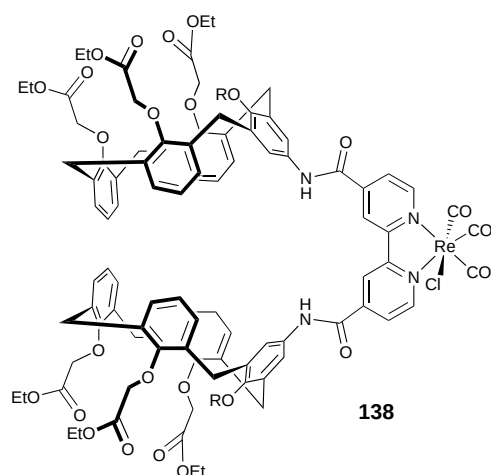
Figure 19. The X-ray crystal structure of the potassium fluoride complex of receptor **136** (hydrogen atoms are omitted). Reproduced with permission from ref. [152]. Copyright© VCH 1991.

A series of calixarene-based ditopic receptors have been synthesized by Beer and co-workers. For example, receptor **137** consists of two benzo[15]crown-5 moieties attached to the lower rim of calix[4]arene through an amide linker. In the absence of an alkali metal cation, receptor **137** showed very little interaction with anions in CD_3CN . Upon addition of potassium ions, a sandwich complex is formed between the two benzocrown ether units. This results in the amide groups being held close together, and along with the electrostatic attraction of the alkali metal cation, preorganizes **137** to bind anions. Dihy-



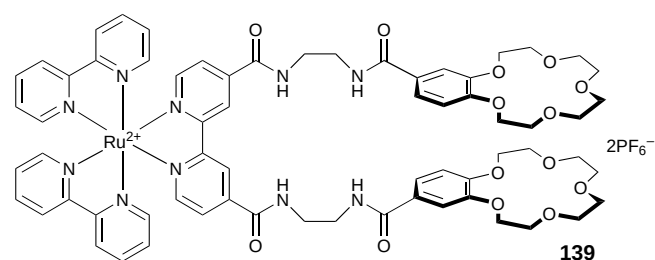
drogen phosphate was found to be particularly strongly bound ($\lg K > 4$) in CD_3CN .^[154]

The bis(calixarene)rhenium(i) receptor **138** has been shown to simultaneously bind alkali metal cations and iodide ions with positive co-operativity. The enhanced affinity of the bis(calixarene) lower rim ester metal complexes of **138** for iodide ions is believed to result from electrostatics and a rigidifying effect of the ester-bound metal cation on the calixarene frameworks, which results in a central cavity that is preorganized for iodide binding.^[155]

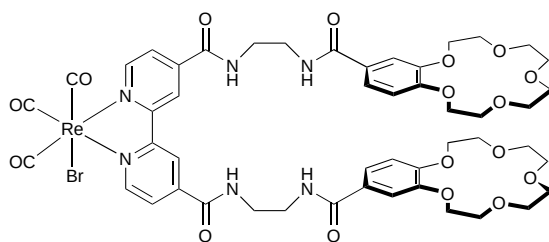


138

Beer and Dent have also recently reported the synthesis of new heteroditopic ruthenium(II)- and rhenium(I)-bipyridyl-bisbenzocrown ether receptors which, as evidenced from stability constant evaluations, complex KCl ion pairs in a co-operative fashion.^[156] It is noteworthy that the anion selectivity properties of the bisbenzo[15]crown-5 receptors **139** and **140** are dramatically switched on binding K^+ ions. In the



139



140

absence of K^+ the receptors are selective for H_2PO_4^- over Cl^- , whereas following the formation of the intramolecular K^+ -biscrown sandwich complex the reverse selectivity (Cl^- over H_2PO_4^-) is exhibited. The K^+ -induced co-operativity of Cl^- binding may be a consequence of favorable electrostatic attraction and conformational effects wherein the sandwich complex results in a pseudomacrocyclic preorganized structure suitable for Cl^- binding (Figure 20).

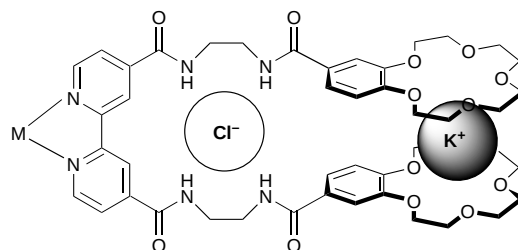
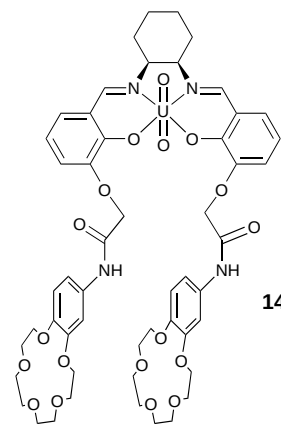


Figure 20. A pseudo-macrocyclic cavity is formed upon addition of potassium ions to **139** or **140** that switches on binding chloride ions.

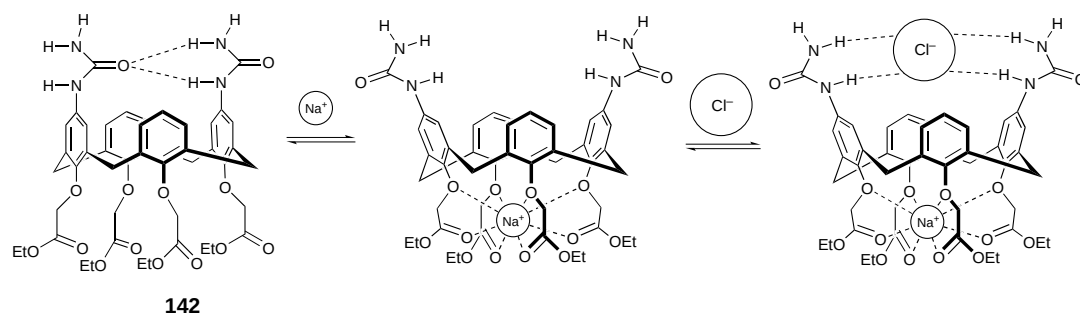
Using a similar strategy, Reinhoudt and co-workers constructed a receptor containing anion-binding Lewis-acidic UO_2^{2+} and amide moieties together with cation-binding crown ether groups.^[157] A variety of complexation experiments revealed that receptor **141** is capable of binding potassium and dihydrogen phosphate ions simultaneously.



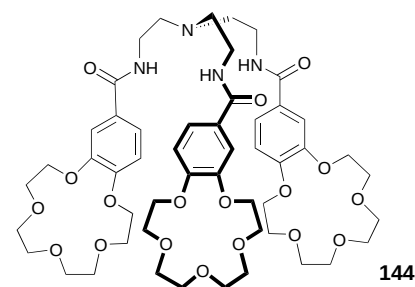
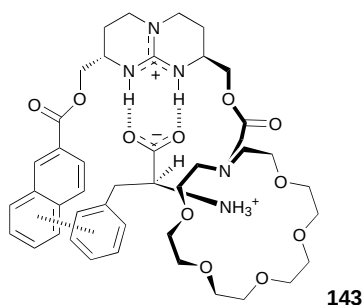
141

By taking the ditopic receptor strategy a step further the same workers have produced a switchable anion receptor. Receptor **142** consists of a calix[4]arene with cation-binding ester groups at the lower rim and anion-binding urea groups at the upper rim (Scheme 13).^[158] The two urea groups are hydrogen-bonded together in chloroform, and so are not available for hydrogen bonding to any putative anionic guest species. However when sodium ions are added, they bind to the ester groups of the calixarene, which causes the lower rim to contract. This rearrangement forces the urea groups at the upper rim apart breaking the hydrogen bonds between the urea groups, thus making them available for anionic guests.

Receptor **143**, synthesized by de Mendoza, Lehn, and co-workers, provides an elegant example of zwitterion recognition.^[45] The receptor extracts amino acids from aqueous solution into dichloromethane. This occurs selectively, with a strong preference for amino acids with aromatic side chains, such as phenylalanine and tryptophan. A three-point binding mode has been proposed, with the carboxylate ion bound by the guanidinium unit, the protonated amine by the aza-crown, and π - π interactions between the phenyl side chain of the amino acid and the receptor's naphthalene unit enhancing the strength and selectivity of complex formation. Additionally,

Scheme 13. The Na^+ dependence of chloride binding by **142**.

receptor **143** is optically active, and is selective for L- over D-amino acids. In fact, no extraction of D-amino acids is observed.



The use of ditopic ion-pair receptors as sequestration agents for environmentally deleterious pollutants has recently begun to be explored. Radioactive pertechnetate anions are generated during the nuclear fuel reprocessing process and are currently discharged into the sea. Beer and co-workers have reported that the tren-based receptor **144** (tren = tris(2-aminoethyl)amine), which contains an amidic anion-binding cavity linked to three cation-binding benzo[15]crown-5 groups, has been shown to efficiently extract sodium pertechnetate from simulated aqueous nuclear waste streams.^[159] In the absence of a co-bound cation, the anion binding affinity of the receptor was considerably reduced.

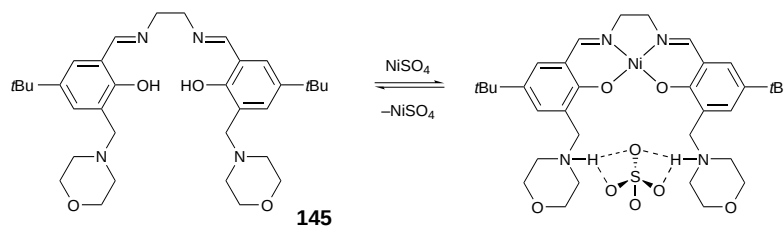
White et al. have produced a receptor that contains a dianionic binding site for transition metal cations and a dicationic binding site for anions.^[160] Receptor **145** (Scheme 14) contains a salen-based binding site (salen = *N,N'*-bis(salicylidene)ethylenediamine dianion) capable of co-

ordinating to transition metal cations such as Cu^{II} or Ni^{II} . Upon complexation, the phenolic protons transfer to the morpholine nitrogen atoms. Additionally the presence of the transition metal forces the receptor into a conformation such that the protonated morpholine groups are in proximity, and define an anion-binding site. Metal binding therefore enhances the anion-binding affinity of the receptor. Extraction experiments at pH 3.8 demonstrated that **145** is capable of extracting CuSO_4 into chloroform with a near 100 % loading of receptor.

5. Conclusion

As this brief review has illustrated with a discussion of a range of artificial anion receptor systems which function through a variety of molecular interactions, the relatively new field of anion coordination chemistry has become an established area in supramolecular chemistry. Additionally, many of the well-known concepts of cation coordination chemistry such as the chelate, macrocyclic, and template effects have transferred across to the sister field of anion coordination.

Generally, it is possible to rationalize thermodynamic stability and selectivity trends exhibited by abiotic anion receptors on the basis of complementary receptor–anion size and shape, binding site topology, and anion basicity. Calorimetric studies are essential in order to elucidate the specific contributions such as electrostatics, hydrogen bonding, hydrophobicity, and the crucial role the solvent has on the anion-recognition process. To date there is unfortunately a paucity of enthalpic and entropic data available.^[161, 162] As a consequence there is little doubt that this is an area of anion coordination chemistry that will have to be addressed in order for the field to develop further. However, based on our current understanding, it is possible to make simple predictions. Consideration of the nature of the solvent medium in

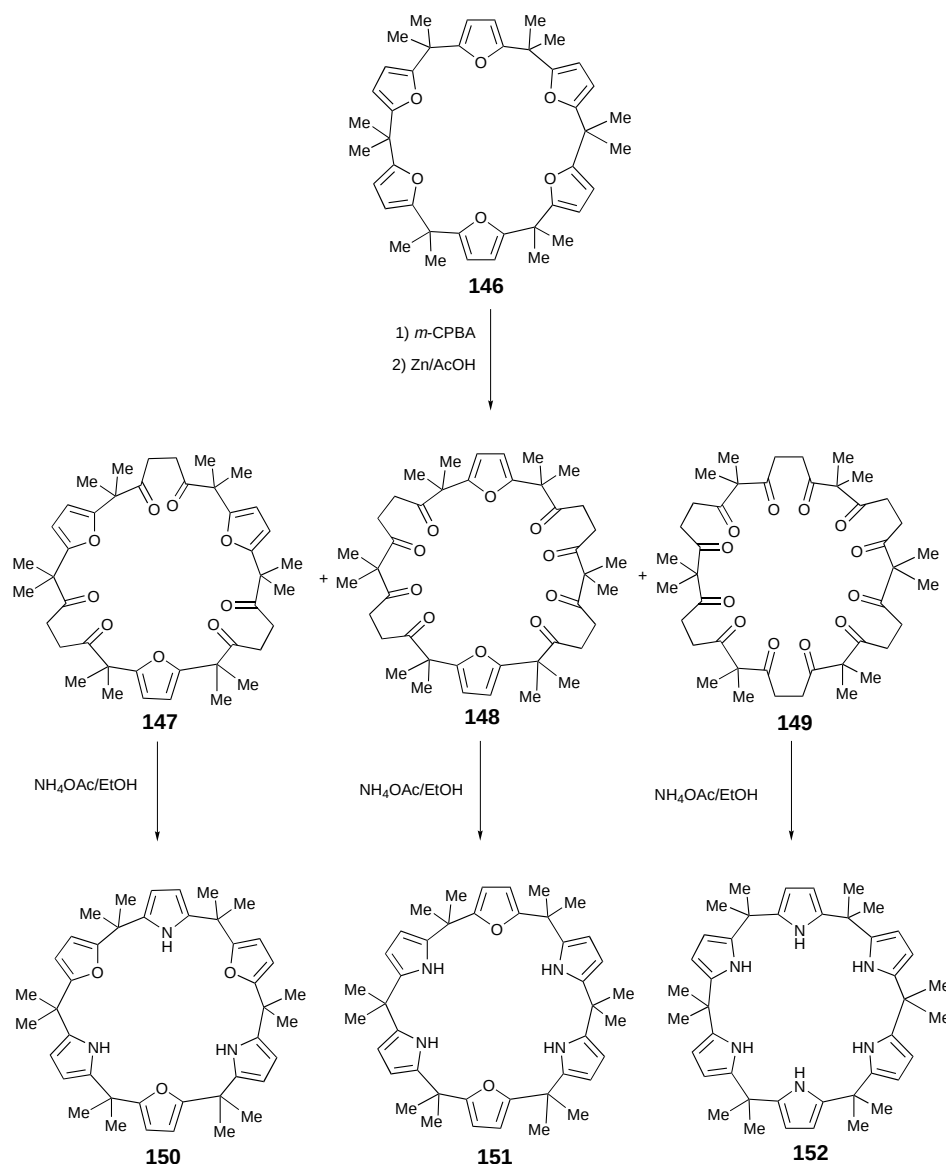
Scheme 14. The Ni^{2+} dependence of sulfate binding by **145**.

which the anion recognition event takes place is of paramount importance. For example, in aqueous solvents receptors that bind anions solely by hydrogen bonding will not function efficiently, and positively charged receptors or ones that employ a combination of hydrogen bonds and electrostatic interactions are required to overcome competing solvation effects. Correlations between the anion stability/selectivity properties of neutral ferrocenyl receptors and the solvent Gutmann acceptor number have been noted.^[163] The nature of the target anion must be taken into account: Multidentate guanidinium receptors, for example, are more effective for coordinating oxoanions such as phosphate or carboxylate wherein convergent preorganized hydrogen bond donor groups complement the hydrogen bond acceptor sites of the guest anion.

Ultimately, we hope to fully understand how nature selectively binds, functionalizes, and transports negatively charged species and so reach a stage where a specific receptor can be readily chosen when a target anion is to be bound in a particular environment. At the start of the new Millennium, it is predicted that the anion coordination chemist will meet this challenge and so provide answers to the many exciting environmental, biological, and medicinal challenges.

Addendum

Since the submission of this manuscript there have been considerable advances in the synthesis of expanded or “higher-order” calix[*n*]pyrrole macrocycles (*n* > 4).^[164, 165] Very recently, Kohnke and co-workers found that *meso*-dodecamethylcalix[6]pyrrole **152**, *meso*-dodecamethylcalix[3]furan[3]pyrrole **150**, and *meso*-dodecamethylcalix[2]furan[4]pyrrole **151** may be prepared from *meso*-dodecamethylcalix[6]furan **146** (Scheme 15).^[166] Reaction of the calix[6]furan **146** with *meta*-chloroperbenzoic acid (*m*-CPBA) followed by zinc/AcOH opens either some or all of the furan rings to afford a mixture of macrocycles **147**–**149** containing α,δ -diketone functionalities. These groups can be converted into pyrrole by treatment with ammonium acetate (Scheme 15).



Scheme 15. Synthesis of the expanded calix[*n*]arene macrocycles **150**–**152**. *m*-CPBA = *meta*-chloroperbenzoic acid.

Although the anion–calix[6]pyrrole stability constants for calix[6]pyrrole **152** have not been reported, transport studies have been carried out in order to compare the abilities of *meso*-octamethylcalix[4]pyrrole and *meso*-dodecamethylcalix[6]pyrrole **152** to transport halide ions from an aqueous (D₂O) to an organic (CD₂Cl₂) phase.^[167] These studies show that **152** extracts chloride ions from D₂O to CD₂Cl₂ most efficiently. The crystal structures of both the chloride and bromide complexes of *meso*-dodecamethylcalix[6]pyrrole **152** were obtained and revealed that the anions are coordinated at the center of the macrocycle through six N–H⋯Cl/Br hydrogen bonds. The crystal structure of the chloride complex is shown in Figure 21.

Sessler et al. have discovered a direct synthetic route to expanded calixpyrroles. Reaction of acetone with 3,4-difluoropyrrole, rather than pyrrole, gives amongst its products significant quantities of calix[5]pyrrole **154** and calix[8]pyrrole **155** (Scheme 16, Figure 22).^[168] The use of the less

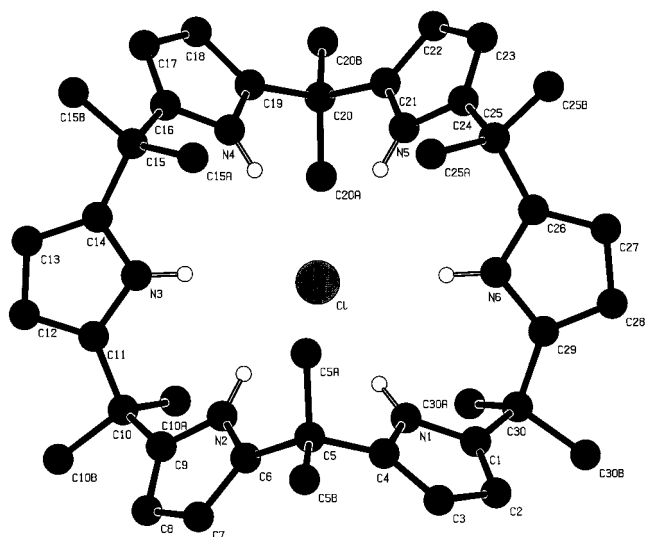
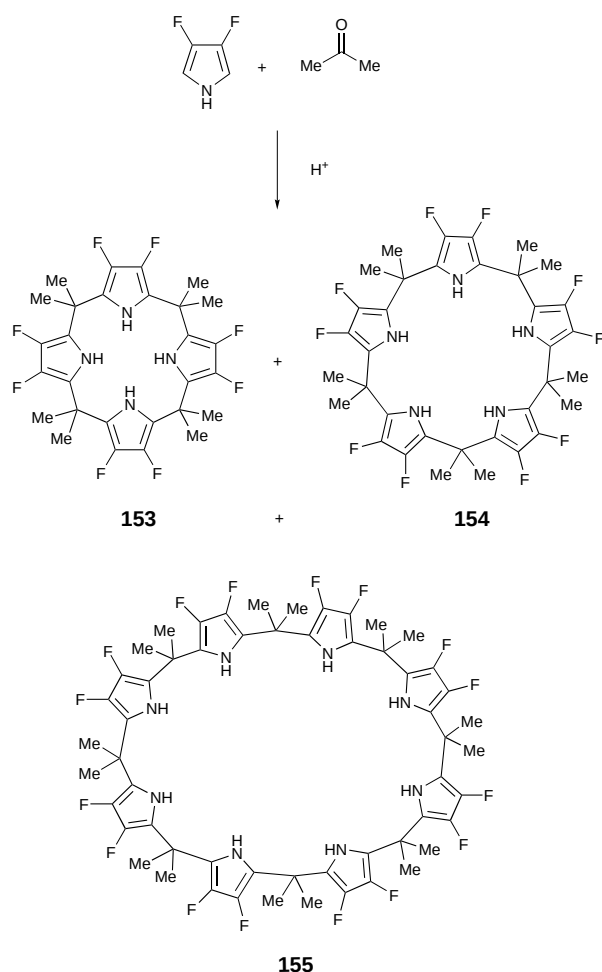


Figure 21. The X-ray crystal structure of the chloride complex of *meso*-dodecamethylcalix[6]pyrrole **152** (hydrogen atoms are omitted). Reproduced with permission from ref. [166].



Scheme 16. Synthesis of fluorocalixpyrroles **153**–**155**.

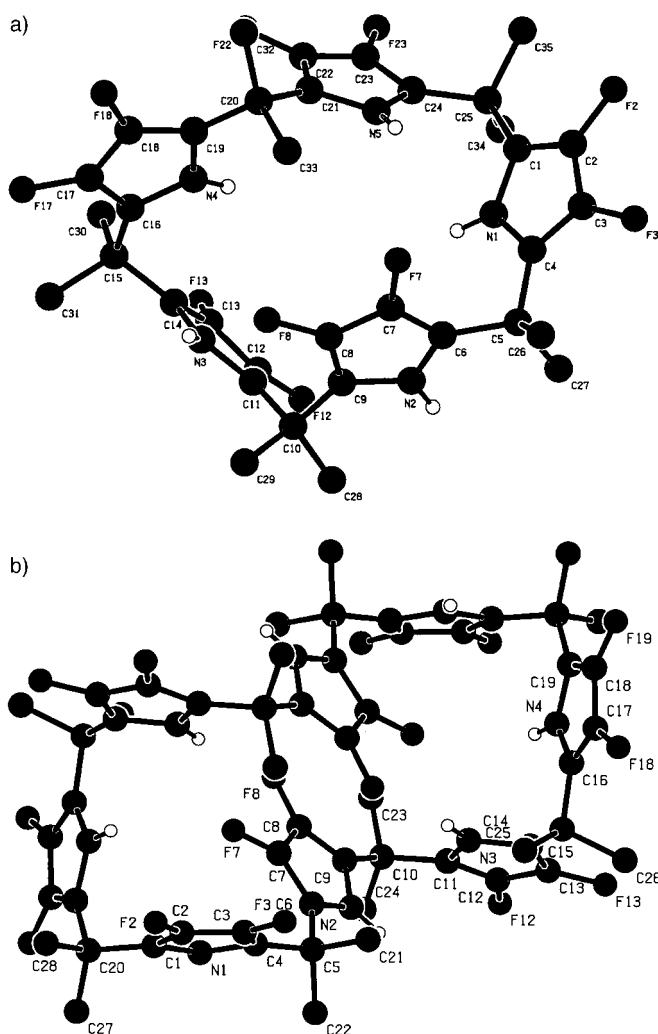
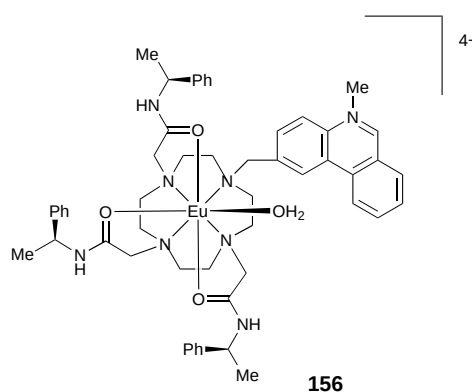


Figure 22. The X-ray crystal structures of decafluorocalix[5]pyrrole **154** and dodecafluorocalix[8]pyrrole **155** (hydrogen atoms are omitted). Reproduced with permission from ref. [168].

reactive 3,4-difluoropyrrole in the condensation allows the macrocyclization reaction to proceed under kinetic, rather than thermodynamic, control at room temperature. In preliminary work, Sessler et al. have found that decafluorocalix[5]pyrrole **154** exhibits a higher affinity for chloride ions ($K = 41\,000\text{ M}^{-1}$) than the corresponding octafluorocalix[4]pyrrole analogue **153** ($K = 11\,000\text{ M}^{-1}$) as determined by ^1H and ^{19}F NMR titration experiments in $[\text{D}_3]\text{acetonitrile}$ (0.5% D_2O).

Significant progress has also been made recently in the detection of oxyanions by lanthanide-containing receptors.^[169] Parker has shown that reversible anion binding to alkylphenanthridinium chromophore appended heptadentate cyclen-triamide or polycarboxylate Eu^{III} - or Tb^{III} -containing receptors such as **156** in aqueous solution is signalled by changes in the ^1H NMR spectrum, emission intensity, and circular polarization following excitation with the more highly charged anions (citrate, malonate) forming the strongest complexes.^[170]

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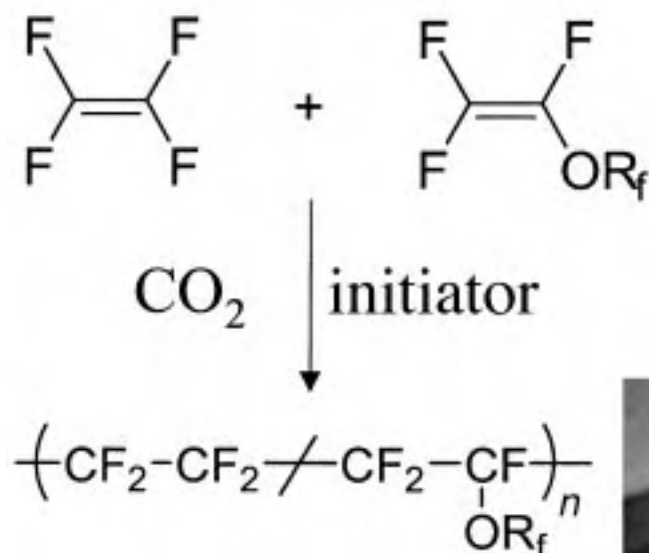
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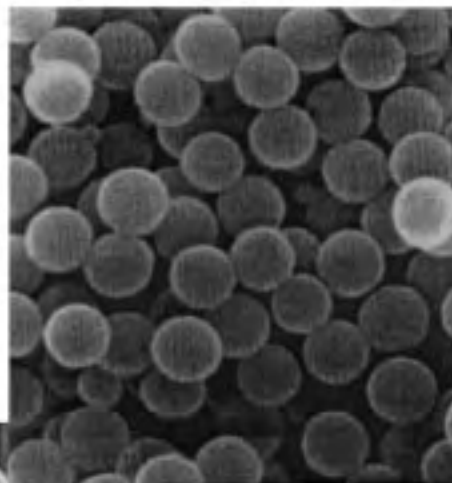
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CO₂ Technology

synthesis of fluoropolymers
in scCO₂



dispersion polymerization



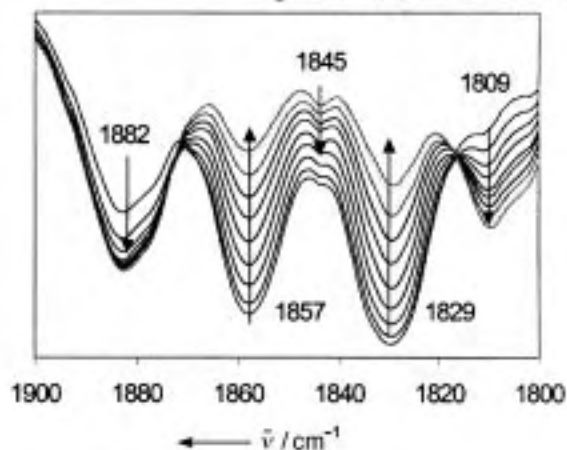
spin-coating
from liquid CO₂



crystallization of
polycarbonates with scCO₂



the decomposition
kinetics of
perfluoralkyl diacyl
peroxides in scCO₂



Sustainable Pollution Prevention

CO₂ Technology Platform: An Important Tool for Environmental Problem Solving**

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CO₂ is a good solvent for many substances when compressed into its liquid or supercritical fluid state. Above the critical temperature and critical pressure ($T_c = 31^\circ\text{C}$, $P_c = 73.8$ bar, see Figure 1 for the phase diagram for CO₂), CO₂ has both gaslike viscosities and liquidlike densities. These moderate

critical conditions allow CO₂ to be used within safe commercial and laboratory operating conditions. Small changes in temperature and pressure cause dramatic changes in the density, viscosity, and dielectric properties of CO₂, making it a tunable solvent that can be tailored for various applica-

tions. Combined, these unique properties make CO₂ a "solvent of choice" for the new millennium.

Keywords: carbon dioxide • micelles • polymers • supercritical fluids • surfactants

1. Introduction

Rapid technological advances have presented many complex ecological issues. As a result, pollution prevention and waste management represent two of the most profound challenges of the 21st century. The proliferation of the use of organic solvents, halogenated solvents, and precious water in manufacturing and processing industries, such as electronics, pharmaceuticals, dyes, and coatings, has created the right atmosphere for the creation and development of environmentally responsible and energy efficient processes. In the past decade, in an effort to meet these challenges, research groups have focused on making liquid and supercritical carbon dioxide (scCO₂) a viable solvent alternative. This pollution-prevention approach is much more sustainable and appropriate than the "end-of-pipe" approach embodied in many waste-management methods.

Carbon dioxide is a natural solvent (phase diagram in Figure 1) that could replace water and many other solvents in many applications. CO₂ is advantageous because it is inexpensive, nonflammable, environmentally benign, and can be

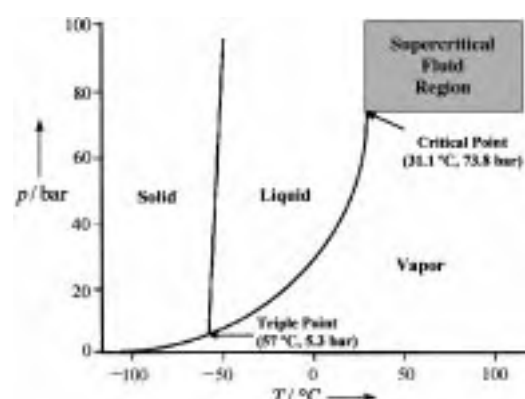


Figure 1. One-component phase diagram for CO₂.

completely and easily removed from products.^[1] CO₂ is also naturally occurring and readily available; it can be found in natural reservoirs and is a by-product from the production of ammonia, ethanol, hydrogen, and natural gases.^[2, 3] CO₂ is routinely handled on a commercial scale using pressurized and refrigerated tanks for storage and processing liquid CO₂ and cylinders for compressed CO₂ gas. When released to the atmosphere, liquid CO₂ leaves no residue to contaminate either the environment or personnel.^[2]

Processes that use CO₂ do not add directly to the greenhouse effect (global warming caused by the entrapment of heat into the atmosphere by gases that are emitted into the environment) but rather aid in the reduction of emitted CO₂. Most of the CO₂ sold today (82 %) is a by-product from other industries.^[4] In addition to environmental benefits, CO₂-based processes can also be more energy efficient than those based on water or conventional solvents. The low heat of vapor-

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[**] A list of abbreviations can be found at the end of the article.

ization of CO₂ significantly reduces the energy costs that are associated with water-intensive processing industries and also eliminates the inevitable contamination problems associated with the pollution of water effluent streams.

The highly versatile nature of CO₂ has been exploited in numerous industries and applications. CO₂ has been used for decades for food freezing and for pH control in the textile and pulp-and-paper industries.^[2] Commercialized in the 1970s as a “natural” extractant in decaffeination processes, coffee, tea, and spice industries have used scCO₂ to replace dichloromethane and ethylene dichloride.^[5] In 1997, Ford Motor Company switched some of their bumper-coating processes from hazardous solvent-based paints and primers to utilize CO₂ technology.^[6] More recently, Micell Technologies has commercialized an innovative process wherein molecular-engineered surfactant molecules, combined with CO₂, provide an environmentally friendly alternative to the traditionally hazardous solvents used today, such as perchloroethylene (PERC).^[7]

A steady stream of emerging technologies has brought CO₂ all the way from a potential alternative solvent in the early 1970s, to its ever growing present day use in many industries and applications. The most recent example is DuPont's announcement to build a \$275 million dollar manufacturing plant that will employ carbon dioxide technology to produce Teflon and other fluoropolymers.^[8]

This review will discuss the technology platform that allows CO₂ to be an environmental problem-solving tool for sustainable economic growth.

2. From Polymer Synthesis to Molecular-Engineered Surfactants

Although CO₂ is a good solvent for many small molecules, most polymeric materials have a very low solubility in CO₂.^[9] This presents major limitations for the applicability of CO₂ in

many processes. These limitations lead researchers to the design and synthesis of molecules that would bring CO₂ into a new application areas.

2.1. Homogeneous Fluoropolymer Synthesis

Only two classes of polymers are significantly soluble in CO₂ at practical operating conditions; these are amorphous (and low melting) fluoropolymers and polysiloxanes^[1, 10, 11] (for other in-depth studies on polymer solubility in CO₂, see refs. [12] and [13]). DeSimone et al. were the first to report a homogeneous free radical polymerization using a semi-fluorinated acrylate monomer in scCO₂.^[11] This milestone led to the homogeneous synthesis of many other fluorinated polymers including poly(2-(*N*-ethylperfluorooctanesulfonamido) ethyl acrylate), poly(1,1-dihydroperfluorooctyl acrylate), and poly(perfluoroethyleneoxymethylstyrene).^[14–17]

The polymerization of tetrafluoroethylene to PTFE in CO₂ is of particular importance because it emphasizes a safe new route to fluorolefin polymers. Conventional routes to fluoropolymers typically employ aqueous or chlorofluorocarbon (CFC) based solvent systems that do not have readily abstractable hydrogen atoms, which leads to premature chain termination. Aqueous based processes also generally produce carboxylic acid and acid fluoride end groups that can only be removed by expensive steps, such as high-temperature hydrolysis or fluorination. The Montreal Protocol banned the use of CFCs because of their deteriorating effect on the earth's ozone layer.^[18] CO₂ provides several advantages; no production of unstable end groups, elimination of expensive energy-intensive heating and fluorination steps, and easy separation of the polymer from solution. (For a more detailed review of the synthesis of fluoropolymers in CO₂ see refs. [16–18].)



Joseph M. DeSimone was born in 1964 in Norristown, Pennsylvania. He received his B.S. degree in chemistry in 1986 from Ursinus College in Collegeville, Pennsylvania and his Ph.D. degree in 1990 from the Department of Chemistry at Virginia Polytechnic Institute and State University where he worked with Professor James E. McGrath. He joined the Department of Chemistry at the University of North Carolina at Chapel Hill (UNC-CH) in July 1990, as an Assistant Professor. The University named Dr. DeSimone as the Mary Ann Smith Professor of Chemistry in 1995. In 1995, he was also appointed as a Professor in the Department of Chemical Engineering at North Carolina State University (NCSSU). On July 1, 1999, Professor DeSimone was named the William R. Kenan, Jr. Distinguished Professor of Chemistry at UNC-CH and Chemical Engineering at NCSSU. His research efforts are focused on developing synthetic pathways for polymer synthesis and processing in liquid and supercritical carbon dioxide. In 1992, he was a recipient of a National Science Foundation Young Investigator Award and in 1993 he was honored by the White House with his naming as a Presidential Faculty Fellow, one

of the only thirty given nationally to young faculty members in science and engineering. In 1996, Professor DeSimone co-founded MICELL Technologies, INC, a start-up company focused on using detergent-modified carbon dioxide as an environmentally responsible replacement for organic and halogenated solvents used in a variety of applications ranging from precision cleaning of microelectronics to garment dry cleaning. In 1997, the White House honored Professor DeSimone again with his selection to receive the 1997 Presidential Green Chemistry Award. In 1999, Professor DeSimone was awarded the American Chemical Society's Carl S. Marvel Creative Polymer Chemistry Award. Joe, his wife Suzanne, their son Phillip and daughter Emily, reside in Chapel Hill, North Carolina.

2.2. Molecular-Engineered Surfactants

Fluoropolymers and siloxanes represent a very small fraction of the industrially important polymers; therefore, surfactants are needed to broaden the efficacy of liquid and supercritical CO₂ to include the synthesis of other polymers using heterogeneous polymerization methods. Just as surfactants are important to aqueous technologies, surfactants are also the key to extractions, coatings, cleaning, drug delivery, and heterogeneous polymerizations in CO₂. The lack of commercially available CO₂ surfactants led researchers to develop CO₂ soluble amphiphilic block-copolymer surfactants that incorporated “CO₂ philic” fluorinated or siloxane components and “CO₂ phobic” hydrophilic or lipophilic components.

2.2.1. Fluoroacrylate-Based Polymeric Surfactants

As a result of the inherent incompatibility of the fluorocarbon monomers with other synthetic methods, controlled free radical polymerization techniques were the first to be employed for the synthesis of the amphiphilic block copolymers for use in CO₂-based systems. Because of the insolubility of most fluoropolymers in common organic solvents and the presence of some special features in several fluorinated monomers (e.g. two acidic hydrogens on the methylene adjacent to the ester group in 1,1,2,2-tetrahydroperfluorooctyl acrylate (TAN)), controlled free radical polymerization methods appeared to be the most versatile available. Specifically iniferter polymerization^[19] and atom-transfer radical polymerization (ATRP)^[20] techniques were implemented for the synthesis of the block copolymers.

The iniferter technique has been used to synthesize a wide range of hydrophilic, lipophilic, and fluorocarbon polymers including poly(2-dimethylaminoethyl methacrylate) (PDMAEMA), polystyrene (PS), poly(vinyl acetate) (PVAc), poly(1,1-dihydroperfluorooctyl acrylate) (PFOA), and 1*H*,1*H*-perfluorooctyl methacrylate (PFOMA).^[21, 22] While ATRP is not as widely applicable to as many monomers as the iniferter technique, ATRP does give much more controlled and well-defined polymers. ATRP has been shown to be effective in synthesizing polymers derived from acrylates, methacrylates, and styrenics as well as fluorocarbon monomers such as FOMA, FOSEA, FOSEMA, and TAN.^[22] Additionally, Xia et al. recently demonstrated the synthesis of PFOA using ATRP in scCO₂.^[23] Several hydrocarbon–fluorocarbon diblock copolymers synthesized by these techniques are listed in Table 1.

2.2.2. Characterization of Fluoroacrylate Polymeric Surfactants

When amphiphilic copolymers are placed in a solvent that is selectively good for one block and a non-solvent for the other, they tend to self-assemble to form micelles in solution. Extending this concept to CO₂ systems, the formation of micelles should occur in a CO₂ medium, where the micellar

Table 1. Hydrocarbon–fluorocarbon diblock copolymers.

Hydro-carbon block	M_n [kg mol ⁻¹]	PDI ^[a]	Fluoro-carbon block	M_n [kg mol ⁻¹]	Techniques
PS	3.7	1.7	PFOA	39.8	Iniferter
PS	6.6	1.8	PFOMA	42.3	Iniferter
PVAc	4.4	1.6	PFOA	43.1	Iniferter
PMMA	8.1	1.3	PFOMA	55.9	ATRP
P(<i>t</i> BuAc)	5.0	1.6	PFOMA	52.6	ATRP
PHEMA	4.0	1.5	PFOMA	40.0	ATRP

[a] PDI = polydispersity index.

core is CO₂-phobic, and the CO₂-philic corona extends into the solvent. The limited solubility of fluorinated polymers in ordinary organic solvents prevents the use of conventional methods for polymer characterization; therefore high-pressure scattering and NMR spectroscopic techniques are employed to study copolymer micelles in solution.^[24–32] Small angle neutron (SANS) and X-ray (SAXS) scattering methods have provided valuable information on the conformational properties of polymeric surfactants in CO₂. In particular, extensive SANS and SAXS measurements were performed on poly(ethylene oxide)-*g*-PFOA, and PS-*b*-PFOA samples in CO₂ over a range of temperatures and pressures.^[24]

Experiments were performed on a PEO-*g*-PFOA sample at 60 °C and three different pressures (470, 300, and 255 bar) in CO₂ in the presence of water, with a water/surfactant ratio of 0.32/1. The oscillatory nature of the scattering curves indicated the formation of spherical core–shell micelles. A depiction of a spherical micelle of PFOA-*g*-PEO with the collapsed PEO chains and water molecules within the core is shown in Figure 2. From core–shell-model fits to the scattering curves, the outer radii of the aggregates were found to be approximately 125 Å and the polydispersities were relatively low. Measurements were also performed on the polymer in CO₂ in the absence of water which showed that the micelle dimensions were smaller. The radius of gyration taken from a core–shell fit increased from ~56 Å (no added water) to 86 Å (H₂O swollen) and 136 Å (D₂O swollen).

The scattering curves from PS-*b*-PFOA in CO₂ also confirmed that core–shell spherical micelles are formed. SANS characterization of micelles with added hydrogenated and deuterated PS oligomer showed >99% of the added oligomer was stabilized in the core of the micelle.^[27] The micellar core volume increased with added oligomer as a function of oligomer concentration (Figure 3). There was approximately an eight-fold increase in the volume of the micelle core with the addition of up to 20% (w/w) oligomer.

Chu and Zhou^[25] and Buhler et al.^[30] were the first to use high-pressure light-scattering methods to study the micellization and critical micelle density (CMD, a reversible unimer-to-micelle transition upon a decrease in CO₂ solvent density). Aided by high-power lasers, static and dynamic light scattering (DLS) methods have also proven to be powerful, reliable, and readily assessable techniques to study the characteristics of polymers in CO₂. Very detailed studies of PVAc-*b*-PFOA and PVAc-*b*-PTAN copolymers, both of which exhibited the CMD transition, were recently reported in the literature.^[30]

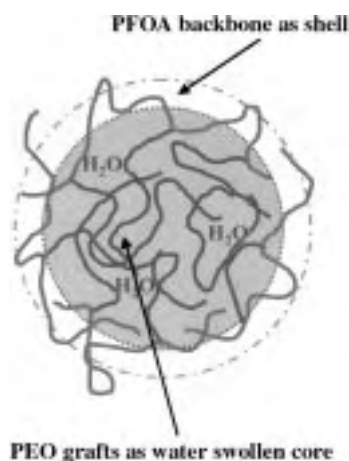


Figure 2. Proposed Structure of a PFOA-g-PEO graft copolymer micelle in supercritical CO_2 .

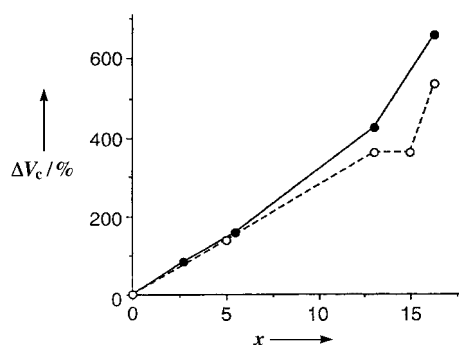


Figure 3. Swelling of 3.7 k -b-39.8 k surfactant micelles in CO_2 (65 °C, 340 bar) with PS oligomers. Surfactant concentration = 4 % (w/v). ΔV_c = change in core volume, x = PS oligomer concentration; ● = H-Oligomer, ○ = D-Oligomer.

Figure 4 shows the hydrodynamic size plotted against CO_2 density for 10.3 k PVAc- b -60.4 k PTAN solution (where the numbers refer to the molar mass of the particular block in 10^3 g mol^{-1} units). In the low-density range 15 nm spherical micelles are found, as the density increases, the CMD transition region is reached leading into the 3–4 nm unimer region. In addition to showing the CMD, the DLS data was used to show the coexistence of unimers and micelles in the transition region. This coexistence prompted the construction of a copolymer–surfactant/ CO_2 binary phase diagram (Figure 5). Three regions on the phase diagram can be identified a) a two phase region at CO_2 densities below 0.82 g cm^{-3} where the polymer was insoluble, resulting in phase separation into polymer rich and solvent rich phases, b) a region of spherical micelles at intermediate CO_2 densities, c) a unimer region at high densities. The coexistence line connecting the micelle and unimer phases not only indicates the CMD at constant copolymer concentrations, but also the CMC at a particular CO_2 density.

2.2.3. Polysiloxane-Based Surfactants

The use of silicone-based surfactants for applications in CO_2 technology is more attractive than the use of fluorinated

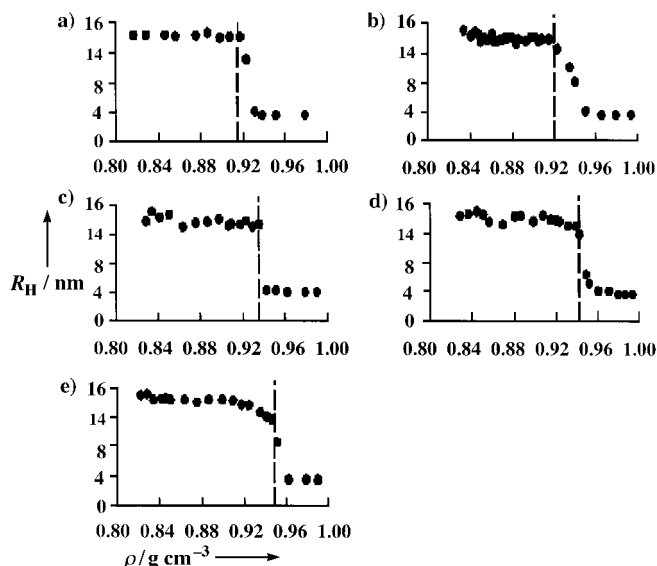


Figure 4. Effect of the CO_2 density (ρ) on the hydrodynamic radius for a copolymer concentration c : a) $1.88 \times 10^{-3} \text{ g cm}^{-3}$, b) $3 \times 10^{-3} \text{ g cm}^{-3}$, c) $6 \times 10^{-3} \text{ g cm}^{-3}$, d) $1.125 \times 10^{-2} \text{ g cm}^{-3}$, e) $2 \times 10^{-2} \text{ g cm}^{-3}$ at temperature $T = 45^\circ\text{C}$. Dashed lines indicate the onset of the micelles $\rightarrow$ unimers transition.

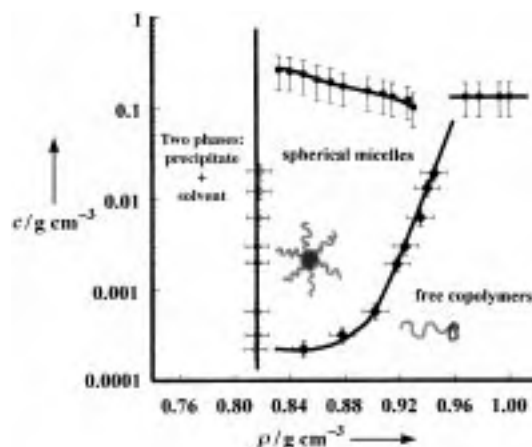


Figure 5. Phase diagram in the copolymer concentration (c) and the CO_2 density (ρ) plane at a fixed temperature $T = 45^\circ\text{C}$. (○) cloud line (solubility line), (◆) spherical micelles $\rightarrow$ unimers transition, and (●) overlap concentration c^* .

materials for a number of reasons. The synthesis of siloxane-based stabilizing systems is cheaper and they are more soluble in conventional solvents which facilitates characterization. Additionally, these surfactants can be synthesized by anionic polymerization methods leading to narrow molecular-weight distributions. Several groups have studied polysiloxanes in CO_2 and reported the high solubility of these materials.^[33, 34] Hoeffling et al. have designed and synthesized silicone-based amphiphiles and explored the relationship between structure and solubility by phase-behavior experiments.^[35] More recently, the design and synthesis of silicone containing “ambidextrous” surfactants was reported by Yates and co-workers.^[36] The surfactants synthesized were a poly(dimethylsiloxane)- b -poly(methacrylic acid) and a poly(dimethylsiloxane)- g -pyrrolidonecarboxylic acid. These surfactants (as discussed in section 3.2) demonstrated the ability to stabilize

an organic latex in either a nonpolar medium, dense liquid CO₂ (CO₂ with a density of $>1.0\text{ g cm}^{-3}$), or water.

2.2.4. Perfluoropolyether Surfactants

In 1985 Krukons reported the solubility of perfluorinated polyethers in carbon dioxide, an observation made while conducting fractionation studies on a commercially available high molecular weight perfluoropolyether oil.^[1] This polymer was fractionated at 80 °C over a pressure range from 82 bar to 275 bar. Since then, a considerable amount of research has focused on the design and synthesis of fluoroether functional surfactants. Hoefling and colleagues demonstrated the high CO₂ solubility of two nonionic perfluoropolyether surfactants, hydroxyaluminum bis(poly(hexafluoropropylene oxide)carboxylate) and poly(hexafluoropropylene oxide)carboxylic acid, and an anionic surfactant, sodium poly(hexafluoropropylene oxide)carboxylate.^[37] The twin-tail surfactant was selected for its potential usefulness as a CO₂-thickener, but no appreciable increase in the solution viscosity was observed.

Fluorinated polyether surfactants have been prepared for CO₂-based applications such as heavy-metal extraction, dispersion polymerizations, and protein extraction.^[38] In the case of heavy-metal extraction, a perfluoropolyether containing a dithiol end group has been synthesized and found to extract as much as 98% of mercury from contaminated soil in laboratory-scale CO₂ extractions. It was determined that over 90% of the total extraction occurred during the first hour. Other functionalities have been incorporated in the polymer chains for use as chelating agents and a review of these materials can be found elsewhere.^[39] (For more details on surfactants, surfactant synthesis and characterization in CO₂ see the review by Carson et al.^[40])

3. Surfactant-Aided Polymerizations

Without the aid of surfactants or stabilizing agents, at a critical chain length, CO₂-phobic polymers will precipitate from a CO₂ solution during synthesis. Many precipitation polymerizations are carried out in this fashion, producing commercially important, melt-processible polymers;^[41, 42] however, for amorphous polymers this method typically results in both undefined morphologies and low degrees of polymerization.^[43] As an alternative approach amphiphilic copolymers of the nature described above (Section 2.2) have been employed in the heterogeneous polymerization of many monomers in CO₂.

3.1. Dispersion Polymerizations

For surface-coating applications, dispersion polymerizations are used to produce uniform polymer particles with diameters ranging from 100 nm to 10 μm . Briefly, a dispersion polymerization is a heterogeneous polymerization process by which latex particles are formed in the presence of a suitable stabilizer from an initially homogeneous reaction mixture.^[44] High degrees of polymerization are observed because the

insoluble polymer is stabilized sterically as a colloid and does not precipitate. In 1994, DeSimone and co-workers performed the first successful dispersion polymerizations in scCO₂ by employing CO₂ soluble amphiphilic stabilizers.^[45, 46] The free radical initiated polymerization of methyl methacrylate (MMA) was the first of a series of dispersion polymerizations of lipophilic monomers using PFOA as the stabilizer.^[47, 48] PFOA behaves very similarly to amphiphilic block copolymers, in that it contains an acrylic-like backbone (CO₂-phobic) which functions as an anchoring unit that can either physically adsorb or chemically graft onto the growing particles, while the fluorinated side groups (CO₂-philic) extend the chain into the continuous phase, preventing flocculation of particles through steric stabilization (Figure 6).

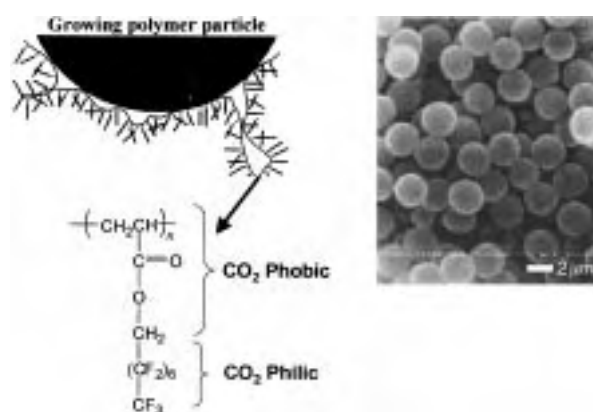


Figure 6. Left: Mechanism of dispersion polymerization and particle formation in scCO₂. Right: Scanning electron micrograph of particles isolated from polymerization run in CO₂.

Until recently there have been few examples demonstrating the synthesis of hydrophilic polymers in CO₂ by dispersion polymerization. Carson et al. recently reported the first dispersion polymerization of a hydrophilic monomer, 1-vinyl-2-pyrrolidone, in scCO₂ also by using PFOA as a stabilizer.^[49] Spherical and relatively uniform particles with diameters ranging from 0.56 and 2.89 μm were produced.

Commercially available and less expensive siloxane-based macromonomers were also found to be effective stabilizers in the dispersion of MMA.^[50] Macromonomers are not amphiphilic in nature, but they contain polymerizable terminal functional groups that are chemically grafted onto the growing polymer, thus providing steric stabilization. By using this method, high molecular weight, well-defined spherical particles of PMMA were obtained with diameters ranging from 1.1–5.8 μm depending on reaction conditions.

The surfactants developed by Yates and co-workers were also reported to stabilize PMMA particles produced by dispersion polymerizations in CO₂; their transfer to water results in an aqueous latex.^[36] Two surfactants were investigated, a block copolymer containing PDMS ($M_w = 5500\text{ g mol}^{-1}$) and methacrylic acid ($M_w = 900\text{ g mol}^{-1}$) and a graft copolymer of PDMS and pyrrolidonecarboxylic acid ($M_{w, \text{total}} = 8500\text{ g mol}^{-1}$). While use of the graft copolymer produced smaller and more uniform PMMA particles (ca. 3 μm), they rapidly flocculated in a dispersed aqueous buffer

solution. However, the particles produced using the block copolymer resulted in an electrostatically stabilized latex in water at concentrations at least up to 10 wt% in buffered solutions of pH 8 and 11.

Amphiphilic diblock copolymers containing fluorinated or siloxane segments have also been employed in the dispersion polymerization of styrene, vinyl acetate, vinyl acetate-*co*-ethylene, and 2,6-dimethylphenol to make poly(2,6-dimethylphenylene oxide).^[47, 48, 51] Diblock copolymers offer steric stabilization, the CO₂-phobic block anchors onto the growing polymer chain while the CO₂-philic block extends out into the solvent medium. These type of stabilizers offer the added ability to control the diameters and size distributions of particles by variations in the ratio of the anchoring (CO₂-phobic) block to the stabilizing (CO₂-philic) block.

3.2. Emulsion Polymerization

Adamsky and Beckman have employed an amide end-capped poly(hexafluoropropylene oxide) surfactant in the inverse emulsion polymerization of acrylamide in CO₂.^[37, 38] These polymerizations were conducted in the presence of water, a co-solvent for the monomer, at a CO₂ pressure of 345 bar and 60 °C using AIBN as the initiator. When surfactant was added to the polymerizations, the CO₂ solution had a milky-white appearance similar to that of conventional inverse emulsion polymerizations. Additionally, intrinsic viscosity measurements of the resultant polymer revealed significantly higher molecular weights than conventional emulsion polyacrylamide. However, in the absence of any surfactant the solution appeared similar to a simple dispersion polymerization of an aqueous solution in CO₂. Phase separation occurred immediately when agitation ceased and a large mass of precipitated polymer was collected.

4. Solving Environmental Problems with CO₂

4.1. Polycarbonate Synthesis

Toughness and optical clarity makes polycarbonates an important class of polymers that are useful in many applications including compact (CD) and digital video disks (DVD), military shields and bullet proof windows. Traditionally two routes have been employed to synthesize high molecular weight polycarbonates: an interfacial route that involves the reaction between phosgene and 2,2-bis(*p*-hydroxyphenyl)propane (bisphenol A) in a biphasic reaction system of methylene chloride and alkaline water; and the melt-phase transesterification between bisphenol and diaryl carbonate.^[52] While the interfacial route requires large volumes of environmentally harmful solvents, it is the predominant method for polycarbonate synthesis. The more environmentally friendly melt-phase process has significant disadvantages including low product molecular weights incurred as a result of high viscosities, and the formation of color bodies which are a result of the high reaction temperatures. The color bodies significantly reduce the optical properties of the material,

making it unsuitable for data storage applications. Recently two new routes have been demonstrated to synthesize polycarbonates: melt-phase transesterification in the presence of scCO₂ and solid-state polymerization (SSP) with scCO₂ as a crystallization agent.

4.1.1. Melt Phase Synthesis

Burke et al. have shown reaction condensates in a melt-phase step-growth polymerization can be effectively removed by swelling or plasticizing the polymer melt.^[53] Plasticizing agents reduce the viscosity, increase chain mobility and free volume, and increase the diffusivity of the small molecule condensate, thus driving the polymerization to higher conversions and higher molecular weights. However, conventional agents are typically expensive, toxic, and difficult to separate from the end product, thus making their usage minimal. In contrast, nontoxic scCO₂ was found to be an excellent easily removable plasticizing agent.^[54, 55] Gross et al. have taken advantage of these properties of CO₂ to swell and melt-phase polymerize bisphenol A poly(carbonate).^[56] Swelling results of two low molecular weight polycarbonates samples indicated that the polymer could be swollen to greater than 50 % of its original volume (Figure 7).

In addition to CO₂ swelling the polymer, it was also used in melt-phase reactions to extract the phenol by-product and thus drive the reaction to higher conversions. The swollen melt-phase polymer system displayed enhanced reaction rates compared to a non-scCO₂ system, as evidenced by higher molecular weights produced in the same reaction time. This is expected since in melt-phase step-growth polymerizations the poor diffusivity of the condensate in viscous polymer melts often limits the reaction rate.

4.1.2. Solid-State Polymerization (SSP)

High reaction temperatures and tedious vacuum techniques are necessary for the operation of melt-phase polymerizations on an industrial scale. Despite solid-state polymerization (SSP) being the method of choice for the preparation of step-growth polymers such as poly(ethylene terephthalate) (PET) in large volume polycarbonate SSP is commercially impractical. In an SSP process, the reaction temperature of precrystallized polymer particles needs to be above the polymer glass transition temperature (T_g) to ensure chain mobility but below the melting temperature (T_m) to prevent sticking and coalescence of particles.

Crystallization is usually induced in polycarbonates by treatment with organic solvents and nucleating agents since the polymer does not crystallize on its own thermally.^[57] The solvents known to induce crystallinity (e.g. acetone and methylene chloride) not only pose potential environmental hazards but are also difficult to handle in an industrial scale plant. Prompted by the discovery by Beckman and Porter of the crystallization of thin films of polycarbonate by CO₂ at elevated temperatures and pressures,^[58] Gross et al. extended the crystallization process to granules and beads of low

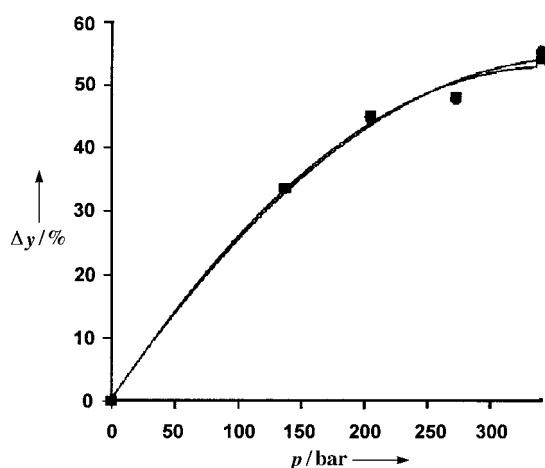


Figure 7. Percent swelling of polycarbonates (M_n of 2500 (■) and 5000 g mol^{-1} (●)) at 235 °C at various CO₂ pressures.

molecular weight polycarbonates in an effort to create materials that could undergo SSP without using toxic organic solvents.^[59] Low molecular weight polycarbonate samples were exposed to scCO₂ and were reported to be between 19 to 30% crystalline, depending on conditions. As a result of exposure to CO₂, the samples lost their transparency and became white and opaque (Figure 8).

The results from the SSP of the precrystallized samples indicated that there could be a seven-fold increase in the

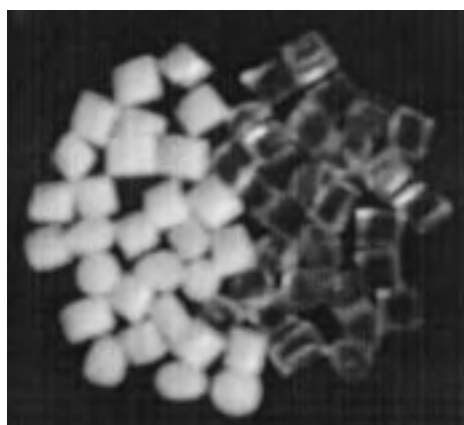


Figure 8. Crystallization of polycarbonate pellets aided by scCO₂. Right: amorphous, left: crystalline.

molecular weight of the final product, depending on reaction conditions. The observed increase in molecular weight demonstrated that the use of scCO₂ to induce crystallinity was effective for the SSP of polycarbonates.

4.2. Coatings in CO₂

Perfluoropolyethers have unique properties that make them suitable for the coating and protection of historical buildings and monuments made of stone.^[60, 61] These transparent, colorless polymers are highly water repellent and have been proven to reduce water absorption into stone by 80 to

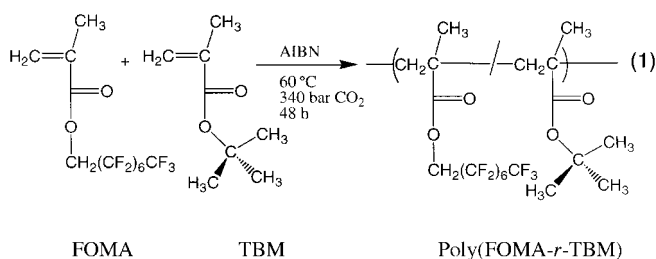
90% for at least 30 months. They have low surface energies and are stable to corrosive acids, high temperatures, UV radiation, and oxidizing agents.^[62] Results in the field of stone protection have shown that perfluoropolyethers offer very encouraging results, however, the only common solvents for these polymers are ozone-depleting CFCs. Hénou et al. have recently shown CO₂ offers several advantages over CFCs for polymeric stone-protective materials.^[63] Aside from previously stated properties of CO₂ and its ability to readily dissolve perfluoropolyethers, its low critical pressure affords the opportunity to spray coat polymers onto the surface of stones. This method of application has the potential to be faster than brush applications and to produce a much more homogenous coating. The atomization of the coating product can be achieved through the rapid expansion of supercritical solution (RESS). In the RESS process, a dilute solution of a solute in the scCO₂ is expanded through a nozzle, from a high upstream pressure to a lower downstream pressure. The polymer then precipitates from the solution because of the lower solubility of the solute at gaslike solvent densities. The solubility properties of perfluoropolyethers in CO₂ are the key parameters in properly designing the RESS process.

Cloud-point and spray-coating measurements of various perfluorinated polymers from CO₂ demonstrate that scCO₂ is a viable solvent for the dissolution and spray application of fluorinated polymers onto stone surfaces and a good alternative to the currently used CFCs.^[63, 64] (For more details about the RESS process and its application to stone protection see refs. [58–61, 65–68].

4.3. Spin Coating and Photolithography

The semiconductor industry has averaged an annual growth of 15% for the last 30 years. Sustained growth is dependent upon the industry's ability to increase microchip performance while decreasing the cost of each microchip. A typical semiconductor processing line producing 5000 wafers per day will generate 8000 liters of waste solvent and 8000 liters of contaminated rinse water per day. These contaminated organic and aqueous solvents are not only environmentally unfriendly, but are also expensive to recover and expensive to dispose. Carbon dioxide provides an excellent opportunity to eliminate hazardous waste produced while spin coating and developing integrated circuits. Several advantages offered by CO₂ include: the easy solvent removal, recovery and drying, the elimination of current ventilation equipment, and the low solvent viscosity makes it ideal for penetrating the increasingly smaller gaps. Despite all the advantages, there are several challenges incurred with the use of CO₂ for this application. Solubility limitations of current photoresist materials necessitate the development of new CO₂ compatible resists that must also be soluble in liquid CO₂ at vapor pressure, that is, CO₂ liquid in coexistence with its vapor. Furthermore, chambers to facilitate high-pressure spin coating must be built. In an attempt to meet and overcome these challenges, Hoggan et al. have reported the synthesis of a suitable resist material and the construction of a high-pressure spin coating apparatus.^[69]

A series of random copolymers of FOMA and *tert*-butyl methacrylate (TBM) have been synthesized [Eq. (1)] as a negative resist for deep-UV lithography. In the presence of a



photoacid generator, the acid sensitive *tert*-butyl groups are cleaved, significantly decreasing the solubility of the polymer in CO₂. This change in solubility is the mechanism by which a pattern can be developed to form an integrated circuit. These photoresist polymers were then spun into films at slightly sub-ambient temperatures and elevated pressures using the liquid CO₂ spin-coating apparatus shown in Figure 9. Initial

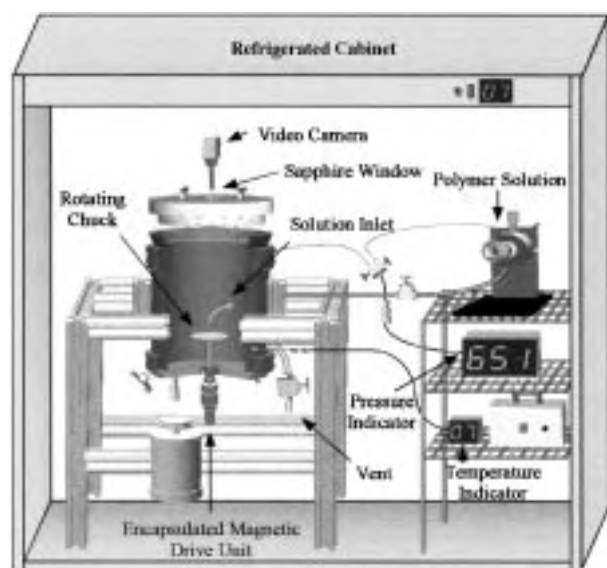


Figure 9. Liquid CO₂ spin-coating apparatus.

results indicated that the films spun were between 1–10 μm with a high level of uniformity. These experiments demonstrated that CO₂ can be used in lithography processing.

5. Barriers and Potential Solutions

While the utilization of CO₂ has significantly increased over the past few years, there are still barriers that hinder its use and acceptance in many industries and applications. The lack of innovative chemistry and fundamental science/theory are two of the major drawbacks. New chemistries are needed to synthesize new CO₂-soluble materials that enable processes that avoid conventional solvents and water, improve properties of current materials, and enable the integration of reaction and separation processes. A better understanding

of interfacial phenomena in compressible media is needed especially as it relates to the solubilization and emulsification of substances in CO₂. An increase in the basic science associated with thermo-physical properties of CO₂ could greatly enhance the understanding of mass-transport phenomenon, multicomponent phase equilibria, reaction kinetics, and thermodynamics. Other barriers that limit the use of CO₂ include: high capital cost, the lack of pollution prevention investment incentives for industry, inadequate communication between industry and academia, and the lack of researchers with an adequate knowledge base. Many of these barriers can be overcome when researchers from various fields start to collaborate to tackle some of the present issues associated with CO₂. Furthermore, the continual and increased support of industry and government would also provide scientists and engineers with both the means and motivation to continue CO₂-based research.

6. Outlook and Summary

A significant amount of research has shown that carbon dioxide can and will have a major impact on many industries in the 21st century. It has been demonstrated for many applications that CO₂ is not only a viable environmentally friendly solvent, but that it also offers improvements over many of the current processes. Recent advances in areas such as dispersion polymerization, polycarbonates synthesis, protective stone coating, and spin coating are representative and predictive of the capabilities of CO₂. With increased collaboration, creative research, and a steady resource base, the possibilities for the broad utilization of carbon dioxide are numerous.

7. List of Abbreviations

AIBN	azobisisobutyronitrile
ATRP	atom transfer radical polymerization
CFC	chlorofluorocarbon
CMD	critical micelle density
DLS	dynamic light scattering
PDMAEMA	poly(2-dimethylaminoethyl acrylate)
PFOA	poly(1,1-dihydroperfluorooctyl acrylate)
FOMA	1,1-dihydroperfluorooctyl methacrylate
FOSEA	2-(N-ethylperfluorooctanesulfonamido)ethyl acrylate
FOSEMA	2-(N-ethylperfluorooctanesulfonamido)ethyl methacrylate
PVAc	poly(vinyl acetate)
PS	polystyrene
MMA	methyl methacrylate
<i>P_c</i>	critical pressure
PDMS	polydimethylsiloxane
PEO	poly(ethylene oxide)
PERC	perchloroethylene
PET	polyethylene terephthalate
PHEMA	poly(hydroxyethylmethacrylate)
SANS	small angle neutron scattering
SAXS	small angle X-ray scattering

sc	supercritical
SSP	solid-state polymerization
TAN	1,1,2,2-tetrahydroperfluorooctyl acrylate
TFE	tetrafluoroethylene
TBM	tert-butyl methacrylate
T _c	critical temperature

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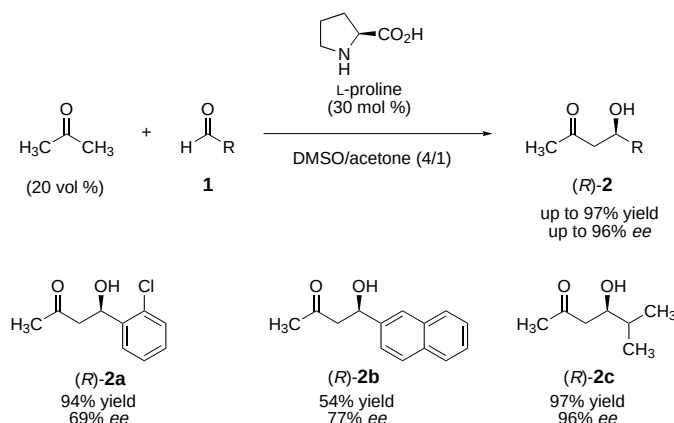
The Application of L-Proline as an Enzyme Mimic and Further New Asymmetric Syntheses Using Small Organic Molecules as Chiral Catalysts

Harald Gröger* and Jörg Wilken

Can a simple organic molecule act like an enzyme? If this were possible, it would represent a remarkable synthetic alternative to many established asymmetric transformations. In particular, such processes would allow the cost effective manufacture of chiral building blocks on an industrial scale. Furthermore, the application of enantiomerically pure, “small” organic molecules represents a promising alternative catalytic concept in addition to other frequently used syntheses based on metal-containing catalysts.^[1, 2] However, these organic catalysts should not only function like an enzyme, but should also—with respect to technical application—show the following characteristics: a) easy availability, b) both enantiomers are available with comparable price, c) low price of the organic molecule (if possible directly accessible without derivatization from the “chiral pool”), d) low molecular weight, e) easy separation from the product, and f) easy recovery after work-up without racemization.

The capability of a simple organic molecule from the “chiral pool” to act like an enzyme has now been shown by List, Lerner, and Barbas III^[3] for one of the most important organic asymmetric transformations, namely the catalytic aldol reaction.^[4] In addition, all the above-mentioned requirements have been fulfilled. The access to the chiral aldol products was realized by means of a simple nonmodified catalytic molecule from the “chiral pool”: L-proline. In the described experiments the conversion of acetone with an aldehyde resulted in the formation of the desired aldol products in satisfactory to very good yields and with enantioselectivities of up to 96 % *ee* (Scheme 1).^[3]

It is noteworthy that, in a similar manner to enzymatic conversions with aldolases of type I or II, a “direct” asymmetric aldol reaction is possible when using L-proline as a catalyst. Accordingly the use of enol derivatives of the ketone component is not necessary, that is, ketones (acting as donors)



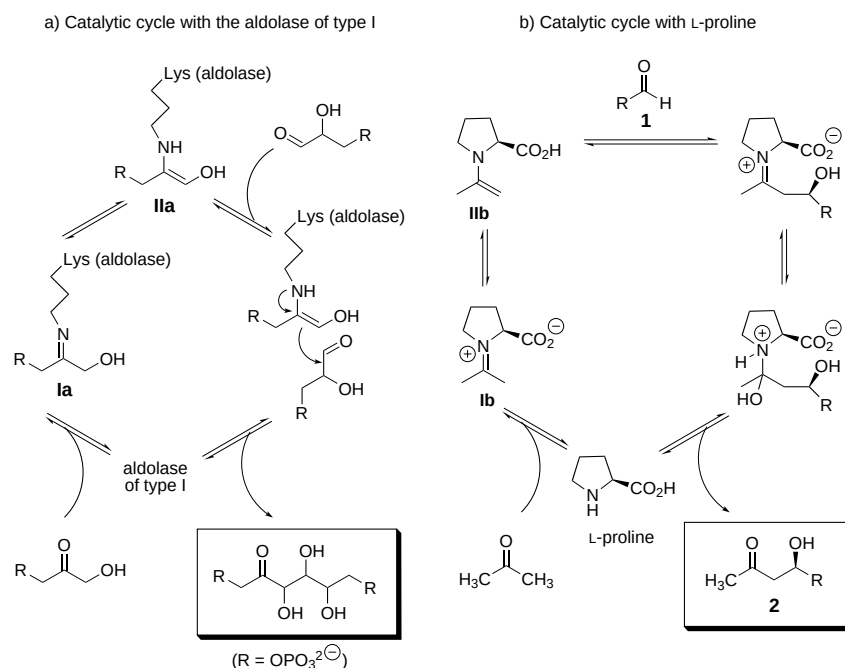
Scheme 1. The direct asymmetric aldol reaction catalyzed by L-proline.

can be used without previous modification.^[5] So far, most of the asymmetric catalytic aldol reactions with synthetic catalysts require the utilization of enol derivatives.^[4] The first direct catalytic asymmetric aldol reaction in the presence of a chiral catalyst has recently been reported by Shibasaki et al.^[6a] In particular, heterobimetallic complexes have been found to be suitable catalysts.^[6] These catalysts can be regarded as enzyme mimics of the metal-containing aldolases of type II (with a zinc cofactor) and they gave excellent yields and enantioselectivities.

In contrast L-proline, which has been used by List et al.,^[3] acts as an enzyme mimic of the metal-free aldolase of type I. Similarly to this enzyme, L-proline catalyzes the direct aldol reaction according to an enamine mechanism. Thus, for the first time a mimic of the aldolase of type I was found. The close relation between the reaction mechanism of the aldolase of type I^[4b] and the postulated mechanism of the L-proline-catalyzed direct aldol reaction^[3] is shown in a graphical comparison in Scheme 2. In both cases the formation of the enamines **IIa** and **IIb**, respectively, represents the initial step. These reactions are carried out starting from the corresponding ketone and the amino functionality of the enzyme or L-proline. The conversion of the enamine intermediates **IIa** and **IIb**, respectively, with an aldehyde, and the subsequent release of the catalyst furnishes the aldol product.

However, a difference between both catalytic cycles can be seen in the reaction sequence for the formation of the

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Scheme 2. The catalytic cycles of the direct aldol reaction with aldolase of type I (a) or L-proline (b).

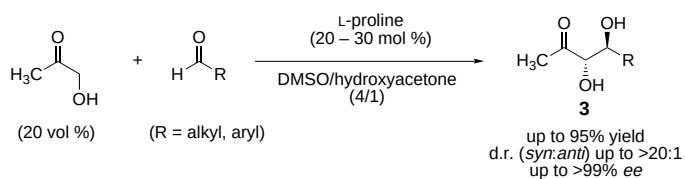
enamines which are key intermediates of these aldol reactions. In the case of the aldolase of type I a primary amino function of the enzyme is used for the formation of a neutral imine (**1a**), while the enamine synthesis proceeds through a positive iminium system (**1b**) when starting from L-proline (Scheme 2). In this connection, investigations by List et al. on the dependence of the catalytic potential from the type of amino acid are of particular interest. In these studies it has been shown that for the catalytic activity the pyrrolidine cycle (in L-proline) is required as well as the carboxylic acid group.^[3]

Promising prospects for synthetic applications in the future were opened up by List et al.'s experimental studies into the substrate range (Scheme 1). The reaction proceeds well when using aromatic aldehydes as the starting material, with enantioselectivities of 60–77% *ee* and yields of up to 94%. The direct L-proline-catalyzed aldol reaction proceeds very efficiently when using isobutyraldehyde as a substrate. For this reaction the product **2c** has been obtained in a very good yield of 97% and with an excellent enantioselectivity of 96% *ee*.

The concept of the proline-catalyzed aldol reaction has recently been extended by List et al. towards the synthesis of aldol products with two stereogenic centers.^[7] The desired *anti*-diols have been obtained in a regio-, diastereo- and enantioselective step starting from achiral compounds. Impressive diastereo- and enantioselectivities were observed, with a diastereomeric ratio up to >20:1 and *ee* values of up to >99% (Scheme 3). In addition, the reaction leads to a high regioselectivity, >20:1.

From an industrial point of view, the following characteristics of these aldol reactions developed by List et al. are noteworthy and could make this process into a synthetic alternative for existing asymmetric methods: the *direct* aldol

reaction possesses a high synthetic value, since the use of modified starting materials is not necessary, and the ketones can be used directly instead of enol derivatives. Furthermore, the price of L-proline—which is available on technical scale in both enantiomeric forms—is only about 40 \$ kg⁻¹. This represents a highly economically attractive access to a chiral catalyst—in particular compared with other types of chiral catalysts.^[8] In addition, the possibility of easily separating the proline catalyst from the product and recovering it by aqueous work-up (due to its water solubility) is also of economical interest. At present, the increase of the enantioselectivity and the improvement of the substrate range indicate the challenge of the future. Such improvements could enable the realization of a technical applicability of the direct asymmetric aldol reaction using L-proline. Another disadvantage is the large excess of the ketone component. Furthermore, for an efficient catalytic process, a

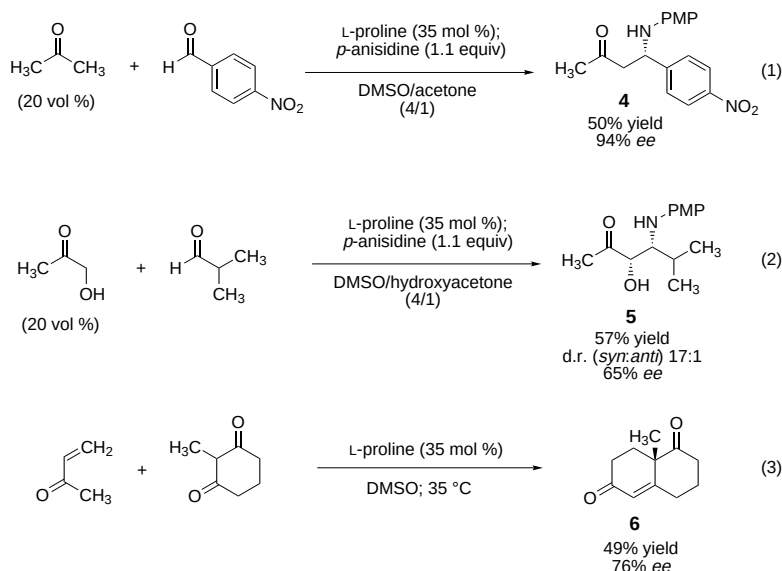


Scheme 3. Diastereo- und enantioselective aldol reactions.

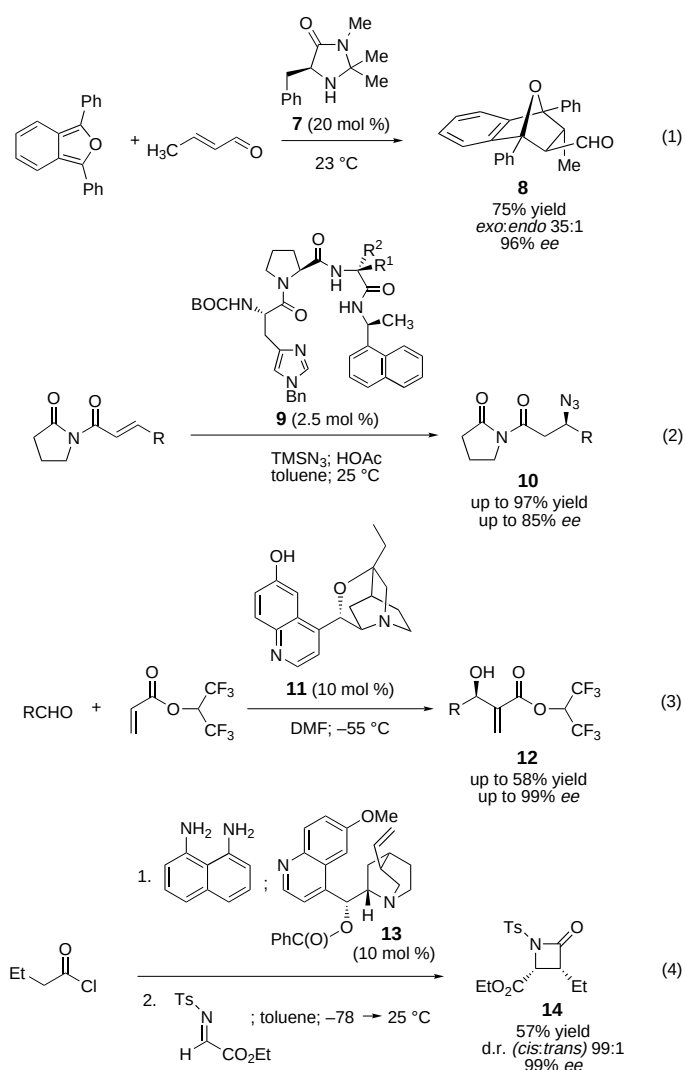
decrease of the required catalytic amount of 20–30 mol % would be desirable.

Nevertheless, the aldol reaction with L-proline as an enzyme mimic is a successful example for the concept of using simple organic molecules as chiral catalysts. However, this concept is not limited to selected enzymatic reactions, but opens up a general perspective for the asymmetric design of a multitude of catalytic reactions.^[2, 9–14] This has also been demonstrated by publications in recent months about developments in the field of “asymmetric syntheses with chiral organic molecules as catalysts”. In the following paragraphs this will be exemplified by selected excellent contributions (Scheme 4 and Scheme 5).

To start with a further application of L-proline as a catalyst in asymmetric synthesis, List developed an efficient three-component Mannich reaction for the preparation of β -amino ketones.^[9] In the presence of L-proline as a catalyst the Mannich product **4** has been obtained in 50% yield and with 94% *ee* (Equation (1) in Scheme 4). This method can be applied to a series of different aldehydes, whereby *ee* values of up to 96% are obtained. It is noteworthy that—similarly to the proline-catalyzed aldol reaction—the Mannich reaction can also be extended to an enantio- and diastereoselective process. So, the *vic*-amino alcohol **5** is formed with a



Scheme 4. Further asymmetric reactions with L-proline as a catalyst. PMP = *p*-methoxy-phenyl.



Scheme 5. Current contributions in asymmetric synthesis with small organic molecules as catalysts. BOC = *tert*-butoxycarbonyl, Bn = benzyl, TMS = trimethylsilyl, Ac = acetyl, Ts = *p*-toluenesulfonyl.

diastereomeric ratio of 17:1 and an enantioselectivity of 65 % *ee* (Equation (2) in Scheme 4).

In addition, Bui and Barbas III reported an optimized protocol for the Hajos-Eder-Sauer-Wiechert reaction, which was found in the 1970s. This reaction furnishes the chiral Wieland-Miescher ketone **6**. It has now been shown, that this synthesis (which comprises three reactions) can be carried out as a one-pot synthesis (49 % yield, 76 % *ee*, Equation (3) in Scheme 4).^[10] Proline functions as an efficient catalyst for all three reaction steps (Michael addition, cyclization, and dehydration).

From a mechanistic point of view, an approach that is comparable to the L-proline-catalyzed asymmetric reactions has recently been described by MacMillan et al. for the asymmetric catalytic Diels–Alder reaction.^[11] As a catalyst the chiral amino acid derivative **7** was used. The catalytic cycle is again based on the formation of an enamine as a key step; the enamine is formed from an amino functionality (of **7**) and the C=O bond of the α,β -unsaturated carbonyl compound. This “organo-catalytic” Diels–Alder reaction proceeds with a high diastereoselectivity (*exo:endo* ratio of up to 35:1) and with up to 96 % *ee* (Equation (1) in Scheme 5).

An asymmetric version of a Michael addition can be also realized with simple chiral organic molecules as catalysts. This has been demonstrated by Miller et al. for the addition of an azide to α,β -unsaturated carbonyl compounds.^[12] In the presence of the tripeptide **9** as the catalyst (2.5 mol %) the products **10** have been formed in excellent yields and with up to 85 % *ee* (Equation (2) in Scheme 5). In addition, this reaction represents an attractive access to β -amino acids.

Recently, Hatakeyama et al. succeeded in developing the first highly efficient asymmetric catalytic Baylis–Hillman reaction.^[13] It is remarkable that this was also achieved by using the concept of small organic molecule catalysis. In the presence of 10 mol % of catalyst **11** the products **12** have been obtained with enantioselectivities of 90 % *ee*, in many cases even of up to 99 % *ee*. Interestingly, in the case of this reaction with the alkaloid derivative **11**, a chiral (tertiary) amine structure has once again been found to be an efficient catalyst (Equation (3) in Scheme 5).

A further application of nucleophilic amines as chiral catalysts has been reported by Lectka et al. in the first highly enantioselective synthesis of β -lactam ring systems with one or two stereogenic centers.^[14] In the first step a ketene is formed from the corresponding acid chloride. Subsequently, the ketene reacts with an imine in a diastereo- and enantioselective reaction under formation of the β -lactam. For example, the preparation of the pharmaceutically interesting product **14** has been realized with a diastereomeric ratio of 99:1 and an *ee* value of 99 % (Equation (4) in Scheme 5).

In conclusion, the recent contributions by List et al., as well as MacMillan, Miller, Barbas III, Hatakeyama, and Lectka with their respective co-workers, towards the application of simple small molecules as efficient chiral catalysts in asymmetric synthesis appear to be very interesting for chemists

from academia as well as from industry. Without doubt it is also surprising to observe that a simple amino acid molecule—as described by List et al.—can, in principle, act like an enzymatic system, thus representing an efficient enzyme mimic.

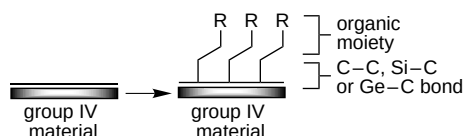
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Diamond Surfaces: Just Big Organic Molecules?

Jillian M. Buriak*

While the organometallic surface chemistry of oxide-free semiconducting group IV materials has been dabbled in since the early 1960s,^[1] an incredible explosion of interest and resources directed to this area has taken place in the latter half of the 1990s (Scheme 1).^[2] Silicon has received the bulk of the



Scheme 1. Modification of the surfaces of group IV elements.

attention because of its applications in micro- and optoelectronic devices, MEMs (microelectromechanical machines), and sensors, to name a few.^[3] Derivatization through Si–C bonds appears promising due to the stability of this bond and to tap into the vast repertoire of known organic reactions that

will allow for precise tailoring of surface characteristics and functions.^[2] Recent work concerning silicon's heavier congener, germanium, appears to demonstrate similar reactivity patterns under ultrahigh vacuum (UHV) conditions to that of silicon, allowing access to Ge–C derivatized surfaces, although much research remains to be done to generalize this.^[4]

The surface chemistry of silicon's more "northerly" and expensive neighbor, carbon in form of diamond, is even more poorly understood.^[5] The chemistry of the unsaturated carbon allotropes, including C₆₀ and carbon nanotubes, have been, and are, the subject of intense investigation.^[6] Unfortunately, the inertness at room temperature and expense of studying diamond has inhibited the same level of fundamental research. Because of the unique characteristics of diamond, such as mechanical hardness, wide band gap, and optical transparency, among others, interest in diamond surface chemistry has both academic and potential technological appeal.^[7]

One of the more pressing questions concerning diamond reactivity is whether its surface chemistry parallels that of Si(100) and Ge(100), or is it more similar to solution phase, molecular organic compounds? Certainly, molecular silicon and germanium compounds have differing reactivity from structurally similar carbon-based molecules in heterolytic reactions due to the availability of empty *nd* orbitals, which

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permits five- and six-fold coordination. Fascinating work from the groups of Bent at Stanford,^[8] and Hamers at the University of Wisconsin, Madison,^[9] in collaboration with researchers at the Naval Research Laboratory (NRL) in Washington D.C. and the GE Corporation, have shown that the surface chemistry of diamond under UHV conditions is analogous to that of molecular olefins and that, unlike the corresponding Si and Ge surfaces, the bulk material underneath has a weaker effect on the chemistry.

Like Si(100) and Ge(100) orientations, C(100) surfaces can undergo a 2×1 reconstruction under ultrahigh vacuum (10^{-10} Torr) conditions, yielding a surface with oriented carbon–carbon bonds (Figure 1). The two carbon atoms are linked by a σ - and a partial π bond, which endows the dimer

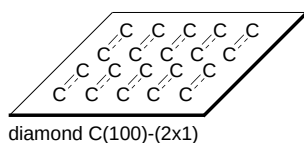


Figure 1. The ordered carbon–carbon dimers with partial double-bond character present on the reconstructed diamond C(100)-(2 × 1) surface, formed under UHV conditions.

[4+2] cycloaddition as the major reaction pathway at room temperature, a Diels–Alder reaction by definition (Scheme 2 a). An alternative [2+2] reaction is not observed with the

with olefinic character. The ultimate test of the nature of the C=C bond is an examination of its reactivity: Will it react in a similar fashion to known, solution phase alkenes? As demonstrated by Bent and co-workers,^[8] the surface reacts with the diene, 1,3-butadiene, to give a

diene or is only a minor product. Bent and co-workers had already demonstrated Diels–Alder-like behavior with dienes on oriented dimers on the Si(100) surface^[10] and thus they confirm that the carbon and silicon surface chemistries under these conditions are similar and closely related to each other and to solution phase organic olefins.

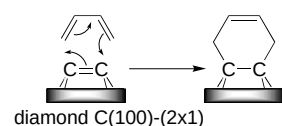
Because the Diels–Alder reaction yields an organic moiety with an isolated olefinic group, the potential exists to carry out further functionalization to produce more highly sophisticated surfaces. Unfortunately, the surface-bound olefin has not yet been coaxed to react with an additional molecule of 1,3-butadiene through a secondary Diels–Alder reaction, as might be expected from known organic reactivity; Diels–Alder reactions with dienes and an alkene lacking an electron withdrawing group require high pressures and temperatures to proceed.^[11] It would be interesting to see if further chemistry carried out on this double bond produces doubly derivatized surface terminations.

In the same issue of the *Journal of the American Chemical Society*, Hamers and co-workers reported on the [2+2]

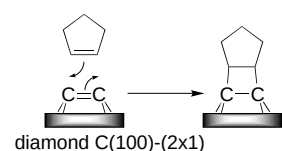
reaction of olefins with the same C(100)- 2×1 reconstructed diamond surface (Scheme 2 b).^[9] Such [2+2] cycloadditions between olefins are usually not observed as ground-state concerted reactions because they violate the Hückel $4n + 2$ rule. These workers and others had previously shown, however, that this cycloaddition is very facile on the corresponding Si(100) and Ge(100) reconstructed surfaces and also terminated with unsaturated dimers.^[4, 12] Their main motive for examining the reaction on diamond was to probe the reactivity differences between the elements—is the ease of the [2+2] reaction on silicon and germanium due to unusual chemistry unique to these elements or to the fundamental differences in reactivity between surface dimers and molecular analogues? Interestingly, they found that the [2+2] addition of cyclopentene takes place on C(100), as observed on Si(100) and Ge(100), but with a much lower probability (sticking coefficient is 10^{-3} smaller than that on silicon) because of a higher energy barrier. The lower activation energy of the Si(100) and Ge(100) surfaces, according to calculations made by Hamers et al., is due to a distortion of the dimers on these surfaces, in which the Si=Si and Ge=Ge species tilt out of the surface plane. This lowers the symmetry of the dimer, thus permitting the [2+2] addition to take place with a low energy barrier. On C(100), however, the dimers do not appear to tilt and, thus, a more concerted and unfavorable [2+2] addition must occur. This work indicates that the surface chemistry on group IV materials may differ from that of molecular analogues due to distortions induced from the underlying bulk, with diamond being most closely related to the solution phase species.

Overall, the reactivity trends suggest that the chemistry on the C(100) dimer diamond surfaces is very similar to that of molecular olefins. Si(100) and Ge(100) surfaces also have related chemistries but differ in that the underlying material distorts the surface dimers, thus lowering energy barriers and inducing subtle effects on the reaction mechanism. This chemistry also permits the diamond surfaces to be terminated with organic monolayers in a rational fashion. To summarize, this research is important not only for possible materials applications of diamond but also from a very fundamental perspective of surface reactivity as well.

a) [4+2] cycloaddition (Diels–Alder)



b) [2+2] cycloaddition



Scheme 2. a) Diels–Alder reactivity on the reconstructed diamond surface with dienes, as demonstrated by Bent and co-workers. b) The [2+2] cycloaddition chemistry with olefins, studied by Hamer's group.

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Olefin Polymerization by Late Transition Metal Complexes— A Root of Ziegler Catalysts Gains New Ground

Stefan Mecking*

Introduction

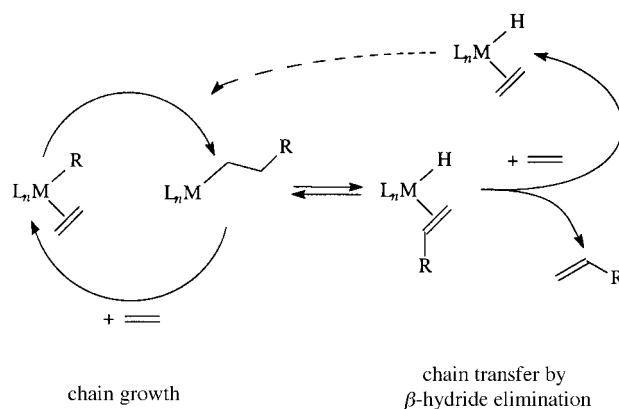
Polyolefins are of vast economic importance, which is reflected by an annual production of more than 70 million tons of polyethylene and polypropylene. While the major portion of these materials is produced with Ziegler- and chromium-based catalysts, the older free-radical process that affords low-density polyethylene (LDPE) has maintained its significance.^[1] Despite the necessity of working at over 1500 bar, 16 million tons of LDPE are currently consumed annually and new large plants continue to be built.^[1d,e] One attractive feature of the high-pressure process is the possibility of incorporating functionalized olefins, such as vinyl acetate or acrylates. Incorporation of even small amounts of polar moieties can increase adhesion properties and compatibility of polyolefins with other materials. Another attractive feature is the different property profile of LDPE compared to the linear ethylene homo- and copolymers produced by Ziegler catalysts. In the free-radical polymerization of ethylene, short- as well as long-chain branches are formed without any added co-monomer. Short-chain branches affect polymer properties, such as crystallinity and melting temperature, and are important in controlling polyolefin application properties. Long-chain branches (typically containing 100 or more carbon atoms) particularly influence the rheology of polyolefin melts, and result in good processing properties of LDPE.

These considerations exemplify existing challenges for transition metal catalyzed coordination polymerization in low-pressure processes. In regard to the desirable incorporation of polar monomers, early transition metal based Ziegler catalysts and metallocenes are, unfortunately, highly sensitive to polar reagents. By comparison, late transition

metal complexes are generally much more functional-group tolerant as a result of their less oxophilic nature. In addition, they can provide access to unique polyolefin branching structures. Recent discoveries of novel olefin-polymerization catalysts based on late transition metals represent major advances. These findings are highlighted and put into perspective with previous developments, by using ethylene polymerization as a guideline.^[2, 3]

General Aspects of Catalyst Design

Polymerization of ethylene or α -olefins by Ziegler-Natta or metallocene catalysis and C–C linkage by late transition metal complexes rely on the same basic types of reactions, namely chain growth by migratory insertion in alkyl-olefin complexes and chain transfer by various mechanisms. However, late transition metal catalysts usually yield dimers or oligomers because of the propensity of alkyl complexes of late transition metals for chain transfer by β -hydride elimination (Scheme 1).^[4, 5c] A prominent example is the Shell Higher Olefin Process (SHOP), developed by Keim et al. in the 1960s and 1970s, in which linear α -olefins are obtained by nickel-

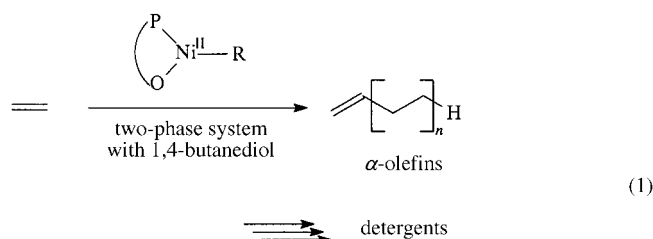


Scheme 1. Simplified schematic representation of ethylene oligomerization and polymerization by late transition metal (M) complexes (R = growing polymer/oligomer chain).

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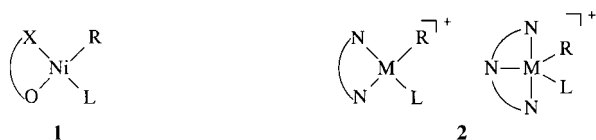
catalyzed oligomerization of ethylene [Eq. (1)].^[4] A late transition metal catalyzed ethylene oligomerization reaction



can also be regarded as a direct forerunner of today's polyolefin industry. After all, it was the observation that a combination of trace impurities of nickel compounds with aluminumalkyl compounds catalyzed ethylene dimerization (the famous "nickel effect") that led directly to the discovery of Ziegler catalysts.^[5]

A prime objective of research on olefin polymerization by late transition metal complexes is the design of catalysts capable of producing high molecular weight products. In mechanistic terms this translates to a suppression of chain transfer, while at the same time maintaining a high chain-growth rate (Scheme 1). For a given chain-growth rate, an increase in the barrier to chain transfer of $\Delta\Delta G^\ddagger \approx 3\text{--}4$ kcal will turn an oligomerization into a polymerization catalyst.

Most known effective polymerization systems are based either on neutral nickel(II) complexes of formally monoanionic bidentate ligands (Scheme 2; **1**) or on cationic iron,

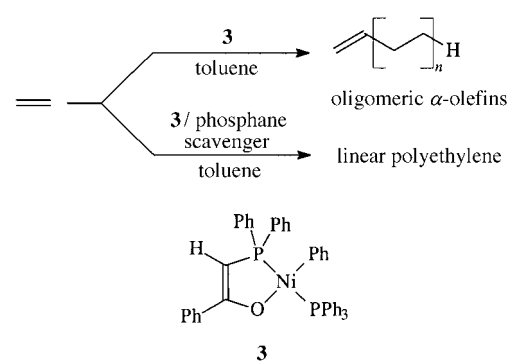


$\widehat{XO}$: formally monoanionic bidentate ligand ($X = P$ or N)

$\widehat{NN}$, $\widehat{NNN}$: neutral bi- or tridentate ligand, respectively

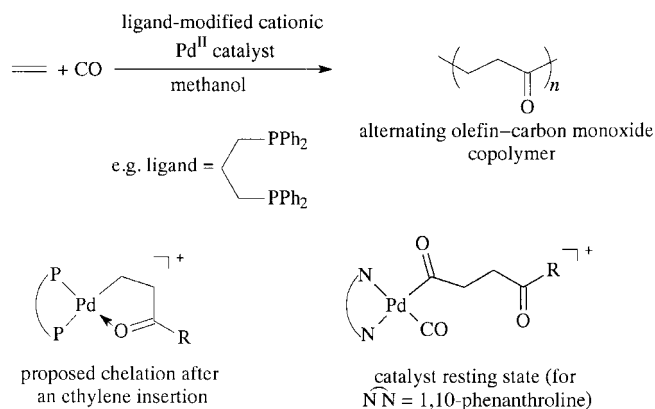
Scheme 2. Structure of some ethylene polymerization catalysts based on neutral or cationic late transition metal complexes. In well-defined catalyst precursors R is either a Ph or Me ligand which is capable of initiating chain growth. L is a monodentate ligand which is generally weakly coordinating and capable of being displaced by the monomer. In the presumed active species, R is usually the growing polymer chain and L is usually the monomer or solvent.

cobalt, nickel, or palladium complexes of neutral multidentate ligands with nitrogen donor atoms substituted with bulky groups (**2**).^[6, 7, 15, 16, 21, 25, 27, 28] The molecular weight of the polymer produced is controlled by both electronic and steric properties imparted by the bi- or tridentate ligands alike (see below). The chelating ligands in **1** and **2** will keep the growing polymer chain and coordinated monomer relatively close (for example, in a *cis* position in square-planar complexes).^[7] Also, most catalyst systems are characterized by the absence of additional strongly coordinating ligands (L), which can block coordination sites during catalysis and favor the formation of low molecular weight products.^[4b] Thus, the typical SHOP-type oligomerization catalyst **3**^[4b,c] produces linear polyethylene upon scavenging of the triphenylphosphane ligand (Scheme 3).^[16]



Scheme 3. Effect of a monodentate triphenylphosphane ligand on the molecular weight of the product.

In the context of preparing functionalized olefin polymers by late transition metal catalysis, it is interesting to note that for the particular case of alternating copolymerization of olefins and CO by cationic palladium complexes (Scheme 4),



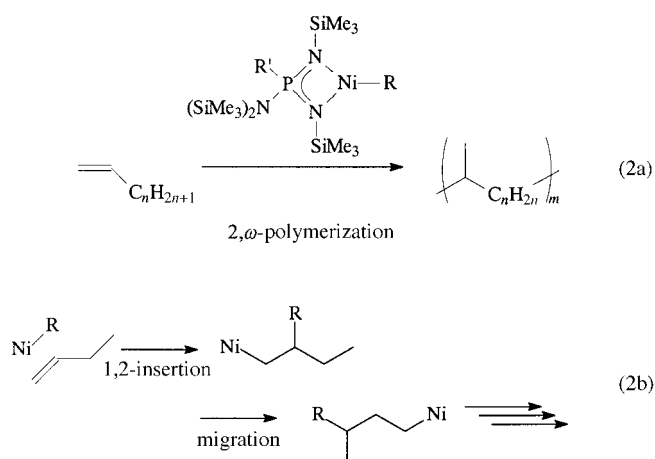
Scheme 4. Copolymerization of olefins with carbon monoxide and the effect of CO monomer on chain transfer.

a much larger variety of bidentate ligands can be used.^[8] It has been suggested that steric constraints imposed by chelating coordination of a β -carbonyl group after an ethylene insertion are responsible for preventing β -hydride elimination.^[8a] Furthermore, ethylene insertion is followed by a rapid CO insertion, such that an acyl complex (not susceptible to β -hydride elimination) is the catalyst resting state.^[9c] Accordingly, the bisphosphane-based catalysts typically used for ethylene/CO copolymerization dimerize ethylene in the absence of CO.^[9] The strictly alternating polyketones obtained by ethylene/CO/propylene terpolymerization have good chemical resistance and mechanical wear properties. However, the presence of a large number of carbonyl groups renders these polymers sensitive to UV light; furthermore, undesired condensation cross-linking during processing can occur. Such semicrystalline engineering thermoplastics have been produced commercially by Shell since 1995 but it was recently announced that this business is to be abandoned.^[10] The vinyl-type polymerization of functionalized norbornenes can also be performed using a variety of palladium(II) and also nickel(II) catalysts.^[11] Again, steric constraints most likely contribute to retardation of chain transfer.

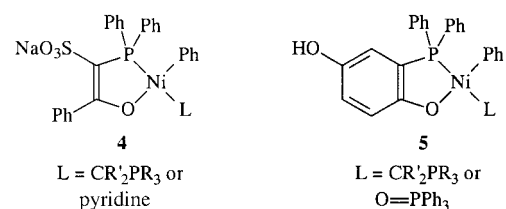
Previous History—Polymerization by Neutral Nickel(II)
Catalysts with a Chelating Ligand

In the SHOP, ethylene oligomerization is catalyzed by neutral nickel(II) complexes with chelating P $\hat{\text{O}}$ ligands [Eq. (1)]. The functional-group tolerance of the nickel(II) catalyst allows for the use of 1,4-butanediol as a polar catalyst phase. Hereby, the process can be run in a two-phase mode, and allows for the simple separation of the apolar products from the catalyst.^[4d] In the development of the SHOP, and in subsequent related academic research, a number of ethylene polymerization catalysts were discovered.^[4c, 12, 13b] Mostly, they convert ethylene into linear polyethylene with moderate activities (some 1000 TO h⁻¹; M_v up to 10⁵ g mol⁻¹; TO = turnover = mol substrate converted per mol metal). By contrast, the catalyst system [Ni(cod)₂]/(Me₃Si)₂N-P(=NSiMe₃)₂ (cod = 1,5-cyclooctadiene) was found to convert ethylene into a branched polymer.^[13] The moderate molecular weight polyethylene ($M_n \approx 7 \times 10^3$ g mol⁻¹) possesses methyl and longer chain branches. This surprising microstructure was proposed to result from simultaneous linear oligomerization of ethylene and subsequent incorporation of the resulting oligomers into the polymer.^[13b,c] A detailed investigation by Fink and co-workers of α -olefin polymerization by such catalysts revealed polymerization occurred in a 2, ω fashion, to yield polymers containing only methyl branches.^[14] This remarkable polymer results from chain growth by 1,2 insertion, followed by a nickel migration prior to the next olefin insertion [Eq. (2)].

In the 1980s, Ostoj-Starzewski and co-workers^[15] and Klabunde et al.^[16] extensively investigated ethylene polymerization by neutral nickel(II) complexes with P,O ligands. In comparison to **3** (Scheme 3) the replacement of the strongly binding triphenylphosphane ligand by a weakly coordinating phosphane oxide^[15] or pyridine^[16] eliminates any need for a phosphane scavenger. Complexes with electron-rich ylide ligands ($L = \text{CR}'_2\text{PR}_3$) have also been investigated intensive-



ly.^[15, 17a] These nickel(II) complexes are single-component, activator-free catalyst precursors for ethylene polymerization. By variation of the ligand structure (for example, **4** and **5**),



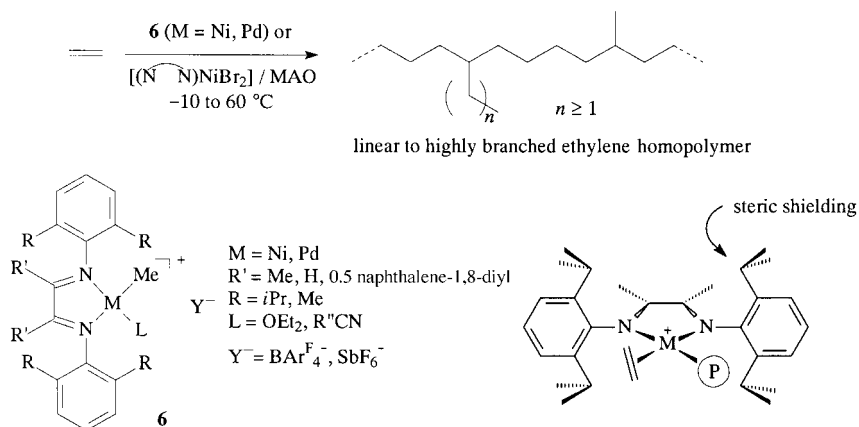
linear polyethylenes of very high molecular weight are accessible (Table 1).^[15, 17b] Productivities of 5×10^4 TO h⁻¹ were observed in typical polymerization experiments, and up to 1.8×10^5 TO h⁻¹ (at 17 bar ethylene) were reported with further optimized P,O ligands.^[18] These polymerization catalysts are also active in polar organic reaction media, such as acetone, DMF, or alcohols.^[15b,d,e, 16b] Attempted copolymerization of ethylene with methyl acrylate or vinyl acetate was

Table 1. Examples of ethylene polymerization by late transition metal complexes.^[a]

Year	Catalyst type	Typical activity ^[a,b] [TO h ⁻¹]	Typical polymer molecular weights obtainable [g mol ⁻¹] ^[a]		Polyethylene branching structure	Functional group tolerance
			M_w	M_w/M_n		
1960s	neutral Ni ^{II} P $\hat{\text{O}}$ complexes (SHOP)	6×10^3	α -olefin oligomers	Schulz-Flory	linear oligomers	two-phase process in butanediol
1980s	neutral Ni ^{II} P $\hat{\text{O}}$ complexes, optimized for polymerization (4 , 5)	1.8×10^5	10^6 (M_v)	25 ^[c]	essentially linear ^[17b]	Stable in various polar organic media; copolymerization of special functionalized monomers
1995	cationic Ni ^{II} and Pd ^{II} complexes 6	4×10^6 (Ni) 4×10^3 (Pd)	$> 8 \times 10^5$	1.5 to 3	highly branched to linear; Me, Et, Pr, Bu and longer. Hyperbranched structures (Pd)	Copolymerization of simple polar monomers, such as acrylates (Pd); stable in esters, acetone or water (Pd)
1998	cationic Fe ^{II} and Co ^{II} complexes 7	10^7 (Fe)	6×10^5	9	highly linear	not reported to date
1998	neutral Ni ^{II} P $\hat{\text{O}}$ complexes 8	2.3×10^5	5×10^5	1.5 to 3	moderately branched to linear; predominantly Me, also Et, Pr, Bu	stable to added amounts of polar organic solvents and water; copolymerization of functionalized norbornenes

[a] Activities have been determined under strongly varying conditions, thus they should only be taken as a measure of the order of magnitude. The same holds for molecular weights, which were determined by different methods. [b] In ethylene homopolymerization. TO = turnovers $\equiv$ mol(substrate) per mol of metal. [c] For low molecular weight materials, narrow distributions of $M_w/M_n = 2$ have also been reported.^[15c] [d] Polymerization in water as a reaction medium has been investigated only recently.^[29a,b]

unsuccessful.^[16a] However, copolymerization of monomers containing a spacer between the vinyl moiety and the functional group, such as $\text{H}_2\text{C}=\text{CH}-(\text{CH}_2)_8-\text{C}(\text{O})\text{OMe}$, has been reported.^[16] Recently, copolymerization of ethylene with polar functionalized norbornenes by these types of nickel(II) catalysts has also been claimed.^[19] In the context of the preparation of branched polyethylenes with late transition metal catalysts, it can be noted that oligomerization of ethylene by P,O-chelated nickel(II) catalysts and subsequent copolymerization of the linear oligomers with ethylene using a typical chromium-based catalyst has been described as a route to long chain branched polyethylenes.^[15c, 20]

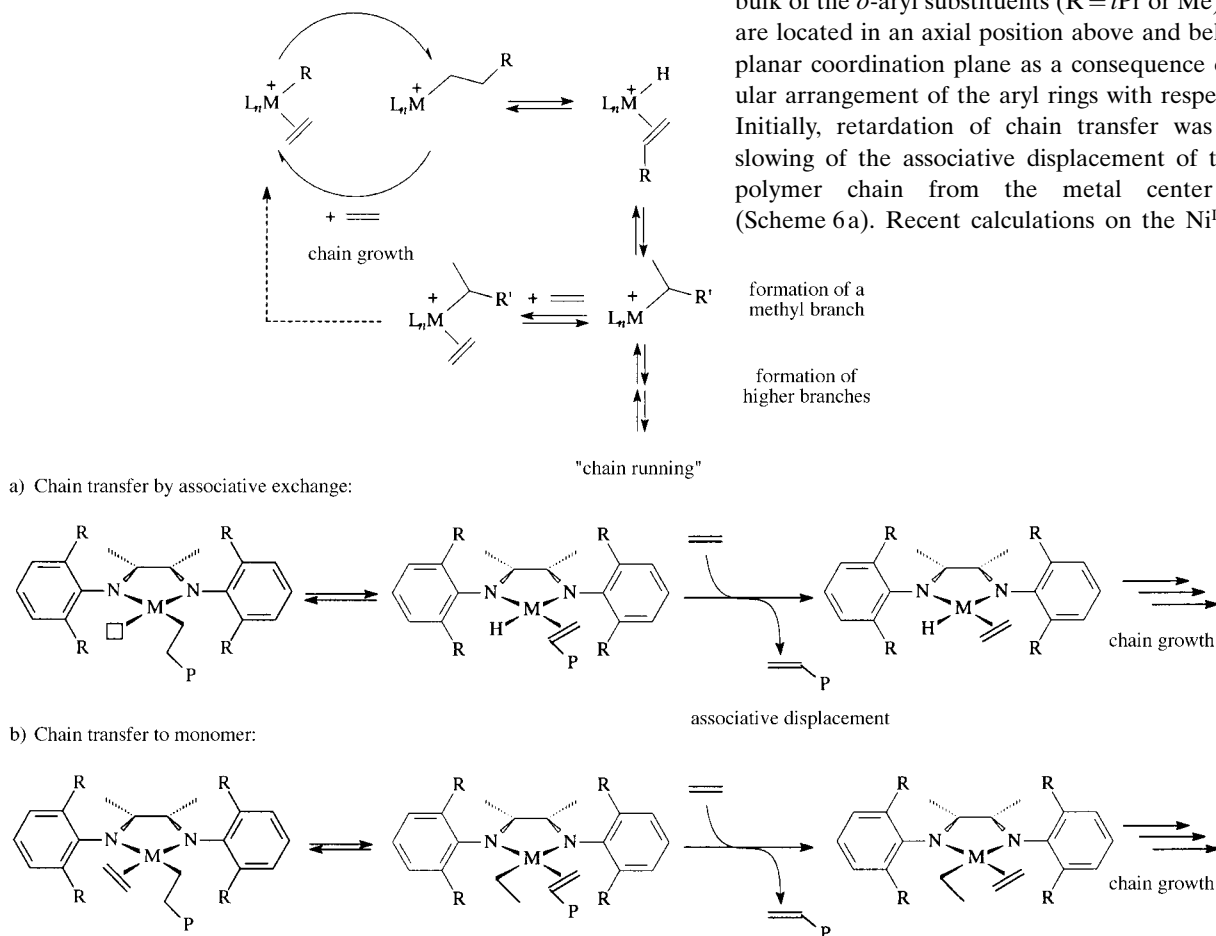


Scheme 5. Polymerization of ethylene by cationic Ni^{II} and Pd^{II} complexes with diimine ligands. MAO = methylalumoxane.

Recent Findings—Cationic Catalysts with Multidentate Ligands

In 1995, a report by Brookhart and co-workers on the discovery of a new class of catalysts for the polymerization of ethylene and α -olefins was received with strong interest in academia and industry alike.^[21] These catalysts, based on known nickel(II) and palladium(II) complexes of bulky substituted diimine ligands,^[22] are unique in polymerizing ethyl-

ene to highly branched, high molecular weight homopolymers at remarkable reaction rates (Scheme 5). Activities of up to $4 \times 10^6 \text{ TO h}^{-1}$ were reported for the cationic Ni^{II} catalysts, which thus approach rates typical of metallocenes.^[23] Polymer molecular weight distributions are relatively narrow and lie in the range expected for single-site catalysts. A key feature enabling polymerization to occur to very high molecular weights (Table 1) is retardation of chain transfer by the steric bulk of the *o*-aryl substituents ($\text{R} = i\text{Pr}$ or Me). The R groups are located in an axial position above and below the square-planar coordination plane as a consequence of a perpendicular arrangement of the aryl rings with respect to the latter. Initially, retardation of chain transfer was ascribed to a slowing of the associative displacement of the unsaturated polymer chain from the metal center by ethylene (Scheme 6a). Recent calculations on the Ni^{II} catalysts alter-

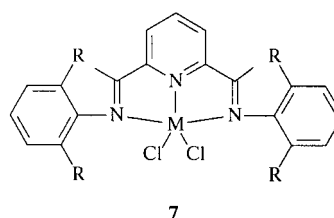


Scheme 6. Mechanism of branch formation in ethylene polymerization by cationic diimine-substituted Pd^{II} and Ni^{II} catalysts. Typical branching distribution^[21b] (per 1000 CH_2) obtained with a) a Pd^{II} catalyst: Me 36, Et 26, Pr 3, Bu 12, amyl 2, hexyl and higher and end of chains 34; b) a Ni^{II} catalyst: Me 41, Et 6, Pr 3, Bu 2, amyl 1, hexyl and higher and end of chains 5.

natively suggest a direct β -H transfer to the monomer (Scheme 6b), the barrier of which increases with increasing bulk of the *o*-substituents.^[21g] Introduction of the less bulky $R=H$ in the Ni^{II} catalysts yields a highly active cationic catalyst for oligomerization of ethylene to linear α -olefins.^[21d]

The polyethylenes possess even- and also odd-number carbon branches (Me, Et, Pr, Bu, amyl, and longer branches). Whereas the polymers obtained with Ni^{II} catalysts are dominated by methyl branches, the Pd^{II} catalysts yield a large portion of longer branches and even a branch on a branch moiety, that is, an element of a hyperbranched structure.^[21h,j] These microstructures arise from a "chain-running" process (Scheme 6), similar to the aforementioned $2,\omega$ polymerization reported by Fink et al.^[21a] The Pd^{II} catalysts yield highly branched amorphous polymers (approximately 100 branches per 1000 carbon atoms) irrespective of the ethylene concentration,^[24] whereas branching can be controlled with the Ni^{II} catalysts by varying the ethylene concentration and polymerization temperature (1 to 100 branches per 1000 carbon atoms). Accordingly, the macroscopic properties of these polyethylenes—obtained from ethylene as the sole monomer—range from highly viscous (high molecular weight) liquids with a T_g of -70°C , over rubbery elastomeric materials, to rigid linear polyethylenes.

Remarkably, the Pd^{II} catalysts also allow for the coordination copolymerization of ethylene and simple polar functionalized olefins, such as acrylates.^[21b,e] With increasing acrylate incorporation into the copolymer, catalyst activity is lowered as a consequence of a reversible blocking of coordination sites by chelating binding of the carbonyl groups of incorporated acrylate (Scheme 7, equilibrium B). Chain running also results

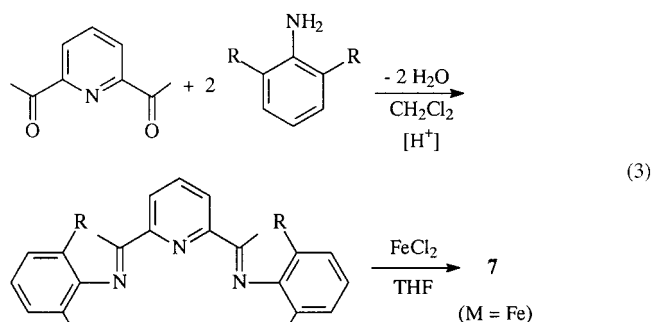


$M = \text{Fe, Co}$
 $R = i\text{Pr, Me}$

activation
e.g. by MAO

7

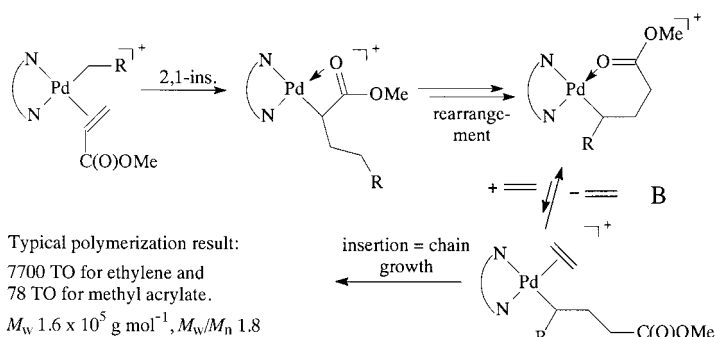
to highly linear, crystalline high-density polyethylene (HDPE).^[25a-d] Astounding rates of up to 10^7 TO h^{-1} (at 40 bar ethylene pressure) have been reported for the iron catalysts. The typical relative ease of preparation for many of the late transition metal catalyst systems highlighted is exemplified by the preparation of the iron catalysts from commercially available compounds as shown in Equation (3).



Broad or bimodal molecular weight distributions are obtained with the Fe catalysts as a result of chain transfer to aluminum as well as β -H elimination (Table 1). By contrast to the other catalyst systems discussed, up to now no single component catalyst precursors suitable as an alternative to the in situ aluminumalkyl-activated systems have been reported. BP-Amoco and DuPont have announced a joint agreement aimed at a commercialization of the rigid polyethylenes prepared with iron catalysts.^[25g] In analogy to the previously mentioned diimine-substituted Ni^{II} and Pd^{II} catalysts, the steric bulk of the *o*-aryl substituents retards chain transfer. Reducing the steric bulk of the *o*-aryl substituents R in the iron complexes again yields catalysts for ethylene oligomerization.^[25e,f] Astonishing activities of up to 10^8 TO h^{-1} for formation of $>99\%$ linear α -olefins were observed, far exceeding the activities reported for SHOP catalysts. From a viewpoint of historical development, it is interesting to note that the search for new polymerization catalysts and the resulting understanding has in turn yielded highly active new oligomerization systems.

New Neutral Nickel(II) Catalysts with $\widehat{NO}$ Chelating Ligands

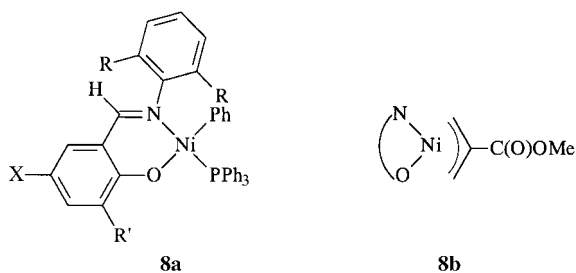
Approximately simultaneously with the cationic iron and cobalt catalysts, a new class of neutral nickel catalysts based on salicylaldimine ligands^[26] (**8**) was reported independently by Johnson et al.^[27] and Grubbs and co-workers.^[28] These neutral nickel(II) complexes contain a formally monoanionic bidentate ligand and are thus related to SHOP-type catalysts.



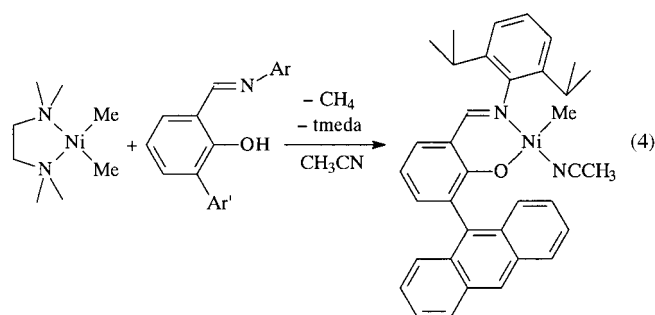
Scheme 7. Copolymerization of ethylene with acrylates yielding branched copolymers.

in predominant incorporation of acrylate at the ends of branches in the highly branched, amorphous copolymers. To date, there is no catalyst system capable of incorporating conventional polar monomers such as acrylates into the backbone of a linear polyethylene.

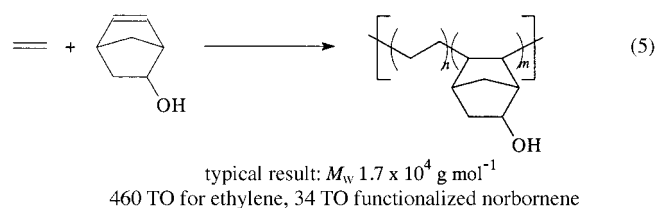
Brookhart and co-workers findings have resulted in a strongly increased interest in late transition metal olefin polymerization catalysis, and spurred an intense search for other suitable ligand structures. Subsequently, three different research groups (Brookhart, Gibson, and Bennett of DuPont) independently reported cationic iron and cobalt catalyst systems of structural type **7** for the polymerization of ethylene



However, the P donor of the latter is replaced by a bulky substituted imine moiety. Moderately branched to linear polyethylenes are obtained with such catalyst systems. Similar weight-average molecular weights but considerably narrower molecular weight distributions are obtained than in materials prepared with traditional P,O-based catalysts (Table 1). Initially, substituted allyl complexes^[27] (**8b**) or triphenylphosphane complexes^[28] (**8a**) were used, which require a Lewis acid or phosphane scavenger, respectively, as a cocatalyst for effective polymerization. Introduction of bulky substituents R' in the *ortho* position of the phenolate moiety enables the use of phosphane complexes as single-component precursors without a phosphane scavenger as a result of facilitated dissociation of the triphenylphosphane ligand.^[28b] Methyl complexes with weakly coordinating acetonitrile ligands, prepared according to Equation (4), represent very versatile



single-component catalyst precursors (tmeda = *N,N,N',N'*-tetramethylethylenediamine).^[27, 28b,c] Activities in ethylene homopolymerization (2.3×10^5 TO h⁻¹ at 17 bar)^[28b] equal those achieved with optimized P,O-based polymerization catalysts. Like P,O-based neutral nickel(II) catalysts, the N,O-substituted nickel systems are functional-group tolerant. Grubbs and co-workers have copolymerized ethylene with 5-functionalized norbornenes [Eq. (5)],^[28b,c] and high molecular weight polymer was obtained in ethylene homopolymerization in the presence of added polar reagents, such as ethers, ethyl acetate, acetone, and also water.^[28b] Such polymerizations in the



presence of added polar reagents are of interest with regard to polymerization of less rigorously purified monomers.^[28b]

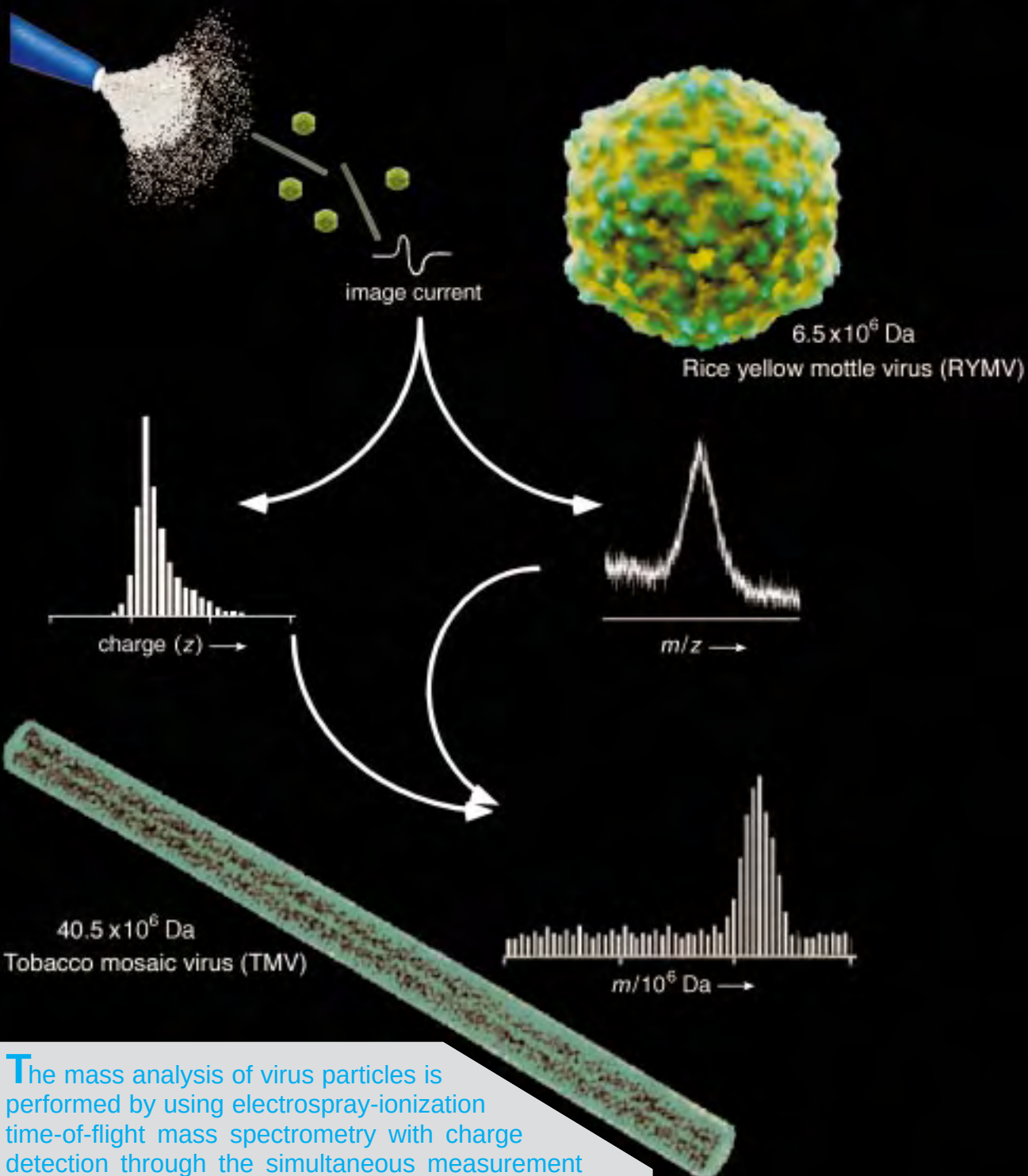
On a different level, utilization of water as a reaction medium for olefin polymerization offers intriguing opportunities. The unique properties of water are illustrated by free radical emulsion and suspension polymerization with which stable polymer latices can be produced directly. Recent reports reveal that such reactions can be carried out by means of vinyl-type coordination polymerization using late transition metal catalysts.^[29, 6]

In summary, major advances have recently been achieved in the field of late transition metal catalyzed olefin polymerization. Novel polyolefin microstructures have become accessible, and copolymerization of simple polar comonomers has been achieved. Also, mechanistic investigations have strongly enhanced an understanding of the underlying principles. This insight has already resulted in a successful rational design of new catalysts. Recently reported neutral Ni^{II} catalysts based on salicylaldimine ligands provide an example. The data currently available does not allow for a concise general picture of the new materials accessible in regard to polymer properties relevant for applications. However, the strong interest in these polymers can be expected to enhance a more comprehensive illumination of this topic in the near future.

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Whole Virus Mass Spectrometry



The mass analysis of virus particles is performed by using electrospray-ionization time-of-flight mass spectrometry with charge detection through the simultaneous measurement of the number of charges on each viral ion and the ion's mass-to-charge ratio (m/z). The m/z ratio is obtained through time-of flight measurements.

Find out more on the following pages.

Mass Spectrometry of an Intact Virus**

Stephen D. Fuerstenau, W. Henry Benner,*
John J. Thomas, Christophe Brugidou, Brian Bothner,
and Gary Siuzdak*

The development of electrospray ionization (ESI) for biomolecular analysis marks one of the historically significant events in mass spectrometry (MS).^[1] As a consequence largely of electrospray, the utility of mass spectrometry has been extended far beyond routine determinations of molecular weight to applications in such diverse fields as chemistry, immunology, and structural biology.^[2] For example, ESI allows for the analysis of noncovalent interactions^[3, 4] such as those that form the basis of supramolecular chemistry,^[5] protein folding,^[3, 6] and viral protein–protein interactions.^[7, 8] In fact, experiments performed on whole viruses^[8] demonstrate that viruses can be observed with mass spectrometry and that noncovalent supramolecular structures can successfully withstand the rigors of vaporization, ionization, and the vacuum of a mass spectrometer. In the initial experiments^[8] viral ions to be analyzed by ESI were nondestructively introduced into the vacuum of a mass spectrometer and electrostatically focused onto a collector plate within the instrument. Interestingly, the virus particle ions were found to retain both their native structure and infectivity; however, mass measurements could not be obtained with the available mass spectrometers. We have circumvented the problems associated with detecting large ions by using charge-detection mass spectrometry to make a simultaneous measurement of charge (z) and mass-to-charge (m/z) ratio for individual particles.

In previous experiments it was found that tobacco mosaic virus (TMV) could be passed through a quadrupole mass analyzer in radio frequency-only mode and weakly detected with an electron multiplier.^[8] Yet in those studies we were unable to perform mass analysis on intact virus ions because their mass-to-charge (m/z) values were too large to yield peaks in our quadrupole mass spectrometer which had a m/z range of 2300. Furthermore, even if our instrument had had sufficient mass range, the limited resolution as well as

formation of adducts during electrospray ionization would have made traditional determination of the mass by assignment of the charge state of adjacent peaks extremely difficult or impossible.^[2] The impressive mass measurements by Robinson and co-workers^[9] of viral capsid ions up to 2.5×10^6 Da and with over 100 charges suggest that traditional ESI-MS methodology will face significant challenges when applied to the measurement of ions with a mean charge state of several hundred. An alternative method based on the direct detection of charge number^[10–14] was explored to overcome these limitations for the analysis of whole viruses.

Charge-detection mass spectrometry is a relatively new technique that circumvents limitations associated with detecting large, highly charged ions by making a simultaneous measurement of charge (z) and mass-to-charge (m/z) ratio for individual ions. The detection technique permits the mass analysis of electrospray ions with virtually unlimited mass^[10–14] and has been performed on both Fourier-transform ion-cyclotron resonance^[14] and time-of-flight^[11–13] mass analyzers. The electrospray ionization source used in these studies^[11] produced an aerosol of highly-charged virus particles in the ion-evaporation region of the electrospray ion source at atmospheric pressure. Virus ions pass one at a time through a small metal flight tube attached to a charge-sensitive preamplifier that captures their image current, the magnitude of which is proportional to the ion's charge. In addition, by measuring the time-of-flight^[15] of each ion through the flight tube the m/z value can be determined. The mass of each ion is obtained from a combination of both the charge and m/z value, where the ion charge can typically be determined with a precision of better than $\pm 75 z$ (as demonstrated in previous experiments with microparticles). A more complete description of the experiments and the system is published elsewhere.^[11]

Two viruses were examined in these studies: rice yellow mottle virus (RYMV) and tobacco mosaic virus (TMV). RYMV is an icosahedral virus (29 nm in diameter) consisting of a single-stranded RNA surrounded by a homogeneous protein shell made up of 180 copies of a single coat protein.^[16] RYMV has a calculated molecular weight of 6.5×10^6 Da and was collected and purified as previously described.^[17, 18] TMV is rod-shaped and is formed from approximately 2140 identical protein subunits wound in a 300-nm long helix with a diameter of 17 nm. A central hollow cylindrical core holds the viral genome—a 6395-nucleotide strand of RNA. TMV has a calculated molecular weight of 40.5×10^6 daltons.^[8] The purified RYMV or TMV were typically diluted in unbuffered water to a concentration of approximately 3×10^{12} particles per mL (5 pM).

The results of these analyses were typically obtained from measuring thousands of individual ions and required approximately 30 minutes for collection. The charge-state distribution of large particles results from factors related to particle shape (where more extended or open conformations often lead to more charges), competition for charge between large particles and easily desorbed low-mass ions, as well as electrospray conditions such as solvent composition and pH value. The most highly charged species we have generated are linear molecules of single-stranded DNA since these ions are

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likely to be elongated in the gas phase, thereby stabilizing or distributing many charged sites along the polymer without significant Coulombic repulsion. Coulombic repulsion limits the maximum number of charges that can reside on the surface of the virus particle. Accordingly, we observed less charging for RYMV and TMV than for significantly smaller DNA biopolymers.^[12] The charge-state distribution observed for TMV (Figure 1) was similar to that previously observed for DNA.^[19] The RYMV and TMV ions possessed a charge distribution of between 300 and 1000 positive unit charges with higher charge states observed for TMV.

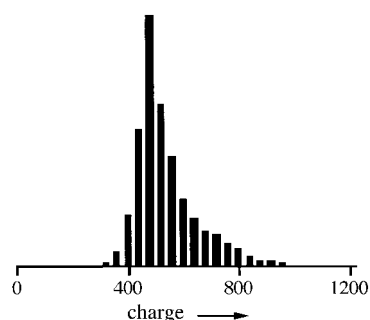


Figure 1. Histogram showing the charge spectrum obtained for tobacco mosaic virus (TMV) using a time-of-flight mass analyzer with charge detection.

The mass spectrum obtained on RYMV (Figure 2) showed a maximum signal centered between 6×10^6 and 7×10^6 Da with tailing on the high mass end. This data corresponds well

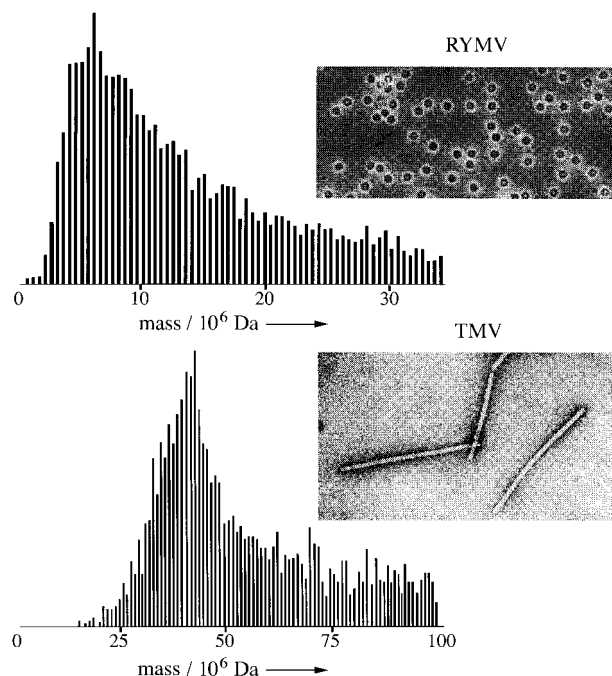


Figure 2. Mass spectra of rice yellow mottle virus (RYMV, top) and tobacco mosaic virus (TMV, bottom) particles analyzed with an electrospray-ionization charge-detection time-of-flight mass spectrometer. Insets: electron micrographs of the icosahedral RYMV (diameter 28.8 nm; top) and the cylindrical TMV (approximately 300 nm long and 17 nm in diameter; bottom). The known molecular weights of RYMV and TMV are 6.5×10^6 and 40.5×10^6 Da, respectively.

to the theoretical mass of a single intact RYMV particle (6.5×10^6 Da) within the error of the instrument ($\pm 15\%$). The mass spectrum on the TMV particles (Figure 2) generated a mass centered between 39×10^6 and 42×10^6 Da, which is consistent with the calculated mass of 40.5×10^6 Da and also within the error of the instrument. While the mass measurements were quite accurate, the relatively large error in the mass determination is derived from both the charge detection and m/z time-of-flight measurements. To improve the accuracy of these measurements we are developing a more stable charge-detection approach to reduce the variation in the signals from ion to ion. In addition, by increasing the length of the mass spectrometer's flight tube we also hope to further reduce the error in the m/z value through more accurate time-of-flight mass measurements. It should also be noted that the mass spectral data show a broadening commonly observed with electrospray time-of-flight analysis of porous protein assemblies with irregular surfaces.^[20–22] While the soft ionization conditions of electrospray help to maintain the macromolecular structure, these conditions also allow for the formation of adducts and incomplete desolvation of large porous structures, thereby contributing to the broad peak shape of the gas-phase particle.

Mass spectrometry has made significant strides into the realm of clinical applications,^[23] and this approach could present another diagnostic method for pathogenic diseases. Currently, mass spectrometric measurements provide valuable insight into virus identification, structure, and function,^[24] and mass measurements of whole viruses would be advantageous. For example, examination of the charge-state distribution on viruses could further reveal different dynamic conformers. Charge detection could also be used to monitor biologically important interactions such as DNA–protein, virus–antibody, and virus–cell receptor complexes since the flexibility, and thus the charge state of macromolecules, can change with intermolecular interactions. Additionally, the mass measurement of viral subgroups within a population would allow virologists to better understand the diversity of viruses or to measure members of a population that have been labeled, for example, with antibodies. Far from being merely a routine mass-measurement tool, mass spectrometry continues to offer new perspectives on the solution and gas-phase properties of biomolecular complexes, including whole viruses.

Experimental Section

Virus preparation and purification: Plants were infected from seed stocks of RYMV (ATCC PV-515) and TMV (ATCC 135P-PV) which had been purchased from American Type Culture Collection. The purification was performed by the protocol of Fauquet and Thouvenel.^[25] Briefly, infected leaves were ground and homogenized in 0.1 M phosphate buffer with 0.2% β -mercaptoethanol (pH 5.0), and filtered through cheesecloth (Fisher Scientific). The homogenate was centrifuged with an equal volume of water and the aqueous phase was collected and stored overnight at 4°C with 6% polyethylene glycol. Samples were then pelleted and the virus was collected through a 20–30% sucrose gradient. Samples were stored at 4°C , and dialyzed prior to mass spectrometric analysis.

The RYMV virus solutions were infused into the heated capillary at $0.5 \mu\text{L min}^{-1}$. The solutions containing TMV were infused at $0.05 \mu\text{L min}^{-1}$. A counter-flow gas of nitrogen assisted the desolvation and direction of the

electrospray ions. A voltage of -2500 V was applied to the electrospray needle, which was held $1\text{--}3\text{ cm}$ away from the inlet to the vacuum.

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Engineering Catalysts for Enantioselective Addition of Diethylzinc to Aldehydes with Racemic Amino Alcohols: Nonlinear Effects in Asymmetric Deactivation of Racemic Catalysts**

Jiang Long and Kuiling Ding*

“Asymmetric amplification” or the “positive nonlinear effect” ((+)-NLE) is a very attractive phenomenon in catalytic asymmetric processes, since it gives enantioselectivities which are improved with respect to the expectations based on the *ee* value of the auxiliary.^[1–7] Therefore, because of asymmetric amplification, high-enantiopurity chiral ligands need not necessarily be applied to achieve high enantiopurities of product. Nevertheless one has to make a partial resolution of the chiral ligands from their racemic forms. Interestingly, asymmetric catalysis with racemic catalysts has been successfully achieved by “chiral poisoning”^[8] or “asymmetric activation”^[9] strategy.

After the first report on the nonlinear effect in asymmetric catalysis by Kagan and co-workers,^[2] the early experiments with strong asymmetric amplification were demonstrated by Oguni et al. in 1988 and by Noyori et al. in 1989 for enantioselective addition of diethylzinc to aldehydes.^[3] In this type of alkylation, the asymmetric amplification is well recognized to be a consequence of an in situ increase in the *ee* value of the active catalyst, since racemic ligand is trapped in the more stable, unreactive *meso* species.^[7] The recent treatment by Noyori and co-workers^[7b] of the systems involving the dynamic monomer–dimer equilibria where the monomers are active species is complementary to the ML_n models of Girard and Kagan.^[1b] In principle, if racemic ligands are used alone, the reaction will definitely give racemic product. The addition of an alternative nonracemic additive (which should be cheap and easily obtainable) to the racemic catalyst system may enantioselectively generate a new species of dinuclear zinc complex with one enantiomer of racemic ligand through “non-self-recognition”^[7a] to release the opposite enantiomer of catalyst for asymmetric catalysis. To exemplify this strategy, we choose Oguni et al.’s racemic amino alcohols to carry out asymmetric catalysis by adding nonracemic additives. In this contribution, we report our results on the first example of highly enantioselective addition of diethylzinc to aldehydes with the catalysis of racemic amino alcohols in the presence of chiral additives.

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

We began this work by investigating the effect of various random chiral additives, such as amino acids, tartaric acid, diols, diamine, diimine, and simple amino alcohols, on the enantioselectivity of ethylation of benzaldehyde (**1a**) with diethylzinc catalyzed by racemic DB1. In some cases, we could really see the influences of the chiral additives on the asymmetric induction of the reaction. For example, (*R*)-1,1'-bi-2-naphthol (BINOL) alone catalyzed the reaction to give the *R* product (8.2% *ee*), but the addition of (*R*)-BINOL to the reaction system catalyzed by racemic DB1 resulted in the formation of *S* product (8.5% *ee*). Similarly, the reaction promoted by (*S*)-2-*N,N*-dimethylamino-2'-hydroxy-1,1'-binaphthyl (DM-NOBIN) yielded *S* product (89% *ee*) and the addition of (*S*)-DM-NOBIN to the racemic DB1 system gave *R* product (38% *ee*). These data could be interpreted by a phenomenon where a catalytically inert heterochiral dimeric zinc complex may be formed between the chiral additive and one of the enantiomers of racemic amino alcohol through non-self-recognition; as a result the zinc complex of racemic amino alcohol is enantioselectively enriched and catalyzes the reaction to give the nonracemic product. From the primary random screening, we found amino alcohols to be one type of effective chiral additive candidates for this purpose (Scheme 1).

High-throughput screening (HTS) is essential for tuning a variety of modifications in lead optimization^[10] and has been found to be an effective technique for finding the most efficient catalysts for asymmetric reactions as well.^[11] With the lead result mentioned above, a library of optically active amino alcohols (AA1–AA13; Scheme 1) was then created by parallel synthesis from amino acids, and a family of racemic amino alcohols (DB1–DB5), which have been reported to show significant asymmetric amplification,^[3a] was also formed. The combined use of 10 mol % of the racemic amino alcohols (DB1–DB5) and half an equivalent amount (5 mol %) of optically active additives (AA1–AA13) in the presence of diethylzinc formed a chiral catalyst library of 65 members, which were then evaluated with HPLC-CD techni-

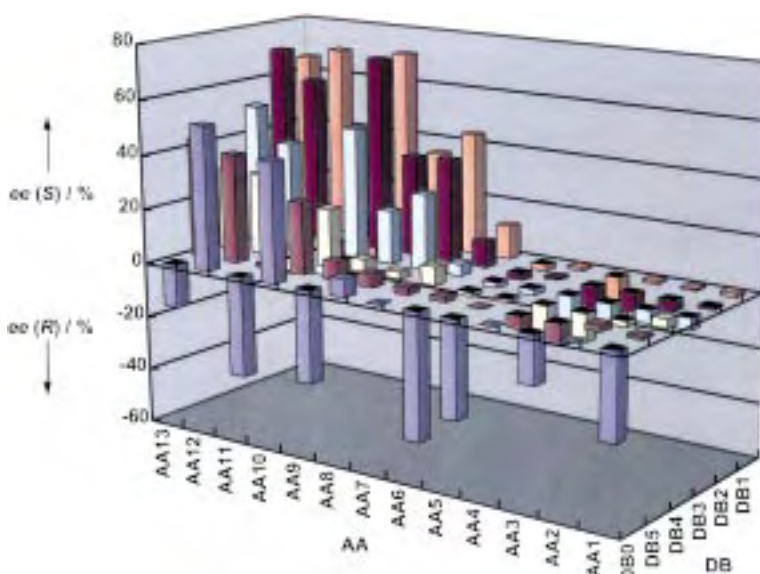
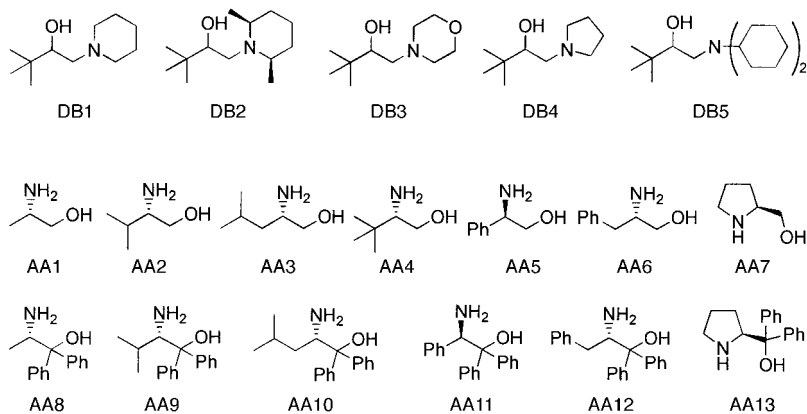


Figure 1. High-throughput evaluation of the catalyst library generated from racemic amino alcohols (DB1–DB5) and chiral additives (AA1–AA13) for enantioselective addition of diethylzinc to benzaldehyde.

ques.^[9f] Figure 1 shows the details of the screening results. It is obvious that the chiral additives with large steric hindrance at the hydroxy-functionalized carbon, AA8–AA13, were more influential on the enantioselectivity of the reaction than the simple amino alcohols, AA1–AA7. Particularly AA10, AA12, and AA13 showed significant synergetic effects on the enantioselectivity of the reaction. For example, with only AA13 (5 mol %) as the chiral inducer, (*R*)-1-phenylpropanol was obtained with 15.6% *ee*. However, the addition of racemic DB1 or DB2 (10 mol %) to the AA13-catalyzed reaction system resulted in the formation of the *S* product in 65.8% and 70.4% *ee*, respectively.

The reactions catalyzed by the better combinations, AA12/DB1, AA12/DB2, AA13/DB1, and AA13/DB2, were further optimized in parallel by varying the molar ratio of racemic DB to chiral AA and decreasing the reaction temperature to -20°C and -40°C . We were pleased to find that (*S*)-1-phenylpropanol could be obtained with up to 92.7% *ee* and in >95% yield under the catalysis of AA13/DB2 (ratio: 1/2; 5 mol % of AA13) at -40°C . Catalyst combinations AA12/DB1, AA12/DB2, AA13/DB1, and AA13/DB2 also proved to be effective for the ethylation of a variety of aldehydes under the optimized conditions (Table 1). To the best of our knowledge, this work represents the first example of highly enantioselective addition of diethylzinc to benzaldehyde with the catalysis of racemic amino alcohols in the presence of chiral additives.

In an effort to elucidate the mechanism for the asymmetric induction, the quantitative effect of chiral additive on the reaction rate was investigated by rapid quenching of the reaction and HPLC analysis with 1-phenylethanol as internal standard (Table 2). It was found that both (*R*)- and (*S*)-DB1 homochiral



Scheme 1. Racemic (DB) and nonracemic (AA) ligands employed for creating the chiral catalyst library.

Table 1. Enantioselectivities for the ethylation of aldehydes with catalysis by racemic DB in the presence of optically active AA.^[a] Parallel screening of matched substrate/catalyst pairs.

$$\text{RCHO} \quad \mathbf{1} + \text{Et}_2\text{Zn} \xrightarrow[\text{CH}_2\text{Cl}_2/\text{hexane}]{\text{DB/AA}} \text{R-CH(OH)Et} \quad \mathbf{2}$$

Entry	R	<i>ee</i> values [%]			
		AA12/DB1	AA12/DB2	AA13/DB1	AA13/DB2
1	phenyl (a)	86.0	86.1	92.7	90.6
2	<i>p</i> -chlorophenyl (b)	69.9	82.3	84.6	92.1
3	<i>m</i> -tolyl (c)	85.7	81.0	90.1	87.3
4	<i>p</i> -anisyl (d)	87.5	90.3	90.0	91.4
5	<i>trans</i> -styryl (e)	67.7	82.3	69.4	69.4
6	<i>o</i> -anisyl (f)	69.8	76.7	74.5	86.3
7	ferrocenyl (g)	81.9	90.6	91.7	72.9
8	<i>p</i> -dimethylamino-phenyl (h)	23.6	55.6	36.2	81.0 ^[b]
9	α -naphthyl (i)	69.9	72.2	69.3	86.3
10	<i>p</i> -tolyl (j)	74.7	80.0	82.4	80.0
11	<i>m</i> -anisyl (k)	79.2	80.7	76.9	76.4
12	<i>p</i> -bromophenyl (l)	76.6	73.6	82.7	79.5
13 ^[c]	<i>trans</i> -propenyl (m)	78.3	84.4	80.7	84.4

[a] All of the reactions were carried out at -40°C in CH_2Cl_2 /hexane mixed solvent for 48 h with catalysis by racemic DB1 (10 mol %) and optically active AA (5 mol %) unless otherwise stated. The conversions of the aldehydes were $>90\%$. All the *ee* values were determined by HPLC or GC on chiral columns. [b] The reaction was carried out at 0°C . [c] The reaction was carried out at -20°C .

Table 2. The quantitative effect of chiral additive AA13 on the rate of reaction, with **1a** as the substrate and DB1 as the catalyst.^[a]

Entry	Config. of DB1	DB1 [mol %]	AA13 [mol %]	Yield [%] ^[b]	<i>ee</i> value [%] ^[c]	Config. of 2a ^[d]
1	<i>S</i>	5	0	16.0	95.0	<i>S</i>
2	<i>S</i>	5	5	6.0	91.1	<i>S</i>
3	<i>R</i>	5	5	1.6	66.2	<i>R</i>
4	$\pm$	5	0	1.6	0	–
5	–	0	5	0.7	15.9	<i>R</i>
6	$\pm$	10	5	5.7	65.8	<i>S</i>

[a] The reaction was carried at 0°C and quenched with an aqueous solution of NH_4Cl after 5 min. [b] The yield was determined by HPLC with 1-phenylethanol as the internal standard. [c] Determined by HPLC on a Chiralcel OD column. [d] Determined from optical rotation measurements and HPLC retention times on a Chiralcel OD column in comparison with authentic samples.

catalysts were deactivated by AA13 (entry 1 compared with entries 2 and 3, respectively), which indicated some interactions between them. However the levels of deactivation for the *R* and *S* catalysts by AA13 were quite different. The reaction catalyzed by (*S*)-DB1/AA13 is 3.8 times as fast as that catalyzed by (*R*)-DB1/AA13 (entries 2 and 3, respectively). ($\pm$)-DB1 and AA13 on their own were found to be catalytically much less reactive (entries 4 and 5). However, use of ($\pm$)-DB1 combined with half an equivalent of AA13 yielded the product 3.6 and 8.1 times as fast as the reactions with the separate component ligands, respectively (entry 6 versus entries 4 and 5). Obviously, such synergetic effects are due to the interaction differences between the AA13–zinc complex and the complexes of (*S*)-DB1 and (*R*)-DB1 with zinc.

The nonlinear effect in the present catalytic system was also disclosed by an investigation of the influence of molar ratios between AA13 and (*R*)-DB1 or (*S*)-DB1 on the enantioselectivity of the reaction.^[12] The different behavior of the nonlinear effects in the AA13/(*R*)-DB1 and AA13/(*S*)-DB1 systems again supported the presence of non-self-recognition between AA13 and DB and also indicated the differences in their non-self interactions.

In conclusion, we have shown the first examples of a highly enantioselective addition of diethylzinc to aldehydes with the catalysis of racemic amino alcohols in the presence of chiral additives, through an asymmetric deactivation strategy with a combinatorial approach. The mechanism of asymmetric induction and the nonlinear effect in chiral deactivation were also studied. This work demonstrated that clever combined use of asymmetric deactivation strategies and combinatorial chemistry approaches will provide a powerful tool for designing and finding new, practical, and efficient asymmetric catalytic systems.

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SrN and SrN₂: Diazenides by Synthesis under High N₂-Pressure**

Gudrun Auffermann, Yurii Prots, and Rüdiger Kniep*

In the binary system Sr–N, only the existence of Sr₂N is certain.^[1] This compound crystallizes in the CdCl₂ structure (layers of octahedra, Figure 1 left). Reports on a binary phase with the stoichiometry “SrN”^[2] were corrected afterwards as these solids also contained hydrogen or carbon.^[1, 3]

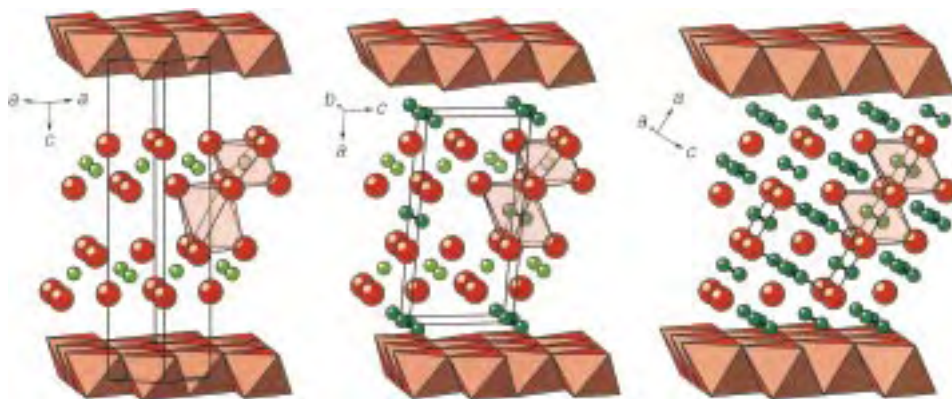


Figure 1. Crystal structures of Sr₂N (left), SrN ≡ (Sr²⁺)₄[N³⁻]₂[N₂²⁻] (center), and SrN₂ ≡ Sr²⁺[N₂²⁻] (right). The top and bottom boundaries of the figures are represented by layers of Sr₆ octahedra (polyhedral representation), occupied by [N³⁻] (Sr₂N, SrN) or [N₂²⁻] (SrN₂), respectively. Ball-and-stick representations between the polyhedral layers: Sr²⁺, red; [N³⁻], light green; [N₂²⁻], dark green. The transparent octahedra contribute to a better visualization.

Recently, we carried out high-pressure experiments for the preparation of strontium–nitrogen compounds using our modified high-pressure equipment, which was originally constructed by Bronger and Auffermann^[4] for the syntheses of extremely air- and moisture-sensitive metal hydrides and hydridometalates.

Using Sr₂N (blue-black powder with metallic luster) as the starting material (reaction temperature 920 K, reaction time 72 h), we obtained single-phase SrN (black-gray powder) under an N₂ pressure of 400 bar and single-phase SrN₂ (brown powder) under an N₂ pressure of 5500 bar.^[5] No impurities of the phases were detected by X-ray and neutron diffraction investigations at ambient pressure^[6] nor by chemical analysis.^[12] The contents of carbon, hydrogen, and oxygen were below the detection limits.

The crystal structures of SrN and SrN₂ were solved by a combination of X-ray and neutron diffraction experiments on air- and moisture-sensitive microcrystalline powders.^[6] The neutron diffraction diagrams (observed, calculated, and difference profile) are given in Figure 2. The crystal structures

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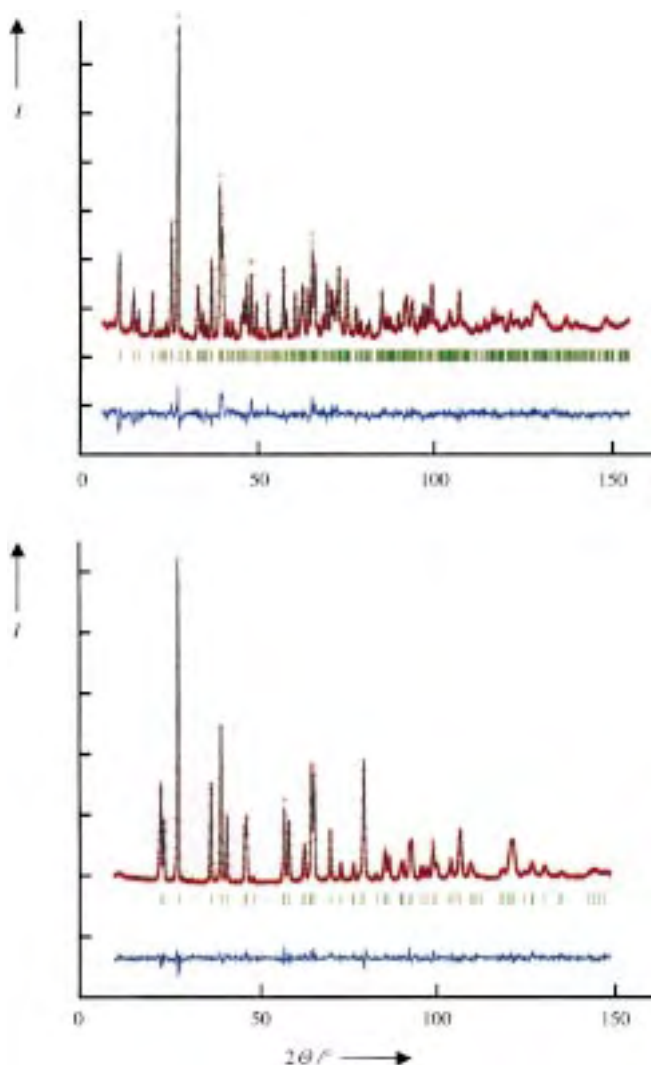


Figure 2. Neutron diffraction diagrams (298 K) of SrN (top) and SrN₂ (bottom).^[6] The observed (red dots), calculated (black solid lines), and difference profiles (blue) are shown. The green ticks mark the positions of the Bragg reflections.

(Figure 1; center and right) can be topologically deduced from Sr₂N ($\rho_{\text{X-ray}} = 3.5 \text{ g cm}^{-3}$): at medium pressure (formation of SrN; $\rho_{\text{X-ray}} = 3.8 \text{ g cm}^{-3}$), one half of the free octahedral holes between the Sr₂N layers are occupied by diazenide ions in an ordered manner; consequently, the Sr₂N layers shift their positions relative to each other (monoclinic unit cell). The high-pressure conditions lead to a tetragonal phase (SrN₂; $\rho_{\text{X-ray}} = 4.2 \text{ g cm}^{-3}$; isotopic relation to the analogous modifications of the alkaline earth acetylides EA[C₂]^[13]) in which all octahedral holes of the nearly close-packed Sr matrix are occupied by [N₂²⁻] ions.

Molecular nitrogen oxidizes strontium (oxidation state “+1.5” in Sr₂N) already at comparatively low nitrogen pressure (400 bar) to Sr²⁺ and is itself reduced to the level of the diazenide [N₂²⁻]. De facto SrN is a nitride–diazenide (Sr²⁺)₄[N³⁻]₂[N₂²⁻]. Whether this step will lead to a better understanding of the effect of the catalyst in the Haber–Bosch process has still to be resolved.

Certainly, the formation of SrN₂ from Sr₂N proceeds via SrN as intermediate because, at a pressure below 5500 bar,

mixtures of SrN and SrN₂ were obtained. No indication for homogeneity ranges of the compounds was observed.^[6, 12] Only use of an elevated pressure of 5500 bar gives the pure diazenide (SrN₂) as a single-phase product. From these results, one can conclude that a comproportionation reaction ($2[\text{N}^{3-}] + 2\text{N}_2 \rightarrow 3[\text{N}_2^{2-}]$) is of crucial importance in the formation of Sr²⁺[N₂²⁻] from SrN ($\triangleq (\text{Sr}^{2+})_4[\text{N}^{3-}]_2[\text{N}_2^{2-}]$).

Thermal decomposition of SrN and SrN₂ takes place (argon; ambient pressure; Netzsch TG/DTA STA409; heating rate 5 K min⁻¹) in the temperature range from 573–673 K and 618–673 K, respectively. These processes are associated with the release of molecular nitrogen and the formation of Sr₂N. The reactions ($(\text{Sr}^{2+})_4[\text{N}^{3-}]_2[\text{N}_2^{2-}] \rightarrow \text{Sr}_2\text{N} + 1.5\text{N}_2$), which correspond to internal redox reactions, are in accordance with the oxidation state “Sr^{+1.5}” in the final product, Sr₂N.

In the crystal structures of SrN and SrN₂, the N–N distances in the diazenide units ($\text{N}=\text{N}^{2-}$) are 1.225(5) and 1.224(2) Å, respectively. These values are in good agreement with the N–N bond length of 1.236(3) Å observed in the diazenide-bridged complex [MoCp*Me₃](μ -N₂)[WCp*Me₃] (Cp* = C₅Me₅; Cp' = C₅H₄Me)^[14] and, as expected, are significantly shorter than the N–N bond length in the protonated diazene ($[\mu\text{-N}_2\text{H}_2[\text{Fe}(\text{“NHS}_4\text{”})]_2]$; N–N: 1.300(7) Å).^[15]

The main focus of this contribution lies in the preparative and chemical aspects. Detailed descriptions of the crystal structures, as well as the magnetic susceptibility measurements (the investigations show a weak temperature-independent paramagnetism for all three compounds), will be given in a future paper.^[11] Up to now, Raman spectra of the diazenides could not be recorded owing to the low thermal stability at ambient pressure. Our investigations on the system Ba–N also show the formation of diazenides under elevated nitrogen pressure.^[16]

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- [6] Neutron diffraction experiments were carried out on the high-resolution powder diffractometer E9 at the reactor BER II of the Hahn-Meitner-Institut, Berlin.^[7] The samples were placed under argon into cylindrical vanadium containers (diameter: 8 mm (SrN) and 6 mm (SrN₂), length: 51 mm, wall thickness: 0.15 mm) and closed with a cap containing an indium seal. Two experiments were carried

out for both compounds with the wavelengths $\lambda = 1.7965(1)$ and $\lambda = 1.3066(1)$ Å in the range $2^\circ < 2\theta < 158^\circ$. Crystal structure data for SrN_2 at 298 K derived from neutron diffraction experiments: tetragonal, space group $I4/mmm$ (no. 139), $a = 3.8136(3)$, $c = 6.2855(4)$ Å, $V = 91.4(1)$ Å³, $Z = 2$; Sr in (2a); N in (4e), $z = 0.4026(2)$; $R_{\text{profile}} = 0.0422$, $R_{\text{Bragg}} = 0.0358$; number of observed reflections: 61. Crystal structure data for SrN at 298 K from neutron diffraction experiments: monoclinic, space group $C2/m$ (12), $a = 13.472(1)$, $b = 3.8121(3)$, $c = 6.7284(5)$ Å, $\beta = 94.720(1)^\circ$, $V = 344.4(1)$ Å³, $Z = 8$, Sr1 in (4i) $x = 0.1541(3)$, $z = 0.3926(7)$; Sr2 in (4i) $x = 0.3561(4)$, $z = 0.0922(6)$; N1 in (4i) $x = 0.2442(3)$, $z = 0.7487(6)$; N2 in (4i) $x = 0.0223(3)$, $z = 0.0830(6)$; $R_{\text{profile}} = 0.0527$, $R_{\text{Bragg}} = 0.0663$; number of observed reflections: 690. The refinements have been carried out using the programs WinPLOTR^[8] and FULLPROF.^[9] The following scattering lengths were used: Sr 7.02 fm; N 9.36 fm.^[10] Further details on the crystal structure investigations 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 numbers CSD-411555, and CSD-411556.

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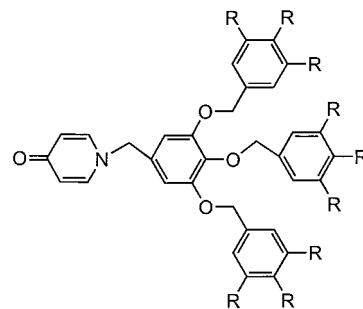
Dendron-Controlled Nucleation and Growth of Gold Nanoparticles**

Ruiyao Wang, Jun Yang, Zhiping Zheng,*

Michael D. Carducci, Jun Jiao, and Supapan Seraphin

Nanoclusters of metals and semiconductors—which exhibit unusual size-dependent electronic, magnetic, optical, and catalytic properties due to the onset of “quantum effects”—are being heralded as the next generation of building blocks for designing modern materials.^[1] However, these particles are metastable and cannot be isolated or manipulated without appropriate stabilization by organic capping ligands.^[2] Various functionalized organic arrays including protein cages,^[3] polymer matrices,^[4] and surfactant vesicles^[5] have been used previously to form nanoparticles by encapsulation. A more recent development is the use of polyamidoamine (PAMAM) dendrimers^[6]—a class of highly branched, monodisperse, and globular synthetic polymers—to passivate nanoclusters of zero-valent metals,^[7] metal oxides,^[8] and metal sulfides.^[8, 9] However, a simple relationship between particle size and dendrimer generation was not established.^[10]

In contrast to classical dendrimers such as the PAMAM species, a dendron is a segment of dendrimer that possesses a focal point onto which the branching units of a dendritic architecture are attached.^[11] If the focal moiety is capable of metal complexation, the specific metal–dendron interactions can be utilized to control reactions at this site.^[12] We envision that such reactivity control in a confined and localized area may be used for the controlled growth and stabilization of nanoparticles. Such a concept is validated here with the production of gold nanocrystals using dendrons G1–G3 with a focal 4-pyridone functionality^[13] as capping agents.



G1 R = H

G2 R = $\text{OCH}_2\text{C}_6\text{H}_5$

G3 R = $\text{OCH}_2\text{C}_6\text{H}_4(\text{OCH}_2\text{C}_6\text{H}_5)_2$

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

The gold–dendron nanocomposites were synthesized by the liquid–liquid phase-transfer reaction^[14] shown in Equation (1) ($Gn = nth$ -generation dendron; $n = 1–3$). In all cases,



wine-red solutions were obtained. These solutions exhibit a characteristic gold surface plasmon (SP) resonance at about $\lambda = 525$ nm (Figure 1) and are stable for at least six months

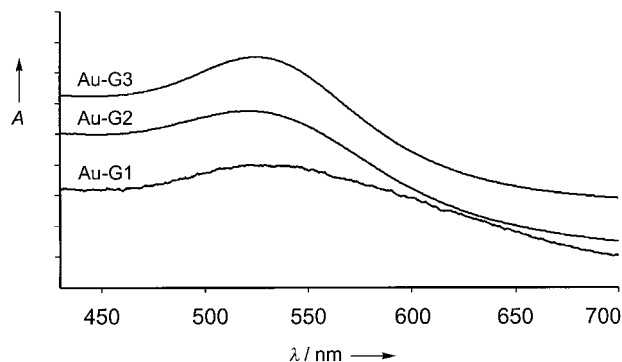


Figure 1. UV/Vis spectra of solutions of nanocomposites Au-Gn ($n = 1–3$). The absorbance A is arbitrarily normalized at $\lambda = 450$ nm.

under ambient conditions. This stability is attributable to passivation of the metal surface by the dendrons, as only insoluble black residues were obtained in the absence of the capping ligands. A similar wine-red solution can also be generated without using any phase-transfer agent, however, with a significant amount of black precipitate. This is presumably due to the inefficient mixing of $\text{HAuCl}_4/\text{NaBH}_4$ with the dendrons in the absence of the agent. These observations lead to the conclusion that the use of a phase-transfer agent facilitates formation of the gold–dendron composites, but is not mandatory.

The gold–dendron nanocomposites can be isolated from the solution as dark crystalline solids that redissolve in dichloromethane without noticeable visual changes. Further purification by recrystallization from dichloromethane/pentane yields analytically pure Au-G1 and Au-G2, but Au-G3 is contaminated with a small amount of free G3 due to similar solubilities. Microanalysis of Au-G1 revealed its composition to be 5% G1 and 95% Au, corresponding roughly to an Au:G1 ratio of 49:1. Based on the packing density calculation for bulk-state gold,^[15] a 2-nm particle (see below) contains 247 gold atoms, leading to the formula $\text{Au}_{247}(\text{G1})_5$. A straightforward calculation^[16] gives an $\text{Au}_{\text{surface}}:\text{G1}$ ratio of 27.5:1, which is not unreasonable considering the coverage offered by the umbrella-shaped dendron.

Transmission electron microscopy (TEM) analysis (Figure 2) of the dropcast films of Au-Gn demonstrates the correlation between the particle size and the generation number of the dendron: The higher the generation, the larger the encapsulated particles. Thus, with G1, G2, and G3 gold particles with an average diameter of 2.0 ± 1.0 , 3.3 ± 1.1 , and 5.1 ± 1.7 nm (measured over 200 particles in each case) were obtained, respectively. The characteristic [111] gold lattice fringes (inset, Figure 2a) manifest crystallinity of the particles.

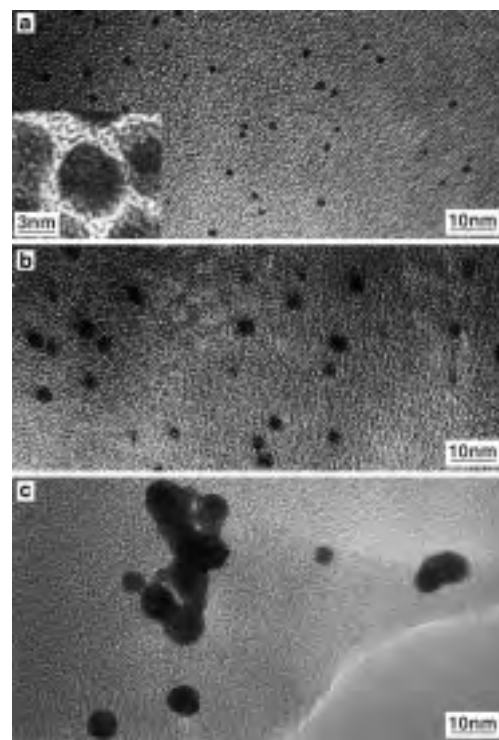


Figure 2. Transmission electron micrographs of a) Au-G1, b) Au-G2, and c) Au-G3. Inset: gold lattice fringes of Au-G1.

The TEM images of differently sized particles were corroborated by the UV/Vis absorption spectra of the particle solution: Going from Au-G3 to Au-G1, the SP band blue shifts slightly (3 nm) and decreases in intensity with decreasing particle size. Similar trends were observed for Au nanocrystals stabilized by PAMAM dendrimers.^[7c,d,10]

Before the size control imposed by different-generation dendrons can be rationalized, the microscopic interactions between the dendron and the gold surface need to be discerned. The dendron focal moiety appears to be the only reasonable site where the particles may nucleate and grow, because the dendron surface lacks metal-stabilizing groups, while the loose dendron may not be able to sustain the confinement of the particles within the branching units. The N atom, the C=O moiety, and even the conjugated six-membered ring can potentially bind metals. Efforts have been made to establish the dendron coordination mode(s), but definitive assignment of a particular type of dendron–gold interaction is difficult owing to the intrinsically weak nature of such interactions. The IR spectra of Au-G1 and Au-G2 are essentially superimposable with those of their respective ligands. This observation is in line with results reported for the similarly weak PAMAM–gold interactions.^[7c,17]

The ^1H NMR signals of Au-G2, though significantly broadened, appear at positions that are almost identical to those of free G2. Similar observations are well documented for gold nanoparticles functionalized with passivating amines^[16] and thiols,^[2a] and the broadening effects have been extensively discussed.^[2a] The XPS studies revealed noticeable broadening of 1s peaks for C, O, and N atoms in Au-G2 relative to free G2, but the changes in ionization energies are

negligible, indicating a rather weak interaction between the metal surface and individual dendrons. Based upon these observations, the possibility of N–Au and focal ring–Au interactions cannot be ruled out. However, such modes of particle stabilization, both involving the seemingly inaccessible N atom, are less likely due to steric encumbrance. The C=O moiety is therefore putatively responsible for binding to the metal, and the observed passivation is provided by the dendron sheath within which the single gold particle resides (Figure 3). To the best of our knowledge, there are no

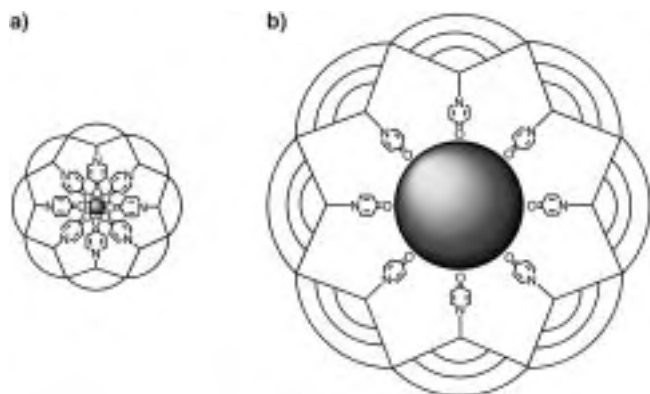


Figure 3. Schematic presentation of Au–Gn nanocrystallite growth controlled by different-generation dendrons: a) G1 and b) G3.

precedents for monolayer formation of pyridone derivatives on bulk metal surfaces of any kind, presumably due to the chemical instability of such monolayers. This work thus represents an exciting departure from the bulk systems in that the high surface curvature (as a result of their finite size) of the Au nanoparticles supports the high-density packing of the capping ligands, which provide concomitant protection of the nanocrystals.^[16]

The systematic variation of particle size may be understood as follows: The higher the dendron generation, the greater the steric requirement of the focal metal-binding moiety, and hence the more room for gold atoms to agglomerate (Figure 3). This steric argument can be easily appreciated by comparing the bulk of a G2 dendron (nine peripheral aromatic rings, Figure 4^[18]) with that of a G1 dendron (only three peripheral aromatic rings). Given the weak force between the particle and the dendrons, particle aggregation conceivably occurs, and the nanocomposite containing the more sterically demanding dendrons is more susceptible to such a coalescence. In other words, the more hindered periphery leads to a less compact and therefore less stable composite structure because of the increasing open space between the branching units. This hypothesis is corroborated by the observation that the particles of Au–G3 (Figure 2c) are not as well separated as those of Au–G1 (Figure 2a) and Au–G2 (Figure 2b). Dendrons with a focal thiol group would be more propitious for stabilizing gold nanoparticles and therefore mitigating particle agglomeration. Experiments with such dendrons are in progress as are studies of other factors that possibly affect the particle size and size distribu-

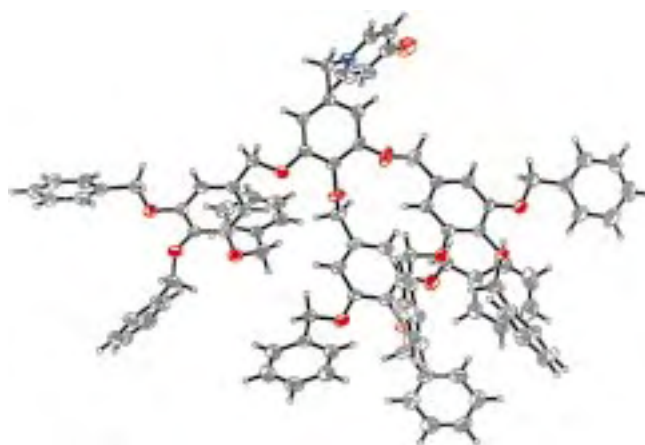


Figure 4. An ORTEP representation of the crystal structure of G2 at the 50% probability level. Carbon: gray, nitrogen: blue, oxygen: red.

tion (for example, dendron:metal ratio, rate of reductant addition, and reaction temperature).

In summary, we have demonstrated that dendrons that are focally modified with a metal-coordinating functionality can be utilized as stabilizing media for the controlled growth of nanocrystals. With 4-pyridone-based dendrons, gold nanoclusters were obtained that are stable for six months both in solution and in the solid state. The average size of the resulting nanoparticles is a direct function of the generation number of the passivating dendron, with higher generation dendrons producing larger particles.

Experimental Section

To a solution of $\text{HAuCl}_4 \cdot 3\text{H}_2\text{O}$ (11.2 mg, 28.4 μmol) in deionized water (5 mL) was added ($n\text{-C}_8\text{H}_{17}$)₄NBr (36.5 mg, 66.7 μmol) in toluene/ CH_2Cl_2 (15 mL, 2/1). An orange-red organic phase and a colorless aqueous phase resulted after 1 h of vigorous stirring. The dendron (310 μmol ; 0.156, 0.452, and 1.34 g for G1, G2, and G3, respectively) in CH_2Cl_2 (15 mL) was added to the above mixture. Subsequent dropwise addition of a freshly prepared aqueous solution (5 mL) of NaBH_4 (16.5 mg, 436 μmol) caused an instant color change of the mixture to wine-red. The resulting mixture was stirred under dry N_2 for an additional 24 h. Decanting the aqueous phase and adding ethanol to the organic phase at -20°C afforded the products as dark purple solids. Recrystallization from CH_2Cl_2 /pentane yielded dark purple crystalline solids (Au–G1 and Au–G2) or dark purple waxy solids (Au–G3). Elemental analysis of Au–G1: C 4.14, H 0.25, N 0.14. Based on this CHN analysis and the molecular formula of G1 ($\text{C}_{33}\text{H}_{29}\text{NO}_4$), O is calculated to make up 0.64% of the Au–G1 nanocomposite, and hence Au makes up 94.8%.

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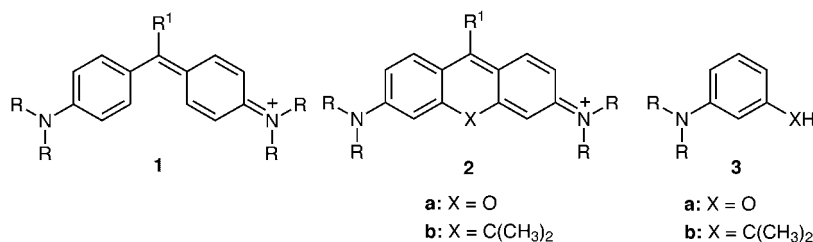
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Alkylene-bridged N,N,N',N' -Tetrasubstituted Bis(2-amino-5-thiazolyl)methinium Salts—A New Class of Strongly Fluorescent Dyes**

Horst Hartmann* and Antje Noack

Owing to their strong fluorescence, pyronines **2a** ($R^1 = \text{H}$)^[1] and rhodamines **2a** ($R^1 = \text{Aryl}$)^[2] have found several practical applications, such as fluorescence and laser dyes,^[3] or, if they are specifically functionalized, for example at the amino groups, as fluorescence markers for biological substrates and polymer characterization.^[4] The fluorescence of the dyes **2a** is in sharp contrast to their unbridged di- and triarylmethane



dye analogues **1** which are nonfluorescent under normal conditions.^[5] The fluorescence-enhancing effect of bridging by heteroatoms is associated, however, with a pronounced hypsochromism of the absorption of these dyes. Thus, the bridged di- and triarylmethane dyes **2a** absorb at about 550 nm. This is a nearly 50 nm shorter wavelength than the absorption wavelength of their unbridged analogue **1**.^[6]

Whereas the fluorescence-enhancement is effected by the increasing rigidity of the molecular system and originates from a restriction or diminishing of the nonradiative deactivation processes^[7] the hypsochromic effect originates from the incorporation of the lone pair of the bridging oxygen atom into the conjugation of the π system responsible for the color. This incorporation gives rise to a stabilization of the electronic ground state and, hence, to a widening of the gap between the ground and first excited state in the bridged compounds.^[6]

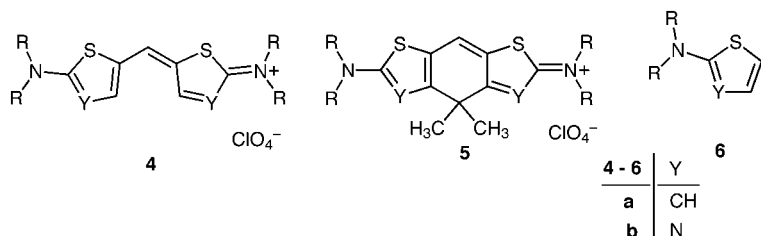
In agreement with this postulate no hypsochromic effect is observed in going from the unbridged compounds **1** to the alkylene-bridged di- and triarylmethane dyes **2b** in which the bridging group has no lone pair. Therefore, these compounds absorb at nearly the same wavelength as their unbridged analogues **1**, but in contrast they exhibit, analogous to the oxygen-bridged compounds **2a**, a strong fluorescence.^[8a] A practical application of the isopropylidene-bridged dyes **2b** has not been reported because the necessary educts for these compounds, the isopropylidene-substituted N,N -dialkylanilines **3b**, can only be prepared by a multistep reaction from commercially available precursors, making them far less

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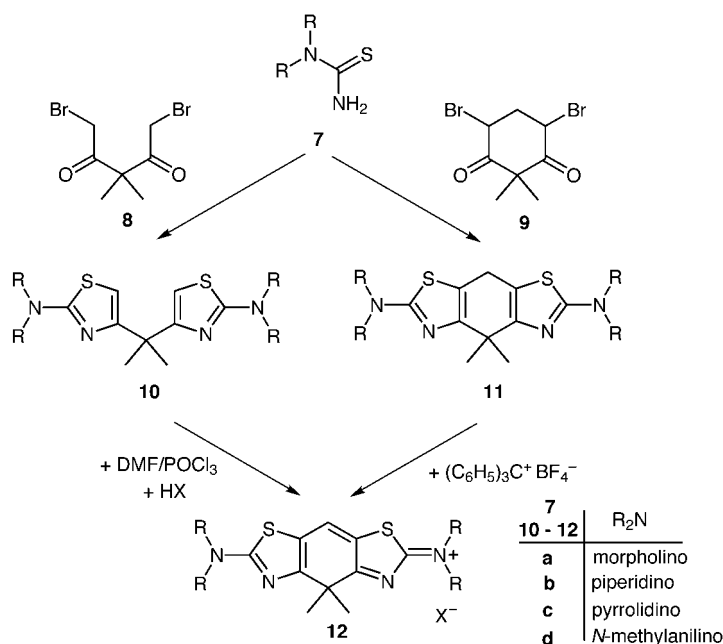
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accessible than the educts **3a** for the oxygen-bridged compounds **2a**.^[8b]

Recently it was demonstrated that some heterocyclic analogues of the di- and triarylmethane dyes **1**, such as the compounds **4**, exhibit similar spectroscopic properties to their carbocyclic parent compounds **1**.^[9] Thus, the maxima of the longest-wavelength absorptions of the bis(2-dialkylamino-5-thienyl)methines **4a**^[10] and bis(2-dialkylamino-5-thiazolyl)-methines **4b**^[9, 11] are found at nearly the same wavelength as the maxima of their nonfluorescent parent compounds **1**.



This parallelism in the spectroscopic properties between the carbocyclic and heterocyclic methine dyes **1** and **4** inspired us to synthesize the alkylene-bridged analogues **5** of the bridged carbocyclic methine dyes **2** and to study their spectroscopic properties, especially their ability to fluorescence. In analogy to the synthesis of the unbridged compounds **4b** from the *N,N*-disubstituted 2-amino-thiazoles **6b**,^[12] the first method studied for the synthesis of **5** was the reaction of *N,N*-disubstituted thioureas **7**^[13] with the dibromo-substituted diketone **8**^[14] (Scheme 1). This method gives the expected bisthiazoles **10**^[15] which were subsequently transformed, by reaction with orthoformate esters and acetic anhydride in the presence of magnesium perchlorate^[16] or, more preferably, by reaction with DMF and POCl₃ and addition of aqueous tetrafluoroboric or perchloric acid, into the bridged methine dyes **12**.



Scheme 1. Synthesis of the bis(2-amino-5-thiazolyl)methinium compound.

Although the desired products **12** could be obtained in this manner their yields were surprisingly low. The yields are reduced by the formation of by-products which probably result from an intermolecular condensation between two thiazole moieties of two educt molecules **10** which competes with the planed intramolecular condensation of the orthoformate esters with the two thiazole groups in **10**. Therefore, a second route for the preparation of **12** was designed. Instead of **8** the dibromo-cyclohexanedione **9** was chosen to react with **7**.^[17] The compound **9** was prepared, analogously to compound **8**, by the bromination of its bromo-free precursor in glacial acetic acid.^[18] The reaction of **9** with the appropriate *N,N*-disubstituted thiourea **7** in a molar ratio of 1:2 gave the tricyclic bisthiazole derivatives **11**.^[19] These products were allowed to react in acetonitrile solution with trityl tetrafluoroborate affording the desired methine tetrafluoroborates **12** in satisfactory yields.

The structures of the isopropylidene-bridged methine dyes **12** were unambiguously confirmed by elemental analysis and NMR spectroscopy (Table 1). The dyes are deep blue and exhibit, as expected, a marked fluorescence. Figure 1 shows the absorption and emission spectrum of the morpholino-substituted compound **12a**. Like most dyes of this type this compound displays a narrow intense absorption band at about 620 nm.^[20] Remarkably the position of this band is shifted to longer wavelength^[21] than the longest-wavelength absorption band of the unbridged methine dye analogues **4b** (552 nm).^[6] The fluorescence maxima from the isopropylidene-bridged methine dyes **12**, which are dependent on the polarity of solvents, are found at about 650 nm in toluene. The small Stokes shift observed is as

Table 1. Selected data for the bridged *N,N,N',N'*-tetrasubstituted bis(2-amino-5-thiazolyl)methinium tetrafluoroborates **12** (X = BF₄).^[a, b]

12a :	Yield 53 % (method A) ^[c] and 51 % (method B); m.p. 209–211 °C (CH ₃ CN/diethyl ether); ¹ H NMR ([D ₆]DMSO): δ = 1.65 (s, 6H, CH ₃), 3.73 (t, 8H, NCH ₂), 3.84 (t, 8H, OCH ₂), 8.83 (s, 1H, CH); ¹³ C NMR ([D ₆]DMSO): δ = 28.16, 45.74, 49.39, 65.18, 120.24, 139.89, 177.83, 181.36; UV/Vis absorption: λ _{max} = 616 nm, log ε = 4.68; emission: λ _{max} = 654 nm, Φ = 56 %
12b :	Yield 49 % (method A) ^[c] and 31 % (method B); m.p. 203–205 °C (CH ₃ CN/diethyl ether); ¹ H NMR ([D ₆]DMSO): δ = 1.63 (s, 6H, CH ₃), 1.70 (m, 12H, CH ₂), 3.81 (m, 8H, NCH ₂), 8.73 (s, 1H, CH); ¹³ C NMR ([D ₆]DMSO): δ = 22.86, 24.91, 28.23, 45.58, 50.75, 119.74, 138.72, 176.95, 181.37; UV/Vis absorption: λ _{max} = 625 nm, log ε = 4.62; emission: λ _{max} = 656 nm, Φ = 37 %
12c :	Yield 32 % (method B); m.p. 160–162 °C (CH ₃ CN/diethyl ether); ¹ H NMR ([D ₆]DMSO): δ = 1.66 (s, 6H, CH ₃), 2.09 (m, 8H, CH ₂), 3.49 (m, 8H, NCH ₂), 8.78 (s, 1H, CH); ¹³ C NMR ([D ₆]DMSO): δ = 24.72, 28.24, 45.40, 51.07, 119.70, 139.91, 173.67, 180.89; UV/Vis absorption: λ _{max} = 616 nm, log ε = 4.57; emission: λ _{max} = 649 nm, Φ = 21 %
12d :	Yield 38 % (method B); m.p. 150–153 °C (CH ₃ CN/diethyl ether); ¹ H NMR ([D ₆]DMSO): δ = 1.71 (s, 6H, CH ₃), 3.76 (s, 6H, NCH ₃), 7.48–7.53 (m, 6H, CH), 7.64 (m, 4H, CH), 8.68 (s, 1H, CH); ¹³ C NMR ([D ₆]DMSO): δ = 28.37, 42.15, 46.05, 121.65, 124.55, 125.73, 130.75, 143.65, 145.02, 172.44, 181.88; UV/Vis absorption: λ _{max} = 623 nm, log ε = 4.64; emission: λ _{max} = 669 nm, Φ = 1 %

[a] For the substituents R₂N pattern, see Scheme 1. [b] Absorption data in dichloromethane, emission data in toluene; fluorescence quantum yield relative to rhodamine B (Φ = 86 %). [c] Determined by ¹H NMR spectroscopy.

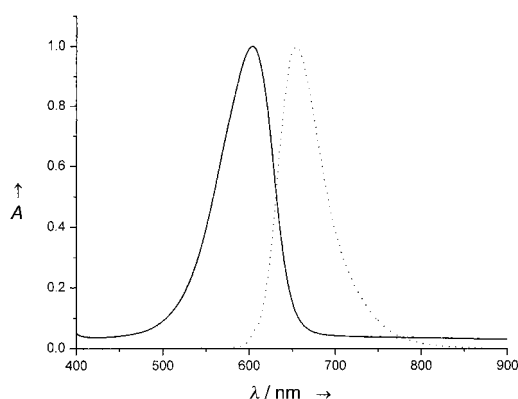


Figure 1. Absorption spectrum (—) and emission spectrum (···) of **12a**.

expected, and in accordance with the rigid structure of the dyes which prevents, or at least largely suppresses, a non-radiative deactivation of the excited state.

The reported route to strongly fluorescent bis(2-amino-5-thiazolyl)methinium salts **12** also indicates a simple way for preparing specially functionalized methine dyes which can be used, analogously to specially functionalized pyronine or rhodamine dyes **2a**,^[4] as fluorescence markers for biological and polymeric substrates.

Experimental Section

Preparation of the isopropylidene-bridged *N,N,N',N'*-tetrasubstituted bis(2-amino-5-thiazolyl)methinium salts **12**:

Method A: To a mixture of a 4-(2-(2-dialkylamino-4-thiazolyl)-2-propyl)-2-dialkylamino-thiazole **10** (0.01 mol) and DMF (20 mL) POCl₃ (0.02 mol, 3.0 g) was added dropwise under stirring at RT. After stirring for 3 h the reaction mixture was added dropwise, to a cooled solution of tetrafluoroboric acid (40%, 5 mL) in methanol (20 mL). The products precipitated after addition of diethyl ether (100 mL) and were isolated by filtration. As indicated by their ¹H NMR spectra the products in each case were a mixture of the corresponding dyes **12** and their dimers, from which the desired products could not be isolated, only identified by their characteristic ¹H NMR spectra and their intense fluorescence.

Method B: A mixture of a 2,6-bis(dialkylamino)-4,4-dimethyl-4,8-dihydrothiazolo[4,5-*f*]benzothiazole **11** (0.01 mol) and triphenylmethyl tetrafluoroborate (3.30 g, 0.01 mol) in acetonitrile (50 mL) was heated at reflux for 24 h. After cooling and reducing the volume to 5 mL diethyl ether (20 mL) was added to the reaction mixture and the precipitated **12** was isolated by filtration.

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- [15] **10a**: Yield 82 %; m.p. 140–143 °C (EtOH); ¹H NMR (CDCl₃): δ = 1.60 (s, 6H, CH₃), 3.39 (t, 8H, NCH₂), 3.77 (t, 8H, OCH₂), 6.15 (s, 2H, CH); ¹³C NMR (CDCl₃): δ = 27.87, 41.93, 48.53, 66.18, 101.58, 160.27, 170.45. **10b**: yield 40 %; m.p. 112–117 °C (EtOH); ¹H NMR (CDCl₃): δ = 1.63 (m, 18H, CH₃/CH₂), 3.41 (t, 8H, NCH₂), 6.10 (s, 2H, CH); ¹³C NMR (CDCl₃): δ = 25.01, 25.83, 28.68, 42.67, 50.24, 101.35, 161.08, 171.35.
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- [17] Yield 61 %; m.p. 83–85 °C (EtOH); ¹H NMR (CDCl₃): δ = 1.41 (s, 3H, CH₃), 1.42 (s, 3H, CH₃), 1.51 (s, 3H, CH₃), 1.52 (s, 3H, CH₃), 2.57 (q, 1H, CH₂), 3.18–3.33 (m, 2H, CH₂), 3.63 (dd, 1H, CH₂), 4.77 (t, 1H, CHBr), 4.98 (dd, 2H, CHBr).
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- [19] **11a**: Yield 76 %; m.p. 220–222 °C (toluene/MeOH); ¹H NMR (CDCl₃): δ = 1.49 (s, 6H, CH₃), 3.41 (t, 8H, NCH₂), 3.78 (t, 8H, OCH₂), 3.82 (s, 2H, CH₂); ¹³C NMR (CDCl₃): δ = 23.33, 28.16, 38.78, 48.57, 66.18, 111.60, 153.49, 169.76; **11b**: yield 66 %; m.p. 275–277 °C (toluene); ¹H NMR (CDCl₃): δ = 1.53 (s, 6H, CH₃), 1.65 (m, 12H, CH₂), 3.43 (m, 8H, CH₂), 3.81 (s, 2H, CH₂); ¹³C NMR (CDCl₃): δ = 24.06, 25.04, 25.78, 28.89, 39.44, 50.25, 111.44, 154.25, 170.66; **11c**: yield 79 %; m.p. 250–252 °C (toluene); ¹H NMR (CDCl₃): δ = 1.59 (s, 6H, CH₃), 2.01 (m, 8H, CH₂), 3.45 (t, 8H, CH₂), 3.83 (s, 2H, CH₂); ¹³C NMR (CDCl₃): δ = 24.20, 26.33, 28.85, 39.56, 50.05, 110.52, 154.47, 166.67; **11d**: yield 66 %; m.p. 153–154 °C (*n*-butanol); ¹H NMR (CDCl₃): δ = 1.64 (s, 6H, CH₃), 3.56 (s, 6H, NCH₃), 3.72 (s, 2H, CH₂), 7.23 (m, 2H, CH), 7.42 (m, 8H, CH); ¹³C NMR (CDCl₃): δ = 23.81, 28.97, 39.41, 40.53, 112.16, 124.99, 126.28, 130.13, 147.36, 153.84, 168.57.
- [20] The UV/Vis absorption and emission spectra were recorded with an MC 40 spectrometer (Zeiss) and Lambda 900 Spectrometer (Perkin-Elmer), respectively, the NMR spectra with a 300 MHz Spectrometer (Varian). The authors are indebted to Mrs. C. Koenig and Mrs. A. Schroeder for recording the NMR and UV/Vis absorption and emission data, respectively.
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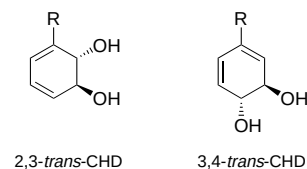
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Synthesis of Functionalized Cyclohexadiene-*trans*-Diols with Recombinant Cells of *Escherichia coli***

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Functionalized cyclohexadiene-*cis*-diols (*cis*-CHD), that are produced by whole-cell bioconversion, have been demonstrated to be valuable precursors in the chemistry of natural products and pharmaceuticals.^[1] Using *cis*-CHD as a starting material, syntheses have been established, for example, for conduritol,^[2] zeylena,^[3] and *ent*-morphinan.^[4]

In contrast, the corresponding cyclohexadienediols with *trans*-configured glycol unit (*trans*-CHD) have not been established as chiral synthetic building blocks yet, mainly due to the poor availability of these substances. On the one hand, *trans*-configured diols cannot be prepared by the dioxxygenase-catalyzed dihydroxylation of arenes, whereas epoxidation with monooxygenases and subsequent nucleophilic opening usually gives racemic products. On the other hand, all chemical routes to *trans*-CHD are characterized by low enantioselectivity or tedious multistep syntheses.^[5, 6] Attempts by several research groups to prepare *trans*-CHD



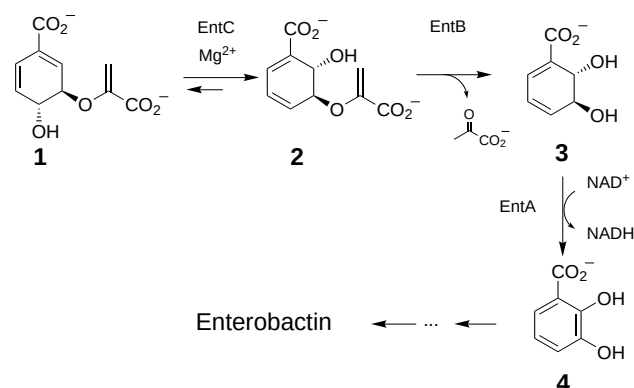
directly from *cis*-CHD have similarly been characterized by low overall yield.^[3, 7] Nevertheless, it was shown that *trans*-CHD and especially derivatives of *trans*-2,3-dihydroxy-2,3-dihydrobenzoic acid (2,3-

hydrobenzoic acid (2,3-

trans-CHD) are ideal precursors for the synthesis of amino-carbasugars (e.g. valienamine)^[5b] and natural cyclohexanebis-epoxides (e.g. crotepoxide).^[8] *trans*-CHDs also appear in nature as secondary metabolites of the shikimate pathway in bacteria, plants, and fungi, and therefore should, in principle, be accessible through metabolic engineering. Using this technique Frost et al., for instance, produced shikimic acid and quinic acid in concentrations up to 27 g L⁻¹ and 13 g L⁻¹, respectively, by fermentation of recombinant strains of *Escherichia coli*.^[9] Microbial production of two *trans*-CHDs (dihydroxydihydrobenzoic acid isomers)

in concentrations up to 200 mg L⁻¹ has been achieved by Leistner and co-workers with strains of *Klebsiella pneumoniae* (potentially human-pathogenic).^[10] Therefore it is evident that *trans*-CHD could be simply and efficiently prepared in a biotechnological process that makes use of the shikimate pathway. Herein we describe the first direct access to (2*S*,3*S*)-dihydroxy-2,3-dihydrobenzoic acid (**3**) starting from glucose and other renewable carbon sources with metabolically deregulated, recombinant strains of *E. coli*.

Compound **3** is an intermediate on the pathway of the iron chelator enterobactin and is produced from chorismate **1** via isochorismate **2** in two catalytic steps (Scheme 1).^[11] Enzymes involved in this process are isochorismate synthase (encoded



Scheme 1. Metabolites of the enterobactin pathway are chorismate **1**, isochorismate **2**, (2*S*,3*S*)-dihydroxy-2,3-dihydrobenzoic acid (**3**), and 2,3-dihydroxybenzoate (**4**). The participating enzymes are isochorismate synthase (EntC), isochorismatase (EntB), and 2,3-dihydroxybenzoate synthase EntA.

by gene *entC*) and isochorismatase (encoded by *entB*). Aromatization to 2,3-dihydroxybenzoic acid (**4**) is catalyzed by 2,3-dihydroxybenzoate synthase (encoded by *entA*, Scheme 1). Intracellular overproduction of **3** can therefore be enhanced by two factors: 1.) by increase of the metabolic flux towards the target product, for example, by amplification of the EntB/EntC activities,^[10] and 2.) by prevention of degradation of the target molecule, for example, by decrease of the EntA activity.

To show that **3** can be overproduced and excreted into culture medium, we have transformed *E. coli entA*⁻ mutants (AN193, H1882) with plasmids containing *entB*, *entC*, or *entB/entC*. In addition, strains without *entA* defect (DH5α, W3110) were transformed analogously (Table 1).

Enhanced expression of the particular genes could be monitored by identification of the respective proteins on sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE) using crude cell extracts of the recombinant strains. An increase of the corresponding enzyme activities could be clearly verified by using HPLC to monitor the degradation of chorismate **1** to **2** and **3**.

Shaking-flask fermentations proved that derivatives of the *entA*⁻ mutants H1882 and AN193 with plasmid-borne genes *entB* and *entC* excreted **3** with a maximum production rate of 27 mg h⁻¹ per g (dry cell mass). Strains DH5α and W3110 (with wild-type EntA activity and EntB/EntC overproduc-

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Table 1. *E. coli* K-12 parental strains in use.

Strain	Relevant genotype	<i>entA</i>	Ref.
DH5 α	F ⁻ <i>endA1 hsdR17(r_K m_K⁺) recA1 supE44 thi-1 Δ(lacZYA-argF)U169 Φ80lacZΔM15</i>	+	[12]
W3110	F ⁻ λ IN(<i>rrnD-rmE</i>) prototroph	+	[13]
AN193	<i>trpE38 leuB6 proC14 lacY1 fhuA23 rpsL109(Str^R)λ⁻ entA403</i>	–	[14]
H1882	<i>araD139 Δ(argF-lac)169 λ⁻ flhD5301 rpsL150(Str^R) Δ(fepA-ent)</i>	–	[15]

tion) also showed excretion of **3**; however, the excretion rate was only about 9 mg h⁻¹ per g (dry cell mass), hence significantly lower than in strains with *entA* mutations (Table 2). Parent strains or strains which overproduced either EntB or EntC, showed no excretion of **3** or of other intermediates in the pathway of enterobactin (**1**, **2**, or **4**) into the fermentation broth.

Table 2. Extent of excretion of **3** in [mg h⁻¹ per g (dry cell mass)] depending on the overexpression of genes encoding for EntB or EntC, respectively. No excretion of **1**, **2**, or **4** was observed. Limit of detection was ≤ 1 mg L⁻¹.

Used strain (chromosomal specificity)	/pJFentB EntB	/pJFentC EntC	/pJFentBC EntB/EntC
DH5 α , W3110 (<i>entA</i> ⁺)	n.q. ^[a]	n.q. ^[a]	9
AN193, H1882 (<i>entA</i> ⁻)	n.q. ^[a]	n.q. ^[a]	27

[a] n.q. = not quantifiable (below limit of detection).

To avoid inhibitory or repressive influences of complex components of the medium on product formation, a minimal salt medium has been developed consisting of mineral salts solution, buffer, and a defined carbon source. Best growth and production rates have been obtained by using a previously published mineral salts medium^[16] with increased concentration of ammonium chloride. In addition, the medium was supplemented with 2,3-dihydroxybenzoate (due to the *entA* deficiency), and growth supplements to satisfy the auxotrophies for thiamine, leucine, proline, and tryptophan were added in all experiments.

Apart from glucose, **3** can be readily produced from other C sources, such as galactose, fructose, glycerol, acetate, or lactate (Scheme 2). The two best C sources (glycerol, gal-

actose) resulted in even better excretion performances (up to 48 mg h⁻¹ per g (dry cell mass)).

With regard to the production of **3**, the strains with an *entA*⁻ mutation showed long-term stability as well as high production rates—basic requirements for high space–time yields in continuously working production processes. By using a pH-controlled stirred tank reactor and applying optimized conditions (pH 6.8, 37 °C, glucose-feeding in a fed-batch mode), the catalytic reaction could be maintained during a process time of more than 40 h. During this time 92 g of **3** were produced from 690 g of glucose monohydrate in a 20 L cultivation experiment at a cell density of 12 g L⁻¹ (dry cell mass), correlating with a molar yield of 17%.^[17] Here again **3** was the major product with no detectable impurities of **1**, **2**, or **4**. Therefore any further purification with laborious separation techniques becomes obsolete.

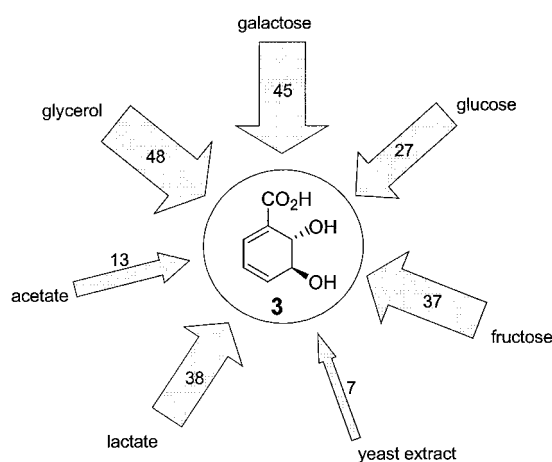
A simple and quantitative separation from the fermentation salts can be achieved by multiple extraction of the acidified (pH 3) permeate of the cell suspension, using short-chain alcohols, (e.g. 1-butanol; extraction coefficient 30%). After purification by column chromatography **3** is isolated in 73 % yield as a yellow solid in highly pure form. Alternatively, the product can be isolated with similar purity and in 75 % yield by using ion exchange chromatography.^[18] At room temperature and moderate pH (3 $\leq$ pH $\leq$ 11) **3** is stable over a period of weeks.

To demonstrate that quite similar follow-up chemistry to that observed with *cis*-CHD is also possible for the substituted *trans*-CHD, we exemplarily worked out highly regio- and stereoselective syntheses starting from **3** towards pharmacologically interesting target molecules.^[19]

In summary, we have demonstrated that (2*S*,3*S*)-dihydroxy-2,3-dihydrobenzoic acid (**3**) can be prepared directly starting from glucose and other renewable carbon sources, using metabolically deregulated, recombinant *E. coli* strains. With these strains at hand, which are both nonpathogenic and are classified as S1 organisms according to German recombinant DNA regulations, it is now possible for the first time to produce **3** on a multigram scale in a cost-efficient manner. It is exceptionally advantageous that the product is free of metabolic impurities, so that it can be isolated easily. We are presently also working on the enantioselective access to derivatives of 3,4-*trans*-CHD through metabolic deregulation in recombinant microorganisms.

Experimental Section

Genes *entB* and *entC* were amplified in vitro by polymerase chain reactions (PCR) using chromosomal DNA of *E. coli* K-12 wild-type strain W3110. The oligonucleotides used were 5'-TATGGATCCACGCGCATCAGCCT-GAA-3' and 5'-GGGCTGCAGACATTTTACCCTG-3' for *entB* and 5'-GGCGAGCTCATTATTAAAGCCTTT-3' and 5'-TGCGGATCCTCGC-TCCTTAATGC-3' for *entC*. The resulting amplification products with



Scheme 2. Microbial production of **3** is possible starting from various renewable carbon sources. The values given refer to the production rates [mg h⁻¹ per g (dry cell mass)] obtained for cells of the *E. coli* strain AN193 with genes *entB/entC* in mineral salts medium with 10 g L⁻¹ substrate.

engineered restriction sites were inserted into the cloning plasmid pJF119EH1^[20] both separately or in tandem. Cloning sites were *Bam*HI and *Pst*I for *entB*, and *Sac*I and *Bam*HI for *entC*, respectively. The *E. coli* strains W3110, DH5 α , AN193, and H1882 were transformed with each of the resulting three plasmids.

Fermentations for product formation analysis were performed in a mineral salts medium (100 mL; pH 7 maintained by addition of 1N NaOH)^[10] in 1 L shake flasks. Cells from a 100 mL preculture in Luria–Bertani medium^[21] (containing 100 mg L⁻¹ ampicillin, 100 μ M isopropyl β -D-thiogalactopyranoside (IPTG) at an optical density (λ = 600 nm) of 2) were harvested in the mid-logarithmic phase and were resuspended in mineral salts medium (containing 100 mg L⁻¹ ampicillin, 100 μ M IPTG) and were incubated at 37 °C and 150 rpm. Product formation was monitored during a period of 10 h by HPLC analysis (maximal excretion was after ca. 4 h).

Mineral salts medium for optimized production and growth (derived from Pan et al.^[16]) contained per liter: KH₂PO₄ (13 g), K₂HPO₄ (10 g), NaH₂PO₄·2H₂O (6 g), (NH₄)₂SO₄ (2 g), MgSO₄·7H₂O (3 g), NH₄Cl (5 g), FeSO₄·7H₂O (40 mg), CaCl₂·2H₂O (40 mg), MnSO₄·2H₂O (10 mg), ZnSO₄·7H₂O (2 mg), AlCl₃·6H₂O (10 mg), CoCl₂·6H₂O (4 mg), Na₂MoO₄·2H₂O (2 mg), CuCl₂·2H₂O (1 mg), H₃BO₃ (0.5 mg), leucine (200 mg), proline (200 mg), adenine (200 mg), thiamine (20 mg), tryptophan (200 mg), 2,3-dihydroxybenzoic acid (20 mg), and ampicillin (100 mg).

The cultivation in a 30 L stirred tank bioreactor (Chemap, Switzerland, 20 L working volume) was performed at pH 6.8 (controlled) and 37 °C with optimized medium. 1 L preculture from complex medium served as inoculum. The initial concentration of glucose was 30 g L⁻¹. The carbon source was added in portions so that the concentration was maintained in the range of 5–10 g L⁻¹. Induction by addition of 100 μ M (final concentration) IPTG was at a cell concentration of 5 g L⁻¹ (dry cell mass). The aeration rate was regulated to 25 L min⁻¹(air).

The crude product was purified by column chromatography on silica gel 60 using ethyl acetate/MeOH (5/1) as eluent. Physical data of **3** (yellow solid): $[\alpha]_D^{25}$ = 3.8 (c = 0.6 in ethanol); ¹H NMR (300 MHz, [D₄]MeOH, 23 °C): δ = 4.10 (d, ³J(H,H) = 2.5 Hz, 1H; CHOH), 4.50 (d, ³J(H,H) = 2.5 Hz, 1H; CHOH), 6.20 (m, 2H; C=CH), 7.06 (dd, ³J(H,H) = 3.3 Hz, ⁴J(H,H) = 3.2 Hz, 1H; C=CH); ¹³C NMR (75 MHz, [D₄]MeOH, 23 °C): δ = 68.8 (CH), 70.4 (CH), 125.1 (CH), 130.8 (C_{quart}), 134.3 (CH), 134.4 (CH), 170.2 (COOH); IR (KBr): $\tilde{\nu}$ = 1699 cm⁻¹ (C=O), 1644 (C=C), 1586 (C=C), 1258, 1075, 1008; UV/Vis (H₂O): $\lambda_{max}(\epsilon)$ = 279 nm (4900); EI-MS (70 eV): m/z (%): 156 (6) [M^+], 138 (100) [M^+ - H₂O], 110 (63) [M^+ - 2H₂O], 93 (10), 82 (29), 65 (13) [C₅H₅⁺]; HR-MS: calcd for C₇H₈O₄: 156.0423; found: 156.0424.

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On the Aromatic Character of Electrocyclic and Pseudopericyclic Reactions: Thermal Cyclization of (2Z)-Hexa-2,4,5-trienals and Their Schiff Bases**

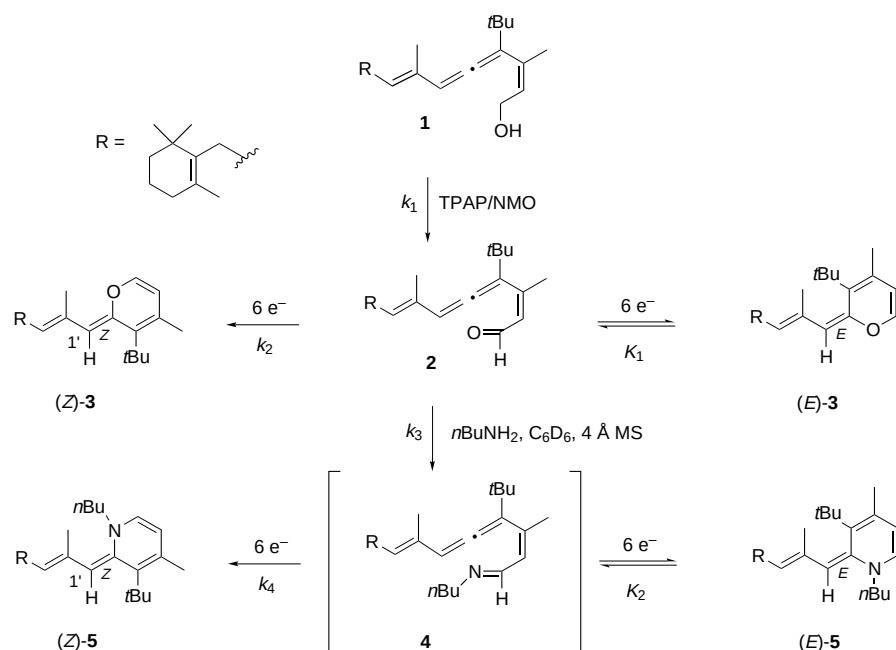
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Recent research on the magnetic characterization of aromaticity^[1] has, over the last few years, promoted the reexamination of the aromatic character of pericyclic reactions.^[2] This idea stems from the pioneering work of Evans,^[3a] Dewar,^[3b] and Zimmerman^[3c] and has been refined by Herges, Jiao, and Schleyer.^[2] Recently, we reported^[4] that the concept of in-plane (σ) aromaticity can be extended to several thermal pericyclic reactions. Within this context, we herein report several ring closures involving (2Z)-hexa-2,4,5-trienals and their corresponding imines (Scheme 1). These compounds are

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



Scheme 1. Synthesis and cyclization of the (2Z)-hexa-2,4,5-trienal **2** and its *N*-butyl Schiff base **4**. TPAP = tetrapropylammonium perruthenate, NMO = 4-methylmorpholine *N*-oxide, MS = molecular sieves.

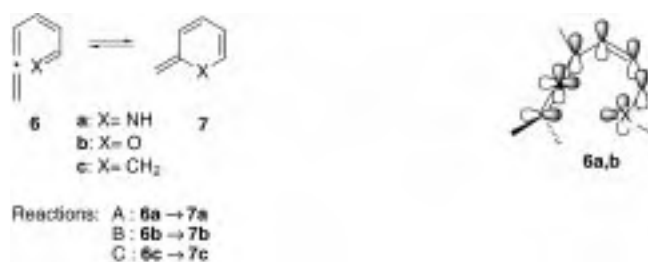
interesting model systems for the study of the chemistry of cumulenes and retinoids.^[5] A common feature of these systems is the presence of a cumulene bond and a heteroatom at one end of the interacting system. This electronic array allows for either one or two orbital disconnections, that is, regions where orthogonal sets of orbitals meet but do not overlap at the transition state associated with their cyclization (see Scheme 2). This situation constitutes a common feature of a subset of pericyclic reactions termed pseudopericyclic.^[6]

We have observed the facile electrocyclic ring closure of (2Z)-hexa-2,4,5-trienal **2** to alkylidene-2*H*-pyran **3**, which proceeds at room temperature upon oxidation of precursor (2Z)-hexa-2,4,5-trienol **1** (Scheme 1).^[7] Detailed kinetic analysis^[8] of the depicted transformation revealed that the divinylallenal **2**, obtained by oxidation of **1** with TPAP and NMO, experienced fast equilibration with the kinetically favored cyclized product, alkylidene-2*H*-pyran (*E*)-**3**, by a process which was interpreted as a sequence of electrocyclic ring-closure and electrocyclic ring-opening reactions. In contrast, the alternative cyclization of **2** leading to the thermodynamically most stable alkylidene-2*H*-pyran (*Z*)-**3** was irreversible. This isomer accumulated in the reaction mixture, becoming the only component after about 48 hours. We also carried out a similar study with the imine derivative. In order to minimize the competing O → C cyclization, the residue obtained upon oxidation was immediately treated with *n*-butylamine (2.0 equiv) in C₆D₆ in the presence of 4 Å molecular sieves. The reaction progress was followed by ¹H NMR spectroscopy.^[8] Upon standing in solution, the ¹H NMR spectra revealed the presence of only two components in a 93:7 ratio after 6 h (no change was detected upon doubling the reaction time). The minor component was identified as the previously characterized^[8] alkylidene-2*H*-pyran (*Z*)-**3**. The major component was shown to be its

nitrogen analogue, the *N*-butylalkylidene-2*H*-pyridine (*Z*)-**5**, which originates from the intermediate Schiff base **4**. Despite the fact that diagnostic signals (the imine hydrogen signal) for the putative Schiff base **4** were not detected in the ¹H NMR spectra throughout the entire experiment, it was considered likely to be an intermediate en route to (*Z*)-**5**. Moreover, close examination of the ¹H NMR spectra at low conversions indicates the presence of signals similar to those of (*Z*)-**5**, which decreased in intensity with time. By analogy to the O → C cyclization, those signals were interpreted as due to the kinetically favored (*E*)-alkylidene-2*H*-pyridine (*E*)-**5** in equilibrium with the putative Schiff base **4**. The cyclization of the imine **4** to (*Z*)-**5** must be irreversible under the reaction conditions, in keeping with the irreversibility of the competing cyclization of **2** to (*Z*)-**3**, but the former is more favorable. The rate constants for the N → C

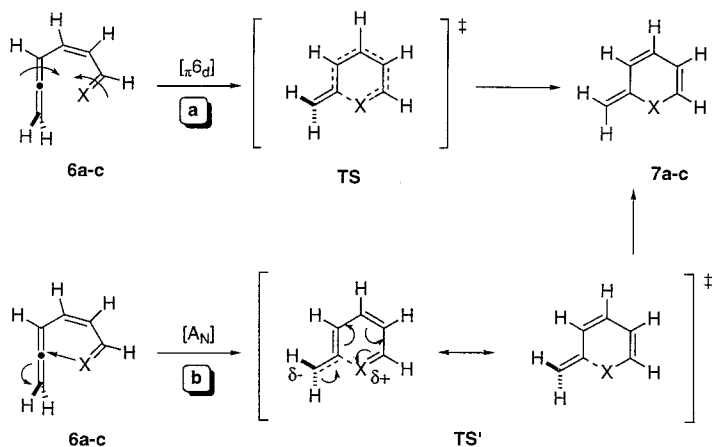
cyclization were shown to be higher than those of the O → C cyclization regardless of the solvent used (see below). The ¹H NMR spectroscopic monitoring and the kinetic analysis did not reveal the intervention of alternative mechanism(s) for the direct conversion of (*Z*)-**3** into (*Z*)-**5**, since heating a solution of isolated (*Z*)-**3** in C₆D₆ to 50 °C with excess *n*BuNH₂ led to the recovery of unaltered (*Z*)-**3**.

In order to understand the mechanistic nature of the above transformations, we have selected the model reactions A–C, the cyclizations of **6a–c** into **7a–c** (Scheme 2). These



Scheme 2. The model reactions A–C.

reactions can proceed through two possible mechanisms. The first, denoted as (a) in Scheme 3, consists of a disrotatory thermal electrocyclization via the transition state **TS**. The second mechanism, denoted as (b) in Scheme 3 involves a nucleophilic addition of the heteroatom lone pair onto the sp²-hybridized carbon atoms of **6a** and **6b**. According to this latter mechanism an appreciable negative charge at the exocyclic carbon atom of **TS'** should be expected. This latter mechanism consists of a pseudopericyclic process since orbital symmetry is not involved and the corresponding transition structure must be planar or nearly planar.^[6b–f]



Scheme 3. Mechanisms of the disrotatory thermal electrocycization (a) and the pseudopericyclic reaction (b).

We have computed the reaction profile associated with the **6a-c**→**7a-c** transformations at the B3LYP/6-31+G*+ΔZPVE level.^[9] In all cases, we have found only one transition structure connecting both stationary points. The chief features of **TSa-c** are depicted in Figure 1. The

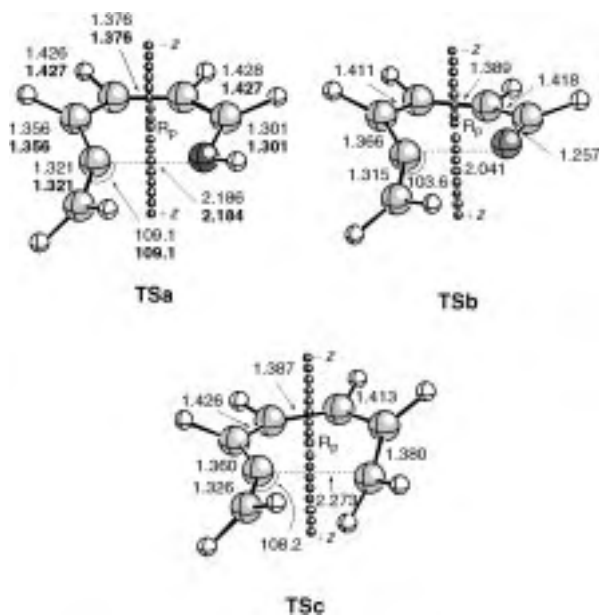


Figure 1. Main geometric features of **TSa-c** computed at the B3LYP/6-31+G* (numbers printed in normal text) and B3LYP(SCIPCM)/6-31+G* (in toluene; bold numbers) levels. Lengths and angles are given in Å and degrees, respectively. R_p stands for the (3,+1) ring point of electron density. The small spheres correspond to the points used in the evaluation of the NICS values (see text).

harmonic analysis of **TSa** reveals that the nuclear motion corresponding to the imaginary frequency of its diagonalized Hessian matrix has no component associated with rotation of the N1-H group with respect to the N1-C2 bond being formed. Instead, aside from indicators for a N1...C2 stretching interaction, there is a component associated with rotation of the exocyclic H-C7 groups with respect to the C2-C7 bond. This rotation corresponds to the rehybridization of the C2 atom and therefore is not associated with disrotatory

motion. In addition, the natural bond orbital (NBO) analysis reveals a charge of $-0.22 e$ at the C7 atom, a value in agreement with the electron distribution expected for the structure of **TS'**. All these data indicate that the mechanism of this reaction is the nucleophilic addition depicted in pathway (b) of Scheme 3. **TSb** exhibits similar geometric and electronic features, except that in this case the oxygen atom does not have any substituents so the absence of rotation around the O1-C2 bond cannot be observed in the corresponding imaginary frequency. In contrast, **TSc** exhibits disrotatory motion in its imaginary frequency, as well as no significant charge redistribution.

We have also tested the dependence of the activation barriers of reactions A-C with the polarity of the solvent. The results are reported in Table 1. All three model trans-

Table 1. Distance R_0 [Å] of the aromaticity with an average radius R_{av} [Å], maximum NICS values^[a] [ppm mol⁻¹], maximum diamagnetic shieldings^[b] σ_{max}^d [ppm mol⁻¹], and activation energies^[c] ΔE_a [kcal mol⁻¹] for transition structures **TSa-c**, as well as the reaction energies^[c] ΔE_{rxn} [kcal mol⁻¹] for reactions A-C.

Parameter	TSa	TSb	TSc
R_0	0.60	0.76	0.38
R_{av}	1.35	1.20	1.25
NICS _{max}	-7.75	-6.80	-13.64
σ_{max}^d	-10.44	-11.74	-11.57
ΔE_a ($\epsilon = 1.00$)	6.4	8.6	17.4
ΔE_a ($\epsilon = 3.39$)	6.3	9.0	17.4
ΔE_a ($\epsilon = 20.56$ (acetone))	6.2	9.4	17.6
ΔE_{rxn} ($\epsilon = 1.00$)	-40.6	-22.1	-29.1

[a] Calculated at the B3LYP-GIAO/6-31+G* level. [b] Calculated according to Equations (1) and (2). [c] Calculated at the B3LYP/6-31+G*+ΔZPVE and B3LYP(SCIPCM)/6-31+G*/B3LYP(L1A1)/6-31+G*+ΔZPVE levels.

formations exhibit low solvent effects. In reactions B and C the activation energies increase when the polarity of the solvent increases. In the case of reaction A, the polarity of **TS'a**, as well as the ability of the nitrogen atom to accommodate the partial positive charge, accounts for the lowering of the activation energy with the polarity of the solvent. These predictions were corroborated experimentally: Solutions of aldehyde **2**, prepared as described above, in different deuterated solvents were treated with *n*BuNH₂ (1.1 mole equiv) in the presence of 4 Å molecular sieves, and ¹H NMR spectra were measured at room temperature to determine rate constants. Figure 2 depicts the dependence of the experimentally determined reaction rates on the polarity of the solvent according to the E_N^T (normalized empirical solvent polarity) parameter.^[10] Similar linear plots were obtained when ln*k* was represented against the Onsager function $(\epsilon - 1)/(2\epsilon + 1)$, with slopes of opposite sign obtained for the **2**→**3** and **4**→**5** cyclizations.

We have also investigated the aromatic character of **TSa-c** by computing the nucleus-independent chemical shifts (NICS)^[11] at the (3,+1) ring critical point of electron density as defined by Bader.^[12] In general, large negative NICS values are associated with aromatic character.^[1b, 11] We report in Figure 3 the NICS values computed along the *z*-axis defined by the points depicted in Figure 1. The NICS values along the

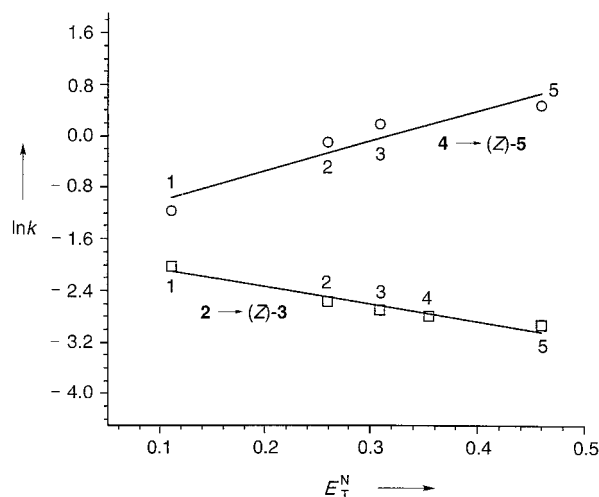


Figure 2. Plot of $\ln k$ versus the solvent parameter E_T^N for the electrocyclizations **2**→**3** and **4**→**5**. 1: Benzene ($E_T^N = 0.111$), 2: chloroform ($E_T^N = 0.259$), 3: dichloromethane ($E_T^N = 0.309$), 4: acetone ($E_T^N = 0.355$), 5: acetonitrile ($E_T^N = 0.460$). Rate constants [h^{-1}] for the **2**→**3** and **4**→**5** reactions, respectively: in benzene: $0.13 (\pm 0.02)$ and $0.31 (\pm 0.02)$, in chloroform: $0.08 (\pm 0.01)$ and $0.90 (\pm 0.10)$, in dichloromethane: $0.07 (\pm 0.01)$ and $1.19 (\pm 0.11)$, in acetone $0.05 (\pm 0.01)$ and not determined, acetonitrile $0.05 (\pm 0.01)$ and $1.61 (\pm 0.09)$.

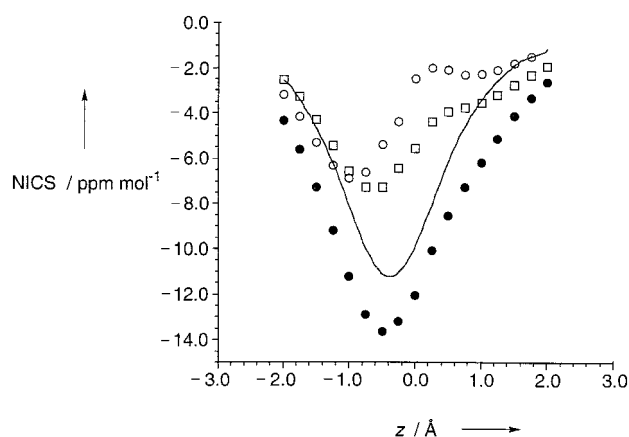


Figure 3. Plot of the calculated NICS versus z for transition structures **TSa** ($\square$), **TSb** ($\circ$), and **TSsc** ($\bullet$). The NICS values have been obtained at the GIAO-SCF/6–31G*/B3LYP/6–31G* level. The z axis has been defined as depicted in Figure 1. The continuous line is the σ_{zz}^d versus z curve for **TSsc**, calculated with Equations (1) and (2) and the values reported in Table 1.

z -axis in pseudopericyclic reactions A and B are different to those computed for the electrocyclic reaction C. In **TSa**, **b** the NICS_{max} values are significantly less negative than for **TSc** (Table 1). In addition, for reaction C the NICS values decrease in negativity monotonously along the z -axis in the region $z > R_0$, whereas in **TSa**, **b** they do not. Indeed, in **TSb** a second local negative maximum (in absolute value) is reached at $z = 0.8 \text{ \AA}$ (See Figure 3).

We have previously demonstrated^[4] that the aromatic character of one given transition structure or stable molecule can be described by means of the ring current model. In general, for a ring current of R_{av} radius and circulating at a certain distance R_0 above the average molecular plane, the variation of the diamagnetic shielding σ_{zz}^d along the axis perpendicular to such a plane can be described by Equations (1) and (2). In these equations σ_{max}^d stands for the maximum (absolute value) diamagnetic shielding.

tions (1) and (2). In these equations σ_{max}^d stands for the maximum (absolute value) diamagnetic shielding.

$$\sigma_{zz}^d = \sigma_{\text{max}}^d \left[1 + \left(\frac{z - R_0}{R_{\text{av}}} \right)^2 \right]^{-3/2} \quad (1)$$

$$\sigma_{\text{max}}^d = -\frac{e^2 \mu_0}{8\pi m_e} R_{\text{av}}^{-1} \quad (2)$$

As shown in Table 1, the σ_{max}^d value obtained for **TSc** is similar, although slightly smaller, than the corresponding NICS_{max} value. Moreover, the variation of the NICS and the σ_{zz}^d values along the z -axis is similar in both cases (Figure 3). This indicates that the ring current model accounts for approximately 85% of the total diamagnetic shielding observed in **TSc**, and that local effects do not vary significantly along the z -axis. Thus we can conclude that **TSc** is aromatic. In contrast, in both **TSa**, **b** neither the NICS_{max} values nor the variation of the NICS and σ_{zz}^d values along the z -axis agree with the behavior described by Equations (1) and (2). In addition, the NICS_{max} values are lower than those predicted by the ring current model for σ_{zz}^d . These results indicate that in both **TSa**, **b** the diamagnetic effects reported in Figure 3 and in Table 1 are due to local effects induced by the heteroatoms and π bonds.

The ring current model and the magnetic criteria permit a clear distinction between disrotatory electrocyclic reactions, which are associated with aromatic structures, and pseudopericyclic reactions, which are not. We can therefore confirm the suggestion we made in previous papers^[4] that the behavior of the diamagnetic shielding along the axis perpendicular to the average molecular plane is useful for distinguishing between different types of aromaticity. Thus, in σ aromaticity there is a maximum diamagnetic shielding at the ring point of electron density (Figure 4). This kind of aromaticity is found in highly planar transition structures involving formation of σ bonds, for example in [3+2] and [2+2+2] cycloadditions. In contrast, in the usual π aromaticity the maximum diamagnetic shielding takes place at a certain distance above and below the

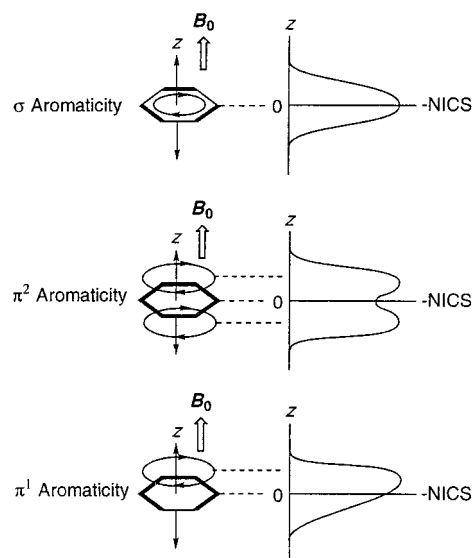


Figure 4. Schematic definition of different types of aromaticity according to the behavior of the diamagnetic shielding along the axis perpendicular to the molecular plane and containing the ring point of electron density.

molecular plane (Figure 4). This effect can be described by means of two ring currents circulating at a certain distance of the molecular plane. In this paper, instead, we have observed one highly aromatic disrotatory ring closure in which there is only one maximum diamagnetic shielding above the molecular plane. In a formal sense this transition structure corresponds to π aromaticity involving only one ring current circulating on the side where the disrotatory movement allows a close proximity between the terminal p atomic orbitals (pAO). We therefore propose the terms π^1 aromaticity and π^2 aromaticity to describe these two different kinds of aromatic transition structures.

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Stereoselective Formation of C_2 -Symmetric ansa-Lanthanocenes by Reductive Coupling of Acenaphthylene with Activated Ytterbium or Samarium**

Igor L. Fedushkin,* Sebastian Dechert, and Herbert Schumann*

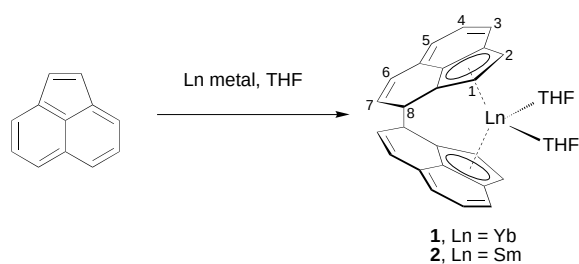
Dedicated to Professor Jörn Müller on the occasion of his 65th birthday

C_2 -symmetric ansa-metallocenes have been studied intensively because of their potential use as catalysts for stereoselective olefin polymerization processes.^[1] Edelmann et al. and, later on, Shapiro et al. and Eisch et al. reported on a method to synthesize interannular ethano-bridged ansa-metallocenes by the reductive coupling of 6-substituted or 6,6'-disubstituted fulvenes with metallic calcium, lanthanide metals, or the dihalides of titanium and zirconium.^[2] The reaction with 6-substituted fulvenes results in the formation of mixtures of *rac* and *meso* isomers. The exclusive formation of just one isomer by fulvene-type coupling has not yet been observed.^[2e] The synthesis of ansa-metallocenes from bridged cyclopentadienyl dianions also produces only mixtures of isomers of variable *rac:meso* ratios.^[3] We now suggest that the reductive coupling of a ligand in which the coupling exocyclic carbon atom of the fulvene moiety is fixed by incorporation into a condensed aromatic ring system such as in acenaphthylene (acene) would probably allow the isolation of an isomerically pure ansa-metallocene. Acene combines one five- and two six-membered rings and its resonance structures reveal the fulvene pattern. The only reductive coupling process of acene known so far is its reaction with [V(CO)₆] which produces the double half-sandwich vanadium complex (μ_2 - η^5 : η^5 -C₂₄H₁₆)[V(CO)₄]₂.^[4] Here we report the reductive coupling of acene by activated metallic ytterbium and samarium, which yields the respective C_2 -symmetric *trans-ansa-lanthanocenes*.

The high electron affinity of acene ($E_{1/2} = -1.65$ V)^[5] allows its reduction with activated metallic ytterbium or samarium, affording the ansa-lanthanocenes [$(\eta^5$ -C₁₂H₈)₂Ln(thf)₂] as dark red (Ln = Yb, **1**) or dark brown crystals (Ln = Sm, **2**) in yields of about 90% (Scheme 1). The ytterbium and samarium are activated by addition of iodine to the respective

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Scheme 1.

suspension of the metal in THF. The release of two electrons from each metal atom leading to the formation of Ln^{II} ions, uptake of one of these electrons per acene molecule, dimerization of the acenyl radicals to give biacenyl dianions, and coordination of the two cyclopentadienyl ring units of the dianion to the Ln^{II} ion are expected as the reaction steps on the way to the isolated ansa-metalloocene complexes.

According to the two different possibilities for the orientation of the two acenyl ring units of the ligand, C_s -symmetric *meso*- and/or C_2 -symmetric *rac*-ansa complexes may be expected. In contrast to the results of the reductive coupling of indenylidenes with metallic calcium^[2c,e] or titanium and zirconium dihalides,^[2d] the described coupling of acene with Yb or Sm, exclusively gives the respective C_2 -symmetric *trans-rac*-ansa complex as confirmed by ^1H NMR spectroscopic measurements and X-ray diffraction analysis of **1** and **2**.

The ^1H NMR spectrum of **1** in $[\text{D}_8]\text{THF}$ shows only one set of eight resonances for the ring protons. Compound **1** could not be characterized by ^{171}Yb NMR spectroscopy because it was not sufficiently soluble in THF or in toluene. As expected, the ^1H NMR signals of the paramagnetic samarium complex **2** in the range from $\delta = 17$ to -10 are broadened, thus preventing the observation of $^1\text{H}-^1\text{H}$ couplings. However, a clear assignment of the ^1H NMR spectrum of **2** could be achieved by $^1\text{H}-^1\text{H}$ COSY experiments and by comparison with the $^1\text{H}-^1\text{H}$ coupling scheme of the diamagnetic complex **1**.

The molecular structures of **1** (Figure 1) and **2** (Figure 2) were determined by single-crystal X-ray diffraction^[6] on crystals obtained from THF. Both complexes crystallize in a centrosymmetric space group, **1** in $P\bar{1}$ and **2** in $P2_1/c$, each with four molecules (two pairs of *R,R* and *S,S* enantiomers) in the unit cell. The two crystallographically independent molecules in **1** show very similar molecular parameters. The lanthanide atoms in **1** and **2** are coordinated to the two cyclopentadienyl units of the biacenyl ligand and to two THF molecules in a distorted tetrahedral fashion with the THF molecules lying in the equatorial wedge of the ansa-lanthanocene moiety. The ansa-metalloocene unit of both **1** and **2** is rather constrained as seen by the $C_g\text{-Ln-}C_g$ angles (C_g defines the center of the five-membered ring units of the ligand) of 119.8° for **1** and 115.0° for **2**. Unexpectedly, these $C_g\text{-Ln-}C_g$ angles are smaller than those of the two-atom bridged ethylenebis(indenyl)(ebi) complexes [(*meso*-ebi)YbN(SiMe₃)₂]^[3] (122.0°) and [(*meso*-ebi)ZrCl₂]^[11] (125.4°) which are already considered as strained molecules. Generally, the $C_g\text{-Ln-}C_g$ angle decreases with increasing size of the metal cation, which in the case of **2** leads to a pronounced slippage of the samarium atom from

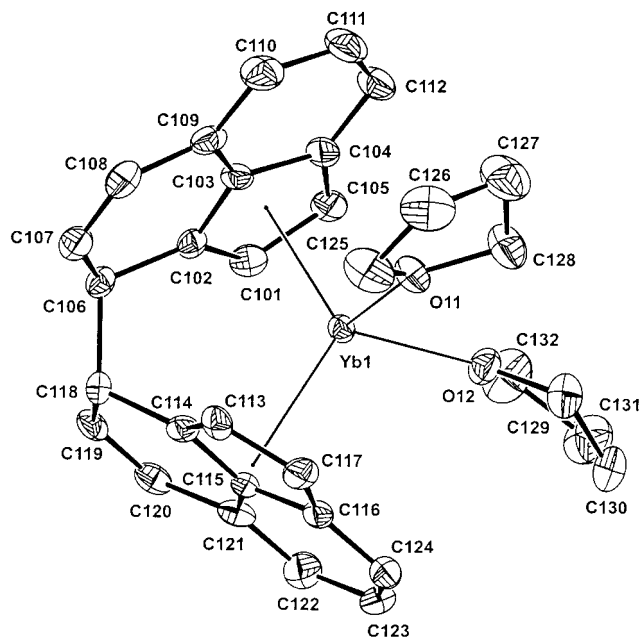


Figure 1. Molecular structure (ORTEP drawing) of one of the two crystallographically independent molecules of **1** (thermal ellipsoids drawn at the 50% probability level). Hydrogen atoms are omitted for clarity. Relevant bond lengths [Å] and angles [$^\circ$]: Yb1- $C_g(1)$ 2.4436(18), Yb1- $C_g(2)$ 2.449(2), Yb1-O11 2.396(3), Yb1-O12 2.364(3), Yb1-C101 2.721(4), Yb1-C102 2.688(4), Yb1-C103 2.705(5), Yb1-C104 2.759(5), Yb1-C105 2.752(4), Yb1-C113 2.714(4), Yb1-C114 2.725(4), Yb1-C115 2.740(5), Yb1-C116 2.759(5), Yb1-C117 2.709(4); $C_g(1)\text{-Yb1-}C_g(2)$ $119.18(6)$, O11-Yb1-O12 $92.91(12)$, $C_g(1)\text{-Yb1-O11}$ $112.89(10)$, $C_g(1)\text{-Yb1-O12}$ $110.20(10)$, $C_g(2)\text{-Yb1-O11}$ $106.74(9)$, $C_g(2)\text{-Yb1-O12}$ $111.79(10)$; ring slippage [Å]: 0.082 ($C_g(1)$), 0.019 ($C_g(2)$).

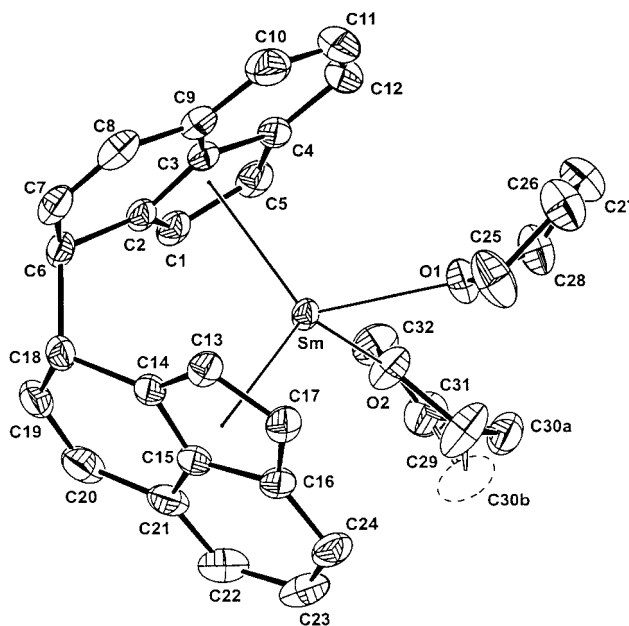


Figure 2. Molecular structure (ORTEP drawing) of **2** (thermal ellipsoids drawn at the 50% probability level). Hydrogen atoms are omitted for clarity. Relevant bond lengths [Å] and angles [$^\circ$]: Sm- $C_g(1)$ 2.5643(10), Sm-O1 2.5167(18), Sm-C1 2.834(2), Sm-C2 2.852(2), Sm-C3 2.827(2), Sm-C4 2.835(2), Sm-C5 2.827(2), Sm- $C_g(2)$ 2.5686(11), Sm-O2 2.5483(18), Sm-C13 2.879(3), Sm-C14 2.825(2), Sm-C15 2.779(2), Sm-C16 2.831(2), Sm-C17 2.876(2); $C_g(1)\text{-Sm-}C_g(2)$ $115.04(4)$, O1-Sm-O2 $83.47(6)$, $C_g(1)\text{-Sm-O1}$ $117.12(5)$, $C_g(2)\text{-Sm-O1}$ $111.82(5)$, $C_g(2)\text{-Sm-O2}$ $120.91(5)$, $C_g(1)\text{-Sm-O2}$ $104.90(5)$; ring slippage [Å]: 0.022 ($C_g(1)$), 0.124 ($C_g(2)$).

the center of one of the two cyclopentadienyl rings (0.124 Å). The C_g-Ln-C_g angles of the less constrained five-atom-bridged bis(indenyl)lanthanocenes $[\{O(CH_2CH_2C_9H_6)_2\}LnCl(thf)]^{[12]}$ (131.4° Ln = Nd, 132.3° Gd, 132.6° Ho) are larger and show little dependence on the size of the central metal cation.

It is expected that **1** and **2** will be useful as reducing agents due to the presence of minor quantities of uncoupled acene radical anionic species in solution, detected by ESR spectroscopy. Reactivity studies of both complexes are in progress.

Experimental Section

All manipulations were performed under nitrogen atmosphere or in vacuum. Elemental analyses were obtained by using a Perkin-Elmer Series II CHNS/O 2400 Analyzer, NMR spectra were recorded on a Bruker ARX 200 instrument. The commercially available acenaphthylene (Aldrich; purity 75%) was purified further to 85% (10 to 15% acenaphthene as impurity) by sublimation (80/10⁻¹ Torr). The given quantities of acenaphthylene and the yields of the products refer to pure acenaphthylene.

1: A mixture of ytterbium metal (7.8 g, 45 mmol) and iodine (1.85 g, 14.6 mmol) in THF (30 mL) was stirred for 1 h at 50 °C, and the resulting suspension of YbI₂ was decanted off. The residual activated metal was washed with warm THF (2 × 30 mL), and then a solution of acenaphthylene (1.23 g, 6.37 mmol) in THF (50 mL) was added. The mixture was stirred for 1 h at reflux. The warm, dark red-brown solution was filtered and then concentrated to 15 mL which yielded **1** as dark red almost black crystals. Yield: 2.34 g (93%); m.p. > 180 °C (decomp); ¹H NMR (200 MHz, [D₈]THF, 20 °C, TMS): δ = 6.87 (d, ³J(H,H) = 8.26 Hz, 2H; CH, H³), 6.65 (dd, ³J(H,H) = 9.7, 2.0 Hz, 2H; CH, H⁶), 6.45 (dd, ³J(H,H) = 8.24, 8.26 Hz, 2H; CH, H⁴), 6.29 (s, 2H; CH, H¹), 6.26 (d, ³J(H,H) = 4.54 Hz, 2H; CH, H⁵), 6.02 (dd, ³J(H,H) = 9.7, 3.56 Hz, 2H; CH, H⁷), 5.59 (d, ³J(H,H) = 3.14 Hz, 2H; CH, H²), 4.45 (s, 2H; CH, H⁸), 3.71 (m, 8H; CH₂), 1.59 (m, 8H; CH₂); elemental analysis (%): calcd for C₃₂H₃₂O₂Yb (621.62): C 61.83, H 5.19; found: C 60.79, H 4.25.

2: The dark brown crystalline compound **2** was prepared as described for **1** using samarium (4.2 g, 28 mmol), iodine (1.3 g, 10.24 mmol), and acenaphthylene (0.76 g, 5 mmol) in THF (50 mL). Yield: 1.34 g (90%); m.p. > 180 °C (decomp); ¹H NMR (200 MHz, [D₈]THF, 20 °C, TMS): δ = 17.67 (s, 2H; CH, H³), 15.52 (s, 2H; CH, H¹), 12.84 (s, 2H; CH, H⁶), 12.01 (s, 2H; CH, H⁴), 6.89 (s, 2H; CH, H²), 5.12 (s, 2H; CH, H⁵), 3.6 (s, 8H; CH₂), 1.73 (s, 8H; CH₂), 0.72 (s, 2H; CH, H⁷), -9.88 (s, 2H; CH, H⁸); elemental analysis (%): calcd for C₃₂H₃₂O₂Sm (598.93): C 64.17, H 5.38; found: C 63.37, H 5.42.

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0.08 Å²) at calculated positions. The PLATON^[10] program was used for the geometric analysis of the structures. Data collection for **1**: crystal dimensions 0.48 × 0.30 × 0.04 mm, triclinic, space group P $\bar{1}$, a = 8.1967(1), b = 15.6420(3), c = 19.9504(2) Å, α = 81.668(1), β = 83.920(1), γ = 89.921(1)°, V = 2516.41(6) Å³, Z = 4, ρ_{calcd} = 1.641 × 10³ kg m⁻³, μ = 3.744 mm⁻¹, F(000) = 1240, 2.08° ≤ 2θ ≤ 55.0°, -10 ≤ h ≤ 10, -20 ≤ k ≤ 20, -25 ≤ l ≤ 24, 19188 data collected, 11429 unique data (R_{int} = 0.0438), 8209 data with I > 2σ(I), 631 refined parameters, GOF(F²) = 0.925, final R indices (R₁ = Σ||F_o| - |F_c||/Σ|F_o|, wR₂ = [Σw(F_o² - F_c²)²/Σw(F_o²)^{1/2}]: R₁ = 0.0348, wR₂ = 0.0658; max./min. residual electron density 1.203/-1.597 e Å⁻³. Data collection for **2**: crystal dimensions 0.50 × 0.42 × 0.22 mm, monoclinic, space group P2₁/c, a = 17.8614(3), b = 8.6231(1), c = 16.4556(2) Å, β = 96.452(1)°, V = 2518.45(6) Å³, Z = 4, ρ_{calcd} = 1.580 × 10³ kg m⁻³, μ = 2.359 mm⁻¹, F(000) = 1208, 2.30° ≤ 2θ ≤ 55.0°, -23 ≤ h ≤ 23, -11 ≤ k ≤ 8, -20 ≤ l ≤ 21, 18413 data collected, 5780 unique data (R_{int} = 0.0374), 4938 data with I > 2σ(I), 326 refined parameters, GOF(F²) = 1.024, final R indices (R₁ = Σ||F_o| - |F_c||/Σ|F_o|, wR₂ = [Σw(F_o² - F_c²)²/Σw(F_o²)^{1/2}]: R₁ = 0.0240, wR₂ = 0.0537; max./min. residual electron density 0.692/-0.641 e Å⁻³. The C30 carbon atom of one of the THF molecules in **2** is disordered about two positions, with occupancy factors of 0.627(18) and 0.373(18). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-149098 (**1**) and CCDC-149099 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Fabrication and Properties of Gold Single-Crystal Ultramicroelectrodes**

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Ultramicroelectrodes (UMEs) are important in electrochemistry and electroanalysis because of the special mass transfer conditions observed with respect to those at electrodes of normal dimensions.^[1] This property has been used to facilitate the measurement of very fast electron transfer kinetics, a well-known example being the electrooxidation of ferrocene.^[2] On the other hand UMEs made from metals in the usual way are necessarily polycrystalline in nature. As a

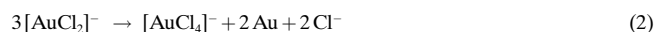
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result, the crystallinity of the electrode and therefore its double-layer properties can vary from electrode to electrode. This fact prevents assessment of the role of interfacial properties in the kinetics of very fast electron transfer processes.

Electrochemical methods for determining slow electron transfer kinetics at gold single-crystal electrodes with well-defined surface properties are now well established.^[3] Gold single-crystals are usually prepared by the Czochralski method or by zone melting and cut with the aid of an X-ray goniometer to expose a face of known crystallographic orientation.^[4] On the other hand it is well known that gold single crystals of nano- and microdimensions can be prepared by techniques involving the use of silicate gels.^[5] An important example is the method described by Kratochvil et al.^[6] which yields thin platelike gold crystals with a (111) orientation on the face. The microcrystals have hexagonal or triangular shapes with effective disc diameters d_{eff} ^[7] between 5 and 200 μm , and a thickness between 0.05 and 0.1 μm . We have fabricated single-crystal UMEs (SCUMEs) using these microcrystals but their thinness makes them fragile and difficult to work with.

Herein we outline a new electrochemical technique for preparing robust Au crystals with mainly (100) and (111) facets in a silicate gel. The gel is formed at low pH with HCl and HAuCl_4 as components. When a small current is passed through the gel between two gold electrodes, Au metal is deposited at the cathode and Cl_2 gas is formed at the anode. Surprisingly, Au crystals are observed in the vicinity of the anode after 24 h. Cl_2 reacts with the Au of the anode to form a metastable Au^{I} complex [Eq. (1)],^[8] which disproportionates further from the anode [Eq. (2)].^[9] The conditions for nucleation and growth of the gold crystals are established by the gel and its pH value.^[5]



A representative sample of microcrystals harvested from the electrochemical cell is shown in Figure 1. The crystals are mainly triangular (b, e) or hexagonal plates (a) with a (111) orientation on the main plane. Rectangular faces (d) correspond to a (100) orientation. The crystals can be further characterized by using an atlas of crystal forms.^[10] The surfaces were smooth on an atomic level without visible terraces or steps when examined with a scanning electron microscope. The density of the gel plays an important role in determining crystal quality.

A selected microcrystal was first attached to a gold microwire using a gold paint which can be converted to metallic gold on heating. It was then aligned under a microscope using a specially designed micromanipulator (Figure 2) with which the operating face of the crystal was set parallel to the microscope table. The crystal and connecting wire were then insulated with epoxy cement so that only the working face was exposed. Figure 3 shows a hexagonal microcrystal with a d_{eff} close to 10 μm mounted for use as a SCUME on a 10 μm wire.

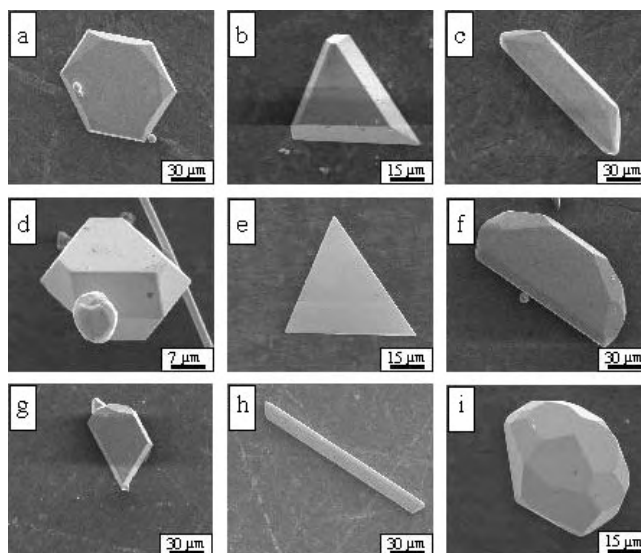


Figure 1. Scanning electron microscope images showing the variety of microcrystals grown in an electrochemical cell containing the silica gel.

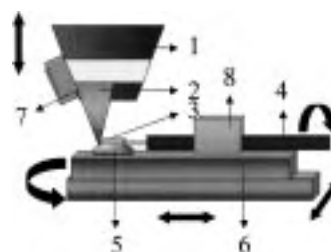


Figure 2. Schematic diagram of the micromanipulator used to attach, align and insulate the SCUME: 1) microscope lens; 2) metal tip used with the epoxy resin; 3) Au microcrystal; 4) copper wire; 5) epoxy resin; 6) stand which is fixed to the microscope table; 7, 8) holders for the copper wire. Two positioning screws were used to achieve exact horizontal orientation of the working face of the Au microcrystal before it was surrounded by insulating epoxy resin.

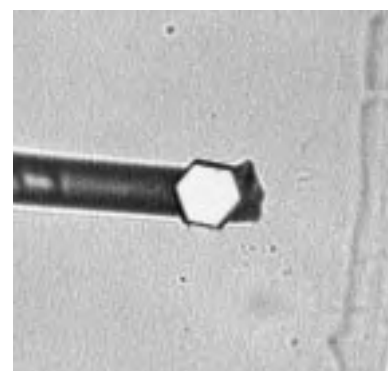


Figure 3. Optical microscope image of a hexagonal Au (111) microcrystal with $d_{\text{eff}} \approx 10 \mu\text{m}$. The crystal has been attached to a 10 μm Au microwire clearly visible in the background and surrounded from all sides by insulating epoxy resin to a level equal to the height of the crystal.

The electrochemical behavior of the SCUMEs having a (111) orientation was compared with that of a gold (111) single-crystal electrode of usual dimensions ($d_{\text{eff}} = 0.145 \text{ cm}$). The current–voltage curve has a characteristic shape in the positive region which is used to identify the orientation of the

surface and confirm that single-crystal quality has been maintained during the surface preparation steps. In the case of a (111) crystal face three anodic peaks are observed in the positive-going sweep, and a large reduction peak corresponding to reduction of gold oxide on the negative sweep (Figure 4a). The corresponding results for a SCUME with a

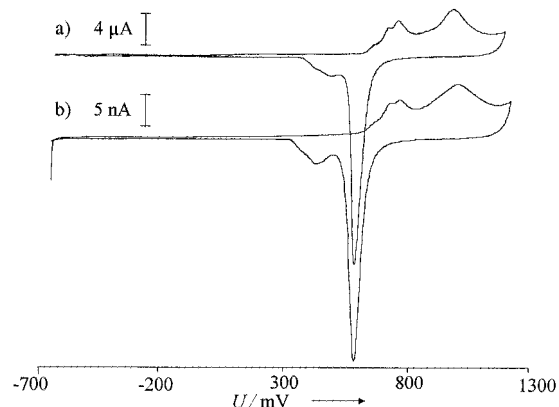


Figure 4. a) Cyclic voltammogram at a Au(111) single crystal with an area of 0.066 cm² recorded in 0.093 M HClO₄ at 20 mV s⁻¹; b) cyclic voltammogram at a Au (111) SCUME with an area of 3500 μm² recorded in 0.01 M HClO₄ at 50 mV s⁻¹.

d_{eff} of 33 μm are shown in Figure 4b. The current is approximately 1000 times smaller than that at the macroelectrode but the features of the current–voltage curve are essentially the same. In the case of the SCUME the electrode must be cycled into the hydrogen evolution region to ensure that the gold oxide is completely reduced in subsequent cycles. On the first cycle for the SCUME, only one oxide formation peak was observed at +1.1 V; on subsequent cycles this peak diminished and shifted in the positive direction. Eventually three oxide formation peaks were observed at +0.65, +0.70, and +0.76 V, just as with the macroelectrode. The double-layer region remains flat indicating that leakage of electrolyte around the microcrystal is not a problem.

Figure 5 shows cyclic voltammograms at an electrode with a d_{eff} of 5 μm for scan rates of 50, 100, and 150 mV s⁻¹. The characteristic features in the oxide formation region only develop clearly at higher scan rates with only two current peaks observed in the positive-going sweep. Otherwise the current–voltage characteristics are the same as those at the SCUME with a d_{eff} of 33 μm, but with currents below 1 nA.

Thus we have produced SCUMEs which are sufficiently small that they could be used to study the kinetics of very fast electron transfer reactions. Work has been carried out with both Au(111) and Au(100) crystal faces. Much more will be done to characterize these systems using established methods,^[11] for example to study the surface properties using scanning tunneling microscopy and impedance spectroscopy. This will allow a more detailed assessment of surface imperfections such as steps. The method is also being extended to other coinage metals, specifically, silver.

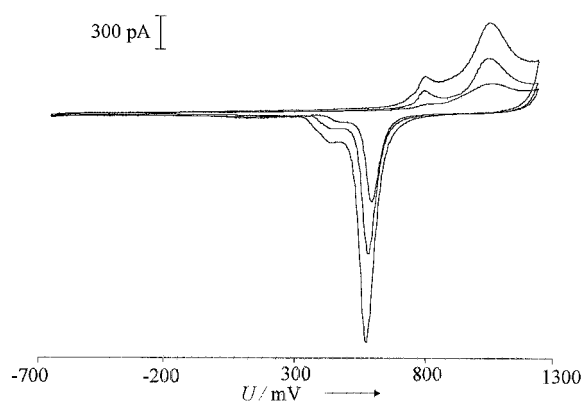


Figure 5. Cyclic voltammograms at a Au (111) SCUME with an area of 80 μm² recorded in 0.01 M HClO₄ at 50, 100, and 150 mV s⁻¹. The current increases with increasing scan rate.

Experimental Section

An excess of pure gold wire (99.99%) was dissolved in hot aqua regia (90 °C). The resulting solution of HAuCl₄ was filtered to remove the undissolved gold after cooling to room temperature. The resulting saturated solution of HAuCl₄ was added dropwise to a solution of sodium metasilicate (Aldrich, $\rho = 1.05 \text{ g cm}^{-3}$) until the HAuCl₄ concentration reached 0.2 M. Then 1 M HCl was added dropwise until the pH value reached 1.0. The solution was then poured into a 2 mL glass test tube which had a gold wire sealed into its bottom. The high HCl concentration in the gel provided the best conditions for microcrystal formation but the gel was formed only after a rather long time (~3 weeks) during which ~35% of the water evaporated.^[12] After the gel was formed a second gold electrode was placed at the top of the glass tube and a current of 14 μA was passed through the cell for three weeks using a 1.5 V battery with a 107 kΩ resistor in series with the cell. The current density at the anode was typically 90 μA cm⁻². Gold crystallites were observed in the vicinity of the anode after one day, but they were harvested after operating the cell for two weeks, that is, after they had reached the optimum size for the present experiments. The gel was then dissolved in 5 M KOH to free the microcrystals which were then thoroughly washed with ultrapure water. They were pipetted as a suspension in the ultrapure water onto a glass slide and the water was allowed to evaporate. After sorting under a microscope, a microcrystal having the desired facet without visible steps or deformations was selected for incorporation in a SCUME.

Attachment of the microcrystal to a gold microwire and alignment were performed in the micromanipulator (Figure 2). Initially a 1 cm length of the gold microwire (10 μm diameter, JMC Puratronic) was soldered to a longer length of copper wire (1 mm diameter). The copper wire was then placed in the holder (7) of the micromanipulator such that the tip of the microwire was exactly in the focus of the microscope. Then the tip was dipped into an organometallic gold paint (Glassgold, Engelhardt) and the selected microcrystal sitting on the glass slide was attached to the painted tip by applying gold paint on one face. Contact between the painted tip and the painted face was achieved by lowering the microscope lens (1). The electrode system was then carefully annealed above a small gas-oxygen flame until all the paint was converted to metallic gold, thereby establishing an all-gold contact between the wire and the crystal. The copper wire was then placed in the holder (8) of the micromanipulator until the desired working crystal face was perfectly aligned in a horizontal position. This was confirmed by reflection of the microscope light source on the working face of the microcrystal.

The final step in the fabrication process was to insulate the conducting parts of the system using epoxy cement so that only the working face was exposed. In the case of the flat trigonal and hexagonal crystal with a (111) face, a drop of epoxy (Devcon, 2-Ton) was placed under the crystal and allowed to harden sufficiently such that the crystal would float on its surface. In this way the back and sides were completely covered and the exposed face was embedded in a smooth epoxy resin background which was the same height as the crystal to within less than 1 μm. After the epoxy

resin had hardened completely the remainder of the uninsulated gold microwire was covered with a thin layer of epoxy resin so that only the (111) face was left exposed. This procedure was successful for microcrystals with $d_{\text{eff}} = 10\text{--}35\text{ }\mu\text{m}$. In the case of smaller SCUMEs, for example with a d_{eff} of $5\text{ }\mu\text{m}$, a slightly different procedure was used to minimize the capacitive current.^[13] In this case a $100\text{ }\mu\text{m}$ length of a gold microwire with a diameter of $3\text{ }\mu\text{m}$ was first fixed to the larger $10\text{ }\mu\text{m}$ wire using the gold paint. The small microcrystal was then fixed to the $3\text{ }\mu\text{m}$ wire using the same procedure described above. Slightly different procedures were used to fabricate SCUMEs with exposed (100) faces.

All electrochemical experiments were carried out in a water-jacketed glass cell with the SCUME, a Pt counterelectrode, and a calomel reference electrode containing 0.05 M KCl. The cell was placed in a Faraday cage and coaxial cables were used to connect the electrodes to the potentiostat. Electrolyte solutions were prepared from HClO_4 (Aldrich, 99.999% pure) diluted to 0.01 M in nanopure water. The solution was purged with argon for 10 min and kept under argon during the measurements. The reference electrode was connected to the body of the cell using a Luggin capillary containing the 0.01 M HClO_4 solution. Cyclic voltammograms were recorded by using a EG&G 283 potentiostat connected to a PC minicomputer by a GPIB IEEE-488.2 interface. The current-potential data were acquired digitally.

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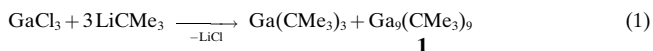
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Ga₉(CMe₃)₉, an Important New Building Block in the Structural Chemistry of the Alkylelement(I) Compounds E_nR_n (E = B – In)**

Werner Uhl,* Lars Cuypers, Klaus Harms, Wolfgang Kaim, Matthias Wanner, Rainer Winter, Rainer Koch, and Wolfgang Saak

Numerous organoelement cluster compounds of the elements boron, aluminum, gallium, and indium have been published in recent literature. Most of them are difficult to prepare and were isolated in only very poor yield. They often contain cluster anions such as $[\text{Al}_{77}\{\text{N}(\text{SiMe}_3)_2\}_{20}]^{2-}$ or $[\text{Ga}_9\{\text{Si}(\text{SiMe}_3)_3\}_6]^-$.^[1] Beside these ionic derivatives a few neutral cluster compounds such as In_8Ar_4 (Ar = 2,6-dimesitylphenyl) or $\text{In}_{12}\{\text{Si}(\text{CMe}_3)_3\}_8$ ^[2] were synthesized in which the number of the cluster atoms exceeds the number of the substituents. To the best of our knowledge there is no systematic approach to the description of their formation and of their fascinating structural chemistry. Element(I) compounds E_nR_n were isolated and structurally characterized before only as monomers ER or as tetrahedral clusters of the type E₄R₄,^[3] in which R denotes very bulky substituents. A neopentylgallium(I) compound was reported in literature,^[4] however, it was not isolated in a pure form. For many years we have tried to control the size of E^I clusters by the systematic variation of the steric demand of their substituents. Smaller groups should lead to the formation of larger clusters, which are of particular interest owing to their bonding and broad preparative application in secondary reactions. However, the tendency to disproportionate as a consequence of insufficient steric shielding prevented the isolation of such derivatives.

The reaction of *tert*-butyllithium with gallium trihalides affords tri(*tert*-butyl)gallium^[5] in a good yield as well as a small quantity of elemental gallium by a redox reaction. By systematically changing the reaction conditions we attempted to stop the partial reduction of trivalent gallium at an intermediate oxidation state. Finally, we obtained a green solution from which black-green crystals of **1** were isolated in 4% yield after separation of the alkylgallium(III) compound [Eq. (1)]. Owing to the easy availability of compound **1** a complete characterization was possible despite its low yield. The crystal structure determination^[6] revealed a tricapped



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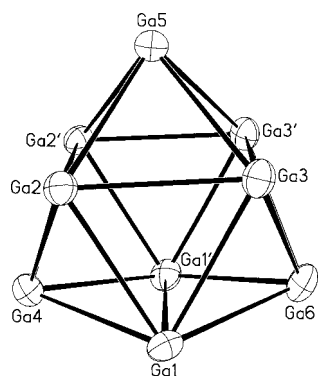


Figure 1. Molecular structure of **1**; the *tert*-butyl groups are omitted for clarity. Only one of the two independent molecules is drawn, the average values are, however, calculated from both independent molecules. Important bond lengths [pm]: Ga–Ga distances to the capping Ga atoms (Ga4, Ga5, Ga6 (Ga7, Ga13, Ga15)): 256.9(1)–261.9(1) (av 258.8); Ga–Ga distances at the edges of the triangle of the prism between the atoms Ga1, Ga2, Ga3 (Ga8, Ga9, Ga13 and Ga10, Ga11, Ga14): 264.06(9)–268.96(9) (av 267.02); Ga1–Ga1' 300.7(1), Ga2–Ga2' 304.6(1), Ga3–Ga3' 291.2(1) [291.39(9)–306.6(1) in the second molecule]; Ga–C 202.5.

228 °C with the formation of elemental gallium. Powdered samples of **1** remained unchanged in air over a period of about 30 min. The UV/Vis spectrum showed two absorptions in the visible region at 480 and 600 nm. In comparison to gallium(III) compounds, the proton resonances of the *tert*-butyl groups in the ¹H NMR spectrum are only slightly shifted to a lower field by about 0.3 ppm ($\delta = 1.48$). However, an extreme low-field shift ($\delta < 30$ in compounds possessing trivalent gallium atoms) was observed for the resonances of carbon atoms attached to gallium ($\delta = 100.4$). Tetrahedral E₄R₄ clusters bearing tris-(trialkylsilyl)methyl substituents showed a less dramatic shift of $\delta = 60$ –64.^[8] An absorption at 513 cm^{−1} in the IR spectrum was assigned to the Ga–C stretching vibration. A ⁷¹Ga NMR spectrum could not be recorded owing to the quadrupole moment of gallium and the low local symmetry at each gallium atom.

According to cyclic voltammetric investigations the uptake of an electron is electrochemically reversible; it leads in *o*-difluorobenzene or dichloromethane to the corresponding radical anion **2**, accompanied by a lightening of the color of the solution.^[9] The radical anion **2** was stable at room temperature and was further reduced at an about 1 V more negative potential in an irreversible two-electron reduction step. Cooling to −78 °C did not lead to an improvement of the reversibility behavior. The oxidation was also completely irreversible in a multielectron process in which the current intensity corresponded approximately to the loss of one electron per gallium atom.

The ESR spectroscopic characterization of the radical **2** was only possible at very low temperature owing to fast relaxa-

tion.^[9] The reason for this may be the relatively high symmetry of **2**, which leads to energetically similar states and the occupation of neighboring, partially degenerate orbitals by the unpaired electron. Similar observations were reported for the distorted octahedral hexaborates [B₆X₆][−] (X = halogen).^[10] Also the splitting of the *g* components of **2** (2.173, 2.06, 1.95) is similar to that of, for example, [B₆Br₆][−] (2.15, 2.09, 1.88).^[10] Thus, these data verify a distribution of the unpaired electron over at least large parts of the cluster skeleton. Accordingly, the hyperfine splitting by coupling with the isotopes ⁶⁹Ga and ⁷¹Ga (each *I* = 3/2) was not observed owing to the overlap of the expected large number of lines.

Compound **1** has a surprisingly high thermal stability and decomposes above

Quantum-chemical calculations of the methyl compound Ga₉Me₉ (**1a**) verified the structural parameters of **1** with three characteristic ranges of Ga–Ga distances and the elongation of the cluster parallel to its threefold rotation axis.^[11] For comparison, we also calculated the radical anion **2a** which was reversibly generated by an electrochemical experiment and detected by ESR spectroscopy.^[11] Remarkably, the nonagallium cluster showed behavior similar to the corresponding boron compounds [B₉X₉]^{*n*−} (X = H, halogen; *n* = 0, 1, 2).^[12] The addition of one electron leads to a strengthening of the Ga–Ga interaction parallel to the long edges of the trigonal prism and to a compression of the cluster (Ga–Ga: from 298.2 in **1a** to 281.6 pm in **2a**). The distances to the capping Ga atoms remained almost unchanged (256.3 (**1a**) and 254.4 pm (**2a**)), while the edges of the triangles of the prism became longer (267.3 (**1a**) and 275.1 pm (**2a**)). Thus, an almost undistorted equilateral trigonal prism is present in the radical anion.

For the first time, the influence of the steric demand of the substituents on the size of a third main group cluster was verified by the synthesis of compound **1**. This will stimulate further experiments toward the synthesis of other alkyl-element(i) compounds bearing smaller alkyl groups and having novel structures. Furthermore, the synthesis of **1** opens the access to a chemistry similar to that of polyborates. As impressively shown with the related compounds E₄R₄,^[3] we expect a broad preparative application of **1**, in particular in those cases in which the high steric shielding of the derivatives previously employed prevented secondary reactions.

Experimental Section

Experimental Section

n-Pentane and *n*-hexane were dried over LiAlH₄. Freshly sublimed GaCl₃ (7.33 g, 0.042 mol) in *n*-hexane (90 mL) was treated with *tert*-butyllithium (78 mL of a 1.6 M solution in *n*-hexane) over a period of 1 h. The mixture was heated under reflux for 16 h, cooled to room temperature, and filtered. The volatile components were removed in vacuum at room temperature. At the same temperature and at a pressure of 10^{−3} Torr tri(*tert*-butyl)gallane was distilled in a trap cooled with liquid nitrogen (yield: 6.83 g, 68 %). The green residue was dissolved in pentane (25 mL) and filtered. The filtrate was evaporated, the residue was thoroughly evacuated and recrystallized from *n*-pentane or diisopropyl ether (yield: 0.19 g, 4 %). Decomposition (under argon, sealed capillary): 228 °C. ¹H NMR (500 MHz, C₆D₆): $\delta = 1.48$; ¹³C NMR (125.8 MHz, C₆D₆): $\delta = 100.4$ (GaC), 32.2 (CH₃). IR (KBr pellet): $\tilde{\nu}$ [cm^{−1}] = 1465 vs, 1387 w, 1358 vs, 1308 m, 1242 vs (δ (CH₃)); 1188 w, 1158 vs, 1005 m (ν_s (C₃C)); 984 m, 937 m (CH₃ rocking); 805 vs (ν_{as} (C₃C)); 513 m (ν (GaC)); UV/Vis (*n*-hexane): λ_{max} [nm] (lg ϵ): 245 (4.6), 480 (3.5), 600 (2.9).

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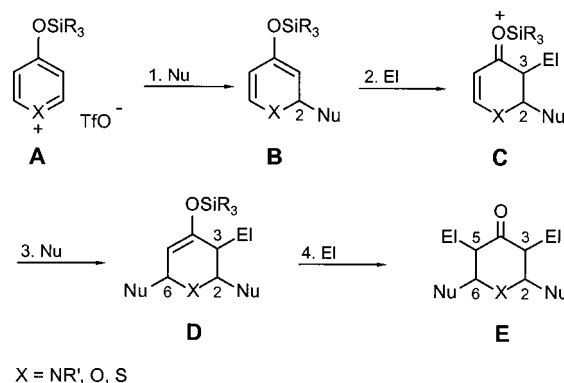
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Stereoselective Multiple Functionalization of Perylium Salts by Domino Reactions with 2-Silyloxybuta-1,3-dienes**

Uwe Beifuss,* Kim Goldenstein, Frank Döring, Christopher Lehmann, and Mathias Noltemeyer

The development of multicomponent domino reactions is particularly attractive as these allow the stereoselective conversion of several simple substrates into complex target molecules, such as annulated or bridged polycycles, in a single step.^[1] Perylium salts are easily accessible, reactive heteroarenes that react preferably with nucleophiles. Apart from transformations that proceed with conservation of the pyran ring, we are also familiar with reactions in which the primary adducts are stabilized by ring opening or subsequent ring transformation.^[2] In contrast, only a few stereoselective reactions that start from perylium salts are known to result in complex ring systems. One exception is the 1,3-dipolar cycloadditions of 3-oxidopyrylium salts, which have initially been developed by Sammes et al. and later by Wender, Mascareñas, and Magnus and co-workers to provide an attractive route to various ring systems and natural products.^[3]

One concept that may be applied to yield products of a higher complexity in diastereomerically pure form from simple components is the multiple functionalization of positively charged heteroarenes. Here, **A** first reacts regioselectively with a nucleophile at C-2. The resulting enol ether **B** can then react with an electrophile at C-3 forming the Michael acceptor **C**. Subsequent transformation with a nucleophile at C-6 and an electrophile at C-5 yield the trisubstituted **D** and the tetrasubstituted heterocycle **E**, respectively (Scheme 1). Following research on the selective mono- and bisfunctional-



Scheme 1. Multiple functionalization of positively charged heteroarenes.

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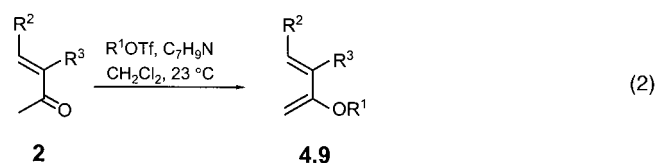
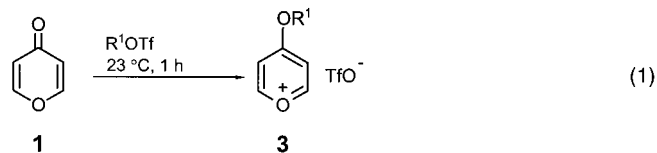
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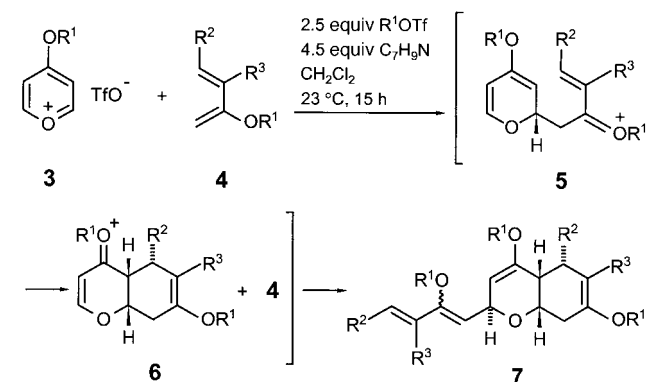
ization of benzannulated systems,^[4] we here report on the first selective tris- and tetrafunctionalization of 4-silyloxyppyrylium triflates by domino reactions with two equivalents of a 2-silyloxybuta-1,3-diene.

The 4-silyloxyppyrylium triflates **3** required as substrates are easily accessible in situ from pyran-4-one (**1**) and silyl triflates R¹OTf under mild conditions [Eq. (1)] and can be reacted with 2-silyloxybuta-1,3-dienes **4** and **9**, respectively. The latter two are also generated in situ in the same flask by the reaction of α,β -unsaturated methyl ketones **2** with silyl triflates in the presence of 2,6-lutidine [Eq. (2)].



The reactions of **1** (1.0 equiv) and **2** (2.0 equiv) with a total of 4.5 equivalents of various silyl triflates led to the tetrahydro-2H-chromenes **7** as their sole products with very good yields in almost all cases. During this trifunctionalization of pyrylium salts a domino 1,2-/1,4-addition between the 4-silyloxyppyrylium triflate **3** and the 2-silyloxybuta-1,3-diene **4** occurs as the first step.^[5] The annulated intermediate **6** formed via **5** is then reacted with another molecule **4** under

Table 1. Tetrahydro-2H-chromenes **7** by domino reactions of **3** and **4**.^[a]

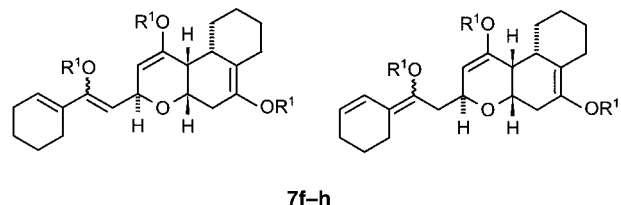


3	R ¹	4	R ²	R ³	7	Yield [%]	E/Z
a	TBDMS	a	Ph	H	a	96	4.0:1.0
b	TES	b	Ph	H	b	98	4.1:1.0
c	TDMS	c	Ph	H	c	90	3.8:1.0
a	TBDMS	d	<i>p</i> -C ₆ H ₄ CN	H	d	80	11.0:1.0
a	TBDMS	e	<i>p</i> -C ₆ H ₄ Cl	H	e	35	1.3:1.0
a	TBDMS	f	(CH ₂) ₄	H	f	86	[b]
b	TES	g	(CH ₂) ₄	H	g	98	[b]
d	TIPS	h	(CH ₂) ₄	H	h	99	[b]
e	TMS	i	<i>p</i> -C ₆ H ₄ CO ₂ Me	H	i	62	3.4:1.0
e	TMS	j	<i>p</i> -C ₆ H ₄ NO ₂	H	j	56	only <i>E</i>

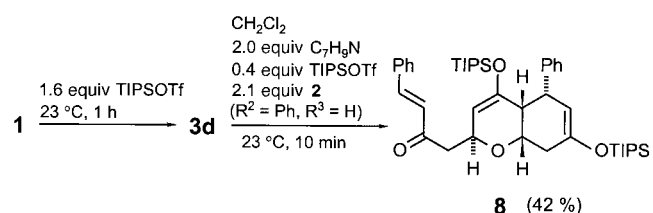
[a] TBDMS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TDMS = thexyldimethylsilyl, TIPS = triisopropylsilyl, TMS = trimethylsilyl. [b] The products **7f–h** were isolated as a mixture of two constitutional isomers.

1,4-addition to give **7** diastereoselectively. In this manner three new C–C bonds and four stereogenic centers can be achieved in a single step (Table 1). Another reason why this new method is quite exciting is that a number of natural products are known to exhibit this ring system.^[6]

Taking the reaction of pyran-4-one (**1**) with benzalacetone (**2**; R² = Ph, R³ = H) and triisopropylsilyl triflate (TIPSOTf) as an example, we were able to show that the amount of the



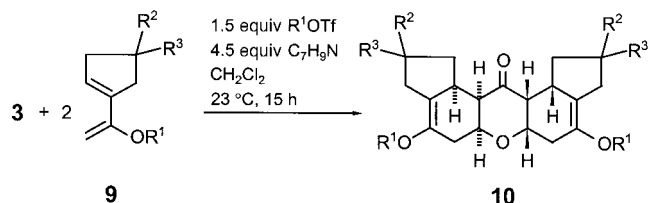
silyl triflate has a significant influence on product formation: for instance, reaction of one equivalent of **1**, 2.1 equivalents of **2** (R² = Ph, R³ = H), and just two equivalents of TIPSOTf gives exclusively **8** (Scheme 2). Evidently, the reactivity of the systems giving **7** or **8** is not sufficient to bring about the second ring closure. In order to direct the reactions in this way, we increased both the reactivity of the 2-silyloxybuta-1,3-diene and of the silyl triflate.



Scheme 2. Influence of the amount of silyl triflate applied.

The importance of the reactivity of the 2-silyloxybuta-1,3-dienes is revealed in reactions of **3** with the silyl enol ethers **9** of different 1-acetylcyclopentenones. With these highly reactive reagents the second ring closure occurs readily to give dicyclopenta[*a,j*]octahydroxanthene-9-ones **10** exclusively (Table 2). We assume that they derive from a sequential domino 1,2-/1,4-addition and a domino 1,4-/1,4-addition between **3** and two equivalents of **9**. In these cases we were able to isolate just

Table 2. Dicyclopenta[*a,j*]octahydroxanthene-9-ones **10** by domino reactions between **3** and **9**.



3	R ¹	9	R ²	R ³	10	Yield [%]
a	TBDMS	a	H	H	a	85
e	TMS	b	H	H	b	75
d	TIPS	c	H	H	c	33
a	TBDMS	d	CO ₂ Me	CO ₂ Me	d	58
e	TMS	e	CO ₂ Me	CO ₂ Me	e	51
a	TBDMS	f	=CH(CH ₃) ₂	H	f	31
a	TBDMS	g	CH(CH ₃) ₂	H	g	61

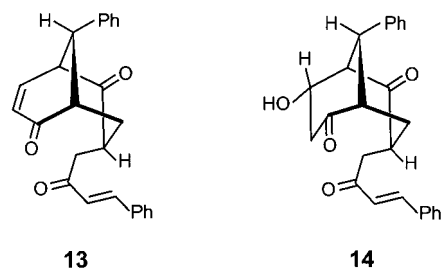
one of the 32 possible diastereomers. The relative configuration follows from the analysis of the NMR spectra, which is made a lot easier by the C_2 symmetry of the compounds. The structural assignments are corroborated by X-ray structural analysis of **10d**.^[7]

Product formation could also be governed by the reactivity of the silyl triflate, although the direction taken was somewhat unexpected: It came as a surprise that the reactions of the trimethylsilyloxypyrylium triflate **3e** with two equivalents of the 2-trimethylsilyloxybuta-1,3-dienes **4k–o** in the presence of the highly reactive TMSOTf selectively yielded the bicyclo[3.3.1]nona-2,6-dienes **12** (Table 3). We assume that cleavage of the pyran ring occurs in this three-component reaction after the formation of **7** by TMSOTf that then generates the bisallyl cations **11**, which are rearranged in an

Table 3. Bicyclo[3.3.1]nona-2,6-dienes **12** by domino reactions between 4-trimethylsilyloxypyrylium triflate **3e** and 2-trimethylsilyloxybuta-1,3-dienes **4k–o**

3	R ¹	4	R ²	R ³	12	Yield [%]
e	TMS	k	Ph	H	a	94
e	TMS	l	<i>p</i> -C ₆ H ₄ OMe	H	b	51
e	TMS	m	<i>p</i> -C ₆ H ₄ Cl	H	c	80
e	TMS	n	<i>p</i> -C ₆ H ₄ CN	H	d	54
e	TMS	o	(CH ₂) ₄	H	e	96

intramolecular and stereocontrolled fashion to give the end products **12**. Four new C–C bonds and five stereogenic centers are formed when these highly functionalized bridged systems are established in a single step. This is all the more interesting as there are a number of bioactive natural products with a bicyclo[3.3.1]nonane framework, but with hardly any stereo-selective routes available that lead to this particular ring



system.^[8] The structure of the products was determined by NMR analysis of compounds **13** and **14** resulting from derivatization or hydrolysis, respectively, of **12a**.^[9] An X-ray structural analysis for **13** is also available.^[7] Only **4i,j** and **9b,e** deviate from this reactivity pattern in that they exclusively yield **7i,j** and **10b,e**, respectively.

Experimental Section

Pyran-4-one (**1**) (1.00 mmol) was treated with silyl triflate (4.50 mmol) under argon and left at room temperature for 1 h. Then dichloromethane (3 mL), 2,6-lutidine (4.50 mmol), and a solution of the α,β -unsaturated ketone **2** (2.0 mmol) in dichloromethane (2 mL) were added and the mixture was stirred for 15 h at room temperature. The reaction mixture was treated with a solution of saturated sodium hydrogen carbonate (10 mL) and extracted with dichloromethane (3 $\times$ 10 mL). After the combined organic layers had been dried over sodium sulfate, the solvent was removed in vacuo. The workup was performed under argon, and purification of the crude products was accomplished by flash chromatography on silica gel.

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Water-Assisted Intramolecular Electron Transfer from the Ring to the Side Chain in *N,N,N',N'*-Tetraalkyl-*para*-phenylenediamine Radicals—The Reverse of Side Chain Deprotonation of Radical Cations

Steen Steenken* and Abel J. S. C. Vieira

For arenes containing (substituted) alkyl groups as substituents, “activation” of the side chain is often possible by changing the “oxidation state” of the arene, for example, by one-electron reduction,^[1–7] or more often, one-electron oxidation.^[8–13] A very characteristic process for the side chain reactivity of radical cations is deprotonation from carbon which leads typically to (neutral) benzyl-type radicals. The reciprocal reaction, protonation on carbon, has also been observed (with radical anions),^[14–20] but it typically takes place *not* on the side chain but on the ring. We have now found evidence for the protonation of a side chain carbon atom (a reaction which involves a neutral radical), electron transfer from the ring to the side chain providing the (high) electron density necessary for the protonation on carbon to occur.

N₂O-saturated aqueous solutions at pH 7–12 containing *N,N,N',N'*-tetramethyl-*p*-phenylenediamine (TMPD; used as the dihydrochloride) were irradiated with the 100 ns pulses from a 3 MeV van de Graaff electron accelerator, and the time-resolved changes in the transmission or of the conductance of the solution monitored. Irradiation of water leads to the radicals $\cdot\text{OH}$ (45 %), $\text{H}\cdot$ (10 %), and e_{aq}^- (45 %). The latter reacts with N₂O within 20 ns to yield another $\cdot\text{OH}$ radical. In the presence of 0.2–0.5 mM TMPD, its radical cation $\text{TMPD}^{+\cdot}$ is produced, whose λ_{max} values are at 330, 565, and 610 nm (Figure 1).^[21, 22] $\text{TMPD}^{+\cdot}$ is formed by two routes, a direct and an indirect one. The direct (“fast”) reaction accounts for (55 ± 5) % of the total formation of $\text{TMPD}^{+\cdot}$ (Figure 1, inset b). The rate, but not the yield, of this reaction depends on the concentration [TMPD],^[23] whereas the rate of the second, slower reaction ($k = (6.6 \pm 1) \times 10^4 \text{ s}^{-1}$ at 20 °C^[24]) turned out to be independent of [TMPD] (0.1–1 mM) and pH (7–12), but dependent on temperature (between 0 and 50 °C), the resulting Eyring parameters for the electron transfer and side chain protonation (see Scheme 2) being $\Delta H^\ddagger = (4.9 \pm 0.5) \text{ kcal mol}^{-1}$ and $\Delta S^\ddagger = (-19 \pm 1.6) \text{ cal mol}^{-1} \text{ K}^{-1}$. Furthermore at pH 8–11 the reaction of $\cdot\text{OH}$ with TMPD leads to an increase in conductance of the solution (Figure 1, inset c) assignable^[25] to the formation of an organic (radical) cation and the OH[−] ion, again in a two-step process, as observed with optical detection. The rate of the slow process and the step height of the change in conductance were independent of the pH value (8–11)^[26] and of the [TMPD] (0.1–1 mM), and were

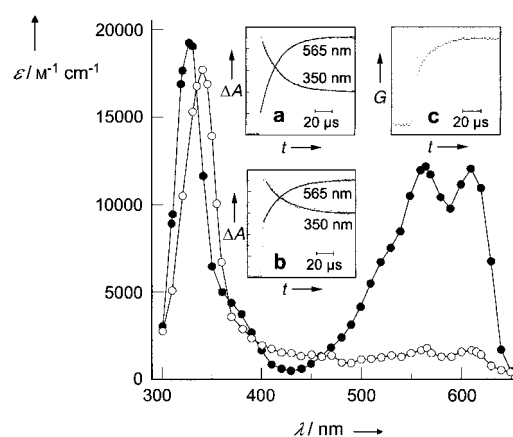


Figure 1. Absorption spectra recorded after reaction of $\text{O}^{\cdot-}$ with 0.4 mM TMPD in N₂O-saturated water ([KOH] = 0.4 M, 20 °C). ● = spectrum of $\text{TMPD}^{+\cdot}$, ○ = spectrum of $>\text{NCH}_2\cdot$. Insets a and b show the decay of $>\text{NCH}_2\cdot$ (350 nm) and the build up of $\text{TMPD}^{+\cdot}$ (565 nm) at 0.4 M KOH and pH 7.4, respectively. Inset c shows the increase in conductance *G* at pH 10, which primarily reflects the formation of OH[−].

equal (within 10 %) with those optically measured (compare with inset b).

On replacement of $\cdot\text{OH}$ by $\text{O}^{\cdot-}$, the conjugate base of $\cdot\text{OH}$ ($\text{p}K_{\text{a}}(\cdot\text{OH}) = 11.9$), the height of the initial step at 565 nm (see insets) was found to be much smaller than at pH 7–8.^[27] Under these conditions,^[28] the first process contributed only 15 % of the total formation of $\text{TMPD}^{+\cdot}$, and the main reaction was the slow formation of $\text{TMPD}^{+\cdot}$ with $k = 6.0 \times 10^4 \text{ s}^{-1}$, that is with essentially the same rate constant as for the reaction at pH 7–12, where, however, $\cdot\text{OH}$ is the reactant.

Based on the fact that $\text{O}^{\cdot-}$ reacts with arenes typically by H-abstraction from the side chain,^[29] the side-chain-derived radical $>\text{NCH}_2\cdot$ is expected to be formed in its reaction with TMPD (see Scheme 1). Similar to other α -aminoalkyl-type radicals,^[30] $>\text{NCH}_2\cdot$ should be a good one-electron reducing agent, and this was in fact found to be the case since this radical could be scavenged by the mild oxidant methylviologen (MV^{2+}) to yield $\text{MV}^{+\cdot}$ ($k = 2.8 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$). The yield of $>\text{NCH}_2\cdot$, determined at pH 9 with this method,^[31] is 53 % relative to the initial $\cdot\text{OH}$ present. This value is in agreement with the numbers derived from the optical and conductance step heights (Figure 1, insets b and c).

The reaction of $\cdot\text{OD}$ with TMPD in heavy water (D₂O) also led to the formation of $\text{TMPD}^{+\cdot}$ in two steps. However, the rate constant for the second, slow process, which is assigned to the conversion of $>\text{NCH}_2\cdot$ to $\text{TMPD}^{+\cdot}$ (see Scheme 2), was smaller than that for the reaction in H₂O by the factor 3.0; thus, the solvent kinetic isotope effect (KIE) is 3.0, a value that is consistent with the (heterolytic) rupture of an O–H bond in the transition state. The activation entropy of $-19 \text{ cal mol}^{-1} \text{ K}^{-1}$ is in agreement with this concept, since motional degrees of freedom are lost by participation of a water molecule in the transition state of the intramolecular electron transfer from the ring to the side chain.

To study the effect of the alkyl substituent on the amino nitrogen atom of the *para*-phenylenediamine moiety, the OH radical was also allowed to react with the *N,N,N',N'*-tetraethyl and *n*-propyl derivatives. As with TMPD, the corresponding radical cations were formed in two steps; the yields for the

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“fast” (bimolecular) reaction were 70–80%.^[32] The subsequent unimolecular reaction revealed k values of 1.2×10^4 and $7.1 \times 10^3 \text{ s}^{-1}$ for the ethyl^[33] and *n*-propyl derivatives, respectively. Figure 2 shows a Taft plot (σ^* values) of the rate

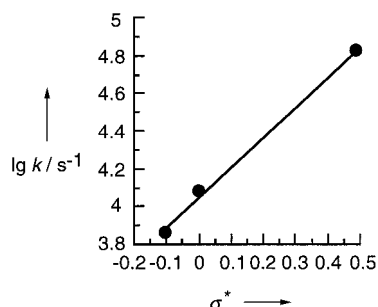
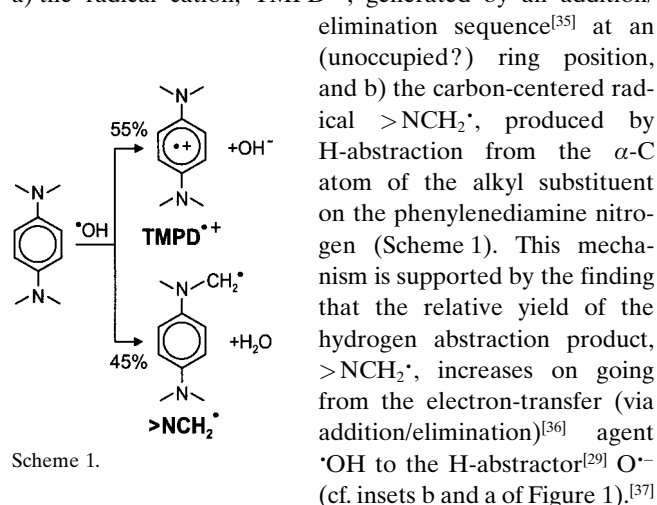


Figure 2. Taft plot of the transformation of $>\text{NCH}_2\text{R}$ ($\text{R} = \text{H, Me, Et}$) into the corresponding radical cation. The Taft parameter was determined to be $\rho^* = 1.6$ from the slope.

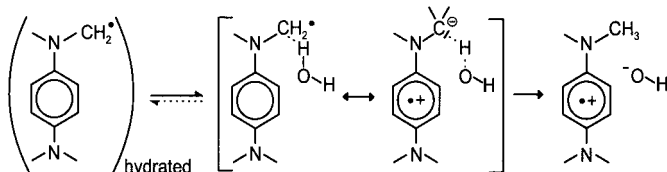
constants for the transformations of the α -aminoalkyl-type radicals into the corresponding phenylenediamine radical cations. The deceleration of the reaction on going from Me to *n*Pr, reflected in the positive apparent ρ^* value of 1.6, may be due to an increase of electron density at the carbon carrying the unpaired electron^[34] or to steric effects.

On the basis of the experimental data presented, a mechanism is suggested which involves the formation of two different radicals from the reaction of $\cdot\text{OH}$ with TMPD:



Scheme 1.

Clearly, for the “unimolecular” transformation of $>\text{NCH}_2\cdot$ to $\text{TMPD}^{\cdot+}$ a proton donor is necessary, and it is proposed that a water molecule serves this purpose. The mechanism suggested (Scheme 2) involves the transfer of an electron from the ring to the N-substituted alkyl



Scheme 2.

radical; a water molecule acts as the protonating agent^[38, 39] (and possibly as an electron transfer mediator) in the transition state of the electron transfer. Evidence for this comes from the kinetic isotope effect of 3 and the negative activation entropy. The anion complementary to the radical cation is OH^- , and this was detected directly (as a hydrated ion) by time-resolved measurement of the conductance (see Figure 1, inset c).

To summarize, evidence has been presented for a water-assisted intramolecular transfer of an electron from the ring as the electron donor to a carbon-centered radical located on the side chain at a position β to the ring as the (weak!) electron acceptor. Formally, the result of this electron transfer would be a *carbanion* on the side chain. However, as concluded from the solvent kinetic isotope effect which indicates the breakage of an O–H bond in the transition state of the electron transfer, protonation by water of this carbon atom is concerted with the electron transfer. The (new) mechanism presented in Scheme 2, which corresponds to the reverse of side chain deprotonation^[40] of radical cations,^[41] is an example of the importance of proton transfer in electron transfer processes in aqueous solution.

Experimental Section

The pulse radiolysis experiments were performed by using a 3 MeV van de Graaff accelerator which supplied 100 ns pulses with doses such that radicals were produced in concentrations of 0.5–3 μM . A thermostatable quartz flow cell, typically set at 20°C, was employed in all experiments. Dosimetry was done with N_2O -saturated 10 mM KSCN solutions taking $G(\cdot\text{OH}) = 6.0 \times 10^{-7} \text{ mol J}^{-1}$ and $\epsilon[(\text{SCN})_2^{\cdot-}] = 7600 \text{ M}^{-1} \text{ cm}^{-1}$ at 480 nm.^[42] The solutions were prepared by dissolving the tetraalkyl-*p*-phenylenediamine dihydrochlorides in water deoxygenated with N_2O and then adjusting the pH to ≥ 7 by addition of KOH or Na_2HPO_4 . The radiation-induced changes of the solution were digitized and analyzed by an on-line DEC-PDP 11/73+ computer system which also controlled the apparatus and pre-analyzed the data. For the time-resolved conductance changes, an AC system with 1 μs time resolution was used.

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Liquid-Phase Synthesis of Colloids and Redispersible Powders of Strongly Luminescing LaPO₄:Ce,Tb Nanocrystals**

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An increasing number of nanocrystalline materials have been synthesized in high-boiling coordinating solvents, since binding of the solvent molecules to the particle surface leads to colloidal solutions of well-separated particles.^[1] If process parameters such as concentration and temperature are properly adjusted^[2] and, most importantly, a suitable solvent for the reaction is found, colloidal solutions of highly crystalline nanoparticles with very narrow particle size distributions are the result. Examples for this method are the synthesis of high-quality cadmium chalcogenide nanoclusters^[1a] and TiO₂ nanoclusters^[1b] in trioctylphosphine oxide (TOPO) and the preparation of InP^[1c,d] and InAs nanoclusters^[1e] in trioctylphosphane (TOP). Similarly, ZnSe,^[1f] Fe₂O₃, Mn₂O₄, and Cu₂O nanoclusters^[1g] have been prepared in long-chain alkylamines. Our synthesis of LaPO₄:Eu and CePO₄:Tb in tris-ethylhexylphosphate^[1h] shows that the method is also applicable to *doped* nanoparticles.

Oxide materials form the active material of most solid-state lasers and are technologically important as phosphors in cathode ray tubes, X-ray detectors, and in lighting applications.^[3] The latter group includes the mixed phosphate La_{0.40}Ce_{0.45}Tb_{0.15}PO₄, which is used in luminescent lamps as highly efficient emitter of green light.^[4] The material is chemically very stable, even in the presence of the mercury plasma discharge inside the lamp, and has an overall luminescence quantum yield of 93%.^[5] Redispersible nanoparticles of La_{0.40}Ce_{0.45}Tb_{0.15}PO₄ may therefore form a stable and efficient substitute for organic laser dyes in various applications. In fact, semiconductor nanoparticles such as CdSe have successfully been applied, for instance, as luminescing labels for biomolecules^[6] and as light-emitting molecular substances in electroluminescent devices.^[7]

Herein we present an improved synthesis that yields more than 10 grams of the ternary system La_{0.40}Ce_{0.45}Tb_{0.15}PO₄ in a simple one-pot reaction which does not involve rapid mixing of dissolved compounds. Rapid mixing at elevated temperatures is often applied to separate nucleation and growth of the nanoparticles,^[8] but becomes increasingly difficult with larger amounts of reactants. Nevertheless, our procedure yields a remarkably narrow particle size distribution even on this preparative scale. This is shown by transmission electron

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micrographs (TEMs, Philips CM 300 UT electron microscope) given in Figure 1. The TEM images further show that the nanoparticles have a mean diameter of 5 to 6 nm and that their shape varies from almost spherical to ellipsoidal with

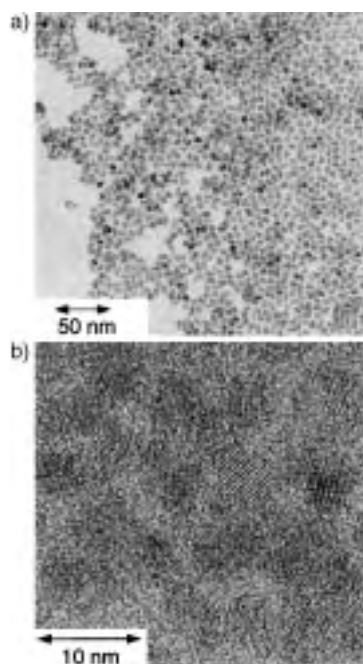


Figure 1. a) TEM image of $\text{LaPO}_4\text{:Ce,Tb}$ nanoparticles. b) High-resolution TEM image of the particles.

aspect ratios of up to two. Many particles display well-defined edges, indicating faceting of these crystallites. High crystallinity is also inferred from the high-resolution TEM images of the material (Figure 1b) showing lattice fringes for most particles and from the powder X-ray diffraction (XRD) data given in Figure 2. Figure 2 displays not only the measured

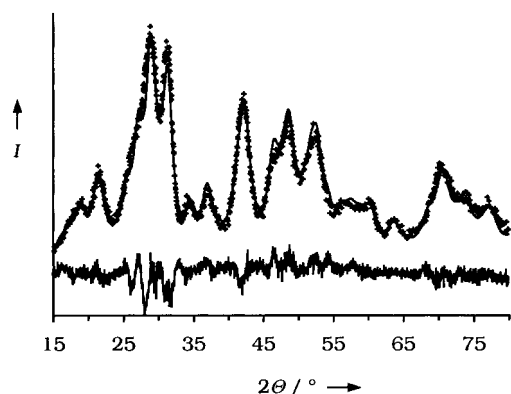


Figure 2. X-ray powder diffraction data (+), Rietveld fit (solid line through data points), and difference curve (solid line below data points) of $\text{LaPO}_4\text{:Ce,Tb}$ nanoparticles.

XRD pattern (for clarity, only every second data point (+) is given), but also a simulation of the XRD pattern based on the Rietveld method^[9] (line through data points) and the difference curve between the XRD data and the Rietveld fit. The numerical values used in the Rietveld simulation (Table 1)

Table 1. Results of the Rietveld fit given in Figure 2 and unit cell parameters of the $\text{LaPO}_4\text{:Ce,Tb}$ nanoparticles as well as of bulk CePO_4 and LaPO_4 .

	Nanoparticles	Bulk LaPO_4	Bulk CePO_4
space group (no.)	$P12_1/n1$ (14)	$P12_1/n1$ (14)	$P12_1/n1$ (14)
a [Å]	6.80	6.83	6.80
b [Å]	7.03	7.07	7.02
c [Å]	6.47	6.50	6.47
α [°]	90	90	90
β [°]	103.9	103.3	103.5
γ [°]	90	90	90
$\langle D_V \rangle$ [Å]	57	∞	∞

reveal that the observed XRD pattern is well in accord with a nanocrystalline monazite phase. The fit yields a volume-averaged mean domain size of 5.7 nm which is roughly consistent with the particle size observed in the high-resolution TEM images and shows that the dimensions of the unit cell are similar to those of bulk LaPO_4 and bulk CePO_4 .

Powders of the nanocrystals are easily redispersed in polar solvents. The agglomeration of particles in these solutions was investigated by small-angle X-ray scattering (SAXS) experiments (Kratky compact camera). Figure 3a shows the scattering curve of a colloidal solution containing 0.2 wt % of nanoparticles and a small amount of tetra-*n*-butylammonium hydroxide in 2-propanol. By assuming the scatterers to be homogeneous spheres, the size distribution can be calculated

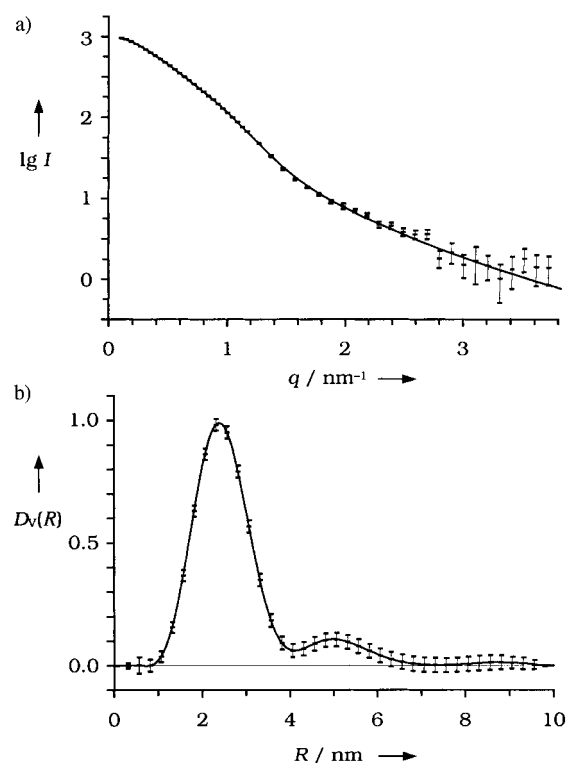


Figure 3. a) Small-angle X-ray scattering (SAXS) curve of a colloidal solution containing 0.2 wt % of $\text{LaPO}_4\text{:Ce,Tb}$ nanoparticles in 2-propanol. The length of the so-called scattering vector q is related to the scattering angle θ , that is, the angle between the directions of incidence and detection, by $q = (4\pi/\lambda_0) \sin(\theta/2)$. $\text{Cu}_{K\alpha}$ radiation was used ($\lambda_0 = 0.154$ nm). b) Normalized particle size distribution deduced from the scattering curve by assuming spherical scatterers of radius R .

from the scattering curve by means of the indirect transformation method^[10] (ITP-software, University of Graz, Austria). The resulting distribution curve (Figure 3b) shows that most scatterers (90% by volume or 98% by number) have diameters $2R$ below about 8 nm, indicating well-separated particles. The weak additional peak in the distribution curve at about $2R \approx 10$ nm proves that the size of agglomerates is restricted to values below about 15 nm. The position and the width (at half-maximum) of the main peak indicates particle diameters in the range of $2R = 4.8 \pm 1.5$ nm, that is a broader size distribution and a slightly smaller mean particle size than expected from the TEM images. This deviation is very likely caused by the nonspherical shape of many particles which was not accounted for in the calculation of the distribution curve. The high degree of deagglomeration may indicate partial capping of the particle surface by ethylhexanol or ethylhexylphosphate moieties, similar to TOP/TOPO-capped semiconductor nanoparticles.^[1a-c] The composition and the properties of the surface of the nanoparticles, however, have not been investigated yet.

The optical properties of $\text{LaPO}_4\text{:Ce,Tb}$ colloids are similar to those of $\text{CePO}_4\text{:Tb}$ nanoparticles^[1h] and are determined by transitions between f-electron and d-electron states of cerium and between different f-electron states of terbium, as schematically depicted in Figure 4. Upon UV excitation,

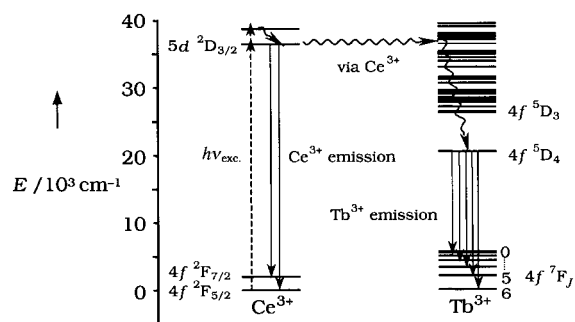


Figure 4. Energy level scheme of $\text{LaPO}_4\text{:Ce,Tb}$ with optical transitions and energy transfer processes as indicated. For simplicity, relaxation of the excited Ce^{3+} state to the lowest vibrational level is not shown in the figure.

colloidal solutions as well as powders of $\text{LaPO}_4\text{:Ce,Tb}$ nanoparticles exhibit strong yellowish-green luminescence (Figure 5) due to transitions between the excited $^5\text{D}_4$ state and the $^7\text{F}_j$ ($J=0-6$) ground states of terbium.^[5] The luminescence spectrum shows no significant differences to the spectrum of the bulk material. In fact, particle size effects on the luminescence are expected to be weak, since transitions of the well-shielded f electrons are mainly affected by the local symmetry of the crystal site. In addition to the terbium lines, the luminescence spectrum shows a rather broad emission between about 300 and 400 nm which is caused by the $5d-4f$ emission of cerium. The cerium emission consists of two transitions from the lowest component of the ^2D state to the spin-orbit components of the ground state, $^2\text{F}_{7/2}$ and $^2\text{F}_{5/2}$. In contrast to the f electrons of terbium, the d electrons of cerium couple strongly to the lattice phonons resulting in broad overlapping bands and a significant Stokes shift. The latter becomes evident by comparing the fluores-

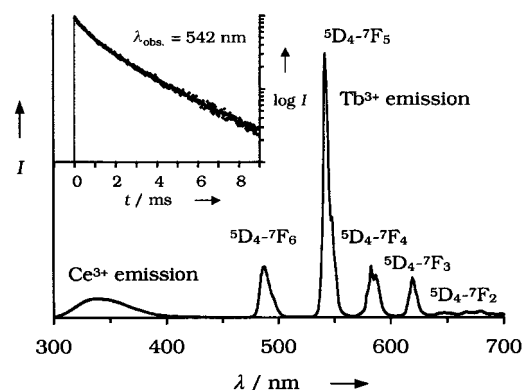


Figure 5. Luminescence spectrum ($\lambda_{\text{exc}} = 275$ nm) of a dilute colloid containing about 0.02 wt % of $\text{LaPO}_4\text{:Ce,Tb}$ nanoparticles. Inset: Luminescence decay curve of the same colloid ($\lambda_{\text{exc}} = 266$ nm, $\tau_{\text{exc}} = 15$ ns; detection wavelength $\lambda_{\text{obs}} = 542$ nm).

cence spectrum in Figure 5 with the absorption spectrum of the colloid given as dotted line in Figure 6. Since the spin-orbit components of the excited cerium $5d$ state, $^2\text{D}_{5/2}$ and $^2\text{D}_{3/2}$, are strongly split by the crystal field the absorption spectrum shows peaks at 214, 236, 258, and 274 nm. The intensity pattern and the position of the peaks are identical to those

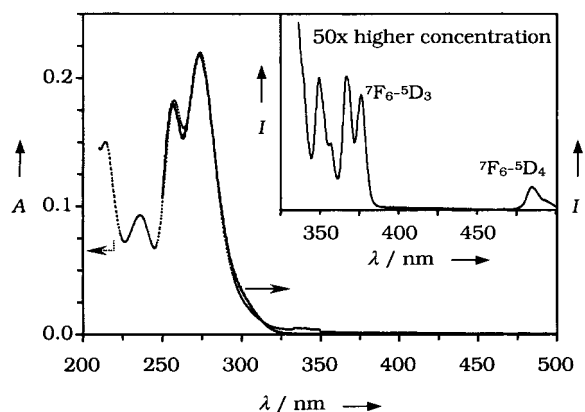


Figure 6. UV/Vis absorption spectrum (dotted line) and luminescence excitation spectrum (solid line, detection wavelength $\lambda_{\text{obs}} = 542$ nm) of a dilute colloidal solution containing about 0.02 wt % of $\text{LaPO}_4\text{:Ce,Tb}$ in methanol. Inset: luminescence excitation spectrum ($\lambda_{\text{obs}} = 542$ nm) of a solution of higher concentration ($50\times$) displaying transitions from the terbium $^5\text{D}_6$ ground state into excited terbium states.

observed in the reflectance and luminescence excitation spectrum of bulk $\text{LaPO}_4\text{:Ce}$.^[11] These features are also observed in the luminescence excitation spectrum of a dilute colloidal solution of the nanoparticles (Figure 6, solid line). The spectrum, monitored at the main terbium line at 542 nm, is identical to the absorption spectrum, verifying energy transfer from Ce^{3+} to Tb^{3+} .^[11, 12] Upon UV excitation of the cerium absorption band, a quantum yield of 42% is observed for the terbium emission of $\text{LaPO}_4\text{:Ce,Tb}$ nanoparticles dispersed in a 1:50 mixture of *N,N*-dimethylformamide and methanol. If the cerium emission is included, the total quantum yield is 61%, which is among the highest values observed for uncoated nanocrystals. Higher quantum yields have only been reported for semiconductor core-shell nano-

particles,^[13] that is, if a sufficiently thick shell of a wide-band gap material with similar lattice constants is grown onto the semiconductor particle cores. This shell reduces luminescence quenching at the particle surface and increases the stability of semiconductor nanoparticles to photochemical corrosion. However, it also complicates the synthesis of larger amounts of material.

Since energy transfer via the particle surface remains possible, the quantum yield of LaPO₄:Ce,Tb nanoparticles depends on the solvent and the termination of the particle surface. Due to their large ratio of surface area to volume, nanocrystalline systems are much more strongly influenced by properties of the particle surface than is the case for bulk materials. Particles in methanol containing some tetra-*n*-butylammonium hydroxide, for instance, show a reduced quantum yield upon UV excitation of the cerium band of $\phi = 17\%$ and $\phi = 24\%$ for the terbium and the total emission, respectively. Since the cerium emission and the terbium emission are both reduced by the same factor (0.4), we have to assume that the excited state of cerium is not only depleted by energy transfer to terbium but also by a competing process involving the solvent or the base used. In fact, the luminescence quantum yield of organometallic cerium complexes^[14] is known to depend on the ligands binding to the cerium atom. Even for cerium complexes, however, the quenching mechanism seems to be not very well understood.^[14] Therefore, we are presently investigating the influence of surface modifications on the luminescence quantum yield of the particles.

In contrast to the optically allowed d–f transitions of cerium, transitions from the terbium ⁷F₆ ground state into the higher excited terbium states are spin- and parity-forbidden and are only observed in the luminescence excitation spectrum of rather concentrated colloidal solutions (inset of Figure 6). The low transition probabilities of the terbium f–f transitions are also reflected in their long luminescence lifetime. The luminescence decay curve of the colloid (inset of Figure 5) shows a lifetime in the range of 3–4 ms, that is a value similar to the 3.2 ms observed for the bulk material.^[11, 12]

The kinetics of the luminescence decay deviates slightly from single-exponential behavior. This can be explained by energy transfer from the excited state of terbium to quencher ions as recently discussed for CePO₄:Tb nanoparticles.^[1b] The origin and the exact nature of these quenchers is not yet understood. However, if energy transfer from the excited terbium state could be reduced even higher quantum yields of the terbium emission may be achieved.

Experimental Section

Synthesis: Tris(ethylhexyl)phosphate (300 mL) was purged with dry nitrogen and a solution containing LaCl₃·7H₂O (7.43 g, 20 mmol), CeCl₃·7H₂O (8.38 g, 22.5 mmol), and TbCl₃·6H₂O (2.80 g, 7.5 mmol) in methanol (100 mL) was added. Then, water and methanol were distilled off by heating the solution to 30–40 °C in vacuum. A freshly prepared solution of crystalline phosphoric acid (4.90 g, 50 mmol) dissolved in a mixture of trioctylamine (65.5 mL, 150 mmol) and tris(ethylhexyl)phosphate (150 mL) was added. The clear solution was repeatedly evacuated and purged with nitrogen in order to minimize oxidation of Ce³⁺ to Ce⁴⁺ at elevated temperatures, and was subsequently heated at 200 °C. During heating, some of the phosphoric acid ester was cleaved and the boiling point of the colloid decreased slowly. Heating was stopped when the

temperature had dropped to about 170–175 °C (after about 30 to 40 h). After the mixture had been cooled to room temperature, a fourfold excess of methanol was added to the transparent colloid, resulting in precipitation of the nanocrystals. The latter were separated by centrifugation, washed with methanol, and dried. (Yield: 10.8 g, 89 %).

Transparent and scatter-free colloidal solutions were obtained by redispersing the powder (50 mg) either in *N,N*-dimethylformamide (5 mL) at 100 °C or in methanol (5 mL) containing a few drops of a 25 wt % solution of tetra-*n*-butylammonium hydroxide in methanol. Before spectroscopic measurements, both solutions were diluted with methanol or 2-propanol by a factor of 50.

The room-temperature quantum yields of the colloids were determined by comparing the emission of the colloidal solution with the emission of a solution of rhodamine 6G (Lambda Physics, laser grade; in spectroscopic grade ethanol) of identical optical density at the excitation wavelength.

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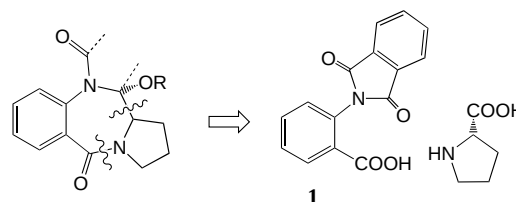
Diastereo- and Enantioselective Synthesis of Pyrrolo[1,4]benzodiazepines through Decarboxylative Photocyclization**

Axel G. Griesbeck,* Wolfgang Kramer, and Johann Lex

The concept of “memory of chirality” has recently been introduced by Fuji and Kawabata as a useful principle for asymmetric synthesis.^[1] It involves the planarization of a stereogenic center during a multistep reaction with subsequent formation of chiral nonracemic products. No asymmetric induction by chiral auxiliaries controls the transformation, only the remaining chirality memory of the intermediates. The lifetime of these intermediates and their conformational flexibility is decisive for the degree of stereoselectivity. Besides reactions with carbanions,^[1] monoradicals,^[2] or carbenium ions,^[3] combination reactions of diradicals are promising due to the very low (if present at all) activation barriers. This approach was described recently by Giese and co-workers for the cyclization of photochemically generated 1,5-diradicals with singlet multiplicity.^[4] The lifetimes of these intermediates are extremely short and near complete memory of chirality resulted. The corresponding triplet diradicals are expected to show strongly reduced memory effects due to their higher lifetimes.^[5] In order to corroborate this assumption, we investigated the decarboxylative photocyclization of phthaloylanthranilic acid derivatives^[6] and now report surprisingly high enantiomeric excesses for the radical combination of a triplet 1,7-diradical.

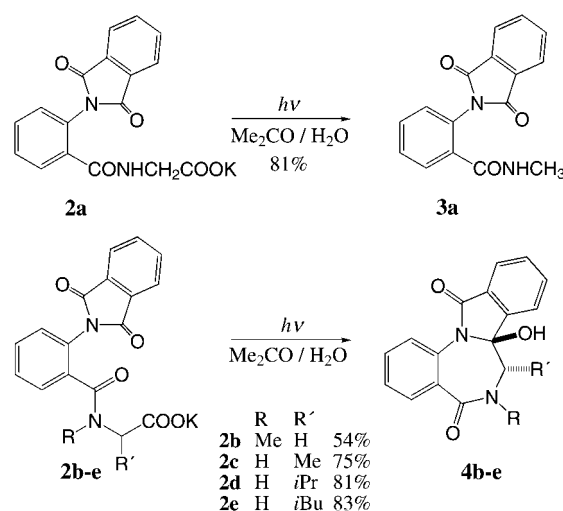
The decarboxylative photocyclization of ω -phthalimido carboxylates is initiated in the triplet channel of the electronically excited phthalimido chromophore.^[7] Intramolecular electron transfer and extrusion of carbon dioxide lead to the 1, ($\omega + 1$)-triplet diradical which, after spin inversion, combines to form the closed-shell products. This process allows, for example, the synthesis of diastereo- and enantiomerically pure benzopyrrolizidines from glutamic acid derivatives.^[8] Another interesting target family in this context are pyrrolo[1,4]-benzodiazepines. These molecules show highly selective binding to DNA and thus exhibit a strong potential as regulators for gene expression.^[9] Taking our photocyclization method into consideration, the retrosynthesis showed C,N-activated anthranilic acid building blocks to be suitable substrates (Scheme 1).^[10]

N-Phthaloyl anthranilic acid (**1**) is a photolabile substance under basic conditions. When it was irradiated in acetone/water mixtures (95/5), only *N*-phenyl phthalimide resulted as a reduction product and no cyclization was observed. If **1** was condensed with glycine to give **2a**, the photochemical



Scheme 1. Retrosynthesis for pyrrolo[1,4]benzodiazepines.

reactivity was decreased and only after prolonged irradiation was the reduction product **3a** formed (Scheme 2). These results are in agreement with the photochemistry of *N*-phthaloyl dipeptides.^[6b] The increased photostability of these substrates is probably caused by an intramolecular hydrogen bond between the amide-NH group and one of the imido carbonyl groups. Thus, *N*-alkylated substrates should exhibit higher reactivities.



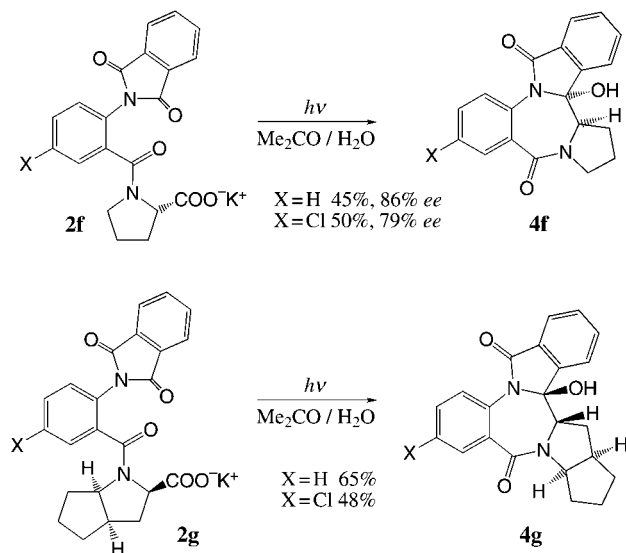
Scheme 2. Photochemistry of the anthranilic acid derivatives **2a–e** of acyclic amino acids.

The switch to sarcosine as the amino acid component did in fact drastically change the (secondary) reactivity: Substrate **2b** cyclized efficiently to give the benzodiazepine **4b** in 54% yield. It was surprising to notice that not only *N*-alkylation favored ring formation but branching of the amino acid component also had the same effect: Irradiation of the alanine, valine, and leucine derivatives **2c–e** gave the corresponding benzodiazepines **4c–e** in good yields. The products were formed diastereoselectively as the pure *trans* isomers, but only when the photolyses were performed on a small scale. Large-scale (0.1 mol) irradiation of **2e** using a 3 kW XeCl excimer system resulted in **4e** as a 1:1 mixture of diastereoisomers.^[11] This mixture could also be produced from pure *trans*-**4e** by treatment with catalytic amounts of trifluoroacetic acid (via the corresponding acyl iminium cation)^[12] which clearly shows, that the photocyclization is kinetically controlled. As we had now established the structural requirements for efficient and selective photocyclization, we started to investigate cyclic α -amino acids as substrate components.

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The proline derivative **2f**-H ($X = H$) was synthesized with $ee > 95\%$ by coupling its benzyl ester and *N*-phthaloyl anthranilic acid (**1**) with DCC/HOBT and subsequent debenzoylation with H_2/Pd . Photodecarboxylation of the corresponding potassium salt in an acetone/water mixture (1/1) resulted in the formation of the pentacyclic product **4f**-H (Scheme 3 and Table 1) in 45% yield and with a diastereoselectivity of



Scheme 3. Decarboxylative photocyclization of anthranilic acid derivatives **2f**-H, **g**-H.

Table 1. Characteristic data for **4f**-H and **4g**-H.^[a]

4f-H: mp 113–116 °C (acetone); $[\alpha]_D^{20}$: +71.2° (methanol, $c = 1$); IR (CsI): $\tilde{\nu} = 3460, 2363, 1717, 1616, 1559, 1506\text{ cm}^{-1}$; $^1\text{H NMR}$: $\delta = 1.1\text{--}1.30$ (m, 1H), 1.71 (dt, $J = 12.7, 7.2\text{ Hz}$, 1H), 2.06–2.20 (m, 1H), 2.50 (dd, $J = 13.7, 7.1\text{ Hz}$, 1H), 3.05 (dt, $J = 11.2, 8.7\text{ Hz}$, 1H), 3.21–3.31 (m, 1H), 4.00 (d, $J = 8.6\text{ Hz}$, 1H), 4.96 (s, 1H; OH), 7.29 (dd, $J = 7.7, 1.1\text{ Hz}$, 1H), 7.43–7.77 (m, 7H); $^{13}\text{C NMR}$: $\delta = 22.7$ (CH_2), 26.8 (CH_2), 45.2 (CH_2), 63.4 (CH), 96.9 (C_q), 123.9 (CH), 124.1 (CH), 129.2 (CH), 129.9 (CH), 130.4 (CH), 131.1 (CH), 132.2 (C_q), 132.3 (CH), 132.8 (C_q), 134.0 (CH), 134.6 (C_q), 143.2 (C_q), 167.5 (C_q), 167.9 (C_q); HR-MS (ESI, reference = PPG): m/z calcd for $[M + \text{Na}]$: 343.10586, found: 343.1060.

4g-H: mp 131–135 °C (acetone); $[\alpha]_D^{20}$: –96.5° (methanol, $c = 1$); IR (CsI): $\tilde{\nu} = 3345, 2958, 1716, 1622, 1486, 1405\text{ cm}^{-1}$; $^1\text{H NMR}$: $\delta = 1.39\text{--}1.49$ (m, 2H), 1.58–1.65 (m, 2H), 1.81–1.89 (m, 2H), 2.03–2.17 (m, 2H), 2.54 (dd, $J = 14.0, 8.3\text{ Hz}$, 1H), 3.57 (dt, $J = 8.1, 4.3\text{ Hz}$, 1H), 4.04 (d, $J = 9.0\text{ Hz}$, 1H), 7.22–7.71 (m, 8H); $^{13}\text{C NMR}$: $\delta = 23.7$ (CH_2), 30.1 (CH_2), 31.5 (CH_2), 32.2 (CH_2), 40.9 (CH), 63.8 (CH), 65.8 (CH), 96.8 (C_q), 123.5 (CH), 124.2 (CH), 128.8 (CH), 128.9 (CH), 129.8 (CH), 130.6 (CH), 131.5 (C_q), 131.9 (CH), 132.6 (C_q), 133.6 (CH), 135.6 (C_q), 143.8 (C_q), 166.6 (C_q), 167.6 (C_q); HR-MS (ESI, reference = PPG): m/z calcd for $[M + \text{H}]$: 361.15532, found: 361.15522.

[a] $^1\text{H NMR}$ spectra were measured at 300 MHz in CDCl_3 ; $^{13}\text{C NMR}$ spectra were measured at 75 MHz in CDCl_3 with distortionless enhancement by polarization transfer. PPG = polypropyleneglycol.

$>98\%$ (*trans* with respect to the hydroxy group and the annulated pyrrolidine ring). Its relative configuration was also proven by X-ray crystal structure analysis.^[13] Compound **4f**-H crystallized in nonracemic form in the space group $P2_12_12_1$; the crude material showed an optical rotation of +71.2 ($c = 1$, MeOH). HPLC comparison of racemic ($\pm$)-**4f**-H (from ($\pm$)-**2f**-H) with the product from enantiomerically pure (+)-**2f**-H

resulted in a surprisingly high ee value of 86%.^[14] This result was unexpected because **4f**-H results from the combination of a 1,7-triplet diradical.

The absolute configuration of **4f**-H could not be determined despite several derivatization experiments. Identical results concerning the enantioselectivity of the photocyclization were obtained with the 4-chloro derivative **4f**-Cl (from 4-chloroanthranilic acid). We did not succeed, however, in crystallizing this material. Consequently, a substrate analogous to proline with additional chiral information had to be applied. We did not succeed in isolating the photoproduct from 4-hydroxyproline. The application of (all-*R*)-2-azabicyclo-[3.3.0]octan-3-oic acid was successful. This waste product from the industrial synthesis of the ACE-inhibitor Ramipril^[15] could be readily transformed into the substrate **2g**-H. Photodecarboxylation resulted in 65% yield of the hexacyclic product **4g**-H, whose relative (and thus also absolute) configuration was determined by X-ray crystal structure analysis.^[13] This analysis showed unambiguously that the diradical combination proceeded with complete inversion of configuration at the stereogenic α center.

In order to rule out the possibility that this effect is related to the sterically shielding bicyclooctane skeleton, the CD spectra of the substrates **2f**-H, **g**-H, as well as the products **4f**-H, **g**-H, were compared. As a consequence of the different configurations at the stereogenic α centers, the CD spectra of the starting materials **2f**-H, **g**-H showed opposite Cotton effects at 244 ($\Delta\epsilon = -20.6$) and 243 nm ($\Delta\epsilon = +27.3$), respectively (Figure 1). The size and direction of these Cotton

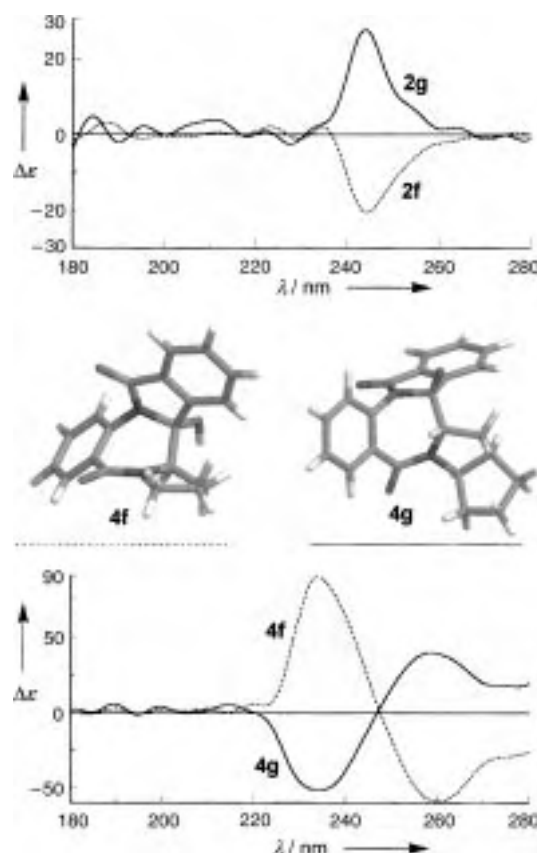


Figure 1. CD Spectra of **2f**-H, **g**-H (top); CD spectra (middle) and X-ray structures (bottom) of **4f**-H, **g**-H.

effects were in agreement with those reported by Gawronski and co-workers for several *N*-phthaloyl amino acids.^[16] Due to the photocyclization, the long-wavelength absorption maximum of the chromophore is shifted hypsochromic (from 290 to <250 nm)^[7] and consequently the maxima in the CD spectra were also shifted to 233 nm (**4f-H**, $\Delta\epsilon = +88.9$) and 234 nm (**4g-H**, $\Delta\epsilon = -51.9$). The absolute configuration of the products were determined through the exciton rule.^[17] Compound **4g-H** shows positive exciton chirality (and thus a negative Cotton effect in the short-wavelength region). The mirror-image behavior of the CD spectra of substrates and products when comparing proline and 2-azabicyclo[3.3.0]octanoic acid derivatives clearly proved that inversion of configuration also occurs for the photocyclization of the proline substrate **2f-H** (Figure 1).

As an explanation for the high degree of memory of chirality, we assume that the intermediary (atropisomeric) 1,7-triplet diradicals exhibit high activation barriers for rotation about the central C–N single bond and thus preserve their absolute axial chirality during the course of the reaction. Force-field calculations for the proline substrate **2f-H** resulted in an activation barrier of approximately 55 kJ mol⁻¹.^[18] This classifies these substrates as non-diaryl atropisomers with restricted single bond rotations in the arylimide, as well as the amide moiety.^[19] The kinetically controlled simple diastereoselectivity (see above) most probably results from diradical conformations determined by spin-orbit coupling that are capable of rapid spin inversion. This model was already successfully applied to cyclization reactions involving 1,4-^[20] and 1,6-diradicals.^[21]

Experimental Section

A solution of carboxylic acid **2** (3.00 mmol) in acetone (10 mL) was treated with a solution of potassium carbonate (1.5 mmol) in water (15 mL) and heated to 50 °C for 2 min. After dilution with acetone (90 mL) and water (90 mL), the solution is irradiated for 12 h under a nitrogen atmosphere in a Rayonet photoreactor ($\lambda = 300 \pm 10$ nm, ca. 800 W) at 15 °C. After treatment with saturated sodium bicarbonate solution (10 mL) and extraction with ethyl acetate (3 × 40 mL), the organic phase was separated, washed with diluted aqueous sodium bicarbonate, and dried. After evaporation of the solvent, **4** was recrystallized or purified by column chromatography.

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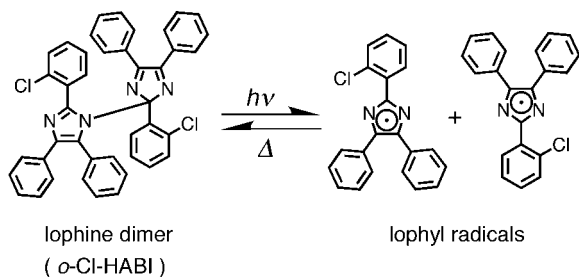
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EPR and Density Functional Studies of Light-Induced Radical Pairs in a Single Crystal of a Hexaarylbiimidazolyl Derivative**

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The intermolecular exchange coupling $2J$ is a measure of the electrostatic energy difference between the singlet and triplet states of a radical pair (RP), and is closely related to such important processes as electron and excitation transfer as well as bulk magnetism in both materials and biological systems.^[1] The photolytic generation of RPs trapped in proximity in the solid state is a well-established phenomenon. Hexaarylbiimidazoles (HABIs) are readily cleaved, both thermally and photochemically, into a pair of triarylimidazolyl radicals called lophyl radicals that can recombine to form the lophine dimer (Scheme 1).^[2] We have recently reported an unprecedented example of the in situ direct observation of a light-induced RP in a crystal of 2,2'-di(*ortho*-chlorophenyl)-4,4',5,5'-tetraphenylbiimidazole (*o*-Cl-HABI) by X-ray diffraction at 103 K.^[3] Radical pairs created by homolysis in single crystals present an opportunity to observe electron–electron through-space coupling between well-characterized



Scheme 1. Reversible photodissociation of *o*-Cl-HABI into two triaryl-imidazolyl radicals (lophyl radicals).

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species.^[4] It enables one to explore systematically the chemistry of the radical pair, a process that is not easily probed by standard solution methods. We report here the first example of the measurement of intermolecular exchange coupling for the light-induced RP in a crystal of *o*-Cl-HABI (Figure 1) and describe the theoretical analyses based on density functional theory.



Figure 1. Perspective views of *o*-Cl-HABI (gray line) and its RP (black line) as determined by X-ray crystallography.

Although the photochromic behavior of HABI and its derivatives in solution and solid matrices has been extensively studied by spectroscopic methods, including electron paramagnetic resonance (EPR), there is practically no knowledge of the intermolecular exchange coupling for the pair of lophyl radicals.^[2b, c, f, 5] Moreover, no EPR studies have been reported on single crystals of HABIs. Although UV irradiation of a single crystal of *o*-Cl-HABI at room temperature leads to no photochemical reaction, the crystal turns from pale yellow to reddish brown on irradiation with UV light at low temperatures ($T \leq 160$ K). The EPR spectrum of the UV-irradiated powder sample of *o*-Cl-HABI at 3.6 K shows a randomly oriented triplet pattern with an overlapping doublet signal derived from a trace of free radicals. The detection of a forbidden weak transition ($\Delta M_s = 2$) at half-field indicates the presence of a triplet-state species, which is assigned to the light-induced triplet RP (pair A). The zero-field splitting (zfs) parameters for the triplet RP are estimated to be $|D/hc| = 0.0111 \text{ cm}^{-1}$ and $|E/hc| \leq 0.0008 \text{ cm}^{-1}$ by simulation of the spectral line shape by the eigenfield method.^[6] The simulated and the experimental spectra are shown in Figure 2a for comparison. However, photolysis of the sample at 50 K gives a different EPR spectrum (Figure 2b) which is characterized by the zfs parameters $|D/hc| = 0.0103 \text{ cm}^{-1}$ and $|E/hc| \leq 0.0007 \text{ cm}^{-1}$ for another triplet state RP (pair B). The zfs parameters are an extremely sensitive probe of RPs since they are inversely proportional to the cube of the distance separating the radical centers. Pairs A and B are chemically identical, differing only in the spatial arrangement of the two lophyl radicals. The average distances between the two radical centers of pairs A and B, as derived from the point dipole approximation, correspond to 6.32 and 6.26 Å, respectively.^[7]

The temperature dependence of the EPR spectral pattern shows that pair A converts irreversibly into pair B on increasing the temperature. The EPR measurement on the single crystal clearly demonstrates this conversion process

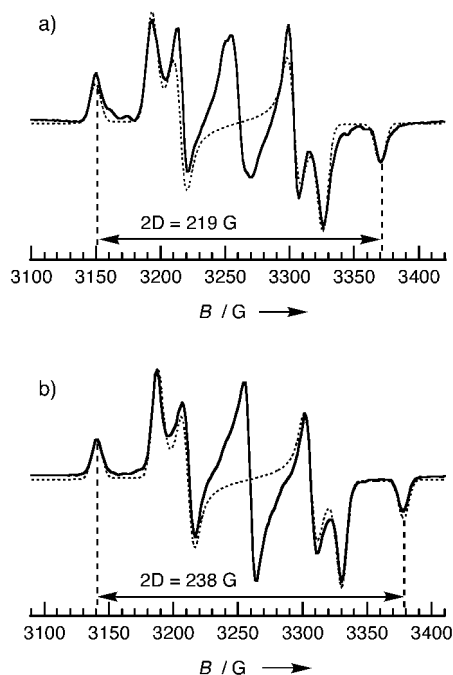


Figure 2. EPR spectra of a UV-irradiated powder sample of *o*-Cl-HABI at a) 3.6 K, and b) 50 K. Dotted curves show spectral simulations. Simulations used $g_{\text{iso}} = 2.003$ and Gaussian line shapes with varying line widths. The yellow single crystal of *o*-Cl-HABI was recrystallized from benzene/acetonitrile solution. The polycrystalline powder used in the powder-pattern EPR measurements was obtained by pulverizing the single crystals. The RP was generated at 2.0 K by the photolysis of the polycrystalline powder of *o*-Cl-HABI. Photolysis was carried out by 365 nm light from a 500 W high-pressure mercury lamp for 1 min. The powder-pattern EPR measurements were carried out at 3.6 and 50 K with a JEOL JES-RE3X spectrometer operating at the X-band.

(Figure 3a). The irradiated single crystal shows a typical triplet EPR signal pattern with doublet splitting arising from electron–electron dipolar interaction within closely spaced RPs. When the crystal irradiated at 2 K was warmed to 140 K, the EPR signal of pair A completely disappeared. In fact, the EPR signal of pair A did not reappear on cooling the sample from 140 to 20 K, but the EPR signal intensity of pair B at 20 K increased relative to that measured at 20 K before the

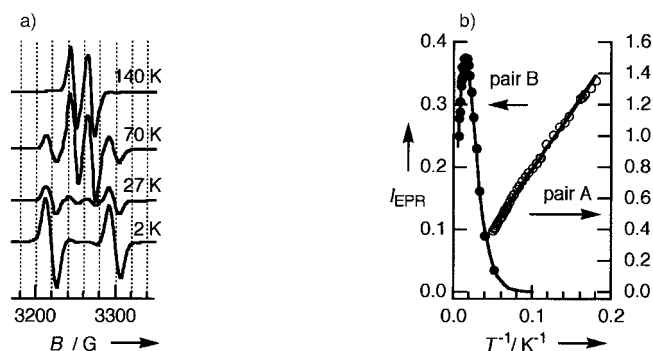


Figure 3. a) EPR spectra at 2 K for a single crystal of *o*-Cl-HABI after photolysis at 2 K and annealing it to the temperatures indicated above each trace. b) Curie plot of the EPR spectral intensity versus reciprocal absolute temperature for pairs A and B. The Curie plot for pair B was measured for the sample free of pair A by annealing to 145 K. The temperature dependence of the EPR spectra of the single crystal was observed between 2–140 K. The fitted curve for pair B was obtained by nonlinear least-squares analysis.

warming process. This observation gives unambiguous evidence for the thermal conversion of pair A into pair B. It is remarkable that the doublet splitting for pair A is significantly larger than that for pair B. The dipole–dipole interaction between the lophyl radicals in pair A seems to have a different magnitude to that in pair B as a result of the difference in their spatial arrangement. Pair A is stable between 2–20 K and does not convert into pair B. Increasing the temperature above 170 K results in the disappearance of the EPR signal of pair B as a result of a reversible radical recombination to form the lophine dimer. Curie analyses were carried out on the intensities of the signals in the EPR spectra for each RP as functions of reciprocal temperatures (Figure 3b). The Curie plot for pair A gives a straight line between 6.1 and 20 K. A linear Curie plot does not prove absolutely that the spectrum observed belongs to a high-spin ground state, but strongly supports that the triplet state of pair A could be the ground state or is nearly degenerate with the singlet state. The Curie plot for pair B, however, shows a maximum at $T \approx 70$ K, which suggests that the observed triplet state is thermally populated and the singlet state is the ground state. By assuming thermal equilibrium between the ground singlet state and excited triplet state, the exchange coupling between the unpaired electrons ($2J$) was determined to be -77 cm^{-1} for pair B.^[8] Thus the energy gap ΔE_{ST} between the ground singlet and the thermally excited triplet states for pair B was determined to be 218 cal mol^{-1} .

Our previous X-ray crystallographic study for a single crystal of *o*-Cl-HABI measured after UV irradiation at 103 K has revealed the molecular geometry of the light-induced RP for pair B. The success of the X-ray analysis makes it possible to explore theoretical analyses of the light-induced RPs of known structures. Density functional theory (DFT) is well-known to handle properly both open-shell and closed-shell structures, and the unrestricted Becke3LYP/6–31G* calculations provide excellent results for the ΔE_{ST} value of diradicals.^[9] We then computed the zfs parameter and ΔE_{ST} for pair B by the spin-polarized DFT method.^[10] The spin-up (α) and spin-down (β) electrons are calculated separately in spin-polarized DFT, which is critical for any system with unpaired spin density where local regions in the system can have different α and β electron densities. As can be seen from Figure 4, electrons with α and β spin can occupy different sets of spatial orbitals even in the singlet RP in order to stabilize the energy of the system. The spin density in pair B is mainly delocalized over each imidazolyl ring. The calculated $|D/hc|$ value of 0.0175 cm^{-1} is in good agreement with the experimental value of 0.0111 cm^{-1} , which indicates that the UB3LYP/6–31G* calculations appear to be promising for determining spin-density distributions in the light-induced RP. The DFT calculations yielded a lower singlet total energy with respect to that of the triplet, which reflects the EPR results. The total SCF energies and the eigenvalues of total spin operator $\hat{S}^2$ for the singlet and triplet RPs are summarized in Table 1. The unrestricted Kohn–Sham wave functions obtained from SCF calculations are eigenfunctions of $\hat{S}_z$ but are not eigenfunctions of $\hat{S}^2$. Therefore, we calculated the spin-projected energies for the triplet and singlet states for the RP in order to determine the value of the exchange coupling $2J$ from the

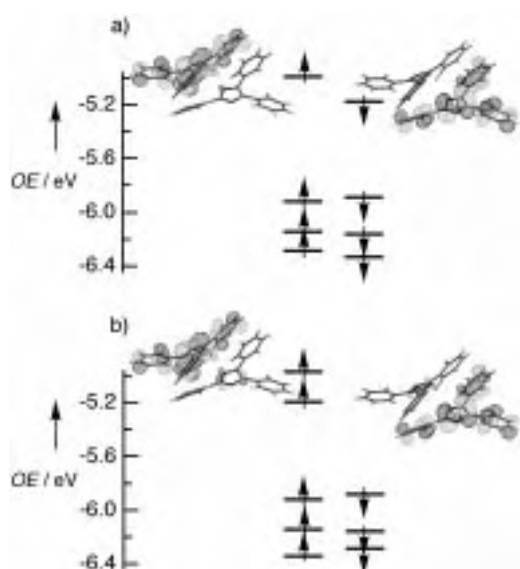


Figure 4. Molecular orbital energy level diagrams and singly occupied molecular orbitals (SOMOs) for a) the singlet state of pair B and b) the triplet state of pair B as obtained from the UB3LYP/6–31G* method. OE = orbital energy.

Table 1. Becke3LYP/6–31G* energies and $\langle S^2 \rangle$ values for the singlet and triplet states for pair B.

Spin state	HF energy (UB + HF-LYP) [hartree]	$\langle S^2 \rangle$
singlet	–2756.15237298	0.3394
triplet	–2756.15211899	2.0013

DFT calculations.^[9a, d, 11] The coupling constant $2J$ was evaluated by calculating the spin-projected energy difference between the singlet and triplet states. The obtained $2J$ value of -45 cm^{-1} compares well with the experimental value of -77 cm^{-1} .

In summary, we have succeeded for the first time in determining the intermolecular exchange coupling for the light-induced RP in a crystal of *o*-Cl-HABI. This study shows that DFT methods can provide an accurate description even for the through-space coupling in RPs. A combination study of X-ray diffraction and DFT calculations for the light-induced RPs in HABI derivatives will lead to a better understanding of radical-pair chemistry and solid-state reactions.

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The First Direct Determination of a Ligand Binding Constant in Protein Crystals

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In the field of protein–ligand interactions there have been many recent attempts to predict protein–ligand dissociation constants by correlating solution binding measurements with structural features from series of protein–ligand crystal complexes.^[1–6] Indeed the whole structure-based design approach relies on the assumption that the thermodynamics of binding and the structures of bound ligands in the crystal will be similar to those in the biological environment. The results presented herein provide the first evidence that this is indeed the case.

Cyclophilins provide a good template for the study of ligand binding as there is relatively little change in their backbone conformation on binding.^[7] To date the only structural data on ligand complexes is for cyclosporin derivatives or proline-containing peptides.^[8–10] The isoform cyclophilin 3 from *Caenorhabditis elegans* (ceCyp3) was selected as the template

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for this binding study because of the availability of high symmetry, well-diffracting crystals which were amenable to ligand-soaking experiments. The enzymatic properties and the X-ray structure of the free form have been described.^[11]

Solution binding and inhibition of ceCyp3 by the Ala-Pro ligand was measured by its ability to inhibit peptidylprolyl isomerase (PPIase) activity. The peptidylprolyl imide bond can adopt *cis* and *trans* conformations and the assay depends on the fact that chymotrypsin can only cleave the imide bond of the chromogenic prolyl substrate when it is in the *trans* conformation. The PPIase activity of cyclophilins catalyzes the rotation about this imide bond, thus speeding up the rate at which the *cis*–*trans* equilibrium is reached.^[12, 13] Ala-Pro acts as a weak inhibitor of the PPIase activity, with a measured K_d value of 23.3 mM (Figure 1).

To measure the binding constant of the Ala-Pro ligand in the crystal a series of native ceCyp3 crystals were equilibrated against different concentrations of ligand (1.2–120 mM) and the individual X-ray structures refined. X-ray refinement statistics for the structures are given in Table 1. The refined structure of the crystal soaked in 120 mM Ala-Pro shows a well-defined ligand structure with seven hydrogen bonds involved in the ligand–protein binding (Figure 2b). The guanidino group of Arg62 adopts a very different orientation to that in the native structure and displaces water molecule W_d which is present in the native structure (Figure 2a). A further three water molecules (W_a , W_b , and W_c) present in the native structure are also displaced by the Ala-Pro ligand. All other residues around the binding site, with the exception of Arg62, adopt an identical conformation to that found in the native structure.

The (2Fo–Fc) electron density maps around the binding site of ceCyp3 complexed with different concentrations of Ala-Pro provide a graphic illustration of the conversion of the native to the ligand-bound structure (Figures 3a–g). The crystal soaked in a 120 mM solution of the ligand (Figure 3g) and the native crystal (Figure 3a) provide pictures of the two extremes. The five structures soaked with intermediate

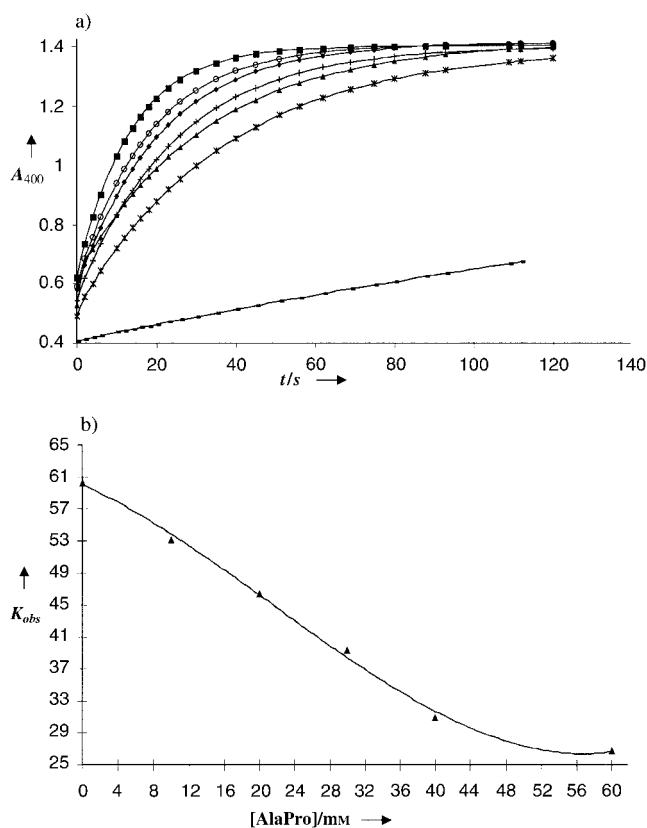


Figure 1. a) Inhibition of PPIase activity of ceCyp3 with increasing concentrations of Ala-Pro. Absorbance values were collected every 0.1 s over 2 min. The protein concentration was 20 nM and concentrations of Ala-Pro ranging between 0 and 60 mM were added. b) Determination of the K_d value for PPIase inhibition of ceCyp3 by Ala-Pro. Initial velocities from Figure 1a were used to determine k_{obsd} ($k_{\text{obsd}} = v/[S]$), where v is the velocity and $[S]$ is the substrate concentration.^[15] A plot of k_{obsd} against inhibitor concentration gives an Ala-Pro concentration of 23.3 mM for 50% inhibition. This IC_{50} value can be taken as an estimate for K_d by using $K_d = [E][L]/[EL]$ and at 50% inhibition $[E] = [EL] = 0.5[E]_T$ (where $[E]_T$ = total protein concentration, $[E]$ = free protein concentration, $[L]$ = free ligand concentration, and $[EL]$ = protein concentration bound to ligand). With a large excess of ligand, the assumption $[L]_{50\%} = [L] \approx [L]_T$ can be made. At the point at which half maximal inhibition occurs $[EL] = [E]$ and $K_d = [L]_T$.

Table 1. Crystallographic statistics of the seven ceCyp3 structures.^[a]

Data collection statistics	Native	1.2 mM Ala-Pro	6 mM Ala-Pro	18 mM Ala-Pro	36 mM Ala-Pro	60 mM Ala-Pro	120 mM Ala-Pro
space group, $P4_22_1$	$a = b = 60.60 \text{ \AA}$ $c = 123.1 \text{ \AA}$ $\alpha = \beta = \gamma = 90^\circ$	$a = b = 60.87 \text{ \AA}$ $c = 122.99 \text{ \AA}$ $\alpha = \beta = \gamma = 90^\circ$	$a = b = 60.74 \text{ \AA}$ $c = 122.72 \text{ \AA}$ $\alpha = \beta = \gamma = 90^\circ$	$a = b = 61.03 \text{ \AA}$ $c = 122.7 \text{ \AA}$ $\alpha = \beta = \gamma = 90^\circ$	$a = b = 61.42 \text{ \AA}$ $c = 122.47 \text{ \AA}$ $\alpha = \beta = \gamma = 90^\circ$	$a = b = 61.05 \text{ \AA}$ $c = 122.67 \text{ \AA}$ $\alpha = \beta = \gamma = 90^\circ$	$a = b = 61.03 \text{ \AA}$ $c = 122.66 \text{ \AA}$ $\alpha = \beta = \gamma = 90^\circ$
resolution range	20–1.8 $\text{\AA}$	25–2.1 $\text{\AA}$	25–2.0 $\text{\AA}$	20–1.9 $\text{\AA}$	20–1.9 $\text{\AA}$	25–2.0 $\text{\AA}$	20–1.9 $\text{\AA}$
number of reflections	145 422	165 474	189 319	146 663	224 150	270 345	152 448
measured number of unique reflections	22 053	14 262	16 311	19 030	19 185	16 443	19 230
completeness	97.0 %	98.9 %	99.7 %	98.6 %	99.5 %	95.8 %	97.6 %
multiplicity	6.59	11.60	11.60	7.70	11.60	16.44	7.92
R_{merge} (outer shell)	8.3 % (27.8 %)	9.9 % (36.2 %)	8.1 % (31.5 %)	6.7 % (34.6 %)	7.2 % (31.3 %)	7.1 % (33.2 %)	7.9 % (33.2 %)
$I/\sigma(I)$ (outer shell)	11.7 (2.60)	12.50 (3.36)	14.88 (3.62)	13.88 (2.34)	14.89 (2.90)	14.44 (2.09)	12.85 (2.13)
R_{final} ($F > 4\sigma$)	20.81 % (19.69 %)	17.65 % (16.52 %)	18.08 % (17.09 %)	20.93 % (19.44 %)	19.49 % (18.32 %)	22.56 % (19.95 %)	18.26 % (17.3 %)
R_{free} ($F > 4\sigma$)	28.47 % (26.61 %)	25.94 % (24.97 %)	26.57 % (24.45 %)	29.58 % (27.20 %)	26.84 % (24.62 %)	29.16 % (26.37 %)	25.05 % (23.77 %)
rms deviations from ideal geometry							
bond lengths [$\text{\AA}$]	0.031	0.030	0.030	0.030	0.031	0.030	0.030
angle distance [$\text{\AA}$]	0.026	0.027	0.027	0.027	0.027	0.025	0.028
mean B-factor [$\text{\AA}^2$]	30.37	33.70	31.93	32.73	30.95	35.84	31.36

[a] $R_{\text{merge}} = \sum_h |I - \langle I \rangle| / \sum_h |I|$, where $\langle I \rangle$ is the mean intensity of all observations of reflection $h = hkl$, $\sigma(I)$ is the standard deviation of the measured intensity, and R_{free} is calculated with 5 % of the data omitted from refinement for cross-validation.

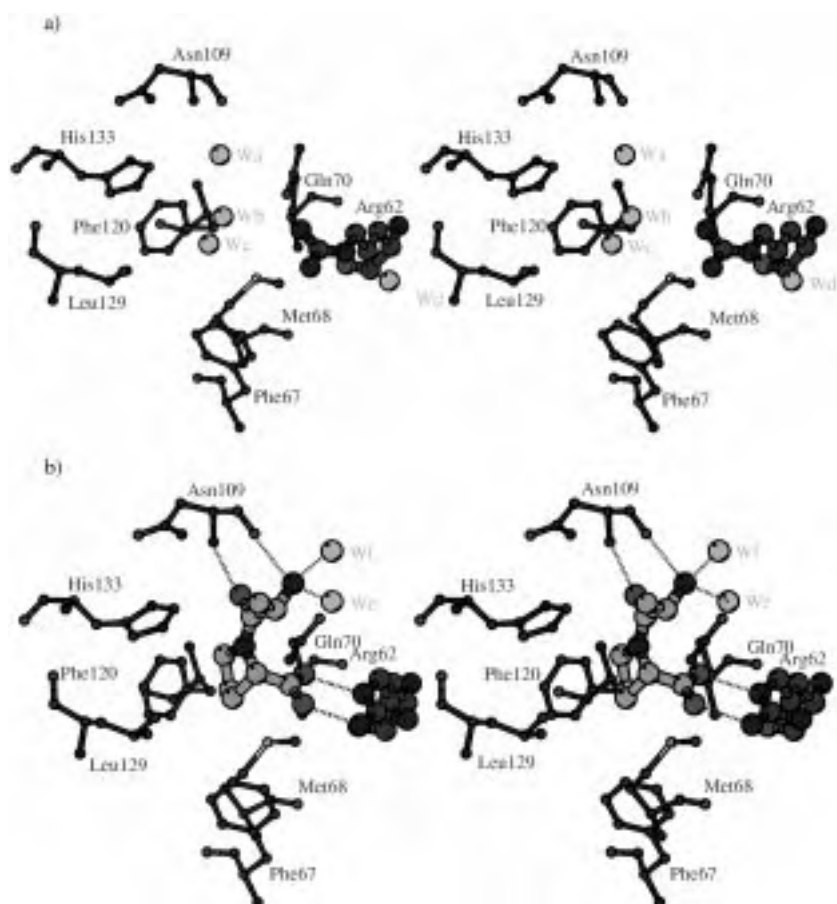


Figure 2. Active site of the structures with and without ligand. a) Stereoview of the active site of native (free) ceCyp3. The four water molecules in the active site (W_a–W_d) are coloured light gray. The side chain of Arg62 adopts a different conformation on ligand binding and is highlighted. b) Stereoview of the active site of ceCyp3 after soaking in a 120 mM solution of Ala-Pro. The seven hydrogen bonds formed by the ligand to N/Asn109, NH₂/Arg62, W_c, O/Asn109, NE/Arg62, W_b, and NE2/Gln70 are shown as dotted black lines.

concentrations of Ala-Pro can be refined as mixtures of these two extreme structures. For example, the electron density maps of the crystals obtained in 18 mM and 36 mM solutions of the ligand (Figures 3d, e) show electron density that can clearly be interpreted as a mixture of the ligand-bound and free structures. The partial occupancy of the ligand (Q_l) is defined as the fraction of the protein molecules in the crystal occupied by the Ala-Pro ligand. Q_n is the fraction of protein molecules in the crystal in the native (free) state. As each molecule in the crystal must be in one of these states then $Q_n + Q_l = 1$. With this simple two-state model, occupancies can be constrained in the following way. The occupancy of the ligand (Q_l) is the same as the occupancy of the Arg62_l in its ligand-bound conformation while the occupancy of the native

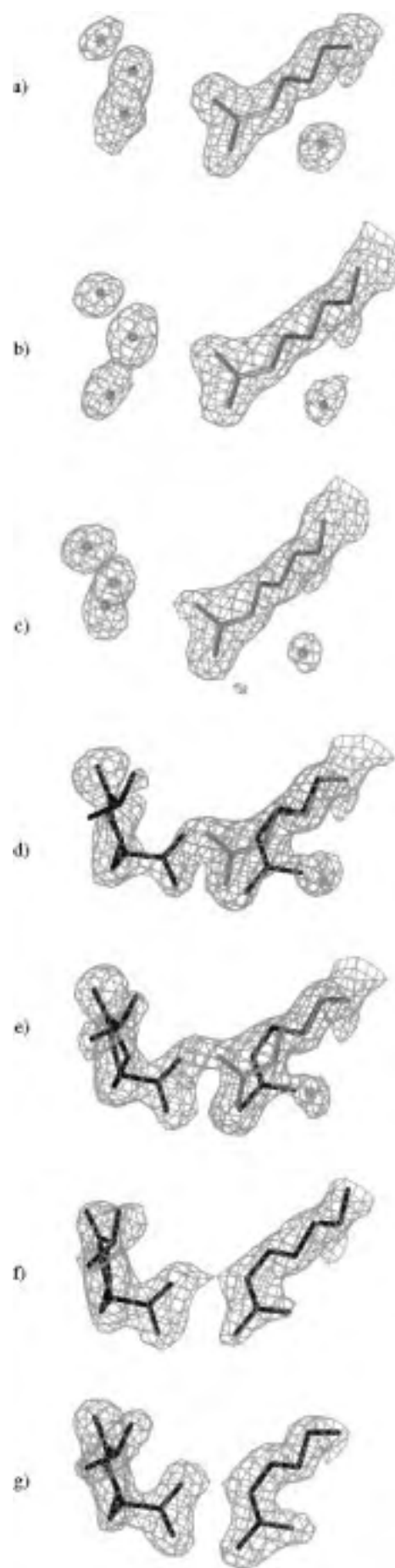
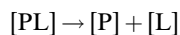


Figure 3. Difference electron density maps of crystals soaked with increasing ligand concentration. The (2Fo-Fc) maps highlighting the ligand, Arg62, and water molecules in the active site are contoured at 1.5 sigma using the program O.^[16] a) The native ceCyp3 structure shows the density of the water molecules. b) and c) The crystals were soaked in 1.2 mM and 6 mM Ala-Pro, respectively. The electron density contoured at 1.5 sigma looks almost identical to the native structure. d) and e) The crystals were soaked in 18 mM and 36 mM Ala-Pro, respectively, and can be clearly interpreted as having features of both the native (light gray) and ligand-bound (black) forms. f) and g) The crystals were soaked in 60 mM and 120 mM Ala-Pro, respectively. The electron density contoured at 1.5 sigma shows only features corresponding with the fully ligand-bound form.

structure (Q_n) is the occupancy of Arg62_(n) in the native conformation, which must be the same as the occupancy of the water molecules W_a , W_b , W_c , and W_d . These occupancy constraints can be conveniently applied using the refinement programme SHELX97,^[14] and the fractional occupancies refined. The occupancy is in fact only one parameter: $Q_l = 1 - Q_n$.

By regarding the crystal soaking experiment as a simple equilibrium in which each protein molecule in the crystal lattice can be bound or free, the fractional occupancy can be related to the dissociation constant in the following way:



$$K_{cd} = [P][L]/[PL]$$

$$[P]_{total} = [PL] + [P]$$

$$[PL] = [P]_{total} Q_l$$

$$[P] = [P]_{total} (1 - Q_l)$$

Thus,

$$K_{cd} = \{[P]_{total} (1 - Q_l)\} [L] / [P]_{total} Q_l = (1 - Q_l) [L] / Q_l$$

$$Q_l / Q_n = [L] / K_{cd}$$

where

K_{cd} is the crystal dissociation constant, $[P]$ is the concentration of free protein, $[L]$ is the concentration of the ligand (it is assumed that the concentration of ligand in the 10 μ L drop is constant throughout the soaking experiment), $[PL]$ is the concentration of protein with ligand, $[P]_{total}$ is the total concentration of protein, Q_l is the occupancy of ligand (fraction of the protein sites in the crystal occupied by ligand), Q_n is the fraction of the protein sites in the free state ($= (1 - Q_l)$).

A value of 26.8 mM was obtained for K_{cd} as calculated from the slope of the plot of (Q_l/Q_n) versus $[L]$ (Figure 4b). This value is in close agreement with the inhibition constant of 23.3 mM measured for the Ala-Pro ligand in solution using the PPIase assay. It is noteworthy that the quality and information content of the X-ray data is sufficient to accurately refine the partial occupancy of the ligand-bound structures even when visual inspection of the electron density maps suggests the electron density is dominated by one of the (native or ligand-bound) forms. In general, interpreting a structure with such low partial occupancy would be almost impossible using conventional map-fitting methods without a well-refined native structure being available. Indeed inspection of the series of electron density maps shown in Figure 3 suggests that, without prior knowledge, side-chain conformations with occupancies less than about 20% would not be readily apparent in electron density maps.

In protein–ligand complexes it can frequently be difficult to distinguish water molecules or disordered water molecules from a weakly bound ligand. A helpful feature of this system is the movement of the Arg62 side chain on ligand binding, as this gives an excellent double-check on the ligand occupancy. In a separate experiment we also showed that diffusion and binding of the ligand in this system took place on a timescale of seconds. A crystal soaked in 120 mM ligand solution for 60 seconds was flash frozen and the refined structure shown to be identical to that from a crystal soaked for 17 hours. The kinetics of ligand–protein binding is likely to vary somewhat from crystal to crystal depending on the crystal packing, solvent channel size, and ligand size. However, we suggest that

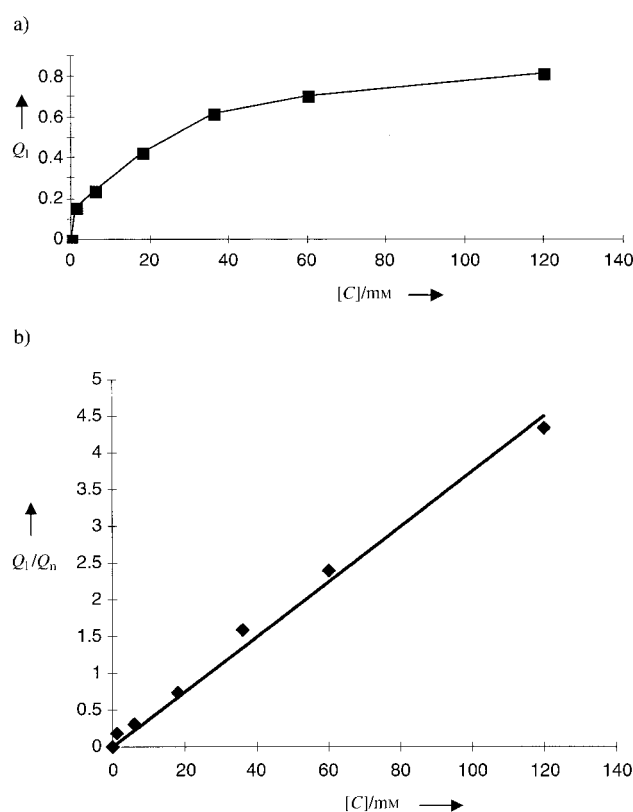


Figure 4. a) Refined occupancy for the seven different crystal structures. Each point on the curve represents the occupancy of the Ala-Pro ligand as determined from an X-ray refinement of a crystal soaked in a given concentration of Ala-Pro.^[17] The ligand concentrations used in the soaking experiments were 0, 1.2, 6, 18, 36, 60, and 120 mM. The corresponding occupancies obtained from crystallographic refinement were 0, 0.155, 0.238, 0.424, 0.613, 0.705, and 0.812. b) Plot of ligand concentration against Q_l/Q_n . Q_l : occupancy of ligand (fraction of the protein sites in the crystal occupied by ligand), Q_n : fraction of the protein sites in the free state ($= (1 - Q_l)$). The ligand occupancies of the different crystals were measured by crystallographic refinement as described in the text. The experimental data fit the theoretical line with a high R^2 value of 0.990 and a slope $1/K_{cd} = 0.0373$. This gives a value for K_{cd} (the crystal dissociation constant) of 26.8 mM.

for a large number of proteins, this crystallographic method of measuring binding constants could be developed into a relatively efficient and routine technique.

Experimental Section

Crystallization and data collection: CeCyp3 was crystallized at 16 °C by the hanging drop vapour-diffusion method using 29–31% poly(ethylene glycol) methyl ether 5000 (MPEG 5000) as precipitant.^[11] Native ceCyp3 crystals (approximately 0.2 × 0.3 × 0.3 mm) were soaked in six 10 μ L drops of well solution containing the Ala-Pro dipeptide at 1.2, 6, 18, 36, 60, and 120 mM, respectively. Crystals were soaked for between 17 and 27 hours.

The composition of the cryoprotectant was glycerol (0.2 mL), MPEG 5000 (0.7 mL), 1.0 M sodium citrate/citric acid (0.1 mL, pH 5.6). Crystals were mounted in a 0.2–0.3-mm cryoloop (Hampton Research, Inc.), dipped in cryoprotectant for a few seconds, and frozen by plunging into liquid nitrogen. The frozen crystal was then transferred to a magnetic goniometer head in a stream of nitrogen at 100 K. All diffraction data were collected on a 300-mm MarResearch imaging plate system mounted on an ENRAF Nonius FR571 rotating anode generator operating at 40 kV, 80 mA, and producing $\text{CuK}\alpha$ radiation from a graphite crystal monochromator.

Refinement: The ceCyp3 native structure was used as a starting model. Positional and B-factor refinement were performed using SHELX97

(Table 1). The coordinates of Arg62_(n), Arg62_(l), Ala-Pro, W_a, W_b, W_c, and W_d were fixed during occupancy refinement. Arg62_(n) represents the Arg62 conformation without Ala-Pro bound and Arg62_(l) represents the Arg62 conformation with Ala-Pro bound to ceCyp3. The B-factors of Arg62_(n), W_a, W_b, W_c, and W_d were fixed to the same B-factor values as those of the native structure. Individual atomic B-factors for Arg62_(l) and Ala-Pro were refined together with occupancy (Figure 4). The restraints applied in the occupancy refinement are summarized below:

$$Q_{\text{Arg62(n)}} + Q_{\text{Arg62(l)}} = 1$$

$$Q_{\text{Arg62(l)}} = Q_l$$

$$Q_{\text{Arg62(n)}} = Q_{W_a} = Q_{W_b} = Q_{W_c} = Q_{W_d}$$

where

$Q_{\text{Arg62(n)}}$: is the occupancy of the Arg62 conformation with no Ala-Pro binding, $Q_{\text{Arg62(l)}}$: is the occupancy of the Arg62 conformation with Ala-Pro binding, and Q_l : is the occupancy of Ala-Pro.

PPIase assay:^[13] α -chymotrypsin selectively hydrolyzes the C-terminal *p*-nitroanilide bond of the substrate in the *trans* X-Pro conformer only. This hydrolysis releases the chromophore 4-nitroaniline, the accumulation of which is recorded by measuring the absorbance at 400 nm as a function of time. Substrate (*N*-succinyl-Ala-Ala-Pro-Phe-*p*-nitroanilide, Bachem AG) was dissolved in LiCl/2,2,2-trifluoroethanol (LiCl/TFE) to give a stock solution of 100 mM. The experiment took place at 4 °C. Constant temperature was maintained within the cuvette by a Peltier (PTP-1) temperature control unit. A Perkin–Elmer UV/Vis Lambda 20 spectrophotometer was used.

Proteins: ceCyp3 solution was freshly prepared before the experiment from frozen stock solution, at the appropriate concentration, by dilution in buffer 50 mM 2-[4-[2-hydroxyethyl]-1-piperazinyl]ethanesulfonic acid (HEPES), 100 mM NaCl, pH 8.0 (buffer A).

α -chymotrypsin (Sigma): In a typical experiment 10 μ L of 20 mM ceCyp3 was made up to 870 μ L with buffer A and the appropriate volume of Ala-Pro in a 1-mL cuvette. The cuvette was then preincubated for 30 min on ice. Immediately before the assay, 100 μ L of chymotrypsin solution (50 mg mL⁻¹ in 10 mM HCl) was added, followed by 30 μ L of a 3.7 μ M stock solution of Suc-Ala-Ala-Pro-PNA in LiCl (470 mM)/TFE. The reaction progress was monitored by the absorbance change at 400 nm that accompanies the hydrolysis of the amide bond and the release of 4-nitroaniline.

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A Heterogeneous *cis*-Dihydroxylation Catalyst with Stable, Site-Isolated Osmium–Diolate Reaction Centers**

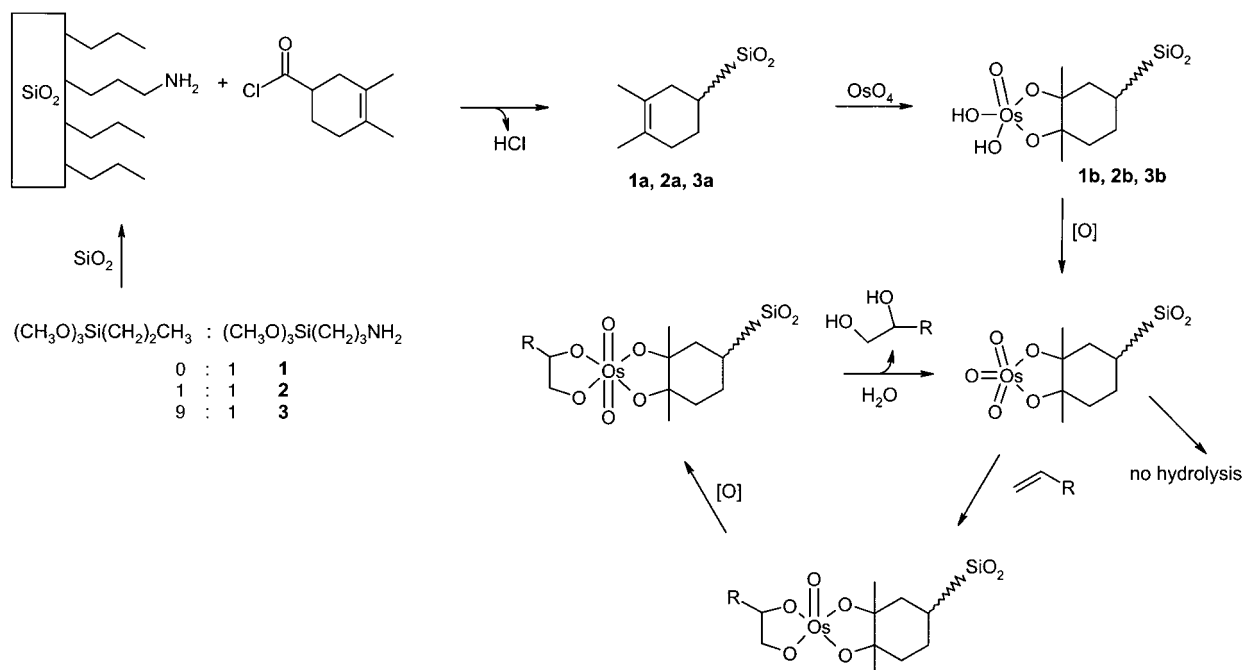
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Osmium tetroxide is by far the most versatile catalyst for *cis*-dihydroxylation (DH) of double bonds.^[1, 2] When homogeneous catalysts are used, free OsO₄ is always present in some step of the catalytic cycle, and the high toxicity and volatility of OsO₄ have hitherto obstructed industrial application. Previous attempts to immobilize OsO₄ used polymers, for example, with coordination of OsO₄ on polyvinylpyridine.^[3, 4] However, hydrolysis of the intermediate Os^{VI} diolate complex requires that Os is detached from the polymeric Lewis base,^[5] and this implies an inherent liability to Os leaching. Similarly, reports on immobilized alkaloids for asymmetric DH mention that Os leaching necessitates Os supplementation in subsequent runs.^[6] In another attempt, OsO₄ was entrapped in polystyrene microspheres, but the mechanism by which OsO₄ is retained within the polymer is not understood.^[7] Herein we report a solid with Os^{VIII} type reactivity, and with a persistent bond between Os and the support. Rigorous heterogeneity tests and reactions with 12 olefins substantiate the value of the new Os catalyst.

Our approach is rooted in the mechanism of the *cis*-dihydroxylation, which comprises two stages: 1) attack of the Os^{VIII} *cis*-dioxo complex on the olefin (osmylation), 2) reoxidation of Os^{VI} to Os^{VIII} and hydrolytic release of the diol. Two points are particularly relevant. First, if the hydrolytic conditions are not too drastic, *tetrasubstituted* olefins are not converted into *cis*-diols.^[8, 9] These olefins are smoothly osmylated to an osmate(VI) ester, but the rate of subsequent hydrolysis is zero (0% yield for a tetrasubstituted olefin vs. 83% for a trisubstituted olefin, ref. [8]). Second, an Os^{VI} monodiolate complex can be reoxidized to *cis*-dioxo Os^{VIII} without release of the diol; subsequent addition of a second olefin results in an Os bisdiolate complex.^[10] These two properties make it possible to immobilize a catalytically active Os compound by the addition of OsO₄ to a tetrasubstituted olefin that is covalently linked to a silica support (**1a**, Scheme 1). The tetrasubstituted diolate ester (**1b**) which is

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Scheme 1. Immobilization of Os in a tertiary diolate complex, and proposed catalytic cycle for *cis*-dihydroxylation ([O] = *N*-methylmorpholine *N*-oxide).

formed at one side of the Os atom is stable, and keeps the catalyst fixed to the support material. The catalytic reaction can then take place at the free coordination sites of Os.

For the preparation of a silica-anchored tetrasubstituted olefin, silica is first functionalized with 3-aminopropyltrimethoxysilane (Scheme 1).^[11] Next 3,4-dimethylcyclohex-3-enylcarbonyl chloride is added, which reacts with the grafted amino groups to form an amide. The 3,4-dimethylcyclohex-3-enylcarbonyl chloride is prepared by the Diels–Alder reaction of 2,3-dimethyl-1,3-butadiene and ethyl acrylate, and conversion of the ester into the acid chloride.^[12] Next, OsO₄ adds to the double bond in the functionalized support **1a** ($\rightarrow$ **1b**). To avoid handling the poisonous OsO₄, hexavalent K₂OsO₂(OH)₄ is used as an Os source, and oxidized in situ to OsO₄ with *N*-methylmorpholine *N*-oxide (NMO) in *tert*-butyl alcohol:dichloromethane (2:1).^[13] Excess OsO₄ is removed from **1b** by threefold washing with the same solvent mixture.

Physicochemical observations confirm that Os is immobilized in surface-linked diolate complexes. In solution chemistry, reaction of OsO₄ with an olefin gives rise to dark brown Os^{VI} complexes. In the reaction of the solid support **1a** with OsO₄, the solid (**1b**) turns dark brown, while no color develops in solution. Diffuse reflectance spectroscopy measurements of the solid show intense absorptions at wavelengths shorter than 700 nm. More detailed information is obtained from solid-state ¹³C NMR spectrometry (Figure 1). The amide signal at $\delta=177$ (for **1a**) confirms the successful attachment of the acyl group to the surface. The spectrum of the Os-free material (**1a**) shows a C=C signal at $\delta=124$, characteristic for the tetrasubstituted olefin. When OsO₄ is added ($\rightarrow$ **1b**), this signal is replaced by a new signal at $\delta=92$. The tertiary alcohol groups in Os(VI) diolate complexes (prepared from OsO₄ and 3,4-dimethylcyclohex-3-enylcarboxylic acid) have a resonance signal in solution NMR spectroscopy between $\delta=90$ and 95. Thus, the intense peak at $\delta=92$ in the solid-state spectrum of

1b confirms that Os is bound by esters of tertiary diols. The immobilized Os is easily observed with X-Ray photoelectron spectroscopy (XPS). Os 4f_{7/2} lines at 53.6 eV and 51.2 eV demonstrate that osmium is in the +VI and +IV state. Based on reported values, this is clear evidence that the octavalent OsO₄ is reduced in the reaction with the covalently linked double bond.^[14]

Catalysis with the new solid Os materials reveals that the activity strongly depends on the concentration of the Os ester groups on the surface: the highest activity is observed for the lowest concentration of Os-binding groups! (Table 1, entries 1–3). The Os loading is easily controlled by performing the surface functionalization with mixtures of silylating agents

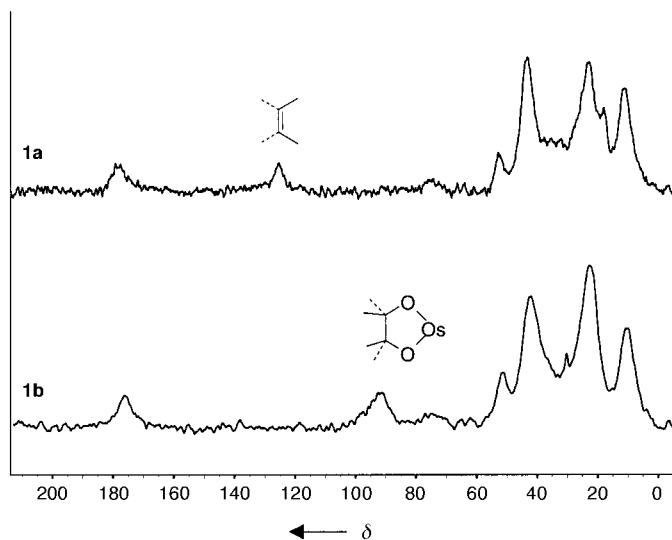


Figure 1. Solid state ¹³C MAS NMR spectra of **1a** (top), with immobilized tetrasubstituted olefin, and **1b** (bottom), that is, **1a** after addition of OsO₄ to the double bond (high power proton decoupling; 45° pulses with 10 s recycle time; spinning rate 10 kHz).

Table 1. Heterogeneous *cis*-dihydroxylation of 1-hexene: effect of the dilution of active sites with propyltrimethoxysilane (PrTMS):^[a] comparison with homogeneous dihydroxylation with or without 2,3,4-trimethyl-2-pentene.

Entry	Catalyst	PrTMS:NH ₂ PrTMS	<i>t</i> [h]	Conversion [%]
1	1b	0:1	24	1
2	2b	1:1	24	5
3	3b	9:1	24	66
4	OsO ₄ ^[b]	–	10	98
5	OsO ₄ ^[c]	–	10	0

[a] 100 mg supported catalyst, 1-hexene (1.6 mmol), NMO (1.6 mmol), solvent (3 mL), and RT unless otherwise stated. [b] NMO:1-hexene:Os = 400:400:1 [c] NMO:1-hexene:2,3,4-trimethyl-2-pentene:Os = 400:400:10:1; 1-hexene is added 4 h after the other reagents.

(Scheme 1). The highest activity is obtained after silylation with a 9:1 mixture of propyltrimethoxysilane (PrTMS) and 3-aminopropyltrimethoxysilane (NH₂PrTMS). This results in a material (**3b**) with the Os centers diluted by propyl groups (Si:Os = 270, as determined by XPS). In contrast, the material is practically inactive when the surface coverage with Os-binding tetrasubstituted alkene groups is raised (for **1b**: Si:Os = 36, XPS). The deactivation of Os by a high surface concentration of Os-binding alkene groups is explained by double-sided binding of Os by two adjacent tetrasubstituted alkenes. This situation is easily mimicked in homogeneous catalytic experiments, by adding 10 equivalents of the tetrasubstituted 2,3,4-trimethyl-2-pentene per Os to the catalytic dihydroxylation of 1-hexene with NMO (Table 1, entries 4 and 5). Product formation from 1-hexene is fully blocked by a small amount of the tetrasubstituted alkene, since the latter forms bisdiolate complexes that are not hydrolyzed in the mild conditions of our experiments. A similar situation arises in the heterogeneous catalyst if the Os-binding tetrasubstituted alkene groups are too close to each other. In contrast, appropriate site isolation, as in **3b**, ensures that a nonhydrolyzable ester is only formed at one side of the Os atom; at the other side, an olefin such as 1-hexene is dihydroxylated at a high rate.

Stringent heterogeneity tests were performed with the **3b** catalyst, by splitting the reaction suspension in the dihydroxylation of 1-hexene at a conversion of 21 %, and monitoring the conversion in the suspension and in the clear supernatant. Zero activity was found in the supernatant, while the reaction continues in the suspension (21 % in the clear solution vs. 60 % in the suspension; Table 2, entry 13). This test was successfully performed for the reaction of **3b** with several olefins, however, it fails for OsO₄ bound on polyvinylpyridine; this is because of the dissociation of the coordinative bond between Os and the nitrogen base in the hydrolytic release of the diol.

With **3b**, we succeeded in oxidizing olefins to the corresponding *cis*-diols with an excellent conversion and selectivity (Table 2). Monosubstituted, *cis* and *trans* disubstituted aliphatic olefins and cyclic olefins are stereoselectively converted to *cis* diols with good conversions and selectivities over 98 % (entries 1–7). Note that the excellent chemoselectivity of the homogeneous reactions with NMO is preserved in the heterogeneous system;^[15] overoxidation products such as the

Table 2. *Cis*-dihydroxylation of olefins with NMO and the heterogeneous **3b** catalyst.^[a]

Entry	Olefin	<i>t</i> [h]	Con- version [%]	Selecti- vity [%]
1	1-pentene	48	83	99
2 ^[b]	1-hexene	48	99	98
3	1-heptene	48	96	99
4	cyclopentene	48	83	98
5	cyclohexene	48	99	99
6	<i>cis</i> -2-hexene	48	99	99
7	<i>trans</i> -2-hexene	48	98	98
8	styrene	48	99	96
9	indene	48	72	99
10	2-methyl-2-pentene	48	50	99
		150	99	99
11	ethyl <i>trans</i> -cinnamate	24	65	99
12	ethyl <i>trans</i> -crotonate	48	85	99
13 ^[c]	1-hexene	10	21	
		20, filtrate	21	
		20, suspension	60	

[a] reaction conditions: 100 mg heterogeneous catalyst (4×10^{-6} mol Os), olefin (1.6 mmol), NMO (1.6 mmol), solvent (3 mL), H₂O (200 μ L), RT. [b] A second run was performed with the used catalyst from entry 2. After 48 h, conversion and selectivity were again 99 and 98 % respectively. [c] Filtrate test: the reaction mixture is splitted after 10 h; further conversion in filtrate and suspension is determined 20 h later.

ketol make up less than 1 % of the products. Aromatic olefins such as styrene and indene are suitable substrates as well (entries 8–9). The reaction proceeds more slowly with a trisubstituted olefin. This is not unexpected, since in our mild conditions, the hydrolysis of the trisubstituted diolate is slow because of steric hindrance. Note that an even greater steric hindrance is at the basis of the stable association between Os and the surface-bound tetrasubstituted diolate. Nevertheless, after a somewhat increased reaction time, 98 % yield is obtained from the trisubstituted 2-methyl-2-pentene. While it is known that more electron-rich double bonds are osmylated at a higher rate,^[16] the reactivity of Os^{VIII} dioxo species is sufficient to even react with relatively deactivated double bonds. Thus, unsaturated esters such as cinnamates or crotonates are dihydroxylated in high yields (entries 11–12).

As is highlighted by the heterogeneity tests, our Os-immobilization concept, and the formation of a stable tetrasubstituted diolate complex, is to date the only solution to the problem of producing such Os supported heterogeneous catalysts. The concept can be expanded to other catalyst carriers that form nonhydrolyzable bonds with Os in the conditions of the catalytic dihydroxylation. Site isolation has been demonstrated to be crucial to obtain an active and truly heterogeneous Os catalyst.

Experimental Section

The support material was commercial SiO₂ 60 from Fluka, predried at 150 °C. Surface functionalization was performed by standard reported techniques.^[11] For the functionalization of the support with Os, a solution containing OsO₄ (4×10^{-3} mmol) was treated for 4 h with the support (100 mg, containing 10^{-2} mmol of double bonds in the case of catalyst **3b**). After all the OsO₄ had reacted with the support, the catalyst was thoroughly washed with *t*BuOH:CH₂Cl₂ (2:1) to remove traces of unbound OsO₄.

In a typical catalytic dihydroxylation, the **3b** material (100 mg) was added to a mixture of the olefin (1.6 mmol), NMO (1.6 mmol), and water (200 μ L) in *t*BuOH:CH₂Cl₂ (3 mL; 2:1) solvent. The mixture was stirred at room temperature and regularly analyzed by GC.

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Stereoselective Nucleophilic Trifluoromethylation of *N*-(*tert*-Butylsulfinyl)-imines by Using Trimethyl(trifluoromethyl)-silane**

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Trifluoromethylated amines are important building blocks for pharmaceutical research.^[1] The CF₃ group, because of its strongly electron withdrawing nature, lowers the basicity of the amide bond towards nonspecific proteolysis^[2] when these amines are incorporated into peptides, as well as modify the solubility and desolvation properties.^[3] In spite of its prime

importance in the drugs industry, direct asymmetric synthesis of trifluoromethylated amines is a challenge. Pirkle et al.^[4] and Mosher and Wang^[5] prepared 2,2,2-trifluoro-1-phenylethylamine, and Soloshonok and Ono^[6] recently reported an elegant method for the preparation of perfluorinated amines by a novel [1,3]-proton shift reaction. However, all of these methods require fluorinated ketones. Nucleophilic transfer of "CF₃" to nitrones and imines for direct preparation of trifluoromethylated amines was recently achieved by Nelson et al.^[7] and Blazejewski et al.,^[8] respectively. These methods suffer from low yield and lack generality. We now report the first stereoselective synthesis of trifluoromethylated amines by using TMSCF₃ **2** (TMS = SiMe₃).

Our systematic investigation began as an extension of our earlier work,^[9] based on the fact that imines are less electrophilic than carbonyl compounds, and that O–Si bonds are stronger than N–Si bonds. We predicted that strongly electrophilic imines might be a solution to this problem under noncatalytic conditions. When *N*-sulfonylaldimines^[10] were used as imine sources the reaction indeed proceeded smoothly in the presence of CsF and gave only the trifluoromethylated adducts in 45–95 % yield. Next we turned our attention to sulfinylimines **1** to make this reaction stereoselective. When chiral sulfinylimines^[11] were subjected to similar reaction conditions little or no products were obtained. Sulfinylimines were recovered intact, but TMSCF₃ decomposed. We surmised that sulfinylimines are not reactive enough to add TMSCF₃. Use of different aprotic solvents and excess of reagents was not helpful. When an excess of TMSCF₃ was used, a number of unidentified fluorinated products with little or none of the expected adduct were obtained. TMS-Imidazole,^[8] was recently reported to facilitate addition of TMSCF₃ to imines. In our case, however, it was ineffective. In all experiments the starting material was recovered.

The above results indicate that TMSCF₃ decomposes prior to reacting with the starting material. Hence, we thought that increasing the substrate concentration might be a solution to this problem. Indeed, when neat TMSCF₃ was added to a concentrated solution of the imines, the desired adduct was obtained. The mass balance corresponds to recovered starting material. Attempts to complete the reaction by using excess of reagent in different solvents was, however, unsuccessful. Imines were treated with TMSCF₃ in the presence of a stoichiometric amount of CsF to give the corresponding trifluoromethylated sulfonamides in 50–65 % yields of isolated products (Table 1, entries 1–7, values in parentheses). Imines with acidic α -hydrogen atoms gave lower yields because of competitive deprotonation. The diastereoselectivity was not very high.

During these investigations we thus encountered two problems: a) Conversion of imines was incomplete even in the presence of excess TMSCF₃ and CsF; b) imines with an α -hydrogen atom failed to react with TMSCF₃ because of the basic nature of CsF. However, we overcame these problems by employing a nonmetallic fluoride source. DeShong et al. reported that tetrabutylammonium difluorotriphenylsilicate (TBAT),^[12] a soluble fluoride source, is very effective for nucleophilic displacement reactions. We found that TBAT is also effective in our system. Reaction of *N*-sulfonylaldimines

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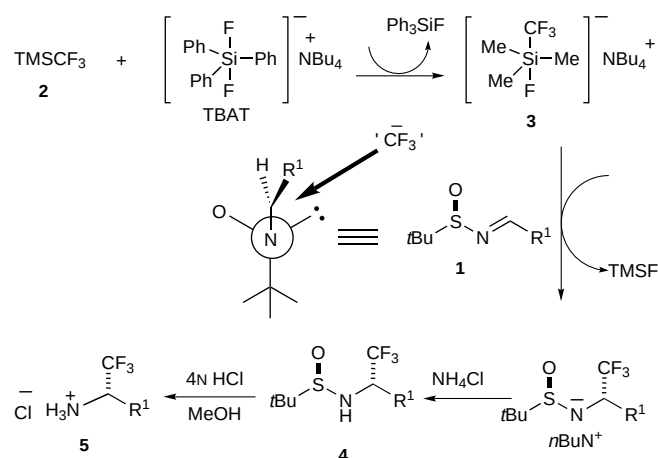
Table 1. Nucleophilic trifluoromethylation of sulfinylimines **1** with CsF or TBAT as fluoride source (see Scheme 1). Unless otherwise mentioned, yields and diastereomeric ratios are for TBAT as the fluoride source.

Entry	R ¹ in 1	Sulfinamide 4		Amine 5	
		Yield [%] ^[a, g]	(R _S ,S)/(R _S ,R) ^[b, c]	Config. ^[e]	[α] _D ²⁵ ^[f]
1	<i>p</i> -ClC ₆ H ₄	95 (53)	> 99 (85:15)	<i>S</i>	+25.9 (<i>c</i> = 0.72)
2	<i>p</i> -BrC ₆ H ₄	90 (50)	> 99 (80:20)	<i>S</i>	+11.2 (<i>c</i> = 1.5)
3	<i>p</i> -CF ₃ C ₆ H ₄	84 (57)	95:05 (85:15)	<i>S</i>	+8.4 (<i>c</i> = 1.5)
4	2-pyridyl	95 (60)	99:01 (90:10)	<i>S</i>	+11.7 (<i>c</i> = 2.0)
5	3-pyridyl	92 (60)	99:01 (85:15)	<i>S</i>	+14.9 (<i>c</i> = 1.0)
6	2-furyl	85 (55)	97:03 (80:20)	<i>S</i>	+6.6 (<i>c</i> = 2.0)
7	Ph	80 (65)	97:03 (75:25)	<i>S</i> ^[d]	+28.6 (<i>c</i> = 0.65)
8	2-Naphthyl	83	96:04	<i>S</i>	+26.0 (<i>c</i> = 0.75)
9	9-Anthryl	90	99:01	<i>S</i>	+28.8 (<i>c</i> = 3.0)
10	Cyclohexyl	88	99:01	<i>S</i>	−2.2 (<i>c</i> = 3.0)
11	<i>t</i> Bu	75	99:01	<i>S</i>	+11.3 (<i>c</i> = 0.65)
12	PhCH ₂ CH ₂	84	90:10	<i>S</i>	−15.7 (<i>c</i> = 1.5)

[a] In parentheses yields with CsF as fluoride source. [b] In parentheses d.r. values with CsF as fluoride source. [c] Diastereomeric ratios were determined by ¹⁹F NMR spectroscopy on the crude reaction mixture. [d] Configuration was determined by comparison with the known compound. [e] Configurations were assigned from transition state model. [f] Optical rotations were measured in methanol. [g] Yields of isolated analytically pure material.

with TMSCF₃ in the presence of TBAT afforded the trifluoromethylated product in good to excellent yields.^[10] When chiral sulfinylimines were subjected to similar reaction conditions, high diastereoselectivities and high yields were obtained.

The above method provides a straightforward and powerful tool for the preparation of trifluoromethylated amines in enantiomerically pure form. A remarkable feature of this reaction is that it can be applied to nonenolizable, enolizable, aromatic, and heterocyclic imines alike. The optimized reaction conditions for the *p*-chlorophenyl derivative (entry 1) in the presence of a stoichiometric amount of TBAT in THF gave the corresponding trifluoromethylated sulfinamide in good yield (95 %) and diastereoselectivity (d.r. > 99 %): TMSCF₃ (1.2 equiv, 0.6 mmol) in THF (2 mL) was added to a mixture of the imine (0.5 mmol) and TBAT (1.1 equiv, 0.55 mmol) in THF (8 mL) at −55 °C. Reaction mixtures were usually stirred over 0.5 to 1 h. Disappearance of the white slurry of TBAT indicates completion of the reaction.



Scheme 1. Mechanism of trifluoromethylation of imines by **2** in the presence of TBAT.

Saturated NH₄Cl solution (2 mL) was added at lower temperature, and the reaction mixture was warmed to room temperature. The quenched reaction mixture was extracted three times with ethyl acetate, and the combined organic layers were dried over anhydrous Na₂SO₄. Evaporation of the solvent under vacuum, Flash chromatography (silica gel, hexanes:ethyl acetate 8:2) gave the sulfinamides as white solids. The above conditions were applied to a wide array of structurally diverse imines (Table 1, entries 2–12). All adducts were hydrolyzed to amine salts by using a reported procedure.^[11]

The rationale for high stereoselectivity is depicted in Scheme 1. In the presence of a stoichiometric amount of fluoride source, pentavalent intermediate^[13] **3** is formed. This pentavalent intermediate, with its large Bu₄N⁺ counterion, preferably adds to the imines from the less hindered *Re* face to give the selective Cram products **4**, which can be transformed to the amines **5**. The preferred conformation of imines^[14] and the addition of organometallic reagents to them under nonchelating conditions^[15] are well documented.

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Hexaphyrin(1.0.1.0.0.0): An Expanded Porphyrin Ligand for the Actinide Cations Uranyl (UO_2^{2+}) and Neptunyl (NpO_2^+)**

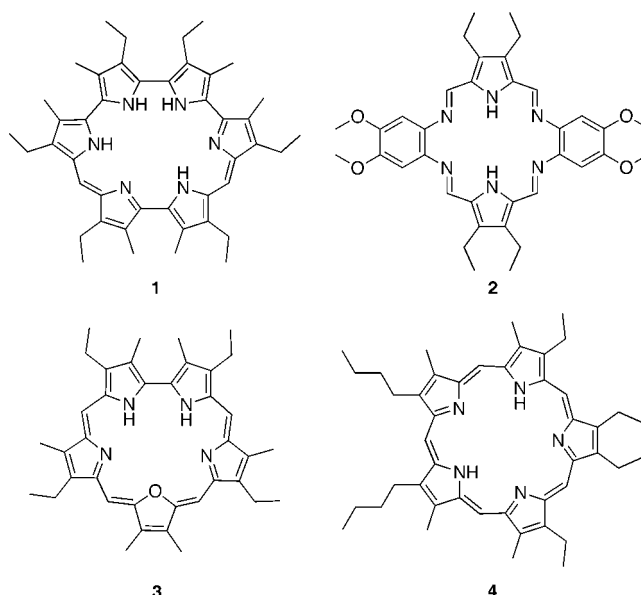
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Dedicated to Professor Ernst-G. Jäger on the occasion of his 65th birthday

Advancements made possible through applications of the unique properties of the actinides have revolutionized our modern era; however, actinide production, whether for defense purposes or the production of electricity, has generated a legacy of environmental problems with serious waste management concerns that must be addressed.^[1] Since actinide production in reactors is accompanied by fission, the ability to isolate the transuranic actinides from a matrix that includes both fission products and uranium remains a problem central to actinide purification. Accordingly, efficient separation processes continue to be sought.^[2]

One proposed solution to this problem involves the coordination of transuranic cations with macrocycles. Incorporation of these macrocycles into cation-selective polymers or placing the metal complex onto silica gel for use in chromatographic separation could lead to the selective isolation of the actinide cations.^[3] To this end, there have been many forays into the realm of the coordination chemistry of transuranic elements with macrocycles.^[4] The more widely studied macrocyclic systems include calixarenes^[5–9] and crown ethers^[10–14] which have been shown to complex UO_2^{2+} ions through both inner-sphere and outer-sphere coordination.^[5–14] In ongoing studies calixarenes have shown some promise as selective actinide extractants,^[8, 9] while the crown ethers have also been found to coordinate NpO_2^+ ions.^[15]

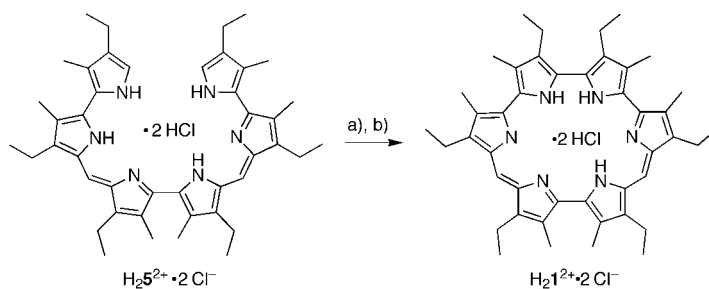
Porphyrins are also macrocycles that are recognized as excellent cation complexation agents, particularly for cations of the late transition series.^[16] While structurally characterized U^{IV} and Th^{IV} porphyrin complexes have been reported,^[17] the expanded porphyrins appear more attractive as ligands^[18] for the specific purpose of actinyl cation coordination, and a select few, such as alaskaphyrin (**2**), oxasapphyrin (**3**), and pentaphyrin (**4**), have been shown to complex uranyl cations



effectively.^[19–21] A uranyl complex of so-called “super phthalocyanine” was also reported early on.^[22]

Of particular interest is the binding of pentavalent actinyl ions AnO_2^+ ($\text{An} = \text{Np}, \text{Pu}$), as these ions tend to be stable under environmental conditions and are notorious for low binding constants with seemingly all available counterions, which leads to higher solubilities and thus high mobilities.^[23] Herein the synthesis and characterization of the hitherto unknown expanded porphyrin, [24]hexaphyrin(1.0.1.0.0.0) (**1**) is reported, as well as the uranyl and neptunyl complexes of its oxidized, aromatic form [22]hexaphyrin(1.0.1.0.0.0).

The precursor for the synthesis of **1**, the linear hexapyrrolic precursor **5**, was obtained from the acid-catalyzed condensation of 4,4'-diethyl-5,5'-diformyl-3,3'-dimethyl-2,2'-bipyrrole with two equivalents of 4,4'-diethyl-3,3'-dimethyl-2,2'-bipyrrole, and isolated as the bis-HCl salt.^[24, 25] Treatment of $\text{H}_2\text{5}^{2+} \cdot 2\text{Cl}^-$ with aqueous $\text{Na}_2\text{Cr}_2\text{O}_7$ in trifluoroacetic acid (TFA)^[26, 27] followed by purification by column chromatography and protonation with HCl gives rise to [24]hexaphyrin(1.0.1.0.0.0) in the form of its diprotonated salt $\text{H}_2\text{1}^{2+} \cdot 2\text{Cl}^-$ in 77% yield (Scheme 1). Subsequent addition of $\text{UO}_2 \cdot (\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ in the presence of base was found to yield the uranyl complex **6** in 74% yield (Scheme 2). Under the latter reaction conditions, the macrocycle undergoes oxidation to produce what is formally an aromatic [22]hexaphyrin(1.0.1.0.0.0) dianionic ligand.

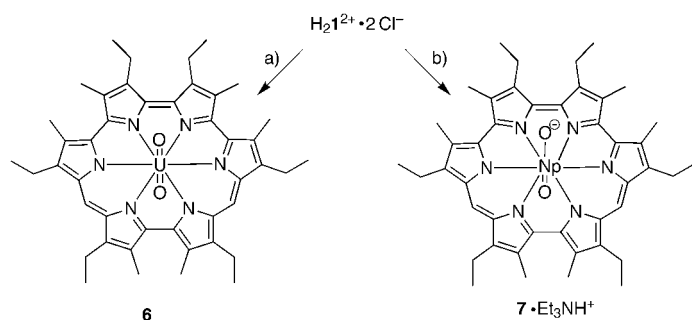


Scheme 1. a) $\text{Na}_2\text{Cr}_2\text{O}_7$, TFA; b) HCl.

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Scheme 2. a) $\text{UO}_2(\text{OAc})_2 \cdot 2\text{H}_2\text{O}, \text{Et}_3\text{N}, \text{MeOH}, \text{CH}_2\text{Cl}_2$; b) NpO_2Cl in 1 M $\text{HCl}, \text{Et}_3\text{N}, \text{MeOH}$.

Compound $\text{H}_2\text{1}^{2+} \cdot 2\text{Cl}^-$ possesses 24 π electrons and is antiaromatic as judged by the strong downfield shifts of its inner NH protons ($\delta = 23.7, 23.9$ and 24.2 , respectively) and the upfield position of the *meso*-CH signal ($\delta = 3.4$) observed in its ^1H NMR spectrum (CD_2Cl_2). The macrocycle experiences a strong ring current effect, with the observed $\Delta\delta$ value of 20.8 being considered indicative of the antiaromaticity. Formation of the uranyl complex **6**, with its proposed 22 π -electron aromatic periphery, is accompanied by a dramatic change in the ^1H NMR spectrum (CD_2Cl_2). For example, the signal ascribed to the *meso*-CH protons is shifted downfield to $\delta = 10.1$. The signals of the methyl groups at the outer periphery of the macrocycle are shifted downfield from $\delta = 0.77, 0.82$, and 1.03 , in the case of $\text{H}_2\text{1}^{2+} \cdot 2\text{Cl}^-$ to $\delta = 3.63, 3.71, 3.79$ in the case of **6**. These findings are consistent with the ring current effects becoming “reversed” as oxidation occurs and aromaticity is induced.

Further support for the proposed aromaticity came from UV/Vis spectroscopic studies. The UV/Vis spectrum of $\text{H}_2\text{1}^{2+} \cdot 2\text{Cl}^-$, recorded in CH_2Cl_2 displays three Soret-like bands at 384 ($\epsilon = 24000$), 497 ($\epsilon = 59000$), and 597 nm ($\epsilon = 25000$), with no Q-like transitions. The uranyl complex **6**, on the other hand, displays a sharp, Soret-like transition at 530 nm ($\epsilon = 330000$) accompanied by two Q-like bands at 791 ($\epsilon = 56000$) and 832 nm ($\epsilon = 81000$). The extinction coefficient of the main transition is also increased by a factor of 5.6.

A neptunyl complex **7**, analogous to **6**, was obtained by treating **1** with a solution of neptunyl(v) chloride in the presence of base (Scheme 2). The UV/Vis spectrum exhibited by this complex also features a sharp, Soret-like band which is seen at 531 nm, but it is accompanied by a single broad Q-like transition at 830 nm, rather than bands at 791 and 832 nm as in the case of **6**.^[28] Perhaps as a consequence of these small differences, solutions of **7** in CH_2Cl_2 solution are a rose color, whereas those of **6** are an intense, bright pink.

The structures assigned for **6** and **7** were confirmed by X-ray crystallographic analyses.^[29] In **6** (Figure 1), the uranium center is bound to two *trans* oxo ligands and six pyrrolic nitrogen atoms from the macrocycle, with the latter donor set completely encapsulating the cation around an equatorial plane. The uranyl center is shifted towards the quaterpyrrolic subunit; as such, the coordination environment of the uranium ion is best described in terms of a distorted hexagonal bipyramid. The U–O bond length of $1.760(2)$ Å is typical for a UO_2^{2+} unit,^[19–21] which indicates that no reduction

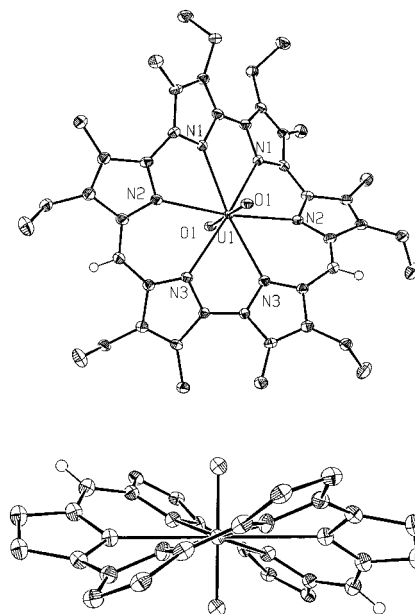


Figure 1. ORTEP diagrams showing the molecular structure of **6**. Upper structure: top view; bottom structure, side view. Most hydrogen atoms are omitted for clarity. Thermal ellipsoids are scaled to 50%.

of the metal center occurred. The average U–N bond length of $2.63(1)$ Å is comparable to that found in the hexacoordinate uranyl complex of alaskaphyrin ($2.63(3)$ Å).^[20] On the other hand, these bond lengths are longer than those found in pentacoordinate uranyl complexes stabilized by pentaphyrin^[19] and oxosapphyrin.^[21] for which average U–N bond lengths of $2.52(1)$ and $2.54(1)$ Å, respectively, were observed. The N–U–N bond angles in complex **6** range from $57.9(1)$ to $65.2(1)^\circ$ with an average value of $61.0(2)^\circ$. The sum of the N–U–N bond angles at 360° reflects the fact that the pyrrolic nitrogen atoms deviate from planarity, presumably as a result of a need to accommodate a metal center that is slightly too small.

The structure of the Np^{V} –hexaphyrin complex **7** (Figure 2) also reveals distortion in the ligand, albeit to a lesser extent than in the corresponding uranium system. These differences are readily apparent upon comparing the side-on views shown in Figures 1 and 2. Presumably, the reduced distortion in the case of **7** is the result of a better intrinsic fit between the hexaaza ligand core and the larger NpO_2^{+} ion. Nonetheless, as in the uranium complex, the neptunium center is contained within a roughly hexagonal bipyramidal structure. The metal center is once again displaced toward the quaterpyrrolic subunit. In this structure the nitrogen atoms are close to planar ($\text{N–Np–N} = 362^\circ$); however, the outer ring of the ligand is forced to twist slightly. The oxo ligands give rise to two unique Np–O bond lengths: Np–O1 is $1.762(1)$ Å and Np–O2 is $1.826(1)$ Å. These distances are short for the NpO_2^{+} ion, for which bond lengths of approximately 1.85 Å are typically seen in simple metal salts.^[30, 31] On the other hand, it is nearly identical to that seen in the Np^{V} –crown ether complex, $[\text{NpO}_2(\text{[18]crown-6})]^+$, for which a Np–O bond length of $1.800(5)$ Å was observed.^[15]

The charge balance of the lattice system, which contains a triethylammonium cation, supports the proposal that the

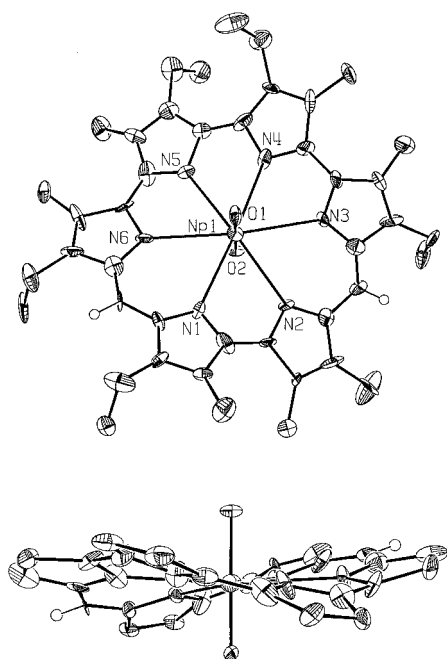


Figure 2. ORTEP diagrams showing the molecular structure of **7**. Upper structure: top view; bottom structure, side view. Most hydrogen atoms are omitted for clarity. Thermal ellipsoids are scaled to 50%.

neptunium center remains pentavalent in **7**. Further, the presence of this cation could explain the distinct difference between the two Np–O bond lengths observed in **7**. Specifically, a short N...O contact (2.70(2) Å), typical of hydrogen bonding,^[32] is seen between the nitrogen atom of the triethylammonium cation and O2. The Np–N bond lengths range from 2.649(1) to 2.880(1) Å, with an average value of 2.77(2) Å. This value is approximately 0.14 Å longer than that of its uranyl analogue **6**. The presence of these longer bonds, as well as the four shorter Np–N bonds with an average length of 2.70(2) Å, is reasonable given the larger size of the neptunyl cation. It is also consistent with what is seen in one of the few structurally characterized macrocyclic neptunyl complexes, namely that of [NpO₂([18]crown-6)]⁺ (see above). In this case, the average neptunium(V)–crown ether Np–O bond length (2.59(1) Å),^[15] was found to be longer than the comparable U–O (2.55 Å) bond found in the corresponding uranyl–crown ether complex.^[33]

In conclusion, a facile synthesis of a new hexapyrrolic expanded porphyrin, namely [24]hexaphyrin(1.0.1.0.0.0) (**1**) has been presented. This system, an isomer of amethyrin,^[34] is the smallest macrocycle known that contains a quaterpyrrole fragment. In its oxidized, aromatic form it is capable of complexing actinide ions, specifically uranyl (UO₂²⁺) and neptunyl (NpO₂⁺), and it represents the first crystallographically characterized neptunium complex stabilized by a macrocycle with an all-aza donor set. The relatively high stability seen for both **6** and **7**, with little evidence of decomposition being seen in CH₂Cl₂ over the course of several weeks, as judged by UV/Vis spectroscopy, leads to the suggestion that these kinds of systems could see application in direct, coordination-based remediation applications. Tests of this possibility are currently in progress.

Experimental Section

H₂I²⁺ · 2 Cl[−]: The linear hexapyrrole H₂I²⁺ · 2 Cl[−] (59.5 mg, 0.08 mmol) was dissolved in trifluoroacetic acid (20 mL). Immediately, a solution of Na₂Cr₂O₇ · 2 H₂O (24.7 mg, 0.083 mmol) in water (1 mL) was added and the resulting mixture was stirred overnight. The solution was added to a mixture of CHCl₃ (50 mL) and water (100 mL). After phase separation, the aqueous phase was extracted with CHCl₃ (3 × 20 mL) and the combined organic phases were then washed twice with a saturated aqueous solution of sodium bicarbonate. After evaporation of the solvent, the remaining residue was subjected to column chromatography, using 230–400 mesh ASTM silica gel as the stationary phase and a mixture of dichloromethane/methanol/triethylamine (99/0.5/0.5; v/v/v) as the eluent. The dark yellow band was collected and the solvent removed in vacuo. The remaining residue was dissolved in CHCl₃ (50 mL) and the resulting solution washed with 1 M HCl (3 × 20 mL). After evaporation to dryness and recrystallization from dichloromethane/hexanes, H₂I²⁺ · 2 Cl[−] (45.7 mg, 77%) was obtained in the form of a dark microcrystalline solid. ¹H NMR (500 MHz, CD₂Cl₂): δ = 0.48 (t, J_{H,H} = 7.5 Hz, 6H, CH₂CH₃), 0.56–0.61 (m, 12H, CH₂CH₃), 0.77 (s, 6H, CH₃), 0.82 (s, 6H, CH₃), 1.03 (s, 6H, CH₃), 1.30 (q, J_{H,H} = 7.5 Hz, 4H, CH₂CH₃), 1.35–1.41 (m, 8H, CH₂CH₃), 3.39 (s, 2H, *meso*-H), 23.66 (s, 2H, NH), 23.86 (s, 2H, NH), 24.19 (s, 2H, NH); ¹³C NMR (125 MHz, CD₂Cl₂): δ = 9.48, 9.57, 10.58, 13.09, 13.82, 14.13, 16.47, 17.11, 17.19, 119.59, 123.94, 126.22, 128.98, 132.04, 132.26, 133.24, 134.91, 137.50, 140.49, 148.90, 152.32, 157.75; HR-MS (CI): *m/z*: found 667.4495 [M⁺ – H⁺, – 2 Cl[−]], calcd for C₄₄H₅₅N₆ 667.4488, found 704.4323 [M⁺ – Cl[−]], calcd for C₄₄H₅₇N₆Cl 704.4333; UV/Vis (CH₂Cl₂): λ_{max} [nm] (ε [dm³ mol^{−1} cm^{−1}]) 384 (24 000), 497 (59 000), 597 (25 000).

6: H₂I²⁺ · 2 Cl[−] (35.6 mg, 0.048 mmol) was dissolved in CH₂Cl₂ and methanol (15 mL each). Triethylamine (1 mL) was then added, an addition that caused the color to change from purple to dark yellow. UO₂(OAc)₂ · 2 H₂O (53 mg, 0.15 mmol) was then added and the resulting mixture was stirred overnight, open to air. The resulting deep red solution was evaporated to dryness on the rotary evaporator. The residue was then subjected to column chromatographic purification, using neutral alumina as the stationary phase and a mixture of dichloromethane/hexanes (2/3, v/v) as the eluent. The red band was collected and the solvent removed in vacuo. After recrystallization from CH₂Cl₂/MeOH, **6** (33 mg, 74% yield) was obtained as a dark microcrystalline solid with a metallic luster. ¹H NMR (500 MHz, CD₂Cl₂): δ = 1.92 (t, J_{H,H} = 7.5 Hz, 6H, CH₂CH₃), 1.98 (t, J_{H,H} = 7.5 Hz, 6H, CH₂CH₃), 2.00 (t, J_{H,H} = 7.5 Hz, 6H, CH₂CH₃), 3.63 (s, 6H, CH₃), 3.71 (s, 6H, CH₃), 3.79 (s, 6H, CH₃), 3.91 (q, J_{H,H} = 7.5 Hz, 4H, CH₂CH₃), 4.15 (q, J_{H,H} = 7.5 Hz, 4H, CH₂CH₃), 4.23 (q, J_{H,H} = 7.5 Hz, 4H, CH₂CH₃), 10.10 (s, 2H, *meso*-H); ¹³C NMR (125 MHz, CD₂Cl₂): δ = 15.52, 16.17, 16.87, 17.34, 17.64, 18.29, 20.46, 20.47, 21.73, 106.96, 134.92, 135.68, 138.96, 144.82, 145.57, 146.80, 147.87, 148.27, 151.20, 151.76, 152.11, 152.68; HR-MS (CI): *m/z*: found 933.4585 (M⁺), calcd for C₄₄H₅₁N₆O₂²³⁸U 933.4581; UV/Vis (CH₂Cl₂): λ_{max} [nm] (ε [dm³ mol^{−1} cm^{−1}]) 530 (330 000), 791 (56 000), 832 (81 000).

7: H₂I²⁺ · 2 Cl[−] (5.0 mg, 0.007 mmol) was dissolved in MeOH (5 mL) and a 0.3 M solution of neptunyl(v) chloride in 1 M HCl was added (160 mL, 0.036 mmol). Triethylamine (4 drops, approx. 80 μL) was then added. The excess solvent was evaporated to dryness and the remaining reddish solid was recrystallized from dichloromethane/hexane. The resulting dichromic (red/green) crystals were analyzed by single-crystal X-ray diffraction methods. After isolation of the complex by column chromatography using dichloromethane/MeOH as the eluent and activated alumina as the solid support, the resulting product (0.9 mg, 0.001 mmol) was dissolved in CH₂Cl₂ (8 mL). Diluting this solution 3:7 in CH₂Cl₂, generated the solution used for the UV/Vis spectroscopic studies. UV/Vis (CH₂Cl₂): λ_{max} [nm] 531, 830.^[28]

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- [28] While experimental difficulties limit the accuracy of these measurements, extinction coefficients [$\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1}$] of $\epsilon = 120\,000$ for the main transition at 531 nm and $\epsilon = 40\,000$ for the Q-like transition at 830 nm were recorded.
- [29] a) Crystallographic parameters for **6** (dark prisms grown from vapor diffusion of CH_2Cl_2 and hexanes): orthorhombic, space group $Pbcn$, $a = 9.0295(2)$, $b = 17.1213(4)$, $c = 24.7737(6)$ Å, $Z = 4$, $R1 = 0.0365$, $wR2 = 0.0612$, $V = 3829.9$ Å³. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with $\text{MoK}\alpha$ radiation ($\lambda = 0.71073$ Å) at -150°C using an Oxford Cryostream low temperature device. The structure was refined by full-matrix least-squares on F^2 to 0.0612, with $R(F)$ equal to 0.0242 and a GOF = 1.009. The complex lies on a crystallographic twofold rotation axis at $0, y, \frac{1}{4}$. The twofold axis passes through the uranium atom and bisects the bipyrrrole and the tetrapyrrole moieties. b) The crystallographic parameters for $[\text{Et}_3\text{NH}][7]$ (red-green dichromic rods, of dimension $0.08 \times 0.08 \times 0.12$ mm³, were grown from vapor diffusion of CH_2Cl_2 and hexanes): monoclinic, space group $P2_1/c$, $a = 15.099(2)$, $b = 22.742(3)$, $c = 14.353(1)$ Å, $\beta = 110.857(4)^\circ$, $V = 4606(1)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.501$ mgm⁻³. The data were collected at 203 K on a Bruker P4/

CCD diffractometer using graphite monochromated $\text{MoK}\alpha$ radiation ($\lambda = 0.71073$ Å). A total of 18883 (5694 independent and $2\theta_{\text{max}} = 45^\circ$) reflections were collected using a combination of ϕ and θ scans. The structure was solved using direct methods, and refined against F^2 to convergence, with $R(I > 2\sigma) = 0.0925$ and $wR(I > 2\sigma) = 0.1371$ for 5694 reflections and 550 L.S. parameters. The final residual electron density was 0.89 e Å^{-3} . Hydrogen atom positions were idealized and refined using a riding model. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-149932 (**6**) and -150148 ($[\text{Et}_3\text{NH}][7]$). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Narrow Molecular Weight Distribution Precursors for Polymer–Drug Conjugates**

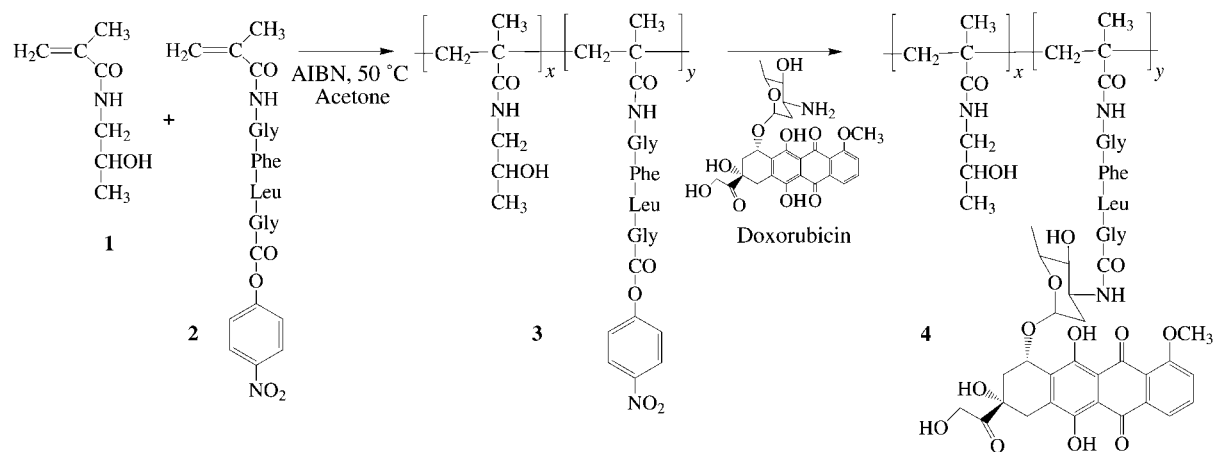
Antony Godwin, Markus Hartenstein, Axel H. E. Müller,* and Stephen Brocchini*

Polymer–drug conjugates derived from copolymers of *N*-(2-hydroxypropyl)-methacrylamide (HPMA) can be prepared from a copolymer precursor such as **3** (Scheme 1).^[1] This methodology has been used for the development of conjugate **4** which is currently undergoing Phase II trials in the UK for the treatment of cancer.^[2]

To exploit more widely the biological advantages of large molecule therapeutics^[1, 3a] and to examine more thoroughly how structure, molecular weight,^[4] and solution properties correlate with biological profile^[3] it is essential to develop preclinical conjugates that have 1) narrow molecular weight

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Scheme 1. Preparation of a polymer–drug conjugate **4** from a copolymer precursor **3** derived from **1** and **2**. AIBN = azobisisobutyronitrile.

distribution (MWD), 2) the same molecular weight characteristics, and 3) uniform pendent chain structure. To address these issues we have prepared a narrow MWD homopolymeric precursor **7** (Scheme 2) by atom-transfer radical polymerization (ATRP) of **5** with **6**.^[5] We have also begun to examine the reactions of **7** with amines to determine if this precursor can be used to prepare families of conjugates.

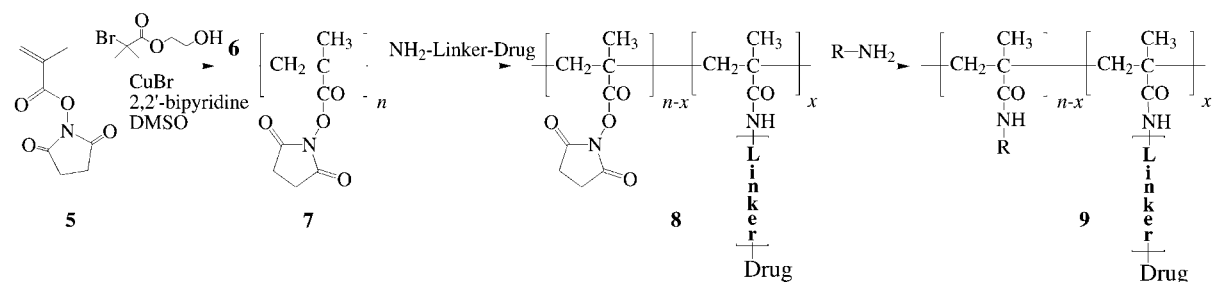
Although the use of active ester homopolymers is known for preparing functionalized polymers,^[6] the preparation of a narrow MWD active ester homopolymeric precursor (for example, **7**) to give water-soluble copolymer conjugates has not been examined. Preparation of narrow MWD methacrylamide copolymers (for example, **3**) is currently not feasible, so the only way to obtain narrow MWD conjugates is by tedious fractionation procedures. By using only the homopolymeric precursor **7**, different stoichiometries of various solubilizing and drug-conjugating pendent chains will give families of conjugates with the same absolute molecular weight characteristics. This is not possible with copolymer precursors (for example, **3**) because each structurally distinct conjugate requires a different copolymer precursor, and each precursor is typically prepared by precipitation free-radical polymerization which results in conjugates with different molecular weights.

We selected *N*-methacryloxysuccinimide **5**^[7] (m.p. 102–104 °C) because these esters can be more hydrolytically stable than other commonly used active esters.^[8] Narrow MWD ($\bar{M}_w/\bar{M}_n = 1.1–1.2$; $\bar{M}_w$ = weight-averaged molar mass, $\bar{M}_n$ = number-averaged molecular mass) polymer **7** was prepared in both THF and acetone, but premature precipitation of the

polymer frequently occurred to limit the preparation of a wide range of molecular weights.^[9] Maintaining a homogeneous reaction mixture seemed the most systematic long-term strategy to prepare polymers at molecular weights which give prolonged circulation times in blood.^[1–3]

Several polymerizations were conducted in DMF (110–130 °C) using monomer concentrations spanning 33–91 wt % in order to maintain solution homogeneity. Although polymer **7** is soluble in DMF,^[7] this solvent is not considered optimal for ATRP because of its possible competitive chelation of copper ions.^[10] The concentration of monomer **5** relative to DMF was critical for the outcome of the polymerization. A 50 % yield of polymer **7** was isolated at 61 wt % of monomer **5** while no polymer was isolated when the reaction was conducted at 33 wt %. The reaction mixture solidified at monomer concentrations above 75 wt % ($M_{\text{target}} \leq 18300 \text{ g mol}^{-1}$). To probe for competing thermal initiation^[11] monomer **5** was stirred alone in DMF at 80 and 110 °C for 8–24 h. This resulted in the formation of some polymer of broad MWD ($\bar{M}_w/\bar{M}_n > 1.5$).

The experiments in DMF suggested that a homogeneous copper-mediated polymerization of **5** in a polar organic solvent was possible. DMSO was examined as the solvent, and homogeneous, reproducible polymerization reactions occurred to give a range of molecular weights (Table 1; entries 1–5). Polymerizations were stopped after 10–15 minutes to give narrow MWD polymer **7** in good yields (80–96 %). Even after 2.5 minutes the yield was nearly 50 % (Table 1, entry 6). These reactions were carried out on a 1.8–2.5 g scale and have also been successfully conducted on a 6 g



Scheme 2. Preparation of polymer–drug conjugates **9** starting from a narrow MWD homopolymeric precursor **7**. The use of **7** as a common precursor enables the synthesis of families of conjugates **9** with similar molecular weight characteristics.

Table 1. Conditions and results for the copper-mediated polymerization of monomer **5** in DMSO.

Entry	5 : 6 :CuBr:bpy ^[a]	<i>T</i> [°C]	<i>M</i> _{target} ^[b]	Yield [%]	<i>M</i> _n ^[c] [g mol ⁻¹]	<i>M</i> _w / <i>M</i> _n	<i>f</i> _{app} ^[d]
1	10:1:1:2	100	1830	85	12300	1.17	0.12
2	20:1:1:2	80	3660	92	16800	1.15	0.20
3	50:1:1:2	100	9150	89	22600	1.20	0.36
4	100:1:1:2	100	18300	96	29000	1.14	0.61
5	150:1:1:2	110	27450	80	40700	1.13	0.54
6 ^[e]	100:1:1:2	100	18300	49	23300	1.15	0.38

[a] Ratio of the initial monomer and initiator concentrations. [b] *M*_{target} = (**5**/**6**) × 183 g mol⁻¹. [c] The molecular weight averages were obtained by GPC using DMF as the eluent (0.1% LiCl) and PMMA standards. [d] Apparent initiator efficiency calculated by: *f*_{app} = (*M*_{target} × yield)/*M*_n. [e] Reaction stopped after 2.5 minutes by dilution with DMSO and rapid cooling.

scale. Like the polymerizations in DMF, the concentration of DMSO similarly influenced the outcome of the polymerization where 57 wt % of monomer **5** was used in the reactions listed in Table 1. Polymer **7** was isolated as a white powdery solid by diluting the reaction mixture with DMSO followed by precipitation of the polymer by adding it to a stirred solution of acetone. Atomic absorption analysis indicated the copper content to be 0.153 ppm at a concentration of 28.0 mg mL⁻¹ of polymer **7** in DMF.^[12]

Molecular weights were obtained by gel permeation chromatography (GPC) using poly(methyl methacrylate) (PMMA) standards and DMF eluent (0.1% LiCl was added to inhibit aggregation). The apparent number-average molecular weight (*M*_n) of polymer **7** was consistently higher than *M*_{target}, and the apparent initiator efficiency (*f*_{app})^[13] increased as the *M*_{target} value increased (Table 1, entries 1–5). To obtain a better indication of the absolute *M*_n value and to determine the degree of polymerization (DP), a sample of precursor **7** was hydrolyzed to the sodium salt of poly(methacrylic acid) (PMAA).^[6a] The apparent *M*_n and DP values of **7** (*f*_{app} = 0.59) prior to hydrolysis was 24800 g mol⁻¹ and 136, respectively (*M*_w/*M*_n = 1.20; *M*_{target} = 18300 g mol⁻¹). After hydrolysis, aqueous GPC analysis (phosphate-buffered saline solution adjusted to pH 8.5) against PMAA sodium salt standards gave *M*_n = 22000 g mol⁻¹ (*M*_w/*M*_n = 1.28). This result indicated that the absolute DP was approximately 200 and *f*_{app} = 0.50 for this sample of **7**.

Before following the general conjugation strategy in Scheme 2 (**7** → **8** → **9**) the first conjugation reaction (**7** → **8**) had to be correlated with the stoichiometry of the added

amine. Precursor **7** was stirred with different stoichiometries of glycine methyl ester in anhydrous DMSO and triethylamine at 60 °C for one hour. The FT-IR spectra obtained by attenuated total reflectance from an aliquot of each reaction mixture displayed a decrease in the height of the active ester imide band at 1735 cm⁻¹ that correlated with the stoichiometry of the glycine methyl ester used (Figure 1).

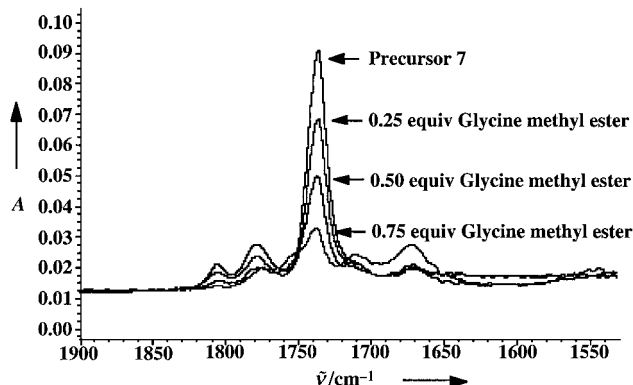
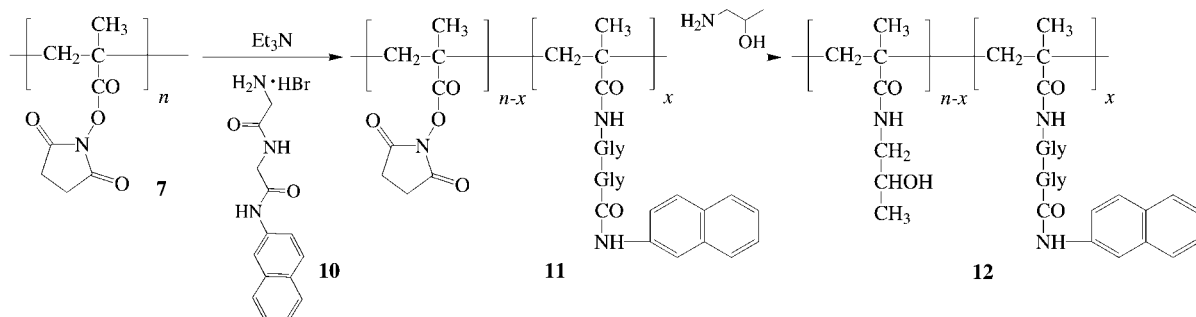


Figure 1. Superimposed IR spectra displaying the decrease in the band corresponding to the carbonyl group at 1735 cm⁻¹ on conjugation of glycine methyl ester (0.25, 0.50, and 0.75 equiv) to precursor **7**. The actual decreases in peak height of 25.7, 53.7, and 74.7% correlated with the amount of added glycine methyl ester.

During the preclinical development of conjugate **4**, *p*-nitroanilide was used as a drug model and the glycine–glycine dipeptide linker was used as a control because it did not undergo lysosomal degradation.^[3a,c] We used commercially available glycine-glycine-β-naphthylamide hydrobromide (**10**) as a linker–drug model to prepare model conjugates **12** (Scheme 3). To prepare a conjugate with 10% loading, 0.1 active ester group equivalents of **10** were conjugated to precursor **7**. A 10% reduction in the peak height of the IR band at 1735 cm⁻¹ was observed from an aliquot of the reaction solution (Figure 2). Excess 1-amino-2-propanol (2.0 equivalents) was then added to the reaction mixture and the band at 1735 cm⁻¹ disappeared. The water-soluble conjugate **12** was isolated after precipitation (acetone:diethyl ether, 1:1 (v/v)). Increasing the stoichiometry of **10** in the first reaction (namely, **7** → **11**) to 0.25 and 0.50 equivalents resulted in a corresponding decrease in the the IR band at 1735 cm⁻¹.

These preliminary experiments indicate that the narrow MWD homopolymeric precursor **7** may be used to prepare



Scheme 3. Conjugation of the drug model **10** to narrow MWD precursor **7** followed by conjugation of 1-amino-2-propanol gives the model polymer–drug conjugate **12**.

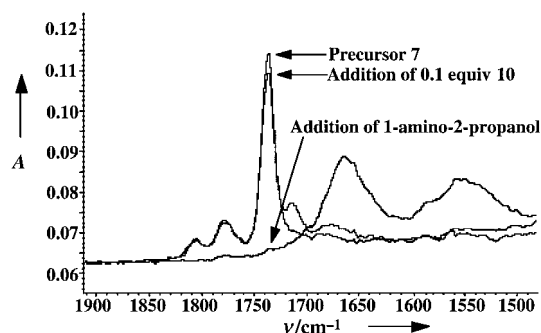


Figure 2. Superimposed IR spectra displaying the changes in the carbonyl band at 1735 cm^{-1} on addition of gly-gly- β -naphthylamide hydrobromide (**10**, 0.1 equiv) to give **11** and then on addition of excess 1-amino-2-propanol (2.0 equiv) to give the final conjugate **12**.

polymethacrylamides if competitive side reactions, for example, hydrolysis and imide formation, can be suppressed. As an example, 1-amino-2-propanol was conjugated to **7** to give a narrow MWD HPA homopolymer (Figure 3) with only trace levels of competitive hydrolysis being observed by FT-IR spectroscopy. Controlled radical-polymerization processes, including ATRP, have successfully been used to prepare many narrow MWD polymers. One exception has been the preparation of a wide range of narrow MWD methacrylamide homo-^[14] and copolymers.

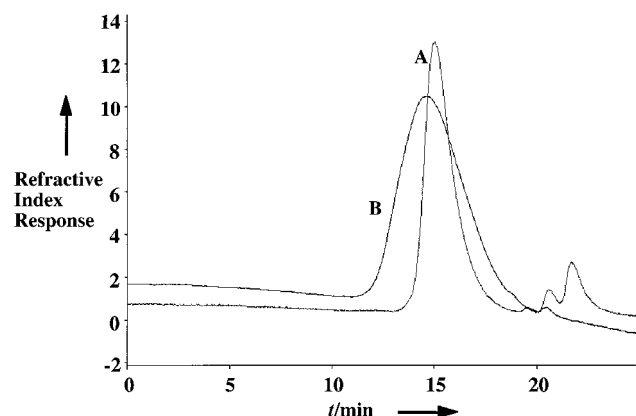


Figure 3. The gel-permeation chromatogram for the narrow MWD HPA homopolymer (labeled A) obtained from the reaction of precursor **7** and 1-amino-2-propanol (2.0 equiv). The trace labeled B shows the HPA homopolymer prepared by conventional free-radical polymerization.

In summary, the narrow MWD, active ester homopolymer **7** was prepared as a precursor for the efficient preparation of families of narrow MWD, water-soluble polymer–drug conjugates. This strategy may have potential for preparing narrow MWD speciality polymers for applications spanning health-care to consumer products.

Experimental Section

7: In a typical polymerization, copper(I) bromide (31.3 mg, 0.2 mmol), 2,2'-bipyridine (bpy, 68.3 mg, 0.4 mmol), and monomer **5**^[7] (2.00 g, 10.9 mmol) were added to a round-bottomed flask which was then sealed with a septum. DMSO (1.3 g) was then injected into the flask. The resulting brown mixture was gently heated until a solution had formed and then purged with argon for approximately 5 min. An argon-purged solution of 2-bromo-2-methyl-(2-hydroxyethyl) propanoate (46.1 mg, 0.2 mmol) in DMSO (0.2 g) was then injected into the mixture and the flask was heated to 100°C in an

oil bath. The reaction mixture became viscous after a few minutes and was removed from the heat after 10–15 min and rapidly cooled. The resulting crude polymeric product was then dissolved by the addition of DMSO (7–8 mL). This solution was slowly added to a stirred solution of acetone (100 mL) to precipitate polymer **7** as a white solid (1.78 g, 89%).

12: **7** (100 mg, 0.55 mmol of reactive groups), H-Gly-Gly- β -naphthylamide $\cdot$ HBr $\cdot$ 0.6 H₂O (**10**, 19 mg, 0.06 mmol, 0.1 equiv), and a magnetic stirring bar were added to a 1.5-mL vial. The vial was sealed with a septum-centered screw-cap lid and purged with argon for approximately 2 min. Anhydrous DMSO (0.4 mL) was injected into the vial once the stirred reaction mixture was homogeneous, and a small sample of the solution was removed by syringe under argon for immediate analysis by FT-IR spectroscopy. Triethylamine (15.2 μL , 0.11 mmol, 2 salt equiv) was then added under argon to the vial and the vial was placed in an oil bath at 50°C for 2.5 h. After cooling the solution, a sample was removed from the vial under argon for immediate analysis by FT-IR spectroscopy. The H-Gly-Gly- β -naphthylamide reaction solution was further heated with 1-amino-2-propanol (82 mg, 1.1 mmol, 2 equiv) at 50°C for 1.25 h. A polymeric product **12** was isolated by precipitation of the DMSO reaction solution with acetone:diethyl ether (50:50) and further purified by precipitation from methanol with acetone:diethyl ether (50:50).

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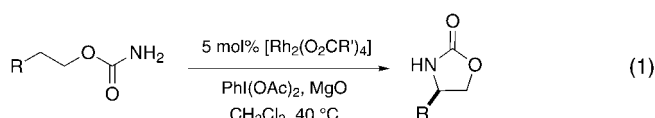
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A Rh-Catalyzed C–H Insertion Reaction for the Oxidative Conversion of Carbamates to Oxazolidinones**

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Vicinal amino alcohols are common structural units in both naturally occurring molecules and pharmaceutical agents.^[1] These groups also appear as auxiliaries in asymmetric synthesis and in ligands for metal catalysts.^[2, 3] The large and varied number of applications for β -hydroxy amines in synthetic, medicinal, materials, and coordination chemistry has fueled interest in the development of methods for their construction.^[2a, 4] We have found a unique, metal-catalyzed C–H insertion process that makes possible the preparation of such compounds from readily available carbamate starting materials [Eq. (1)]. This methodology utilizes catalytic quan-

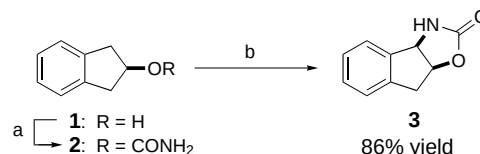


ties of a Rh^{III} carboxylate complex and an inexpensive commercial oxidant, PhI(OAc)₂. The product oxazolidinones are versatile, crystalline materials that can be opened under hydrolytic conditions to furnish 1,2-amino alcohols.^[5, 6]

Transition metal promoted methods for the oxidative conversion of saturated hydrocarbons to amines or amine derivatives have limited precedence.^[7, 8] In one seminal example, both iron and rhodium catalysts were found to react with the iodoimine of 2,5-diisopropylbenzenesulfonamide to furnish a substituted benzisothiazoline product.^[9] This reaction is believed to occur through intramolecular metal–nitrene insertion into an isopropyl methine C–H bond, though no mechanistic data has been offered in support of this claim.^[10] More recently, reports of metal-catalyzed intermolecular allylic and benzylic C–H oxidation with PhI=NSO₂Ar reagents have been described.^[7c–e,h–k] These processes are hampered, however, by the poor shelf life of the iodoimine starting materials, a restricted substrate profile, and the need to often employ large excesses of hydrocarbon substrates.

We wished to explore the use of simple carbamate materials as precursors for the synthesis of substituted oxazolidinones.

The crystalline indanol derivative **2** used for our initial studies was afforded easily upon treatment of alcohol **1** with CCl₃C(O)NCO followed by K₂CO₃/MeOH (Scheme 1).^[11]



Scheme 1. a) CCl₃C(O)NCO; K₂CO₃/MeOH; b) 5 mol % [Rh₂(OAc)₄], PhI(OAc)₂, MgO, CH₂Cl₂, 40 °C, 12 hr.

Control experiments indicate that **2** does not react with PhI(OAc)₂ after > 10 hr at 40 °C.^[12] We were pleased to find, however, that a stirred suspension of **2**, PhI(OAc)₂, and 5 mol % [Rh₂(OAc)₄] at 25 °C produced ~15 % of the desired oxazolidinone **3**. Analysis of the unpurified reaction mixture by ¹HNMR spectroscopy indicated that the sample comprised mostly starting material **2**. Subsequent studies demonstrated that the conversion of **2** into **3** could be improved slightly by warming the mixture of reactants to 40 °C, an observation that intimated a possible problem with slow catalyst turnover. Following a series of control experiments, we concluded that AcOH, generated as a by-product from PhI(OAc)₂, reduced the catalytic activity of [Rh₂(OAc)₄]. The need to scavenge AcOH from the reaction mixture prompted the screening of K₂CO₃, Na₂HPO₄, 2,6-di-*tert*-butyl-4-methylpyridine, BaO, and MgO as base additives. Of these reagents, MgO proved uniquely effective and, in addition, was the most desirable from a cost and convenience standpoint. Thus, the reaction of **2** performs optimally when a CH₂Cl₂ suspension containing PhI(OAc)₂ (1.4 equivalents), 5 mol % [Rh₂(OAc)₄], and MgO (2.3 equivalents) is stirred for 12 hr at 40 °C (Scheme 1).^[13] Reactions conducted under these conditions on scales > 1.5 mmol furnish the product oxazolidinone **3** as analytically pure material in 86 % yield.

Extension of this method to other carbamate starting materials illustrates the potential value of this C–H oxidation reaction (Table 1). Substrates containing both benzylic and tertiary C–H centers are cyclized to oxazolidinone products in yields of 74–84 % (entries 1–5). [Rh₂(OAc)₄] can be used as the catalyst with a number of these starting materials; in some cases, however, the readily prepared triphenylacetate (tpa) complex, [Rh₂(tpa)₄],^[14] is a more effective promoter at a 5 mol % loading. The enhanced performance of [Rh₂(tpa)₄] is ascribed to its greater resistance towards oxidation under the reaction conditions. As evident in entry 6, cyclization of less reactive substrates such as *n*-butylcarbamate requires use of this more robust catalyst.^[15] By contrast, carbamates derived from tertiary cycloalkanols with unactivated CH₂ centers (entries 7 and 8) are converted efficiently into oxazolidinones with [Rh₂(OAc)₄].^[16] Collectively, our findings indicate that substrates having some degree of conformational constraint generally afford superior results.

The carbamate prepared from (*S*)-2-methyl-1-butanol (**4**) was employed as a probe to examine the mechanism of oxazolidinone formation (Figure 1).^[17] Direct insertion of a nitrene or nitrenoid intermediate into the methine center of **4**

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

Table 1. Oxidative cyclization of carbamates.

Entry	Substrate	Product	Catalyst ^[a]	Yield ^[b]
1			B	74
2			B	77 ^[c]
3			A	83
4			A B	77 79
5			A B	82 84
6			B	44
7			A	82
8			A	83 ^[d]

[a] Catalyst: **A** = $[\text{Rh}_2(\text{OAc})_4]$, **B** = $[\text{Rh}_2(\text{tpa})_4]$. [b] All reactions conducted for 12 h with 5 mol % of catalyst, 1.4 equiv $\text{PhI}(\text{OAc})_2$, and 2.3 equiv MgO in CH_2Cl_2 at 40°C ($\sim 0.2\text{M}$ in substrate). [c] Exclusive product as determined by ^1H NMR spectroscopy of the unpurified reaction mixture; *cis* stereochemistry assigned based on ^1H coupling constants. [d] Product isolated as an 8:1 mixture of *cis:trans* isomers; *cis* stereochemistry established by X-ray crystallography. Full experimental details are in the Supporting Information.

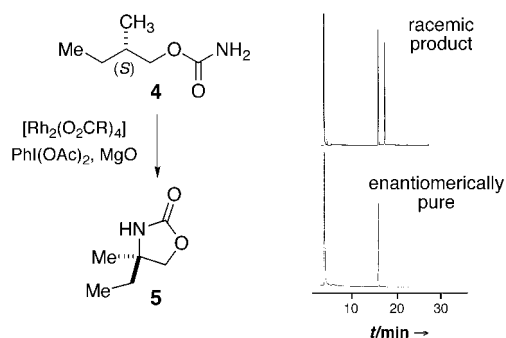
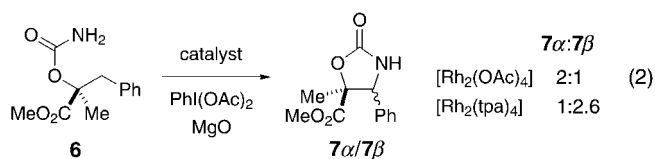


Figure 1. Cyclization of **4** into **5**. Gas chromatograms of the oxazolidinone **5** from racemic (top) and optically pure (bottom) carbamate **4**.

should occur with retention of configuration.^[18, 19] Alternatively, cyclization of **4** through a pathway involving a discrete tertiary radical species is likely to produce a mixture of enantiomeric oxazolidinones. Chiral GC analysis of the product obtained from **4** displayed only a single peak in the chromatogram (Figure 1). This result provides definitive evidence that C–N bond formation is stereospecific. Moreover, the observed reactivity is consistent with that of a nitrene-type oxidant. In practice, stereospecific C–H insertion

makes possible the synthesis of chiral α,α -disubstituted alkyl amines from enantiomerically pure, β -branched primary alcohols.^[20] The potential of this method is considerable given the limited number of asymmetric methods available for preparing this important class of compounds and related quaternary α -amino acids.^[21]

Carbamoylnitrenes, generated in thermolytic or photolytic decomposition reactions of azidoformates, react as powerful, indiscriminate oxidants.^[17c, 18a,b] In the Rh-catalyzed process, the regioselective formation of a single product from substrates capable of generating other oxazolidinone and/or oxazinone derivatives (e.g., entries 2, 4, and 6, Table 1) is evidence against a free nitrene intermediate.^[17c, 18a, 22] Additional data that strongly support this conclusion were obtained from reactions with carbamate **6** [Eq. (2)]. The use



of $[\text{Rh}_2(\text{OAc})_4]$ as a catalyst to effect the cyclization of **6** afforded a 2:1 mixture of diastereomeric products, **7α** and **7β** (79%). In contrast, the $[\text{Rh}_2(\text{tpa})_4]$ complex yielded **7α** and **7β** in a 1:2.6 ratio (74%).^[23] Collectively, these observations confirm that the Rh catalyst is in some way mediating C–N bond formation, and that a free carbamoylnitrene is not the active oxidant. Such a reaction mechanism, in which the metal complex influences the actual C–H insertion step, has significant ramifications for the future development of catalyst systems that enable control over reaction chemo-, regio-, and stereoselectivity.^[24] We believe that our findings represent the most compelling experimental documentation recorded to date for a concerted, metal-directed N-atom insertion process.^[10]

We have described a unique catalytic method for the oxidative cyclization of carbamates to oxazolidinones. The reaction is performed conveniently on the benchtop using readily accessible substrates and catalysts, an inexpensive commercial oxidant, and a common absorbent. C–H insertion is stereospecific, thereby facilitating the preparation of α -branched alkylamines from optically pure alcohol starting materials. Importantly, our data indicate that the active oxidizing species does not display the indiscriminate reactivity patterns characteristic of a carbamoylnitrene. The ability to use simple Rh carboxylate complexes to perform selective intramolecular alkane oxidations has created myriad opportunities for investigations in catalyst design, mechanism, and target-directed synthesis. Efforts along each of these lines are currently in progress.

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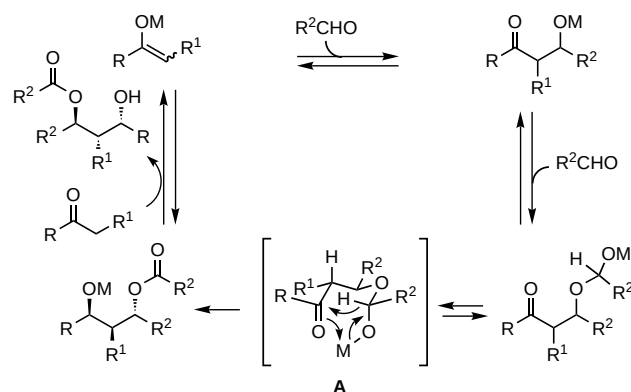
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- [23] Diastereomeric product ratios were determined by ¹HNMR spectroscopy. The stereochemical assignments for compounds **7a** and **7b** are based on difference nuclear overhauser effect (nOe) measurements.
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First Catalytic Asymmetric Aldol-Tishchenko Reaction—Insight into the Catalyst Structure and Reaction Mechanism**

Cheryl M. Mascarenhas, Steven P. Miller, Peter S. White,[†] and James P. Morken*

Since the comprehensive studies of Nord et al. in the 1940s,^[1] the catalytic aldol-Tishchenko reaction has received much attention as a means to couple unactivated carbonyl compounds.^[2] Only more recently have stoichiometric^[3] and catalytic stereoselective reactions^[4] become the focus of development. Mechanistic studies on stereoselective aldol-Tishchenko reactions suggest that the reaction occurs by the mechanism depicted in Scheme 1.^[3a,d,e, 4a] After generation of



Scheme 1. Cycle for catalytic aldol-Tishchenko reactions.

the enolate, a reversible aldolization step is thought to precede a rate-determining reduction via transition state **A**.^[5] The major product stereoisomer is derived from the stereoisomer of structure **A** wherein all substituents at the six-membered ring occupy equatorial positions. Despite the fact that stereocontrol in the aldol-Tishchenko reaction appears to result from a highly organized metal-centered transition state, this reaction has not been subject to enantioselective catalysis under the influence of chiral ancillary ligands. In this report, we describe the first catalytic enantioselective version of this process.^[6]

We recently reported that simple metal alkoxides can catalyze a diastereoselective hetero aldol-Tishchenko reac-

tion thereby offering access to propionate equivalents directly from simple carbonyl compounds.^[7] Expecting that de novo design of chiral metal alkoxide catalysts would be treacherous due to the inherent difficulty in predicting coordination numbers and aggregation states of metal alkoxides, we have used an arrayed catalyst evaluation^[8] protocol to discover promising catalyst candidates. Initial studies with 96 independent complexes revealed the complex of $Y_5O(OiPr)_{13}$ ^[9] and salen (**1a**)^[10] as an effective catalyst for the enantioselective aldol-Tishchenko reaction.^[11]

We now examined the effect of ligand structure on this reaction [Eq. (1)]. As seen in Table 1, the aldol-Tishchenko adduct is obtained with ligand **1a** in 44% overall yield and in a 78:22 enantiomer ratio. The reaction provides two regioisomeric esters **2** in similar enantiopurity

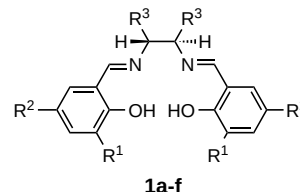
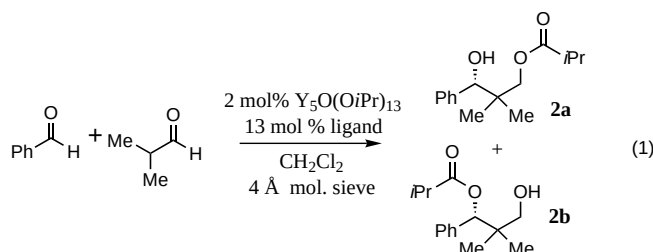


Table 1. Analysis of the effect of ligand structure on the yttrium-catalyzed aldol-Tishchenko reaction (1). In all reactions the ratio of *i*PrCHO:Ph-CHO was 6:1, and they were performed under an inert atmosphere.



Ligand	R ¹	R ²	R ³	Yield [%] (2a:2b) ^[a]	e.r. of 2a ^[b]
1a	<i>t</i> Bu	<i>t</i> Bu	(CH ₂) ₄	44 (3.4:1)	78:22
1b	<i>t</i> Bu	H	(CH ₂) ₄	36 (3.0:1)	87:22
1c	Me	H	(CH ₂) ₄	54 (1.6:1)	57:43
1d	adamantyl	Me	(CH ₂) ₄	42 (3.2:1)	83:17
1e	<i>t</i> Bu	<i>t</i> Bu	Ph	48 (3.3:1)	82:18
1f	adamantyl	Me	Ph	70 (> 15:1)	87:13

[a] Combined yield, after purification by flash chromatography; ratio of **2a:2b** determined by ¹H NMR spectroscopy; identity of major enantiomer determined by comparison to authentic material. [b] Enantiomer ratio determined by GLC (β -Dex column by Supelco).

suggesting a nonselective intramolecular acyl migration after formation of the aldol-Tishchenko adduct. Bulky substituents *ortho* to the salen oxygen atom (R¹) are necessary for reactivity and selectivity, whereas the presence of *para* substituents (R²) is not essential for asymmetric induction. Also of note is that the diphenylethylene-derived ligand **1e** displays greater enantioselection than the corresponding diaminocyclohexane-derived ligand **1a**. With some of the structural requirements for effective ligands exposed, we prepared salen **1f** containing both a bulky *ortho* adamantyl unit and the diphenyl backbone. The use of **1f** in the aldol-Tishchenko reaction (1) results in 70% yield and an 87:13 ratio of enantiomers, the highest selectivity of all ligands examined.

Reaction generality was examined through experiments with different aldehydes as reaction substrates [Eq. (2),

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[†] Crystallography

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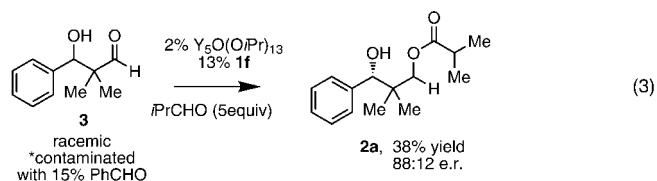
Table 2]. All substrates gave useful product yields, except for the less electrophilic anisaldehyde (entry 4) as might be expected. While comparable levels of enantioselection were obtained with all aromatic aldehydes, α,β -unsaturated aldehydes (entry 5) appear to be less useful under the current reaction conditions.

Table 2. Utility of the catalytic asymmetric aldol-Tishchenko reaction (2).

Entry	Substrate	Yield [%] ^[a]	e.r. (configuration) ^[b]
1		70	87:13 (<i>S</i>)
2		55	85:15 (<i>S</i>)
3		50	82:18
4		21	86:14
5		50	55:45

[a] Yield, after purification by column chromatography. [b] Enantiomer ratio determined by GLC (β -Dex column) or by HPLC (Chiracel OD or Chiracel OJ). The identity of the major enantiomer, where indicated, was determined by comparison to authentic material.

To ascertain whether this catalyzed reaction operates under similar Curtin–Hammett conditions as described in Scheme 1, we prepared racemic **3** (contaminated with 15 % benzaldehyde) and subjected it to the catalytic reaction conditions in the presence of isobutyraldehyde [Eq. (3)].



With ligand **1f**, aldol-Tishchenko adduct **2a** was obtained from **3** in 38 % yield and with an 88:12 enantiomer ratio. These results strongly indicate that, with the yttrium–salen catalyst, the Tishchenko reduction is slower than the retro-aldol reaction and a similar kinetic profile operates as that described previously.

Time-course experiments show that the enantiomer ratio does not change as the aldol-Tishchenko reaction proceeds, indicating that the 1,3-glycol monoester product does not modify the oxophilic yttrium center in any detrimental way during the course of the reaction. Additional experiments in which the enantiomeric excess of ligand **1a** was varied show a linear relationship between ligand enantiopurity and reaction

enantioselectivity thereby suggesting the possibility of a monomeric catalyst structure.^[12] Vapor pressure osmometry experiments provided more definitive evidence of a monomeric aggregation state of the metal complex; a solution prepared to be 0.050 M each in metal and ligand was measured to be (0.057 ± 0.005) M in solute versus a calibration curve prepared for the known monomer triphenylmethane.^[13]

To elucidate the architecture of the catalyst complex, a crystal structure analysis was performed for the complex prepared from $Y_5O(OiPr)_{13}$ and ligand **1a** (Figure 1).^[14] It

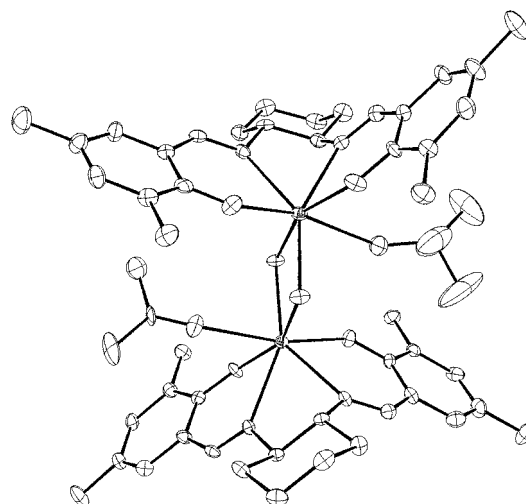
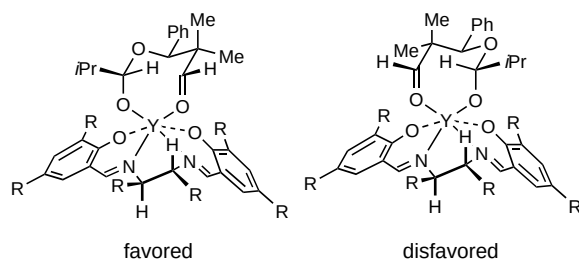


Figure 1. ORTEP diagram of the complex prepared from **1a** and $Y_5O(OiPr)_{13}$ and crystallized from acetone/ CH_2Cl_2 ; *tert*-butyl substituents have been truncated for clarity.

revealed the complex to be a dimer where each yttrium is seven-coordinate, complexed to acetone (crystallization co-solvent) and bridged by two hydroxide ions to a second yttrium center.^[15] Whereas in most salen complexes of d transition and main group metals the ligand structure is planar, the yttrium ion causes significant bending in the four-coordinate ligand. Addition of the crystalline complex to a solution of isobutyraldehyde and benzaldehyde is not sufficient to catalyze the aldol-Tishchenko reaction. We suspect that this catalytic inactivity may be due either to the stability of the dimeric solid-state structure relative to the monomeric structure observed in solution or to the replacement of isopropoxides with hydroxides. Regardless, because the structure shows a salen coordination geometry that is similar to that reported for a salen(amido)yttrium complex,^[16] we expect that the structure is relevant (vide infra).

Considering the correlation between product and ligand configuration, the structural requirements for enantioselection, the evidence for a monomeric yttrium–salen complex and evidence for rate-determining hydride transfer, we propose a predictive model for enantioselection in the aldol-Tishchenko reaction (Scheme 2). Chelate-controlled organization of the intramolecular Tishchenko transition state positions the hemiacetal substituent (*i*Pr) in a pseudoequatorial position about the cyclic transition structure. With a salen ligand coordinated to yttrium, the major product is derived from a structure where the isopropyl group is positioned away



Scheme 2. Predictive model for enantioselection in the aldol-Tishchenko reaction catalyzed by Y-salen complexes.

from the axial salen hydrogen; presumably the diastereomeric transition structure suffers from this steric interaction thereby yielding less of the minor enantiomer.

In conclusion, we have discovered and developed the first catalytic enantioselective aldol-Tishchenko reaction. The mechanistic studies presented herein should provide a useful starting point for the development of more effective catalytic asymmetric aldol-Tishchenko reactions.

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- [14] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-150468. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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Total Synthesis of the Callipeltoside Aglycon**

Ian Paterson,* Robert D. M. Davies, and Rodolfo Marquez

The callipeltosides were isolated by Minale and co-workers from the shallow-water lithistid sponge *Callipelta* sp., collected off the east coast of New Caledonia.^[1a,b] Callipeltoside A (**1** in Scheme 1, obtained in 1.4×10^{-4} % yield) was found to inhibit in vitro the proliferation of KB and P388 cells (IC_{50} values of 11.26 and $15.26 \mu\text{g mL}^{-1}$, respectively). Results indicate this activity to be cell-cycle dependent, blocking proliferation in the G1 phase, highlighting callipeltoside A as a putative, mechanism-based lead.^[1a] Similarly, callipeltosides B and C, differing only in the sugar portion of their structures, also exhibited marked cytotoxic activity.^[1b]

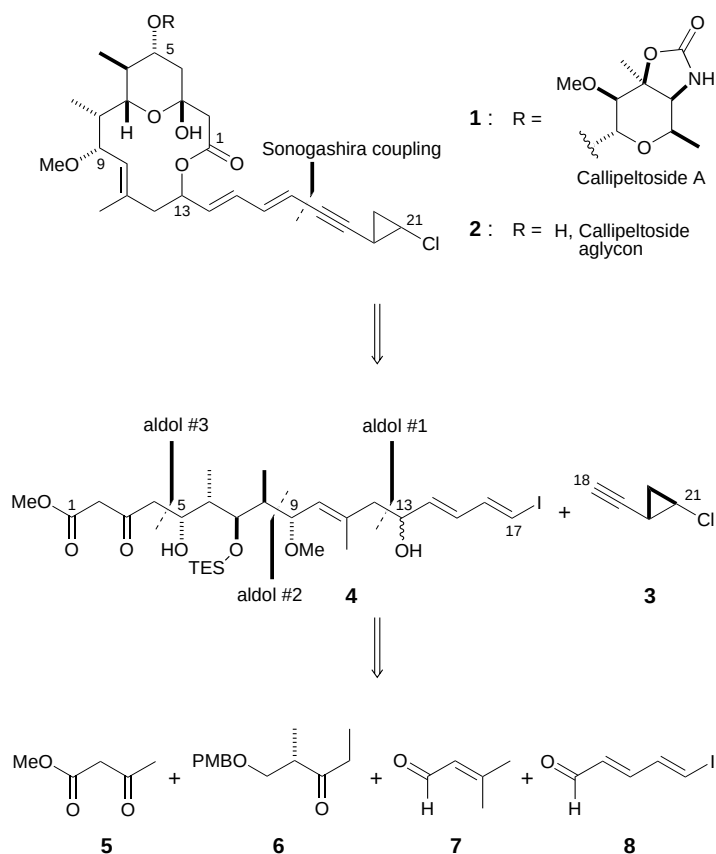
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From extensive two-dimensional NMR analysis, the callipeltoside aglycon (**2**, Scheme 1)^[1c] was characterized structurally as a unique hemiacetal-containing, 14-membered, macrocycle with seven stereocenters and an *E*-trisubstituted alkene. The pendant unsaturated side chain is an unusual feature of this rare marine polyketide, comprising a *trans*-chlorocyclopropane ring adjacent to a dienyne system. Whilst the relative configuration of the callipeltosides has been partly assigned,^[1c] synthetic efforts^[2] are required to resolve the remaining structural ambiguities, and ultimately provide access to additional material for biological evaluation. Herein, we report the first total synthesis of the callipeltoside aglycon (**2**). By adopting a pragmatic approach to stereocontrol and utilizing contemporary aldol methodology, we have synthesized two epimers that differ only in the configuration at C13 and elucidated the relative configuration within the macrocycle ring.

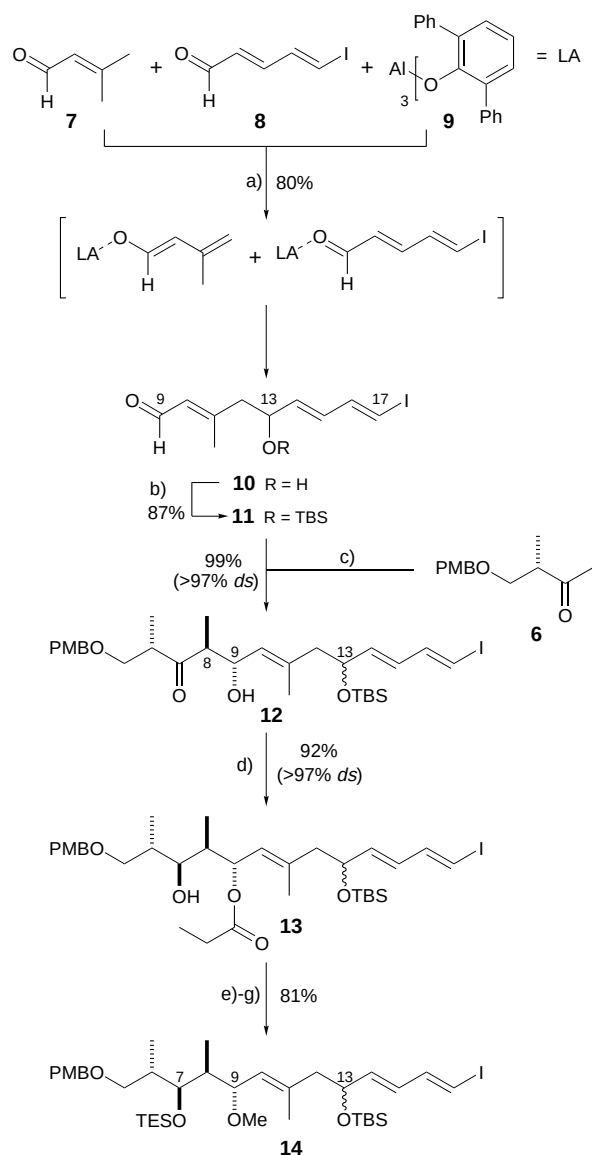
Our synthetic plan relied on the late-stage Sonogashira coupling of alkyne **3** (or *ent*-**3**), preceded by hemiacetalization and macrolactonization, which leads back to the acyclic



Scheme 1. Retrosynthetic analysis of the callipeltoside aglycon (**2**). PMB = *para*-methoxybenzyl.

C1–C17 fragment **4**. This can be further dissembled by three strategic aldol disconnections at C4–C5, C8–C9 and C12–C13, giving β -keto ester **5**, chiral ketone **6** and aldehydes **7** and **8**.

A key objective in the synthesis was to install the *E*-trisubstituted alkene at an early stage. We achieved this (Scheme 2) using the vinylogous aldol reaction developed by

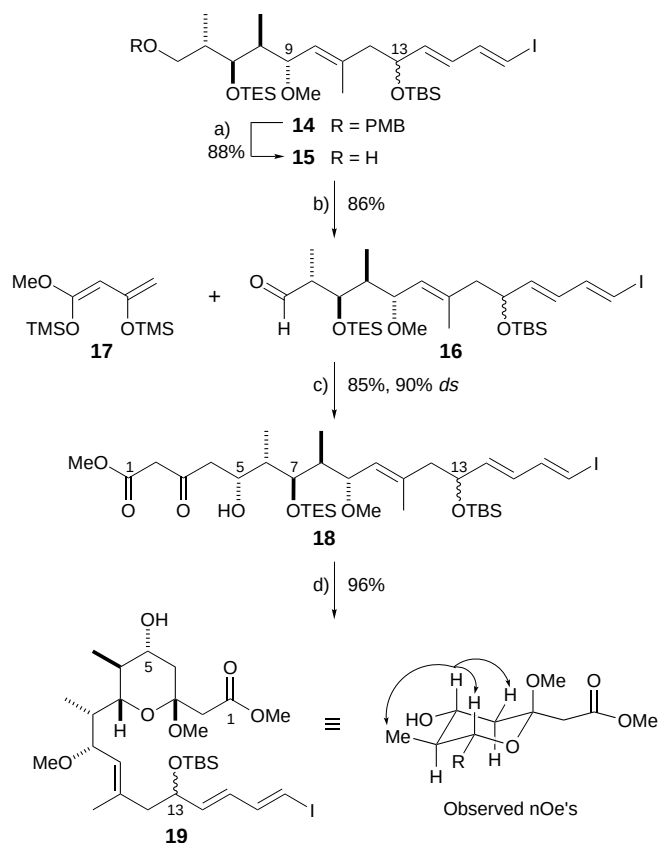


Scheme 2. Synthesis of the C5–C17 subunit **14**: a) toluene, -78°C , 5 min; LDA, THF, -78°C , 15 min; b) TBSCl, Im, CH_2Cl_2 , 20°C , 1 h; **11**, $-78 \rightarrow -27^{\circ}\text{C}$, 16 h; 2) $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$, SiO_2 , 20°C , 30 min; d) SmI_2 , EtCHO, THF, $-20 \rightarrow -10^{\circ}\text{C}$, 2 h; e) TESOTf, 2,6-lutidine, CH_2Cl_2 , -78°C , 1 h; f) DIBAL, CH_2Cl_2 , -78°C , 30 min; g) Me_3OBF_4 , H^+ sponge, CH_2Cl_2 , $0 \rightarrow 20^{\circ}\text{C}$, 1 h. *c*-Hex = cyclohexyl, Im = imidazole, TESOTf = triethylsilyl trifluoromethanesulfonate, DIBAL = diisobutylaluminum hydride, H^+ sponge = 1,8-bis(dimethylamino)naphthalene-*N,N,N',N'*-tetramethyl-1,8-naphthalenediamine.

Yamamoto et al., which is promoted by the aluminum Lewis acid **9**.^[3] Hence, the extended enolate of enal **7** was added to the readily available *E,E*-configured iododiene aldehyde **8**^[4] to provide the C9–C17 subunit **10** in 80% yield, with complete control of double bond geometry. Notably, this opening gambit permitted the flexibility required at the C13 center, whilst incorporating the iododiene precursor to the callipeltoside side chain, latterly to be appended with the cyclopropyl alkyne **3**. However, the survival of this delicate functionality was to be a key concern throughout the remainder of the synthesis.

Protection of aldol adduct **10** as the corresponding TBS ether furnished aldehyde **11**. Application of our boron-mediated anti-aldol reaction^[5] to ethyl ketone **6**^[6] and aldehyde **11** gave adducts **12** in 99% yield and complete selectivity at C8 and C9. The usual oxidative cleavage of the initially formed boronate product with H₂O₂ was found to be incompatible with the iododiene functionality, necessitating an alternative hydrolytic cleavage over silica gel.^[7] At this stage, the mixture of C13 epimers was not readily separable. An Evans–Tishchenko reduction^[8] with SmI₂ and propionaldehyde formed exclusively the 1,3-*anti* diol, protected as the monopropionate **13**. Subsequent TES protection of the C7 hydroxyl, reductive removal of the propionate ester with DIBAL and methylation at the C9 hydroxyl afforded triene **14** (see Scheme 2).

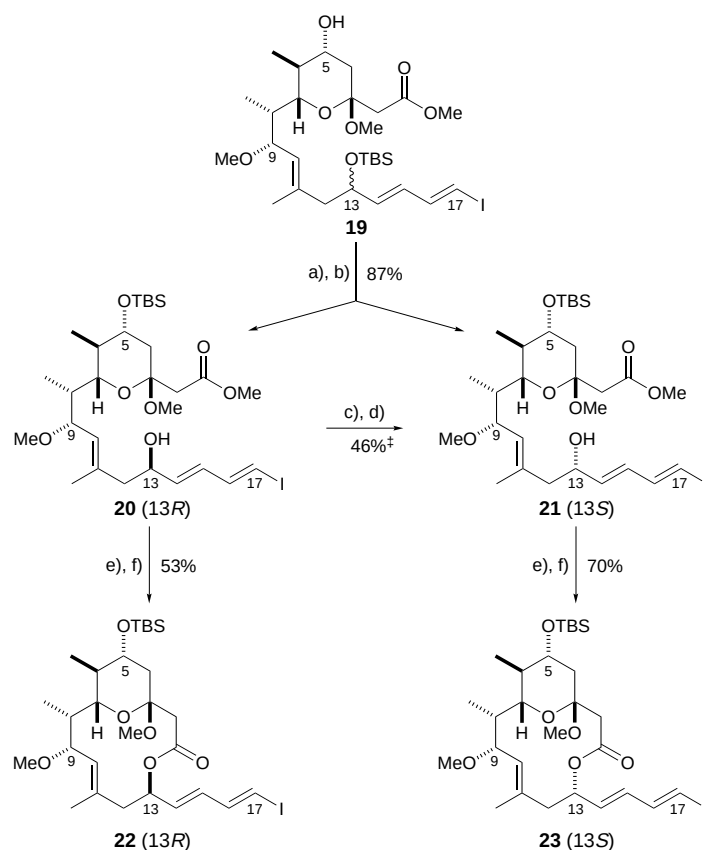
Oxidative removal of the PMB protecting group in **14** (Scheme 3) with DDQ, in the presence of the allylic TBS ether at C13, proved to be problematic. Unwanted oxidation of the latter functionality to the dienone,^[9] as well as substrate instability to the reaction conditions were observed. These issues were ameliorated by refluxing **14** in CH₂Cl₂/pH 7 buffer with DDQ (1 equiv) to provide alcohol **15** (42%; 88% based on recovered starting material). With alcohol **15** in hand, Dess–Martin oxidation provided aldehyde **16**, primed for the final aldol reaction needed to introduce the C5 stereocenter. Indeed, a Mukaiyama aldol reaction, promoted by BF₃·OEt₂,



Scheme 3. Synthesis of the C1–C17 subunit **19**: a) DDQ (1 equiv), CH₂Cl₂/pH 7 buffer (10/1), 40 °C, 10 min; b) DMP, CH₂Cl₂, 20 °C, 1 h; c) BF₃·OEt₂, CH₂Cl₂, –100 °C, 15 min; d) PPTS, (MeO)₃CH, MeOH, 20 °C, 2 h. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMP = Dess–Martin periodinane.

between the O-silylated dienolate **17**^[10] and the α -chiral aldehyde **16** proceeded with Felkin–Anh control^[11] to give β -keto ester **18** in 85% yield and 90% diastereoselectivity. Treatment of **18** with PPTS and trimethyl orthoformate in MeOH effected selective TES deprotection with concomitant methyl acetal formation to provide **19**, allowing assignment of the configuration by NOE analysis.

The subsequent TBS protection of the C5 hydroxyl in **19** (Scheme 4) proved significant, as the selective deprotection of



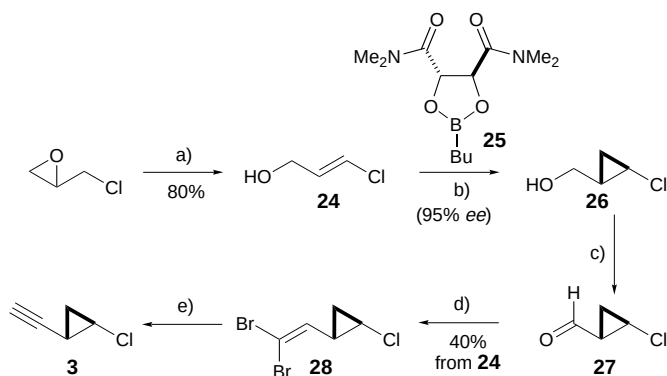
Scheme 4. Synthesis of the C1–C17 macrolides **22** and **23**: a) TBSCl, Im, CH₂Cl₂, 20 °C, 2 h; b) TBAF, THF, 20 °C, 1 h; c) TPAP, NMO, 4 Å molecular sieve, CH₂Cl₂, 20 °C, 50 min; d) NaBH₄, CeCl₃·7H₂O, EtOH, –78 → 0 °C, 40 min; e) Ba(OH)₂·8H₂O, MeOH, 20 °C, 16 h; f) 2,4,6-trichlorobenzoyl chloride, Et₃N, DMAP, toluene, 80 °C, 4 h. TBAF = tetrabutylammonium fluoride, TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine, DMAP = 4-(*N,N*-dimethylamino)pyridine. The reduction gave an approximately 1:1 mixture of **21** and **20**.

the allylic TBS ether at C13 by TBAF revealed alcohols **20** (13*R*) and **21** (13*S*), which were now separable by regular flash column chromatography. At this point, the absolute configuration at C13 was assigned by ¹H NMR MTPA analysis using the advanced Mosher method.^[12]

In parallel studies, saponification of the methyl esters **20** and **21** with barium hydroxide, followed by the key macro-lactonization, provided, after optimization, the diastereomeric macrolides **22** (53%) and **23** (70%), respectively. We first employed the Yonemitsu^[13] variant of the Yamaguchi lactonization^[14] on **20**, which resulted in the formation of mostly macrodiolides and -triolides, with monomer **22** as a minor component. We then turned to the conventional Yamaguchi

protocol which, with the careful control of temperature (80 °C) and slow addition, proved successful.^[15] Before embarking on the synthesis, we probed the configuration at C13 of the two possible diastereomeric macrolides by molecular modeling.^[16] By comparing the reported NOE data^[1a] with the calculated global minimum energy conformation, we found **23** to be the more likely candidate. Subsequent comparison of macrocycles **22** and **23** by ¹H NMR spectroscopy reinforced this conclusion: The spectrum and NOE data of the latter closely matched that recorded for the callipeltosides. At this point, the unwanted diastereomer **20** could be converted to give more of **21** by oxidation with TPAP,^[17] followed by Luche reduction.^[18]

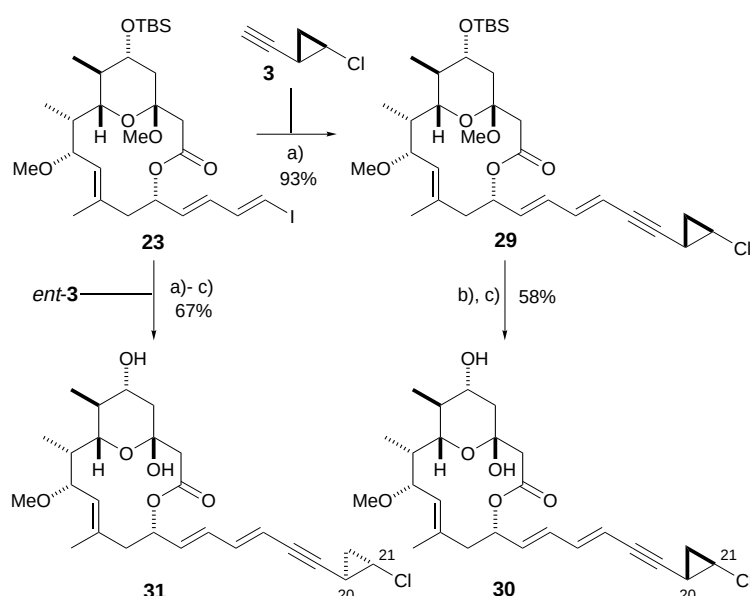
Having assembled the desired 14-membered macrolide **23**, we addressed introduction of the full side chain. The synthesis of alkyne **3** (Scheme 5) commenced with the treatment of *epi*-chlorohydrin with *n*BuLi in the presence of TMEDA, which generated chloroallylic alcohol **24** in 80% yield as a single geometric isomer.^[19] Asymmetric Simmons–Smith



Scheme 5. Synthesis of the C18–C22 alkyne **3**: a) *n*BuLi, TMEDA, THF, –78 → 0 °C, 1.5 h; b) ZnEt₂, CH₂I₂, chiral auxiliary **25**, CH₂Cl₂, 0 → 20 °C, 16 h; c) (COCl)₂, DMSO, CH₂Cl₂, –78 °C, 20 min; Et₃N, –78 → 0 °C, 20 min; d) Zn, py, PPh₃, CBr₄, CH₂Cl₂, 20 °C, 16 h; e) *n*BuLi, Et₂O, –78 °C, 30 min. TMEDA = *N,N,N',N'*-tetramethylethylenediamine, DMSO = dimethylsulfoxide, py = pyridine.

cyclopropanation under the conditions of Charette et al.,^[20] using the dioxaborolane ligand **25** derived from (*S,S*)-(–)-*N,N,N',N'*-tetramethyltartaric acid diamide, supplied alcohol **26** in 95% *ee* (¹⁹F NMR MTPA analysis). In an analogous fashion, the enantiomeric alcohol, *ent*-**26**, was prepared with the (*R,R*)-(+)-dioxaborolane ligand. Swern oxidation of **26** gave aldehyde **27**, which was treated under Corey–Fuchs conditions^[21] to generate dibromo olefin **28** (40% from **24**). Lastly, treatment of **28** with *n*BuLi provided alkyne **3**. The antipodal cyclopropane, *ent*-**3**, was prepared in an identical fashion.

After removing the ether solvent at atmospheric pressure, **3** was used directly in the Sonogashira coupling with the macrocyclic dienyl iodide **23** (Scheme 6). Conventional coupling conditions ([Pd(PPh₃)₄], CuI, *n*BuNH₂ in benzene)^[22] failed to generate any of the desired product **29**. However, conditions developed for the coupling of electron deficient



Scheme 6. Synthesis of the callipeltoside aglycons **30** and **31**: a) [(PPh₃)₂PdCl₂], CuI, *i*Pr₂NH, EtOAc, –20 → 20 °C, 1.5 h; b) TBAF, THF, 20 °C, 50 min; c) PPTS, CH₃CN, H₂O, 20 °C, 16 h.

alkynyl amides^[23] [(Ph₃P)₂PdCl₂], CuI, *i*Pr₂NH, in ethyl acetate) proved successful, affording the protected aglycon **29** in 93% yield with retention of double bond geometry. Finally, deprotection of the TBS ether with TBAF, followed by treatment with catalytic PPTS in wet acetonitrile to hydrolyse the methyl acetal, provided the callipeltoside aglycon **30**. Similarly, the enantiomeric cyclopropyl alkyne *ent*-**3** was coupled with **23** and deprotected to provide the diastereomeric aglycon **31**.

Although the ¹H and ¹³C NMR spectra of these diastereomers were essentially identical, there was a substantial difference in optical rotation: **30** had [α]₂₀^D = –97.8 (*c* = 0.19, CHCl₃) and **31** had [α]₂₀^D = +45.8 (*c* = 0.28, CHCl₃).^[24] The 500 MHz ¹H NMR spectra of both **30** and **31** matched closely with those recorded^[1b] for the callipeltosides in CDCl₃, with divergence in the signals of and around C5 due to the absence of a sugar moiety. The ¹³C NMR spectrum also showed close agreement with the reported data, except for the C20 and C21 resonances of the cyclopropane ring.^[25]

In conclusion, this expedient total synthesis of the callipeltoside aglycon proceeds in 20 steps and 2.7% yield from pyridinium-1-sulfonate (precursor to **8**)^[4] for the longest linear sequence. Attachment of the sugar residue to aglycons **30** and **31** should enable the full stereochemical assignment of callipeltoside A. This work represents the first application of Yamamoto's vinylogous aldol in total synthesis, which has proved highly effective applied in tandem with our own selective boron-mediated aldol methodology. The early incorporation of the delicate iododiene functionality for a late-stage Sonogashira coupling is also noteworthy.

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$\delta = 34.2$. In the callipeltosides a resonance at $\delta = 34.0$ was attributed to the remaining C20 methine. In actual fact, the signal of the C20 methine in the aglycons **30** and **31** lies at $\delta = 12.02$, almost coinciding with the C25 methyl signal at $\delta = 11.98$, which were resolved by a DEPT 90 NMR experiment. Thus, we conclude that the ^{13}C NMR spectra of the callipeltosides may require the reassignment of C20 ($\delta = 12.0$) and C21 ($\delta = 34.0$). For supportive ^{13}C NMR spectral data on chlorocyclopropanes, see: Y. Kusuyama, T. Kagosaku, T. Hasegawa, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2836.

Insights into the Branched-Chain Formation of Mycarose: Methylation Catalyzed by an (S)-Adenosylmethionine-Dependent Methyltransferase**

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Methylation is a common biotransformation that encompasses a wide variety of substrates involved in a myriad of biological processes.^[1] For example, methylation of DNA has been shown to play an important role in gene regulation, and methylation of specific protein targets has been established as a general mechanism to control signal transduction or cell growth and differentiation. In addition, the biological consequences of methylation of rRNA and mRNA are also well documented.^[1] The majority of biological methyl transfers are catalyzed by methyltransferases that use (S)-adenosylmethionine (AdoMet) as the methyl donor. It is of interest that methylation is such a prevalent process in living organisms, considering that methyl transfer from AdoMet to its acceptor is intrinsically a very slow reaction in water.^[2] Although methyltransferases characteristically display low k_{cat} values, their catalysis of methyl transfer can still be considered significant compared to the uncatalyzed reaction.

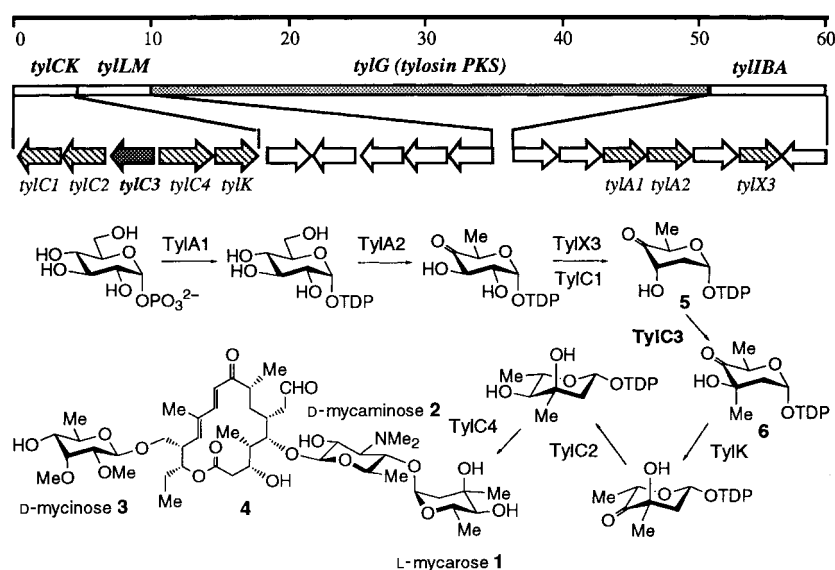
While the flexibility of AdoMet as a methyl donor is apparent from its ability to use carbon, nitrogen, and oxygen as acceptors, methyltransferases that are capable of catalyzing C-methylation are much less common and therefore less well studied.^[3] A specific area in which C-methyltransferases

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clearly play a central role is the production of methyl-branched sugars. On the basis of their biogenesis, branched-chain sugars can be divided into two groups.^[4, 5] Sugars carrying a methyl or a two-carbon side chain are classified as Group I, and those bearing a hydroxymethyl or a formyl branch make up Group II. Branched chains longer than two carbon atoms are extremely rare. Formation of Group I branched-chain sugars most likely involves coupling of a one- or two-carbon unit from appropriate donors such as AdoMet or pyruvate to a diphosphonucleotidyl(NDP)-hexulose.^[5] Unfortunately, information on the biosynthetic pathways of these unusual sugars, especially mechanisms of branched-chain attachment, is sparse and is mostly derived from early tracer experiments.^[4, 5] This paper reports the isolation and characterization of TylC3, the first C-methyltransferase to be purified that is involved in the biosynthesis of a branched-chain sugar, namely, L-mycarose (**1**, Scheme 1). L-Mycarose,



Scheme 1. Top: organization of the tylosin PKS gene cluster; bottom: biosynthesis of tylosin (**4**). **1**–**3** are shown as substituents, not as independent molecules.

along with two other sugars, D-mycaminose (**2**) and D-mycinose (**3**), is an essential component of the macrolide antibiotic tylosin (**4**), which is produced by *Streptomyces fradiae*. Tylosin is used commercially to treat veterinary Gram-positive and mycoplasma infections, as well as to promote livestock growth.^[6] L-Mycarose also forms part of a few other clinically important antibiotics including erythromycin, in which L-mycarose is methylated at O-3 (L-cladinose).

Early genetic studies led to the identification of the entire gene cluster responsible for the biosynthesis of tylosin,^[7] including the genes involved in the biosynthesis of L-mycarose.^[8] Sequencing results and analyses identified *tylC3* as the gene likely to encode the C-methyltransferase required for the attachment of the methyl branched chain to the hexulose precursor **5** (Scheme 1). Although TylC3 did not display significant sequence homology to any characterized AdoMet-dependent methyltransferase, three localized sequences similar to the well-defined binding motifs of Ado-

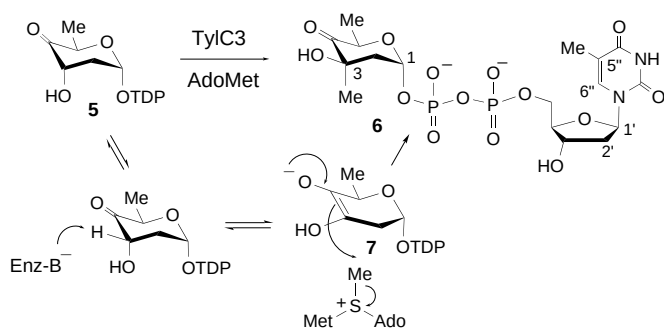
Met-dependent enzymes were identified. One gene product that did exhibit strong homology to TylC3 was EryBIII (68 % identity and 80 % similarity) in the erythromycin-producing strain *Saccharopolyspora erythraea*.^[9] Mutation experiments implicated *eryBIII* as the gene encoding the C-methyltransferase in the biosynthesis of L-cladinose in erythromycin.^[10] However, no biochemical studies were performed on the gene product to confirm its function.

To verify the function of TylC3, the *tylC3* gene was amplified by polymerase chain reaction (PCR) from the cosmid pHJL311^[11] and cloned into a pET-24b(+) vector. The resulting construct, pH34, was used to transform *Escherichia coli* BL21(DE3), from which the expressed C-terminal His-tagged TylC3 was purified to near homogeneity by a Ni-NTA column (Qiagen). N-Terminal amino acid sequencing confirmed the identity of TylC3,^[12] and the subunit molecular mass of 48 kDa, as revealed by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS PAGE), correlates well with the predicted value of 46 423 Da deduced from the amino acid sequence. An M_r of 43.1 kDa, estimated by gel filtration, indicated that TylC3 exists as a monomer in solution.

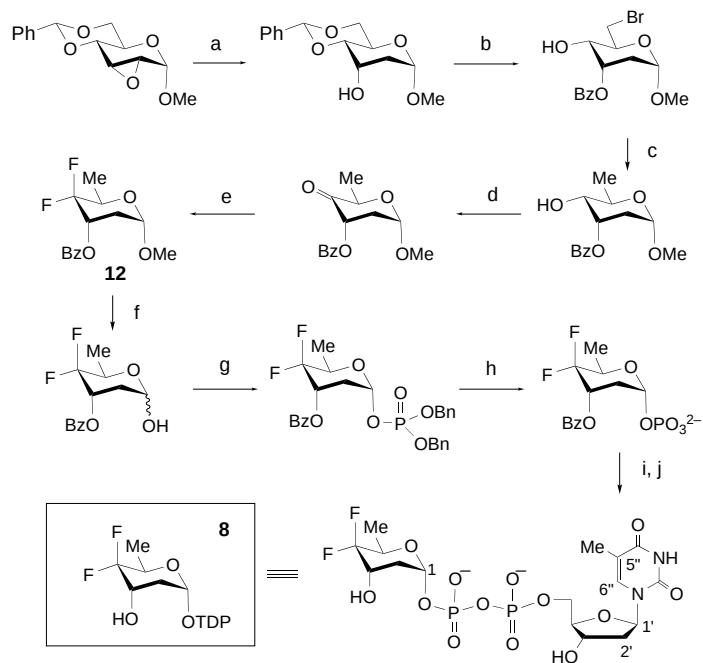
Initial tests with [³H₃C]AdoMet showed that TylC3 does bind AdoMet, even in the absence of sugar substrate. HPLC analysis^[13] of an incubation of this enzyme with the expected substrate **5**^[14] revealed the presence of a new compound. The NMR data identified^[15] this new product as the C-3 methylated sugar **6**, and this firmly establishes the function of TylC3 as the AdoMet-dependent C-methyltransferase required for the biosynthesis of L-mycarose. A positive Nuclear Overhauser Effect (NOE) between the newly installed C-3 methyl group and the C-5 axial hydrogen atom showed the methyl group to be axial; this indicates that TylC3-catalyzed methylation proceeds with overall inversion of configuration at C-3.

An HPLC assay was developed and used to determine the kinetic parameters for the enzyme.^[16] K_m for AdoMet was $1.5 \pm 0.2 \mu\text{M}$, but K_m for the sugar substrate **5** was beyond the sensitivity of the assay and could only be estimated as less than $1 \mu\text{M}$. The small K_m values and a k_{cat} of $1.4 \pm 0.1 \text{ min}^{-1}$ are typical for methyltransferases,^[2] which exhibit large catalytic accelerations as compared to the uncatalyzed reaction even though their turnover numbers are often low. Considering that purified TylC3 is UV/Vis transparent above 300 nm and its activity does not depend on the presence of metal ions,^[17] the enzyme appears not to require the assistance of any cofactor to stabilize the enediolate intermediate **7**, which is likely to be the methyl acceptor in this mechanism (Scheme 2).

To gain evidence for the intermediacy of enediolate **7** in the course of TylC3-catalyzed reaction,^[18] a 4,4-difluoro substrate analogue **8** was synthesized as shown in Scheme 3.^[19–21] It is anticipated that upon incubation with TylC3, **8** may undergo deprotonation at C-3 followed by the elimination of a fluoride



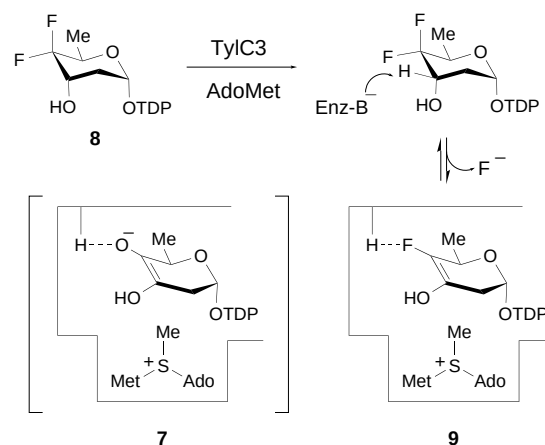
Scheme 2. Essential components of the methylation step 5 $\rightarrow$ 6.



Scheme 3. a) Super-Hydride, THF, 97%;^[19] b) NBS, BaCO₃, CCl₄;^[20] c) Bu₃SnH, AIBN, benzene, two steps, 30%; d) PCC, CH₂Cl₂, 69%; e) DAST, CH₂Cl₂, 82%; f) Dowex-50W(H⁺), MeCN, H₂O, 85%; g) BuLi, THF, then dibenzyl phosphorochloridate, 66%; h) 5% Pd/C, H₂, MeOH, 93%; i) 1H-tetrazole, pyridine, TMP-morpholidate; j) 2M LiOH, THF, two steps, 47%. AIBN = azobisisobutyronitrile, Bn = benzyl, Bz = benzoyl, DAST = (diethylamino)sulfur trifluoride, NBS = N-bromosuccinimide, PCC = pyridinium chlorochromate, TMP = thymidine 5'-trihydrogenphosphate, TDP = thymidine 5'-dihydrogenphosphate.

ion from C-4 to yield a new intermediate **9** (Scheme 4).^[22] Since **9** closely resembles the putative enediolate intermediate **7**, binding of **9** to the active site of TyIC3 may lead to enzyme inhibition. However, to our disappointment, when compound **8** was exposed to TyIC3, no release of fluoride ion could be detected by ¹⁹F NMR, and no inhibition of TyIC3 was observed. Considering that **8** is not even a competitive inhibitor for TyIC3 at a concentration 25 times higher than that of the substrate in a competition experiment, **8** must either have little affinity toward TyIC3 or have difficulty fitting into the active site. Clearly, a full elucidation of the catalytic mechanism of TyIC3 must await further experiments.

Nevertheless, since TyIC3 is a prototypical C-methyltransferase involved in methyl-branched sugar formation, insights gleaned from this study should be applicable to the biosyn-



Scheme 4. Expected effect of TyIC3 on the 4,4-difluoro substrate analogue **8**.

thesis of other methyl-branched sugars such as L-vinlose, D- and L-virenose, D-evalose, L-nogalose, L-chromose B, D-evermucose, and L-axenose.^[4, 5, 23] The present studies on TyIC3 not only expand our knowledge of AdoMet-dependent enzymes, but also add to the tools available for the genetic manipulation of biosynthetic pathways of deoxy sugars. Since the sugar components of macrolide antibiotics are known to be essential for specificity and activity of the parent drug, the ability to genetically engineer microorganisms to produce sugars that contain various structural alterations, such as branched chains, provides an innovative approach to the discovery of clinically useful compounds.

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- [13] Analysis by HPLC was performed with an Adsorbosphere SAX column (5 μ , 4.6 $\times$ 250 mm) with a gradient from 140 mM to 320 mM potassium phosphate buffer, pH 3.5, over 20 min, followed by a 5-min wash with 500 mM potassium phosphate buffer, pH 3.5.
- [14] Substrate **5** was prepared as described previously: H. Chen, G. Agnihotri, Z. Guo, N. L. S. Que, X. H. Chen, H.-w. Liu, *J. Am. Chem. Soc.* **1999**, *121*, 8124–8125.
- [15] **6**: ^1H NMR (500 MHz, $^2\text{H}_2\text{O}$): δ = 1.11 (d, $^3J(\text{H,H})$ = 6.0 Hz, 3H; 5-Me hydrated form), 1.15 (d, $^3J(\text{H,H})$ = 6.0 Hz, 3H; 5-Me keto form), 1.37 (s, 3H; 3-Me hydrated form), 1.45 (s, 3H; 3-Me keto form), 1.82 (s, 3H; 5'-Me), 1.92 (m, 2H; 2-H hydrated form), 2.23–2.32 (m, 2H; 2'-H), 2.40 (m, 2H; 2-H keto form), 4.01–4.10 (m, 3H; 5-H hydrated form, 4'-H, 5'-H), 4.47–4.53 (m, 1H; 3'-H), 4.72 (q, $^3J(\text{H,H})$ = 6.0 Hz, 1H; 5-H keto form), 5.49 (m, 1H; 1-H hydrated form), 5.64 (m, 1H; 1-H keto form), 6.24 (t, $^3J(\text{H,H})$ = 4.2 Hz, 1H; 1'-H), 7.61 (s, 1H; 6''-H); ^{13}C NMR (75 MHz, $^2\text{H}_2\text{O}$, hydrated form): δ = 11.6, 12.0, 23.5, 38.3, 40.9 (d, $^3J(\text{C,P})$ = 7.5 Hz; C-2), 65.3 (d, $^2J(\text{C,P})$ = 5.6 Hz; C-5'), 68.1, 70.7, 71.8, 84.7, 85.0 (d, $^3J(\text{C,P})$ = 7.5 Hz; C-4'), 94.0 (d, $^2J(\text{C,P})$ = 5.3 Hz; C-1), 94.3, 111.6, 137.2, 151.6, 166.5. The ratio of the hydrated form to the keto form is approximately 3:1.
- [16] The HPLC assay used for determining the kinetic parameters was performed on an Adsorbosphere SAX column (5 μ , 4.6 $\times$ 250 mm), which was eluted isocratically with 50 mM potassium phosphate buffer, pH 3.5. The peak integrations of (S)-adenosylmethionine and (S)-adenosylhomocysteine were used to determine the product conversion.
- [17] Inductively coupled plasma (ICP) analysis for metal ions indicated the presence of approximately 0.4 mol of Zn^{II} per mole of TylC3. However, the zinc does not appear to be important for activity, since dialysis of the enzyme against 5 mM 1,10-phenanthroline for 4 d did not reduce the activity, although ICP analysis indicated that approximately half of the zinc was removed. Attempts to reconstitute the enzyme with zinc also failed to increase the activity. Likewise, the addition of Mg^{II} did not increase the activity of TylC3.
- [18] Eneidiolates are common intermediates in many biotransformations. For a few examples, see: a) R. V. J. Chari, J. W. Kozarich, *J. Am. Chem. Soc.* **1983**, *105*, 7169–7171; b) A. E. Johnson, M. E. Tanner, *Biochemistry* **1998**, *37*, 5746–5754; c) C. J. Jeffery, B. J. Bohnson, W. Chien, D. Ringe, G. A. Petsko, *Biochemistry* **2000**, *39*, 955–964.
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- [20] S. Hanessian, N. R. Plessas, *J. Org. Chem.* **1969**, *34*, 1035–1044.
- [21] **8**: ^1H NMR (300 MHz, $^2\text{H}_2\text{O}$): δ = 1.10 (d, $^3J(\text{H,H})$ = 6.6 Hz, 3H; 5-Me), 1.73 (s, 3H; 5'-Me), 1.86 (m, 1H; 2-H_{ax}), 2.08 (m, 1H; 2-H_{eq}), 2.18 (m, 2H; 2'-H), 3.98 (m, 4H; 3-, 3'- and 5'-H), 4.06 (dq, $^3J(\text{H,F})$ = 21.6, $^3J(\text{H,H})$ = 6.6 Hz, 1H; 5-H), 4.44 (m, 1H; 4'-H), 5.40 (m, 1H; 1-H), 6.16 (m, 1H; 1'-H), 7.57 (s, 1H; 6''-H); ^{13}C NMR (75 MHz, $^2\text{H}_2\text{O}$): δ = 11.6, 12.0, 23.5, 38.3, 40.9 (d, $^3J(\text{C,P})$ = 7.5 Hz; C-2), 65.3 (d, $^2J(\text{C,P})$ = 5.6 Hz; C-5'), 68.6 (dd, $^1J(\text{C,F})$ = 31.7, $^1J(\text{C,F})$ = 24.1 Hz; C-4), 70.9, 84.8, 85.2 (d, $^3J(\text{C,P})$ = 9.0 Hz; C-4'), 93.6 (d, $^2J(\text{C,P})$ = 4.6 Hz; C-1), 111.6, 137.3, 151.6, 166.5; ^{19}F NMR (282 MHz, $^2\text{H}_2\text{O}$): δ = -125.9 (d, $^2J(\text{F,F})$ = 253 Hz), -128.3 (dd, $^2J(\text{F,F})$ = 253, $^3J(\text{H,F})$ = 21.2 Hz); ^{31}P NMR (121 MHz, $^2\text{H}_2\text{O}$): δ = -11.2 (d, $^2J(\text{P,P})$ = 20.7 Hz), -12.1 (d, $^2J(\text{P,P})$ = 20.7 Hz); HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{23}\text{F}_2\text{N}_2\text{O}_{13}\text{P}_2$ [$M - \text{H}$] $^-$: 551.0649; found: 551.0669.
- [22] The difluoromethylene moiety is a strongly electron-withdrawing group which can stabilize the corresponding β -anion both by induction and by negative hyperconjugation: B. E. Smart in *Chemistry of Organic Fluorine Compounds II* (Eds.: M. Hudlicky, A. E. Pavlath), American Chemical Society, Washington, **1995**, pp. 979–1010. Although the $\text{p}K_{\text{a}}$ data of protons adjacent to the difluoromethylene group are not available, examples of α -anion-induced β -fluoride elimination in similar structures are well known: A. M. Kornilov, I. B. Kulik, A. E. Sorochinsky, V. P. Kukhar, *Tetrahedron Asymmetry* **1995**, *6*, 199–206; D. Schirlin, S. Baltzer, J. M. Altenburger, C. Tarnus, J. M. Remy, *Tetrahedron* **1996**, *52*, 305–318.
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Oxathiaphospholane Approach to the Synthesis of P-Chiral, Isotopomeric Deoxy(ribonucleoside phosphorothioate)s and Phosphates Labeled with an Oxygen Isotope**

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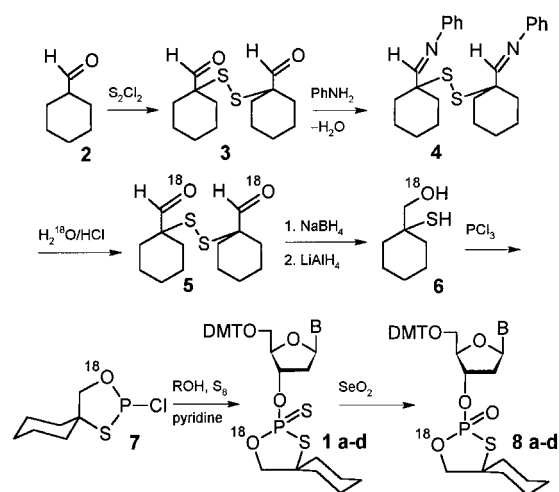
Introduced by Eckstein, phosphorothioate analogues of nucleotides have become an indispensable tool for studying the metabolism of nucleic acids.^[1] Standard chemical methods for the synthesis of oligo(deoxyribonucleoside phosphorothioate)s (PS-Oligos) provide a mixture of 2ⁿ diastereoisomers, where n is the number of phosphorothioate linkages.^[2] The enzymatic synthesis of stereodefined PS-Oligos is limited to the preparation of (all- R_P)-oligomers because of the stereoselectivity of available DNA and RNA polymerases. The first method for stereocontrolled chemical synthesis of PS-Oligos was elaborated in our group,^[3] and several alternative methods were recently reported.^[4, 5] Stereodefined PS-Oligos were used for studying the mode of action of several bacterial and human enzymes^[6–8] and the stereodependent avidity of PS-Oligos toward complementary DNA or RNA.^[9] However, the presence of a sulfur atom affects the properties of internucleotide bonds, mostly due to the different steric requirements of sulfur atoms (P–S vs P–O bond length), different affinity towards metal ions, and changes in the distribution of the negative charge in the phosphorothioate anion.^[10] Therefore, the hydration pattern of PS-Oligos is different from that of natural oligonucleotides,^[11] and this obstructs the evaluation of kinetic data of “rescue effects” of thiophilic metal ions, and makes analysis of direct or water-mediated contacts between metal ions and phosphate groups much more difficult. These inconveniences could be avoided by using P-chiral isotopomeric phosphates.^[12] Here we describe the synthesis of stereodefined oligo(deoxyribonucleoside [^{18}O]phosphorothioate)s (PS ^{18}O -Oligos) and oligo-(deoxyribonucleoside [^{18}O]phosphate)s (P ^{18}O -Oligos), in which both of the nonbridging oxygen atoms of the internucleotide bond were replaced by S and ^{18}O , or one of them was replaced by ^{18}O , respectively. Oligonucleotides containing a single P-chiral [^{16}O , ^{18}O] internucleotide bond were first used by Eckstein^[13] in studies on Eco RI endonuclease. Stereodefined P ^{18}O -Oligos can be used to investigate the interaction of particular oxygen atoms with other molecules or metal ions, given analytical methods that allow the isotopic effect to be measured with satisfactory accuracy.^[14]

To obtain stereodefined PS ^{18}O -Oligos, we synthesized 5'-O-DMT-nucleoside-3'-O-(2-thio-“spiro”-4,4-pentamethylene-

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1,3,2-[^{18}O]oxathiaphospholane)s (**1**), and separated them into diastereomerically pure forms (Scheme 1). Commercially available cyclohexanecarbaldehyde (**2**) was converted into the 2,2'-dithiobis(cyclohexanecarbaldehyde) **3** in 70% yield;^[15] this compound was subsequently transformed into



Scheme 1. Synthesis of **1a–d** and **8a–d**. DMT = 4,4'-dimethoxytrityl, ROH = 5'-O-DMT-3'-OH-nucleoside.

the bis(imine) **4** by treatment with aniline in benzene with azeotropic removal of water. A solution of crude **4** in THF was cooled to 0–5 °C and saturated with anhydrous HCl in the presence of 1.1 mole equivalents of [^{18}O]water (95 atom % ^{18}O) to form the 2,2'-dithiobis([^{18}O]cyclohexanecarbaldehyde) **5**. Its analysis by EI-MS [m/z 286 ($2 \times ^{16}\text{O}$, 18.3%), m/z 288 (^{16}O , ^{18}O , 78.1%), m/z 290 ($2 \times ^{18}\text{O}$, 100%)] showed an isotopic enrichment of 71 atom % ^{18}O . A similar method was formerly applied for almost quantitative incorporation of an ^{18}O label into benzaldehyde,^[16] but in these exploratory studies no special precautions with respect to the dryness of THF were taken. Treatment of **5** with NaBH_4 followed by LiAlH_4 gave (1-sulfanylcyclohexyl)methan[^{18}O]ol (**6**) with retention of the isotopic enrichment. At this stage, **6** was diluted with unlabeled sulfanylalcohol, and the final isotope enrichment was about 45%. Reaction of **6** with PCl_3 provided the [^{18}O]oxathiaphospholane **7**. The ^{31}P NMR spectrum (Figure 1A) contained two peaks at $\delta = 218.88$ and 218.79 corresponding to unlabeled and ^{18}O -labeled compounds. Phosphitylation of 5'-O-DMT-nucleosides with **7** followed by sulfurization gave monomers **1a–d**, which subsequently were separated by chromatography into pure fast- and slow-eluting P-diastereomers, with R_p and S_p absolute configuration, respectively (Table 1). Their ^{31}P NMR spectra consisted of a downfield and an upfield signal (Figure 1B), corresponding to unlabeled and isotopically labeled monomers, respectively. The chemical shift difference of $\Delta\delta = 0.025$ –0.027 indicates that the ^{18}O atom is attached to the phosphorus atom by a single bond.^[17]

The monomers *fast-1a* and *slow-1a* were used for the synthesis of dithymidyl [^{18}O]phosphorothioates. The condensation was performed in CH_3CN on a 40-mg scale with 15 mg of 3'-O-Ac-thymidine in the presence of 1,8-diazabicy-

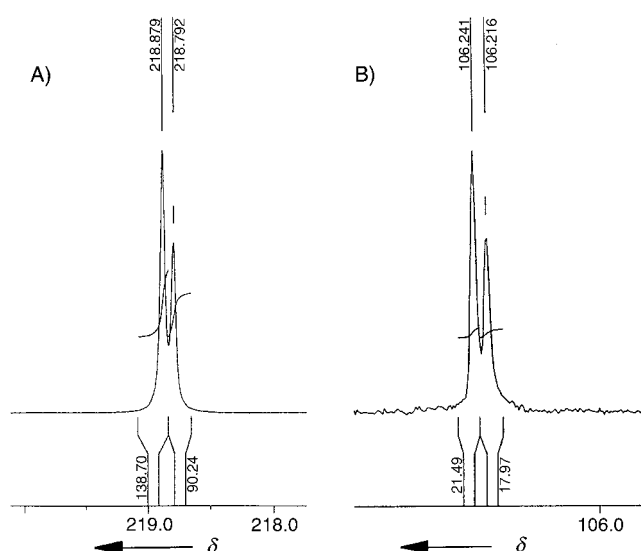


Figure 1. ^{31}P NMR spectra (CD_3CN) of A) **7**, B) *fast-1b*. Spectral parameters: time domain 16 k, size 16 k, sweep width 800 Hz.

Table 1. ^{31}P NMR and FAB-MS characteristics of isotopically labeled monomers **1a–d** and **8a–d**.^[a]

Nucleobase, isomer	$\delta(^{31}\text{P})$ ^[b]			m/z (FAB-MS) ^[c]		Isotope enrichment ^[d] [%]
	^{16}O	^{18}O	$\Delta\delta$	^{16}O	^{18}O	
Thy, <i>fast-1a</i>	106.284	106.258	0.026	749.0	751.0	47
Thy, <i>slow-1a</i>	106.646	106.619	0.027			
Cyt ^{Bz} , <i>fast-1b</i>	106.241	106.216	0.025	838.3	840.2	48
Cyt ^{Bz} , <i>slow-1b</i>	106.621	106.595	0.026			
Ade ^{Bz} , <i>fast-1c</i>	105.910	105.885	0.025	862.4	864.4	46
Ade ^{Bz} , <i>slow-1c</i>	106.402	106.376	0.026			
Gua ^{Bu} , <i>fast-1d</i>	106.353	106.328	0.025	844.3	846.3	46
Gua ^{Bu} , <i>slow-1d</i>	106.838	106.813	0.025			
Thy, <i>fast-8a</i>	44.078	44.060	0.018	733.1	735.0	44
Thy, <i>slow-8a</i>	44.590	44.572	0.018			
Cyt ^{Bz} , <i>fast-8b</i>	44.111	44.091	0.020	822.2	823.9	46
Cyt ^{Bz} , <i>slow-8b</i>	44.551	44.534	0.017			
Ade ^{Bz} , <i>fast-8c</i>	43.799	43.780	0.019	846.0	848.0	45
Ade ^{Bz} , <i>slow-8c</i>	44.204	44.186	0.018			
Gua ^{Bu} , <i>fast-8d</i>	44.749	44.730	0.019	828.2	830.0	44
Gua ^{Bu} , <i>slow-8d</i>	45.426	45.407	0.019			

[a] For compounds **8a–d** the terms *fast* and *slow* refer to the chromatographic mobility of their precursors **1a–d**. [b] ^{31}P NMR spectra were recorded on a Bruker AC 200 spectrometer in CD_3CN . [c] The spectra were recorded for unseparated mixtures of both diastereoisomers. The observed m/z values are in accord with calculated ones. [d] Calculation based on molecular ion intensities for ten averaged FAB-MS scans.

clo[5.4.0]undec-7-ene (DBU). Reaction was complete in 5 min, and the dinucleotides were obtained almost quantitatively (^{31}P NMR). The observed chemical shift difference of $\Delta\delta = 0.04$ indicated a bond order of greater than 1.5 between the ^{18}O and P atoms, while the matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrum recorded for the unprotected dinucleotide confirmed the isotope enrichment [R_p -T_{PS}T, m/z 560.8 (56%), 562.8 (44%); S_p -T_{PS}T, m/z 561.1 (54%), 563.1 (46%)]. Configurational assignments based on the known stereochemistry of the condensation process^[9] allowed us to conclude that *slow*- and *fast-1a–d* provide [^{18}O]phosphorothioate dinucleotides with S_p and R_p absolute configurations, respectively. According to

the Cahn–Ingold–Prelog rules, the isotopic replacement $^{16}\text{O} \rightarrow ^{18}\text{O}$ in dinucleoside phosphorothioates changes neither the sense of chirality nor the absolute configuration of the phosphorus atom, as the atomic numbers of the two oxygen isotopes are the same.

Pure *fast*- and *slow*-**1a** were used for the solid-phase synthesis of octa(thymidine [^{18}O]phosphorothioate)s. The purified oligomers were treated with snake venom phosphodiesterase (svPDE). As expected, the (all- S_P)-octamer was not digested by R_P -selective svPDE. Its (all- R_P)-counterpart was digested by the enzyme, and the reacting mixture containing consecutively shortened, partially digested oligomers (down to a pentamer) was analyzed by MALDI-TOF mass spectrometry (Figure 2). The observed relative intensities of the mass peaks were in accord with calculated values.

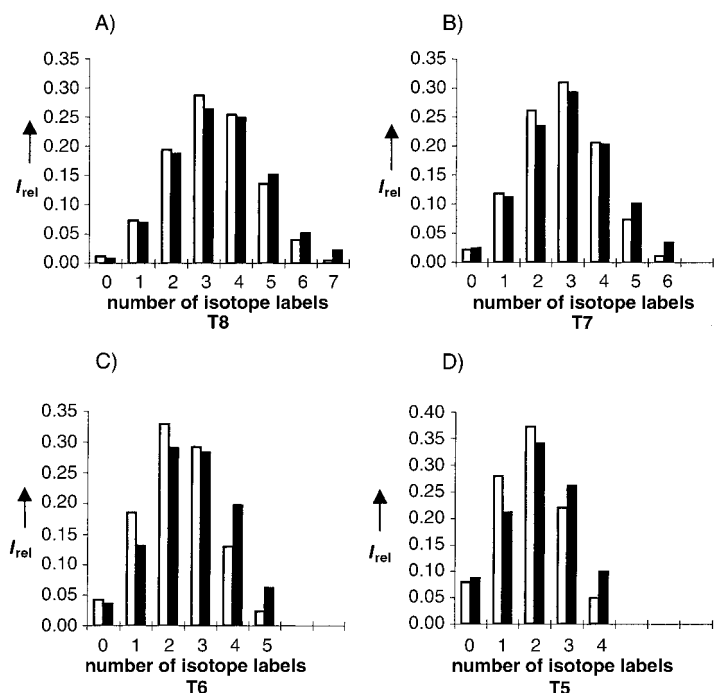
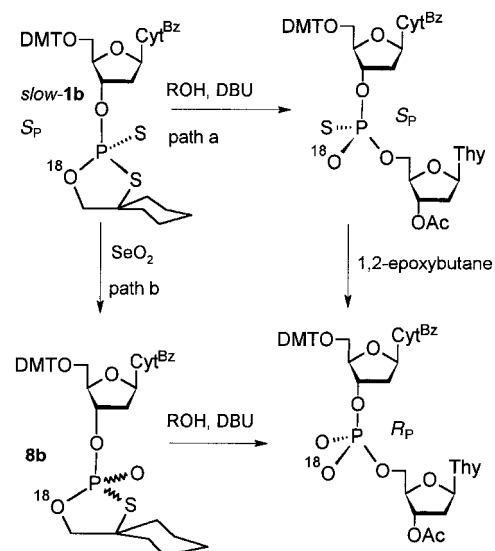


Figure 2. Comparison of calculated (open bars) and measured (full bars) relative intensities I_{rel} of molecular ions and corresponding isotopic bands from MALDI-TOF analysis for oligomers resulting from svPDE digestion of isotopically labeled (All- R_P -PS ^{18}O)-T $_8$. An isotopic enrichment of 47% was used for calculation. A) [starting octamer] m/z = 2482. B) [heptamer] m/z = 2162. C) [hexamer+Na $^+$ +K $^+$] m/z = 1904. D) [pentamer+Na $^+$ +K $^+$] m/z = 1584.

To obtain monomers for direct synthesis of stereodefined P ^{18}O -Oligos, diastereomerically pure monomers **1a–d** (ca. 400 mg) were stereospecifically (as judged by ^{31}P NMR spectroscopy) oxidized with SeO $_2$ (twofold molar excess) in CH $_3$ CN (3 mL) at room temperature with stirring (15 min) to give 5'-O-DMT-nucleoside-3'-O-(2-oxo-“spiro”-4,4-pentamethylene-1,3,2-[^{18}O]oxathiaphospholane)s (**8a–d**, see Scheme 1). The reaction mixture was passed through a dry silica gel column (ca. 1 g), with exclusion of moisture, to absorb traces of dissolved SeO $_2$. The monomers were recovered in amounts of about 350–360 mg and characterized by FAB-MS and ^{31}P NMR spectroscopy (see Table 1).

The applicability of the unlabeled monomer **8a** for synthesis of oligonucleotides possessing phosphate internucleotide bonds has already been reported.^[18] However, the stereochemistry of the isotopomeric P ^{18}O -Oligos had to be determined. For that purpose, the model dinucleotide [PS ^{18}O]-DMTC ^{Bz} T $_{\text{OAc}}$ obtained from *slow*-**1b** was converted with 1,2-epoxybutane in stereoretentive manner^[19] into [P ^{18}O] ^{DMT} C ^{Bz} T $_{\text{OAc}}$ (Scheme 2, path a). The same monomer



Scheme 2. Sequence of reactions used for determining the absolute configuration at the P atom in P ^{18}O -Oligos. ROH = 3'-O-Acetylthymidine.

1b was oxidized with SeO $_2$, and resulting **8b** was used for synthesis of [P ^{18}O] ^{DMT} C ^{Bz} T $_{\text{OAc}}$ (path b). The K $^+$ salt of each [P ^{18}O]dinucleotide obtained via path a and path b, without deprotection, was converted into a methyl ester with MeI/DMSO/[18]crown-6^[20] and analyzed by ^{31}P NMR spectroscopy. The spectra showed identical patterns with isotope chemical shifts of $\Delta\delta$ = 0.04 and 0.02 for the downfield and upfield signals, respectively. These results indicate that a sequence of reactions: *slow*-**1b** $\rightarrow$ **8b** $\rightarrow$ P ^{18}O -Oligo yields the [^{18}O]phosphate internucleotide with R_P absolute configuration. Most probably, the oxidation of **1b** to **8b**, as well as the condensation of **8b** with 3'-O-Ac-thymidine, occurred with retention of configuration.

The two sets of ^{18}O -labeled monomers **1a–d** and **8a–d** and their unlabeled counterparts allow medium-size oligonucleotides to be synthesized with any combination of internucleotide bond with respect to its type (P–S vs P–O) or absolute configuration (R_P vs S_P), as well as to the position and the number of isotope labels along the chain. This flexibility is exemplified by the solid-phase synthesis of (R_P ,Mix)-d(A $_{\text{PS}}$ C $_{\text{PO}}$ T $_{\text{PS}^{18}\text{O}}$ C) (**9**), which was obtained on a 1- μmol scale by using 20 mg of each monomer per coupling followed by two-step HPLC purification. The product was analyzed by polyacrylamide gel electrophoresis (PAGE) and MALDI-TOF mass spectrometry (Figure 3). Both techniques documented its homogeneity and the presence of the isotopic label.

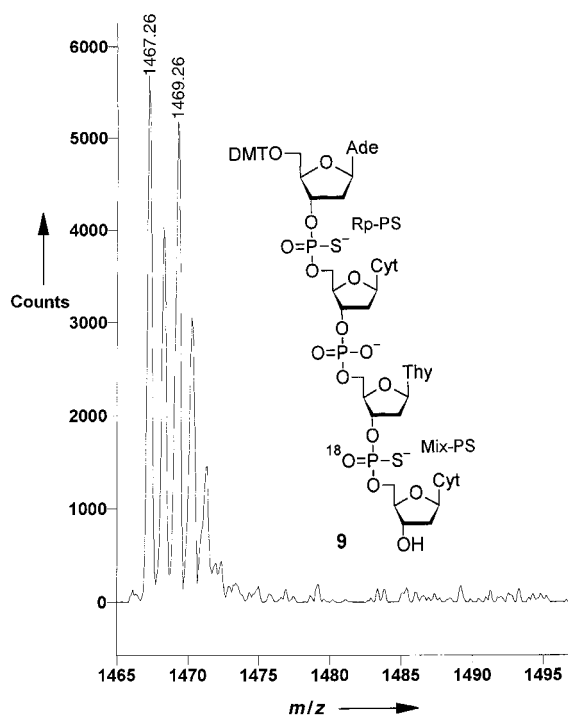


Figure 3. MALDI-TOF mass spectrum for **9** with a 5'-O-DMT protecting group. Spectral parameters: negative-ion spectrometry, reflector mode, accelerating voltage 20 kV, delay 100 ns, 60 scans averaged.

Experimental Section

The detailed reaction conditions for synthesis of unlabeled compounds **1**, **3**, **5**, **6**, **7** and **8**, their full characteristics and chromatographic conditions for separation of **1a–d** into pure diastereomers were published elsewhere.^[9, 18] The ¹⁸O-labeled water (95 atom % ¹⁸O) was supplied by ICON Services, Inc. (Summit, NJ). The FAB mass spectra were recorded on a Finnigan MAT 95 spectrometer (Bremen, Germany) in negative-ion mode. High-resolution MALDI-TOF mass spectrometry (negative ion spectrometry) was performed with a Voyager-Elite mass spectrometer (PerSeptive Biosystems Inc., Framingham, MA) operating in the reflector mode.

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Chiral Recognition in Bis-Urea-Based Aggregates and Organogels through Cooperative Interactions**

Maaïke de Loos, Jan van Esch,* Richard M. Kellogg, and Ben L. Feringa*

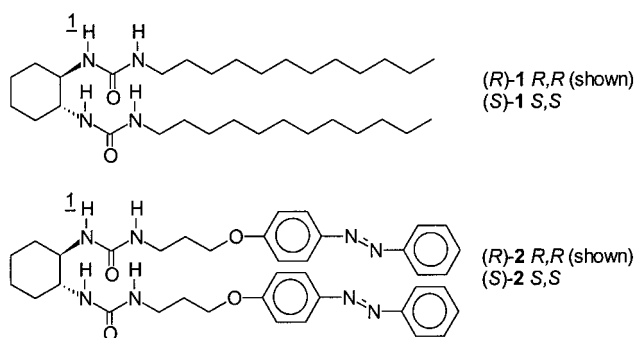
Chiral recognition is indisputably one of the most intriguing phenomena in nature. In chemistry, it is a key feature in applications such as enantioselective catalysis,^[1] separation techniques,^[2] and in the formation of supramolecular systems, both in solid assemblies^[2, 3] and in solution.^[2, 4–6]

Intermediate to solid- and solution-phase systems one might place organogels.^[7, 8] These consist of molecules, self-assembled into large fiberlike aggregates which intertwine to form a reversible gel in organic solvents. Especially the rationally designed 1,2-bis(ureido)cyclohexane derivatives were found to be highly effective gelators for organic solvents.^[9, 10] Furthermore, these compounds contain two stereogenic centers, which for **1** are expressed in the formation of twisted fibers in ethanol with a helicity that depends on the handedness of **1**.^[10b] Related chiral phenomena are found for other gel systems.^[3, 7, 8a,d]

Here we report on chiral recognition through cooperative interactions between aggregates and gels of **1** and a co-aggregating guest **2**.^[11] Guest **2** exhibits the same bis(ureido)-cyclohexane skeleton as **1**, but azobenzene chromophores have been attached to the side chains to differentiate **2** from host **1** and to probe the microenvironment by spectroscopic methods.

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^1H NMR measurements on solutions of **1** in CDCl_3 showed a strong downfield shift of the NH1 proton upon increasing the concentration, which is indicative of self-association through intermolecular hydrogen bonding (Figure 1).^[12]

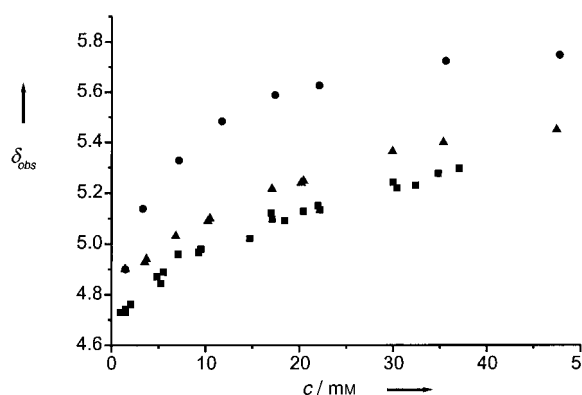
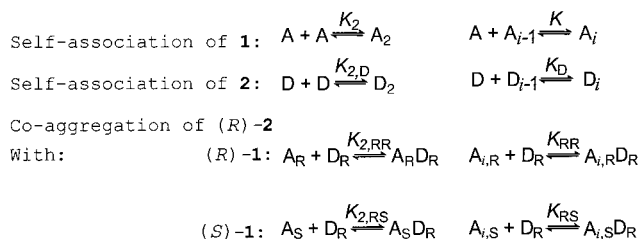


Figure 1. Chemical shifts plotted against the total urea concentration for: NH1 of pure **1** (■), NH1 of (*R*)-**2** in (*S*)-**1** (●), and NH1 of (*R*)-**2** in (*R*)-**1** (▲; CDCl_3 , $T = 50^\circ\text{C}$). (*R*)-**2** was kept at a fixed concentration of 2 mM and the concentration of either (*S*)-**1** or (*R*)-**1** was increased.

The concentration dependency of the chemical shifts could not be described by a dimerization model,^[13] and indicates that higher aggregates were formed. Thus, in accordance with an earlier study on the self-association of mono-urea compounds^[14] the association equilibria of **1** were treated with a cooperative association model in which all but the first association constant K_2 are assumed to be the same (Scheme 1).^[15, 16] The concentration dependency of the chem-



with $K_2 \neq K_3 = K_4 = \dots = K_i = K$

Scheme 1. Cooperative model for a chiral self-associating system (**A**) and the co-aggregation of a second chiral molecule (**D**) with both enantiomers of this system.^[16]

ical shifts can now be described with Equation (1),^[15, 16] and gives the association constants shown in Table 1.

$$\frac{(1 - P_i)^{1/2}}{(2P_i - 1)c^{1/2}} = K_2^{1/2} + K \frac{P_i[(1 - P_i)c]^{1/2}}{2P_i - 1} \quad (1)^{[16]}$$

with

$$P_i = \frac{\delta_a - \delta_{\text{obs}}}{\delta_a - \delta_m}$$

Table 1. Calculated association constants and downfield shifts from the ^1H NMR measurements (CDCl_3 , $T = 50^\circ\text{C}$).

Sample	Calculated for	K_2 [M^{-1}]	K [M^{-1}]	$\Delta\delta_{\text{obs}}^{[a]}$
1	1	25 ± 10	179 ± 18	0.55
(<i>R</i>)- 2 in (<i>R</i>)- 1	(<i>R</i>)- 1	4 ± 1	176 ± 13	0.48
	(<i>R</i>)- 2	5 ± 1	175 ± 17	0.51
(<i>R</i>)- 2 in (<i>S</i>)- 1	(<i>S</i>)- 1	4 ± 1	167 ± 10	0.47
	(<i>R</i>)- 2	6 ± 1	321 ± 21	0.82

[a] $\Delta\delta_{\text{obs}} = \delta_{\text{obs}}(2 \text{ mM}) - \delta_{\text{obs}}(35 \text{ mM})$.

It is clear that the association constant K for the higher aggregates is considerably larger than the dimerization constant K_2 , which indicates that self-association of **1** is indeed a highly cooperative process. This proposal is also supported by variable temperature ^1H NMR measurements: it was found that gelation occurred within 1°C upon cooling a solution at $c > 8 \text{ mM}$.

Co-aggregation of **2** with solution-phase aggregates of (*R*)-**1** or (*S*)-**1** was studied by ^1H NMR titration experiments in which the concentration of **2** was kept constant. Both the NH protons of **1** and **2** could be distinguished. Increasing the concentration of either (*R*)-**1** or (*S*)-**1** caused a downfield shift of the NH1 proton of (*R*)-**2** (Figure 1). Separate FT-IR and ^1H NMR measurements^[17] showed that self-association of **2** is negligible at low concentrations; thus it can be concluded that the downfield shift is the result of co-aggregation of **2** with **1**. CD spectroscopic studies (see below) support this conclusion.

Calculation of the association constants of **1** in the presence of small amounts of (*R*)-**2** revealed that for (*R*)-**1** and (*S*)-**1** the dimerization constants K_2 decreased, but the higher association constants K did not significantly change (Table 1). In contrast, a large difference is observed in the curve shape (Figure 1) and magnitude of the downfield shifts ($\Delta\delta_{\text{obs}}$) when the co-assembly of (*R*)-**2** with (*R*)-**1** and with (*S*)-**1** is compared (Table 1). This observation indicates that both the association constants and the hydrogen-bonded structure in the co-aggregates are dissimilar.

The association constants for the co-assembly of (*R*)-**2** with (*R*)-**1** ($K_{2,RR}$, K_{RR}) and (*R*)-**2** with (*S*)-**1** ($K_{2,RS}$, K_{RS} ; Scheme 1) are also given in Table 1.^[18] For both co-assemblies it can be seen that, as for pure **1**, K_2 is considerably smaller than K , which is indicative of a highly cooperative association process. Furthermore, the dimerization constants $K_{2,RR}$ and $K_{2,RS}$ are of the same magnitude. However, the association constant K_{RS} is almost twice as large as K_{RR} , which indicates that the incorporation of (*R*)-**2** in higher aggregates of (*S*)-**1** is preferred to incorporation in higher aggregates of (*R*)-**1**. Dimerization is apparently not affected by the chirality of the compounds, whereas formation of larger aggregates results in

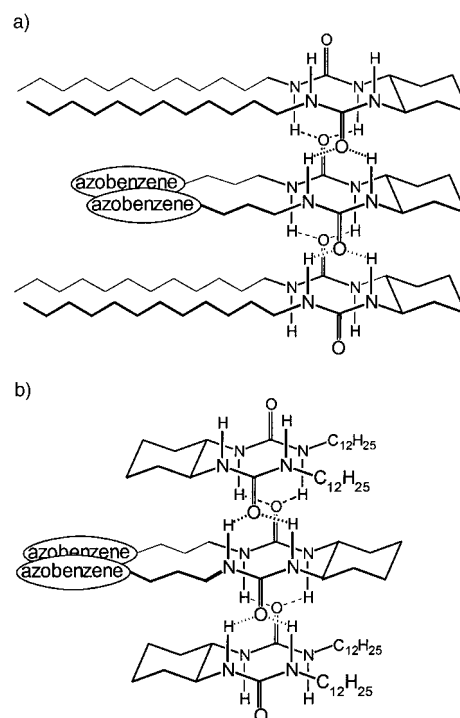
discrimination between the enantiomers. Thus, cooperativity is important for the chiral recognition in these systems. Furthermore, the K_{RR} and $\Delta\delta_{\text{obs}}$ values for the co-assembly of (*R*)-**2** with (*R*)-**1** are similar to those for pure (*R*)-**1**, which indicates they have a comparable hydrogen-bonded structure and strength. However, both the K_{RS} and $\Delta\delta_{\text{obs}}$ values are different for the co-assembly of (*R*)-**2** with (*S*)-**1**, which leads to the conclusion that an aggregate is formed with a different hydrogen-bonded structure and strength.

Chiral recognition in larger aggregates, namely, the gel, was studied by spectroscopic methods and *cis-trans* isomerizations. UV/Vis spectra of solutions of **2** in 1-butanol (0.3 mM) showed strong absorption bands at 238 and 344 nm and a weak band at 440 nm. Incorporation of (*R*)-**2** in 1-butanol gels of (*R*)-**1** or (*S*)-**1** resulted in symmetric absorption bands at 239, 345, and 443 nm, thus indicating the presence of molecularly dispersed azobenzenes.^[19]

CD measurements on pure **2** showed a split CD Cotton effect associated with the UV band at 344 nm for the solvents tested, with the intensity increasing upon decreasing solvent polarity (Figure 2a). The observed exciton coupling exhibits no concentration dependency and thus has to be the result of an intramolecular stacking of the chromophores. The sign of the Cotton effects for (*R*)-**2** and (*S*)-**2** is in agreement with the absolute configuration at the cyclohexane ring.^[20]

The CD spectra of (*R*)-**2** (0.3 mM) in a 1-butanol gel of (*S*)-**1** (18.6 mM) showed a slightly more intense CD effect at room temperature than that of a solution of (*R*)-**2** in 1-butanol (Figure 2). At 45 °C, above the melting point of the gel, the CD effect decreases to a value comparable to that of the solution of (*R*)-**2** in 1-butanol. The change in the CD spectra indicates that (*R*)-**2** becomes incorporated in (*S*)-**1** upon

gelation of (*S*)-**1**. Moreover, the solvent dependency suggests that the slight increase in intensity arises from the environment of (*R*)-**2** being less polar when it is incorporated in the gel of (*S*)-**1** than in 1-butanol itself (Scheme 2b).



Scheme 2. Model for the incorporation of **2** in a) an aggregate of **1** with the same configuration (shown: (*R*)-**2** in (*R*)-**1**) or b) an aggregate of **1** with opposite configuration (shown: (*R*)-**2** in (*S*)-**1**, showing the distinct environments for the azobenzene groups.

In contrast, incorporation of (*R*)-**2** in a gel of (*R*)-**1** results in a strong positive CD effect, from which the exciton coupling has disappeared (Figure 2b). Apparently, (*R*)-**2** has adopted a different conformation upon co-aggregation with (*R*)-**1**; the azobenzene groups are no longer stacked but incorporated between the close-packed alkyl chains of (*R*)-**1** (Scheme 2a). As for (*S*)-**1**, the solution-phase exciton-coupled CD spectrum reappears upon melting of the gel.

Irradiation of the solution and gel samples at 365 nm resulted in isomerization of the azobenzene groups to the *cis* form,^[21] and the disappearance of the CD effect. The *cis* form isomerized thermally (30 °C) back to the *trans* form, with clear differences being observed in the kinetics for the solution and the (*S*)-**1** and (*R*)-**1** gels (Table 2).

The isomerization of (*R*)-**2** in solution followed first-order kinetics. In the gels, however, a deviation from first-order kinetics was observed and the data concur with two simultaneous first-order reactions containing fractions a_s and a_t of a

Table 2. Thermal *cis-trans* isomerization at 30 °C^[a].

Sample	$k_s \times 10^{-5} [\text{s}^{-1}]$	a_s	$k_t \times 10^{-5} [\text{s}^{-1}]$	a_t
(<i>R</i>)- 2 , solution	1.84 ± 0.005	1.0	—	—
(<i>R</i>)- 2 , in (<i>S</i>)- 1 gel	4.6 ± 0.1	0.58	21.9 ± 0.4	0.42
(<i>R</i>)- 2 , in (<i>R</i>)- 1 gel	5.1 ± 0.1	0.59	29.5 ± 0.3	0.41

[a] For an explanation of the symbols, see the text.

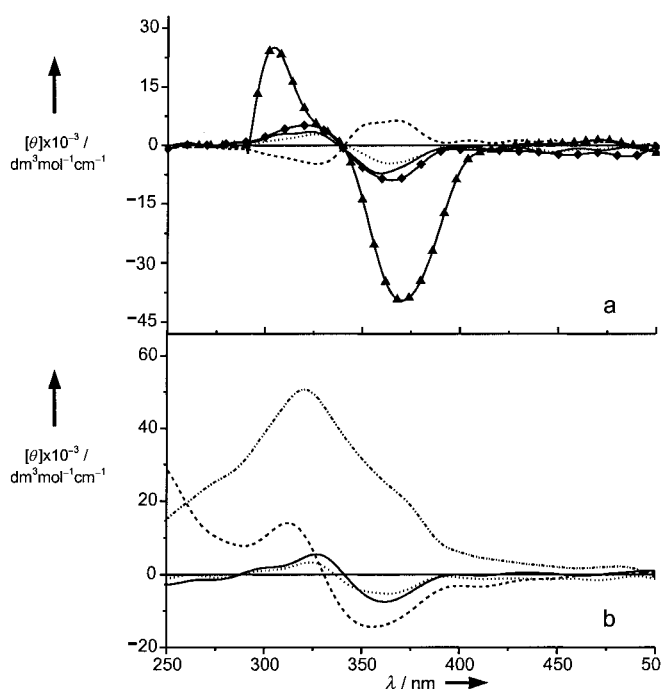


Figure 2. a) CD spectra of solutions of (*R*)-**2** in 1-butanol (—), 1-octanol (—◆—), chloroform (—●—), and *p*-xylene (—▲—), and (*S*)-**2** in 1-butanol (---). b) CD spectra of (*R*)-**2** in a 1-butanol gel of: (*S*)-**1** at 25 °C (----), (*S*)-**1** at 45 °C (—●—), (*R*)-**1** at 30 °C (—○—), and (*R*)-**1** at 45 °C (—).

slow (k_s) and a fast (k_f) reacting component.^[22] Remarkably, the isomerization was found to be slower in 1-butanol than in the gels. Furthermore, isomerization in the (S)-**1** gel was found to be slower than in the (R)-**1** gel, especially for the fast reacting component. Apparently, the azobenzene groups in (R)-**2** experience a more exposed "solvent-like" environment in the (S)-**1** gel than in the (R)-**1** gel (Scheme 2). These results support the CD measurements, and can be explained by the different packing of **2** in aggregates of the same or opposite configuration leading to a difference in the free volume and polarity experienced by the azobenzene groups (Scheme 2).

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- [16] Explanation of the symbols: A = host (R)-**1** or (S)-**1**; D = guest (R)-**2**; c = total urea concentration (M); δ_a = chemical shift of the fully aggregated state; δ_{obs} = observed chemical shift; δ_m = chemical shift of the monomer.
- [17] FT-IR measurements on **2** (CHCl₃; 2 mm) showed a shift of the NH stretch and amide I band from 3435 and 1663 cm⁻¹ for a solution at approximately 50 °C (monomer) to 3322 and 1628 cm⁻¹ for a gel at 20 °C (hydrogen-bonded aggregates), see Y. Mido, *Spectrochim. Acta Part A* 1973, 29, 431. ¹H NMR titration experiments of **2** (CDCl₃; 2–0.5 mm) revealed just a slight change (less than 0.006 ppm).
- [18] It was assumed that as **1** and **2** exhibit the same bis(ureido)cyclohexane skeleton the effect of aggregation on the chemical shift of the NH1 proton of **2** is similar when **2** is incorporated in stacks of **1** as in stacks of pure **2**. It is then possible to treat the chemical shift of **2** (δ_{obs}) as a function of the total concentration (c) of (R)-**2** + **1**, and Equation (1) can be applied. Self-association of **2** is negligible at $c \leq 2$ mm.
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Palladium-Catalyzed Domino Reaction of 4-Methoxycarbonyloxy-2-butyne-1-ols with Phenols: A Novel Synthetic Method for Cyclic Carbonates with Recycling of CO₂**

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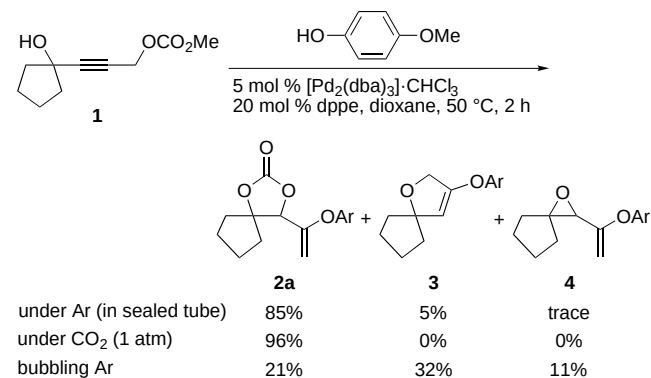
Allylic and propargylic carbonates are well-known compounds that undergo a variety of palladium-catalyzed transformations, which make up an important class of palladium-catalyzed reactions.^[1, 2] The key step in these reactions is the formation of a π -allyl- or -allenylpalladium complex by facile decarboxylation, which undergoes a variety of further transformations under neutral conditions. In these reactions, CO₂ is produced as a co-product in the decarboxylation step, but there are few reports on the recycling of this CO₂ molecule.^[3] Recently, the chemistry of CO₂ has received much attention from the viewpoint of carbon resources and environmental problems,^[4] and the fixation of CO₂ as cyclic carbonates represents an attractive area of organic synthesis.^[5–9] Here we report a novel synthesis of cyclic carbonates by palladium-catalyzed domino reaction of 4-methoxycarbonyloxy-2-butyne-

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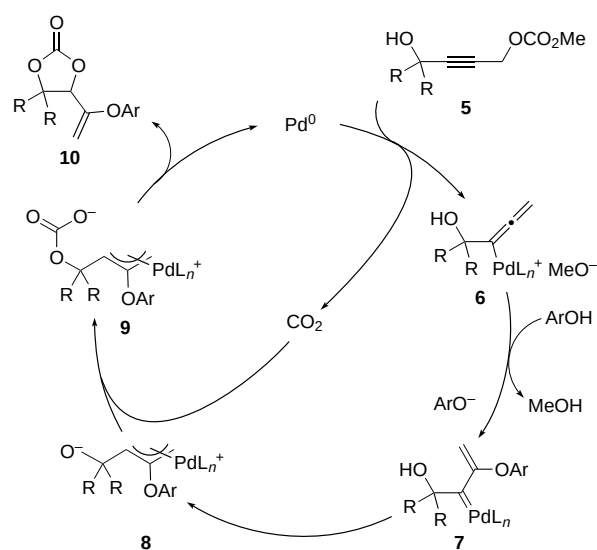
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1-ols with phenols. The reaction enables the efficient construction of cyclic carbonates in a one-pot process with recycling of the CO₂ molecule.

In an initial experiment, we found that the reaction of **1** and *p*-methoxyphenol with [Pd₂(dba)₃]·CHCl₃ and dppe under Ar in a sealed tube provided the cyclic carbonate **2a** in 85 % yield with a small amount of dihydrofuran **3** and traces of epoxide **4** (Scheme 1). A plausible mechanism for the reaction is shown in Scheme 2. By reaction with palladium catalyst, the propargylic carbonate **5** would undergo elimination of CO₂ to give



Scheme 1. Domino reactions of **1** in the presence and absence of CO₂. dba = dibenzylideneacetone, dppe = 1,2-bis(diphenylphosphanyl)ethane, Ar = *p*-methoxyphenyl.



Scheme 2. Proposed reaction mechanism for the type of domino reaction shown in Scheme 1.

the allenylpalladium methoxide **6**, which would be subject to nucleophilic attack by phenols to give the π -allenylpalladium complex **8** via the intermediate **7**. Finally, **8** would re-fix CO₂ to afford the carbonate species **9**, which would subsequently cyclize to produce the aryloxy-substituted cyclic carbonate **10**. It is expected that by-products **3** and **4** would be produced by direct cyclization of π -allenylpalladium complex **8**.^[10] To the best of our knowledge, this is the first example of efficient re-fixation of the CO₂ molecule from a decarboxylation reaction. To confirm this, we examined the reactions in the presence and absence of CO₂ (Scheme 1). When the reaction was

carried out in a CO₂ atmosphere, the yield of **2a** increased to 96 %. In contrast, when the reaction was carried out under bubbling Ar to remove the resulting CO₂, only 21 % yield of **2a** was obtained together with 32 % yield of **3** and 11 % yield of **4**. These results provide strong evidence that decarboxylation is followed by re-fixation of the CO₂ molecule in the reaction cycle.

To examine the scope of this reaction, we next attempted the reaction of **1** with various substituted phenols ArOH [Eq. (1), Table 1]. All of the reactions successfully proceeded

Table 1. Domino reactions of **1** with various substituted phenols [Eq. (1)].

Entry	X	T [°C]	t [h]	Product	Yield [%]
1	4-OMe	50	2	2a	85
2	2-OMe	RT	3	2b	90
3	4-Me	RT	5	2c	87
4	H	RT	9	2d	81
5	[a]	RT	4	2e	74
6	4-Cl	50	2	2f	70
7	4-F	50	2	2g	54
8	4-acetyl	50	5	2h	36

[a] ArOH = 1-naphthol.

to give the corresponding cyclic carbonates **2a–h** in moderate to good yields. In particular, the products were produced in high yields when **1** was treated with phenols bearing electron-donating substituents (entries 1–3). Some results of palladium-catalyzed domino reactions of various propargylic carbonates with *p*-methoxyphenol are summarized in Table 2. The reactions of **1**, **11**, **13**, and **15**, which contain five- to eight-membered rings, with *p*-methoxyphenol provided the corresponding cyclic carbonates in high yields (entries 1–4). Interestingly, **17**, which is known to be transformed into the aryloxy-substituted cyclopentanone at high temperature,^[11] was converted into the cyclic carbonate **18** in 63 % yield at room temperature (entry 5). The reactions of acyclic substrates **19** and **21** also gave the corresponding products **20** and **22** (entries 6 and 7). Although the yield of **22** was not high (42 %), it dramatically increased to 97 % when the reaction was carried out under an atmosphere of CO₂ (entry 7).

The reaction was applicable to 4-aryloxybutyn-1-ols **23** and **25**, in which the nucleophilic phenolic components were present within the molecule [Eq. (2)]. The

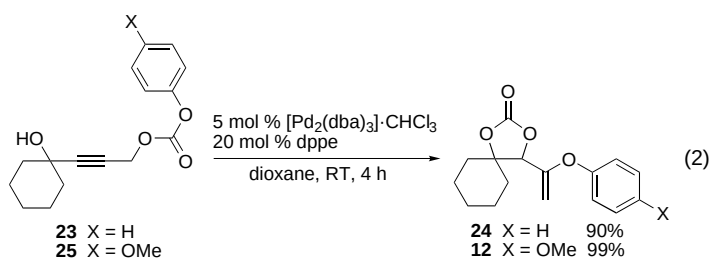
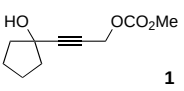
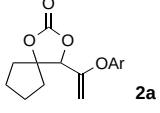
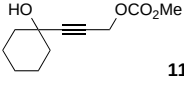
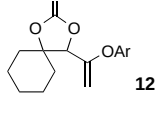
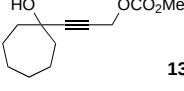
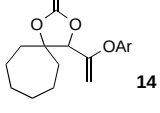
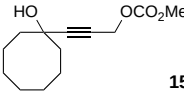
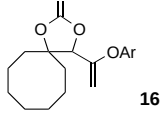
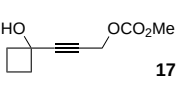
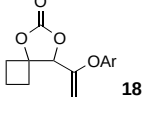
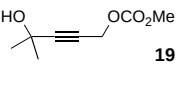
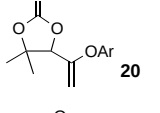
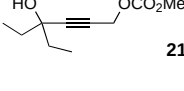
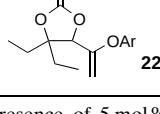
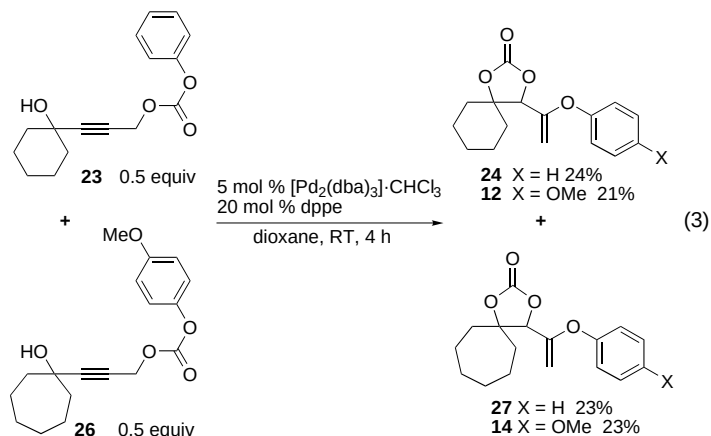


Table 2. Domino reactions of various propargylic carbonates with *p*-methoxyphenol.^[a]

Entry	Substrate	T [°C]	Product ^[b]	Yield [%] ^[c]
1		50		85 (96)
2		RT		91
3		RT		89
4		RT		80
5		RT		63
6		50		83
7		50		42 (97)

[a] Reactions were carried out in the presence of 5 mol % $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3$, 20 mol % dppe, and 1.1 equiv of *p*-methoxyphenol in dioxane under argon for 2–5 h. [b] R = *p*-methoxyphenyl. [c] The yields in parentheses are for reactions carried out under CO_2 (1 atm).

reactions of **23** and **25** with the palladium catalyst gave the desired cyclic carbonates **24** and **12**. Compound **12** was obtained almost quantitatively. A crossover experiment showed that the aryloxy ion was completely dissociated from the propargyl unit in the reaction [Eq. (3)]. This implies



that the reaction proceeds through the degradation of propargylic carbonates into three components—allenylpalladium species, aryloxy, and CO_2 —followed by re-formation of these components with high efficiency.

In conclusion, we have developed a novel synthesis of cyclic carbonates by palladium-catalyzed domino reactions of 4-methoxycarbonyloxy-2-butyn-1-ols with phenols. The reaction enables the construction of cyclic carbonates by efficient re-fixation of the CO_2 molecule under mild conditions, which is a very convenient and environmentally friendly method. The utility of this reaction in organic synthesis and its application to catalytic asymmetric reactions are now under investigation.

Experimental Section

General procedure for the palladium-catalyzed domino reaction of 4-methoxycarbonyloxy-2-butyn-1-ols with phenols: Reaction of **11** with *p*-methoxyphenol (Table 2, entry 2): *p*-Methoxyphenol (26.9 mg, 0.217 mmol), $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3$ (10.2 mg, 0.0099 mmol), and dppe (15.7 mg, 0.0394 mmol) were added to a stirred solution of **11** (41.8 mg, 0.197 mmol) in dioxane (3 mL) at room temperature. After being stirred for 4 h at room temperature, the reaction mixture was concentrated, and the residue was purified by chromatography on silica gel with hexane/AcOEt (90/10) as eluant to give **12** (54.9 mg, 91 %) as colorless needles. M.p. 80–83 °C; IR (KBr): $\tilde{\nu}$ = 2925, 2850, 1795, 1620 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 1.18–1.40 (m, 1H), 1.61–1.85 (m, 7H), 1.97–2.13 (m, 2H), 3.80 (s, 3H), 4.17 (d, J = 3.0 Hz, 1H), 4.47 (d, J = 3.0 Hz, 1H), 4.72 (s, 1H), 6.86–6.92 (m, 2H), 6.95–7.01 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3): δ = 21.8, 21.9, 24.6, 30.6, 36.6, 55.5, 83.1, 85.6, 89.7, 114.9 (2C), 122.1 (2C), 147.1, 153.9, 156.3, 157.0; MS (70 eV): m/z 304 [M^+]; HR-MS calcd for $\text{C}_{17}\text{H}_{20}\text{O}_5$ 304.1311; found 304.1314.

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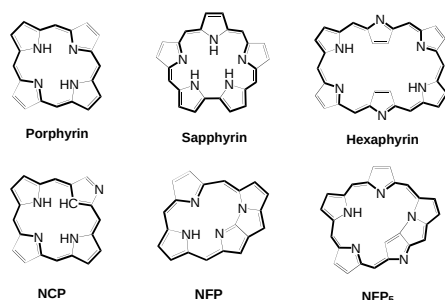
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N-Fused Pentaphyrin

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Porphyrin analogues have been attracting considerable attention not only from the interest of annulenic chemistry but also from their use in a variety of applications.^[1] Recently, reinvestigation of the Rothmund-type pyrrole–aryl aldehyde condensation^[2] has revealed the concurrent formation of a porphyrin isomer, the *N*-confused porphyrin (NCP),^[3] and expanded porphyrins such as sapphyrin^[4] and hexaphyrin^[5].



We have also reported a new analogue, the *N*-fused porphyrin (NFP), in which a unique fused tri-pentacyclic ring exists in the porphyrin core as the result of an inversion of the confused ring in NCP.^[6] Herein we report the first example of a normal-type of fused expanded porphyrin, *N*-fused pentaphyrin (NFP₅), which contains a fused tri-pentacyclic ring in the core.

The title compound was synthesized under similar Rothmund-type conditions, namely, the acid-catalyzed condensation of pentafluorobenzaldehyde and unsubstituted pyrrole, followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Along with the *meso*-pentafluorophenylporphyrin (12%), *meso*-pentafluorophenylhexaphyrin^[5] (20%), and other higher homologues of *meso*-aryl type

(around 13 %),^[7] yellowish (**1-Y**) and reddish (**1-R**) products, both of which show parent mass peaks in the fast atom bombardment (FAB) mass spectra corresponding to the pentapyrrolic macrocycle, could be isolated in a total yield of approximately 15 %. The ratio of the two products **1-R** and **1-Y** changed greatly according to the amounts of oxidant used and converged to **1-R** when DDQ was used in excess (2.5 equiv). The similar products **2** and **3** were also obtained, in yields of 19 and 2 %, respectively, from the analogous reactions with 2,6-dichloro- and 2,4,6-trimethylbenzaldehyde.^[8] Although the reaction is not optimized yet, the relatively high concentration of reactants (> 50 mM) seems effective for the formation of products.

The structure of the *N*-fused product **1-Y** was revealed by X-ray analysis on a single crystal (Figure 1).^[9] A fused tri-pentacyclic ring with inward- and outward-pointing nitrogen atoms was found in a pentapyrrolic core. The inner nitrogen atom N(27) of the fused ring was connected to the β -carbon atom C(3) of the neighboring pyrrole ring. One of the pyrrole rings was canted significantly: the tilting angles of each ring, clockwise from the fused ring, were 24.96, 15.32, 22.46, and 99.18° to the mean plane of the 30 core atoms. Two of the

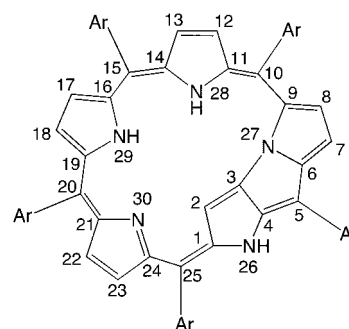
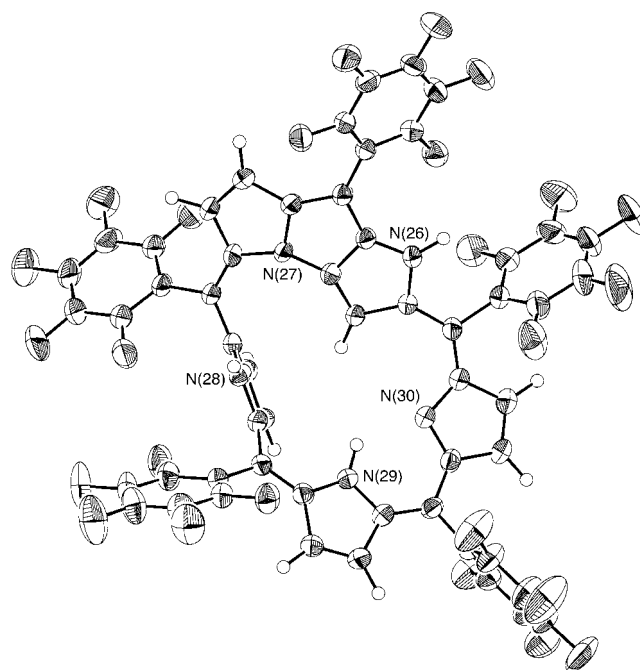


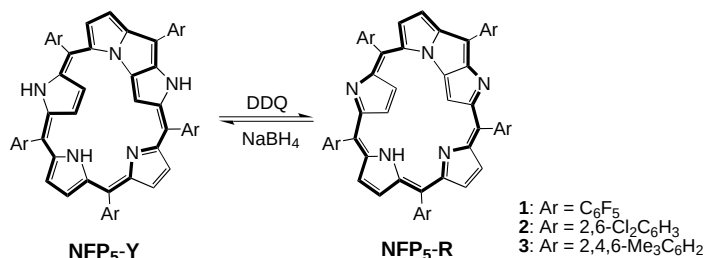
Figure 1. Top: X-ray crystal structure of *meso*-pentafluorophenyl *N*-fused pentaphyrin (**1-Y**). Bottom: Schematic representation of NFP₅-Y showing the numbering scheme.

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three pyrrole rings have protonated nitrogen atoms as judged from the interior angle: $\angle \text{C}(11)\text{N}(28)\text{C}(14)$ 109.6° and $\angle \text{C}(16)\text{N}(29)\text{C}(19)$ 110.6° , and the other is deprotonated $\angle \text{C}(21)\text{N}(30)\text{C}(24)$ 106.0° .^[10] Thus, the structure of **1-Y** can be drawn with a 24π anti-aromatic circuit (Scheme 1). In support of this, the ^1H NMR spectrum of **1-Y** (Table 1) shows three sets of β -H atoms in the range of $\delta = 8.2$ – 5.5 and three NH



Scheme 1. Redox reaction between **NFP₅-Y** and **NFP₅-R**.

Table 1. Selected physical data for **1-Y** and **1-R**.

1-Y: m.p. > 300 °C (decomp); ^1HNMR (500 MHz, CDCl_3): $\delta = 13.73$ (brs, 1 H, N(29)H), 8.16 (d, $^2J = 4.0$ Hz, 1 H), 8.09 (d, $^2J = 3.5$ Hz, 1 H), 7.84 (s, 1 H, C(2)H), 6.69 (brs, 1 H, NH), 6.59 (brs, 1 H, NH), 6.19 (d, $^2J = 5.5$ Hz, 1 H), 6.16 (d, $^2J = 5.5$ Hz, 1 H), 6.03 (d, $^2J = 5.5$ Hz, 1 H), 6.00 (d, $^2J = 5.0$ Hz, 1 H), 5.85 (d, $^2J = 4.5$ Hz, 1 H), 5.58 (d, $^2J = 5.5$ Hz, 1 H); ^{13}CNMR (125.65 MHz, CDCl_3): $\delta = 165.1, 154.3, 150.8, 150.6, 150.2, 142.3, 136.9, 136.3, 133.7, 133.4, 133.3, 132.1, 129.5, 128.4, 126.9, 125.9, 125.0, 112.8, 110.6, 108.5, 106.9, 104.9$ (C(2)), 102.0, 101.5, 93.9, 90.3 (pentafluorophenyl signals could not be assigned because of the multiple coupling of ^{13}C-^{19}F); UV/Vis (CH_2Cl_2): λ_{max} (ϵ [$\text{mol}^{-1}\text{dm}^3\text{cm}^{-1}$]) = 443.0 (51 100), 499.0 (63 100), 771.0 nm (7200); FAB-MS: m/z (% intensity): 1217.0 (100) [$M^+ + 2$] 1-R: m.p. > 300 °C (decomp); ^1HNMR (500 MHz, CDCl_3): $\delta = 9.11$ (s, 2 H), 8.56 (d, $^2J = 4.0$ Hz, 1 H), 8.37 (d, $^2J = 5.0$ Hz, 1 H), 8.35 (d, $^2J = 4.5$ Hz, 1 H), 8.31 (d, $^2J = 4.5$ Hz, 1 H), 2.19 (d, $^2J = 5.0$ Hz, 1 H), 1.70 (d, $^2J = 4.0$ Hz, 1 H), 1.24 (brs, 1 H, NH), -2.26 (s, 1 H, C(2)H); ^{13}CNMR (125.65 MHz, CDCl_3): $\delta = 161.0, 160.9, 160.4, 159.7, 153.4, 152.2, 150.8, 148.0, 146.9, 136.6, 133.7, 133.3, 132.8, 132.4, 132.3, 131.5, 131.2, 129.3, 123.2, 122.4, 120.5, 112.7, 109.6, 100.7, 99.1$ (C(2)), 99.0; UV/Vis (CH_2Cl_2): λ_{max} (ϵ [$\text{mol}^{-1}\text{dm}^3\text{cm}^{-1}$]) = 349.5 (40 600), 460.5 (59 500), 553.5 (62 600), 991.5 nm (2100); FAB-MS: m/z (% intensity): 1217.1 (100) [M^+]

protons at $\delta = 6.69, 6.59$, and 13.73 . The third extremely low-field-shifted signal could be attributed to $\text{N}(29)\text{H} \cdots \text{N}(30)$, in which the distance of $2.728 \text{ \AA}$ between $\text{N}(29)$ and $\text{N}(30)$ is within the range for a hydrogen-bonding interaction. It is noteworthy that one of the nitrogen atoms of the fused ring in **NFP₅** is pointing outward, which is in contrast with the inward-pointing nitrogen atom in **NFP**. Therefore, the *N*-fused porphyrinoids can be classified as *normal*-type (**NFP₅**) and *confused*-type (**NFP**) based on the linkage (α - α and α - β) of the pyrrole rings. When a solution of **1-Y** in CH_2Cl_2 was treated with DDQ the yellow solution changed to red and afforded **1-R** quantitatively. In turn, the **1-R** obtained was reduced to **1-Y** by treatment with NaBH_4 .^[11, 12] The ^1H NMR spectrum of **1-R** (Table 1) showed the aromatic ring current effect: a set of β -C(12 and 13)H atoms of the inverted pyrrole ring, the inner N(29 or 30)H, and inner C(2)H signals of the fused ring appeared at $\delta = 2.19, 1.70, 1.24$, and -2.26 , respectively, while the peripheral β -CH atoms resonated

around $\delta = 9.2$ – 8.3 . Consequently, the structure of **1-R** is inferred to have 22π aromaticity as shown in Scheme 1.

The absorption spectra of both **1-Y** and **1-R** show broad bands relative to that of **NFP**, which presumably reflects the distortion from planarity and the extended π system (Figure 2). The long-wavelength absorption around 1000 nm observed in **NFP** is also observed for aromatic **1-R**. The quantitative interconversion between **1-Y** and **1-R** was confirmed by the observation of isosbestic points in the absorption spectra.

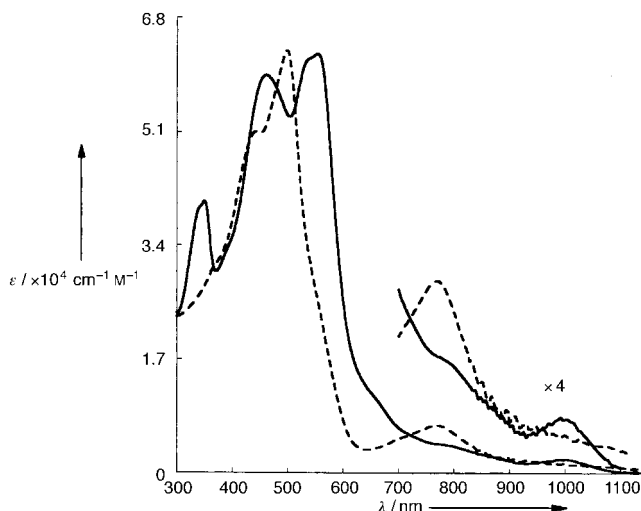
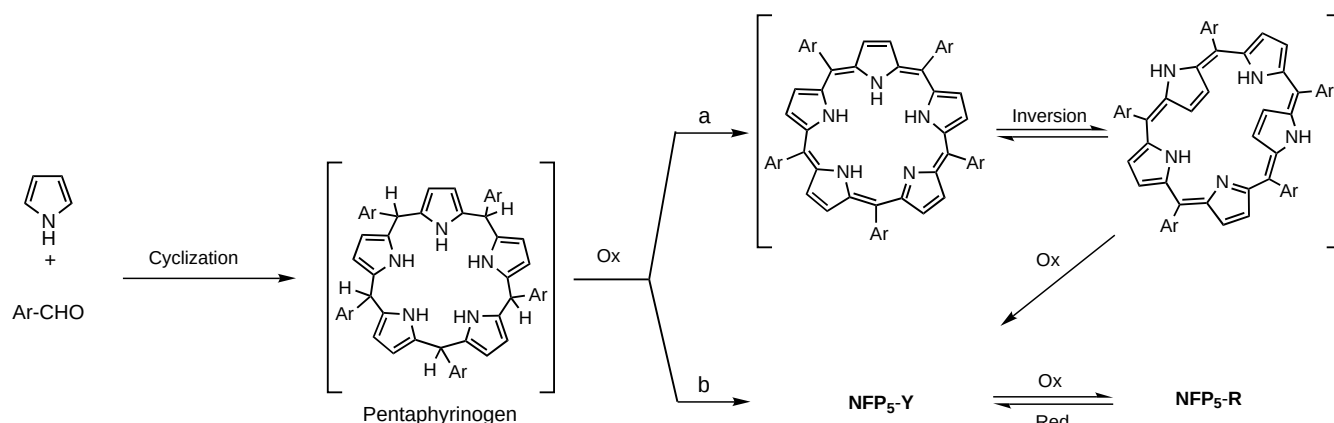


Figure 2. Absorption spectra of **1-Y** (---) and **1-R** (—).

In the porphyrin synthesis, the porphyrinogen is presumed to be oxidized to a corresponding porphyrin.^[13] Mechanistically, therefore, **NFP₅-Y** and **NFP₅-R** might be derived from the putative precursor pentaphyrinogen during the oxidation process (Scheme 2). If the oxidation proceeds by route a, *meso*-pentaarylpentaphyrin, which has not been synthesized so far, could be formed. To release the strain of the molecule, one or two pyrrole rings could be inverted, then oxidized to **NFP₅-Y**. Such a pyrrole inversion was observed in *meso*-arylsapphyrin^[4a] and *meso*-arylhexaphyrin.^[5] On the other hand, route b presumes that a direct oxidation of the pentaphyrinogen occurs. In either way, the proposed mechanism would explain why *meso*-arylpentaphyrin has not been obtained from the standard acid-catalyzed pyrrole–aryl aldehyde condensation reaction. As the total amount of **NFP₅** obtained is comparable to that of porphyrin and hexaphyrin, we believe the absence of *meso*-arylpentaphyrin in the reaction mixture is because of the formation of **NFP₅**. The isolation of *meso*-arylsapphyrin from similar reaction conditions would be also relevant to the intrinsic instability of *meso*-arylpentaphyrin.^[4] Further mechanistic study as well as the investigation of the metal coordination chemistry are currently underway.

Experimental Section

1-R: A solution of $2.5 \text{ M BF}_3 \cdot \text{OEt}_2$ in CH_2Cl_2 ($100 \mu\text{L}$) was added to a solution of pentafluorobenzaldehyde ($494 \mu\text{L}$, 4 mmol) and pyrrole ($278 \mu\text{L}$, 4 mmol) in CH_2Cl_2 (60 mL), and the resulting solution was stirred



Scheme 2. A possible reaction mechanism for the formation of **NFP₅**.

for 2 h under nitrogen. After adding DDQ (2.27 g, 10 mmol), the solution was stirred for 10 h, then passed through a short alumina column to remove the tar. The reaction mixture was then separated by column chromatography on silica gel with CH_2Cl_2 :*n*-hexane (1:4). The red solution of **1-R** was eluted after the purple fraction of *meso*-pentafluorophenylhexaphyrin. The solution of **1-R** was evaporated, and the residue recrystallized from *n*-hexane to give pure **1-R** (146 mg, 15%).

1-Y: NaBH_4 (22.7 mg, 0.6 mmol, 15 equiv) was added to a solution of **1-R** (50 mg, 0.04 mmol) in CH_3OH (10 mL) and the solution was stirred for 10 min under nitrogen. After removing the solvent, the residues were dissolved in CH_2Cl_2 , and filtered through a short alumina column. After evaporation, the residue was recrystallized from *n*-hexane to give **1-Y** (50 mg, 100%).

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- [7] A variety of higher homologues, such as octaphyrins, nonaphyrins, decaphyrins, undecaphyrins, and dodecaphyrins, are isolated from the reaction mixture: J.-Y. Shin, H. Furuta, A. Osuka, unpublished results.
- [8] Spectral data and the X-ray structure of **2-Y** are shown in the Supporting Information.
- [9] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-147880. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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- [11] The absorption spectral changes of the redox reaction between **1-Y** and **1-R** are shown in the Supporting Information.

[12] Supporting this facile interconversion, the two-electron redox processes between **1-Y** and **1-R** were recorded at low potential, -0.447 V and $+0.067$ V (versus the ferrocene/ferrocenium couple (F_c/F_c^+)) by cyclic voltammetry.

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Iron-Catalyzed Regio- and Stereoselective Carbolithiation of Alkynes**

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Organolithium compounds are one of the most popular organometallics and have been used for organic synthesis as nucleophiles in carbon–carbon bond formation, and as transmetalation agents onto other metals.^[1] Carbometallation of alkynes is recognized to be useful in the preparation of stereochemically defined tri- and tetrasubstituted alkenes, while in reactions of alkynes without a conjugated electron-withdrawing group, the regioselectivity becomes the principal problem.^[2] The carbolithiation of alkynes has limited synthetic use because only particular kinds of alkynes can be used, and as for the stereochemistry, the vinylolithium intermediates produced tend to isomerize with ease.^[3] We report herein a preliminary result on the regio- and stereoselective carbolithiation of alkynes by a simple procedure that uses cheap iron salts as a catalyst.

We found that 3-pentynyl 3-phenylpropyl ether (**1a**), upon addition of a catalytic amount of FeCl_3 , reacted with

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butyllithium to yield (*E*)-4-methyl-3-octenyl 3-phenylpropyl ether (**2a**) as a single isomer [Eq. (1)]. As shown in Table 1, the choice of a solvent is crucial for this reaction. In benzene

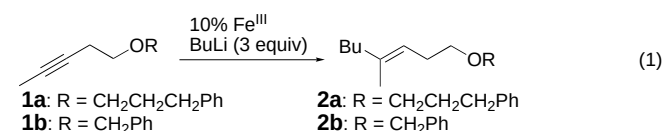


Table 1. Reaction of 3-pentynyl ethers **1** with butyllithium in the presence of Fe^{III}.^[a]

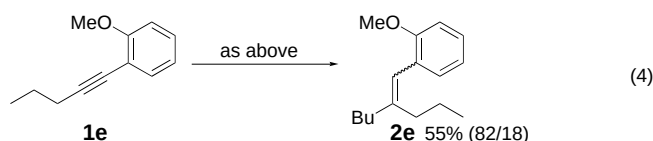
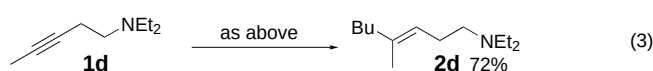
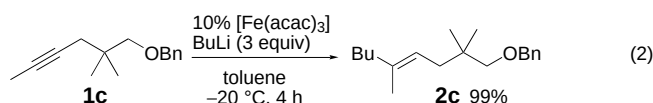
Entry	Substrate	Fe salt	Solvent	Conditions	Yield (2) [%] ^[b]
1	1a	FeCl ₃	THF	−40 °C, 4 h	0 ^[c]
2	1a	FeCl ₃	Et ₂ O	−40 °C, 3 h	79 (2a)
3	1b	FeCl ₃	Et ₂ O	−40 °C, 3 h	79 (2b) ^[d]
4 ^[e]	1a	FeCl ₃	benzene	−20 °C, 2 h	86 (2a)
5 ^[e]	1a	FeCl ₃	toluene	−20 °C, 2 h	97 (2a)
6	1b	[Fe(acac) ₃] ^[f]	toluene	−20 °C, 2 h	97 (2b)
7	1b	[Fe(dbm) ₃] ^[f]	toluene	−20 °C, 2 h	85 (2b)
8	1b	FeCl ₃	toluene	−20 °C, 2 h	13 (2b) ^[g]

[a] All reactions were carried out using 3.0 equivalents of butyllithium and 10 mol % of Fe^{III}, unless otherwise noted. Reactions were quenched with 1N HCl solution. [b] Isolated Yield. [c] **1a** (18 %) was recovered. 3-Phenylpropanol (80 %) and nona-2,3-diene^[7] (20 %) were found in the reaction mixture. [d] Benzyl alcohol (13 %) was produced. [e] Suspension of FeCl₃ in the respective solvent was used. [f] The amount of Fe^{III} was reduced to 5 mol %. [g] **1b** (45 %) was recovered and benzyl alcohol (34 %) was produced. DBM = 1,3-diphenyl 1,3-propanedione (dibenzoylmethane).

or toluene, a butylated product **2a** was obtained in high yield (entries 4 and 5). In diethyl ether or THF, the cleavage of the C–O bond to yield the corresponding alkynyl alcohol or the β -elimination of ROH, such as 3-phenylpropanol or benzyl alcohol, takes place in preference to the desired butylation. As for an iron catalyst,^[4] when an Fe^{III} salt was employed, **2** was produced in high yield, while with FeCl₂, only a poor yield of **2** was obtained. The actual catalyst for the present carbometallation has not been clearly determined. Previously, cross-coupling reactions with catalytic amounts of Fe^{III} species were reported and in those reactions, an Fe^I center generated by the reduction of the Fe^{III} species with a Grignard reagent was proposed as a catalyst.^[5] In our system, a low-valent iron species may possibly catalyze the reactions. To determine the stoichiometry of butyllithium to Fe, we attempted the reaction with an equimolar amount of [Fe(acac)₃] and the substrate **1b** (acac = 2,4-pentanedione (acetylacetone)). When 8 equivalents of butyllithium were introduced, the yield of **2b** was 63 %, and using 12 equivalents of the lithium reagent 89 % of **2b** was obtained.^[6] These experiments suggest that the present iron catalysis may be based on an iron–ate complex. [Fe(acac)₃] is soluble in toluene, thus, we could carry out most of the reactions simply using a stock solution of [Fe(acac)₃] in toluene.

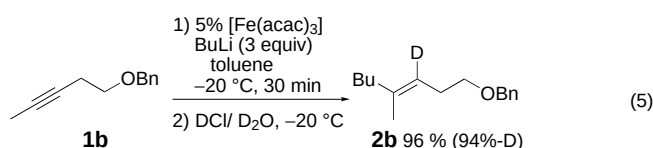
4-Hexynyl ether **1c**, a one-carbon homologue, also reacted with butyllithium in toluene to afford the corresponding addition product **2c** as the sole product in quantitative yield [Eq. (2)], while in diethyl ether the reaction resulted only in the recovery of **1c**, showing a clear solvent effect. The

butylation was not only successful with alkynyl ethers, even the pentynylamine **1d** gave a butylation product (**2d**) in 72 % yield [Eq. (3)]. Interestingly, a simple alkyne, 6-dodecyne did not react at all under the conditions shown in Equations (2)–(4). *o*-Methoxy-1-pentynylbenzene (**1e**) also reacted with



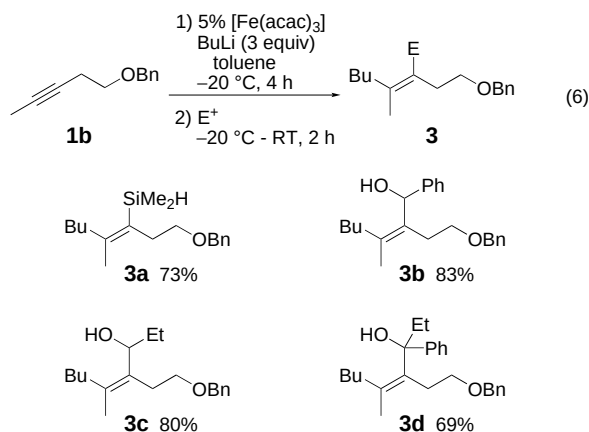
butyllithium to give a mixture of two stereoisomeric products **2e** in moderate yield [Eq. (4)]. In these reactions, a Lewis-basic moiety in a substrate alkyne not only activates the triple bond toward butylation, but possibly also controls stereo-selectivity. Recently, Nakamura et al. reported iron-catalyzed olefin carbometallation, where organomagnesium and zinc reagents were employed.^[8] As for the present reaction, when BuMgBr^[9] was used for the reaction of **1b**, the yield of **2b** was low; 56 % (−20 °C, 4 h), 60 % (RT, 4 h),^[10] and further synthetic use seems to be difficult, as indicated by the low D-content of the product **2b** in a deuteration experiment.

When a reaction of **1b** was quenched with DCl/D₂O, deuterated **2b** (94 %-D) was obtained in 96 % yield [Eq. (5)].^[11] The postulated vinyl lithium intermediate further



reacted with electrophiles (E⁺) such as chlorosilane to afford stereochemically defined vinylsilane **3a** in 73 % yield [Eq. (6)]. Both aromatic and aliphatic aldehydes also reacted to give the corresponding allylic alcohols **3b** and **3c**, respectively, in high yields. Even a ketone could be used as an electrophile, and a tetrasubstituted alkene **3d** was isolated in 69 %, as a single isomer.

It was found that cheap iron salts catalyze carbometallation^[12] of alkynes bearing an alkoxy or amino group. The simple protocol presented here allows us to access tetrasubstituted alkenes in a stereoselective manner. Further synthetic applications of this process are now under investigation.



Experimental Section

Full experimental details are in the Supporting Information. A representative procedure is as follows: to a flask purged with argon, a solution of $[\text{Fe}(\text{acac})_3]$ in toluene (0.025 M, 0.025 mmol, 1 mL), toluene (4 mL), and a substrate **1b** (0.5 mmol) were introduced. The flask was cooled to -40°C and a solution of butyllithium in hexane (1.5 M, 1.5 mmol) was added to the mixture. Reaction temperature was immediately raised to -20°C and the mixture was stirred at -20°C for 2 h. The reaction was quenched with 1 N HCl. After the conventional workup and purification by chromatography on silica gel, a pure product **2b** was obtained in 97% yield.

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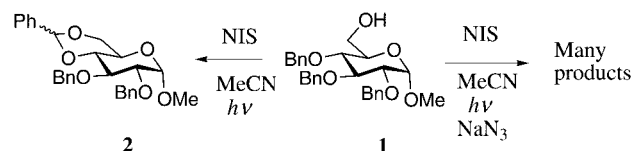
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- [4] In the absence of a catalyst, a complex mixture without a normal product **2b** was produced.
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- [6] Conditions for all reactions reported here are not fully optimized. A sufficient amount of butyllithium per iron catalyst (5 mol %) seems to be required during the reaction for the successful carbolithiation. Therefore, 3 equivalents used in reactions are a large enough amount for the present carbolithiation, and, indeed, a reaction of **1b** with 2 equivalents of butyllithium gave essentially the same result (95% of **2b**, cf. Table 1, entry 6).
- [7] This product was possibly obtained by the addition of butyllithium to pent-1-en-3-yne, produced by the β -elimination of phenylpropanol from **1a**. a) A. A. Petrov, V. A. Kormer, T. V. Yakovleva, *Zh. Obshch. Khim.* **1960**, *30*, 2238; b) A. A. Petrov, Yu. I. Porfir'eva, V. A. Kormer, *Zh. Obshch. Khim.* **1961**, *31*, 1518.
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- [9] BuMgBr was prepared in diethyl ether, and most of the solvent was replaced with toluene before use.

- [10] Only allylmagnesium bromide successfully added to **1b** (in Et_2O at RT for 7 h using 20 mol % of $[\text{Fe}(\text{acac})_3]$) and the corresponding allylated product was obtained in quantitative yield.
- [11] The produced vinyl anion seems to be unstable at room temperature. Yield of **2b** and its deuterium content were decreased to 90% and 82% -D, respectively when the reaction mixture was kept at ambient temperature for 3 h before quenching with DCl/ D_2O , the reaction was conducted under the same conditions as in Equation (5).
- [12] Ethyllithium and hexyllithium were also added to **1b** to afford alkenes in high yields (Et: 96%, Hex: 92%).

Radical Azidonation of Benzylic Positions with Iodonium Azide**

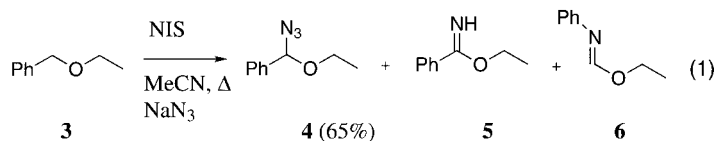
Christel Viuf and Mikael Bols*

We recently reported a procedure for the conversion of benzyloxy alcohols like **1** into benzylidene derivatives like **2** with *N*-iodosuccinimide (NIS) and light (Scheme 1).^[1] During



Scheme 1. The NIS-promoted transformation of benzyloxy alcohols into benzylidene derivatives and the effect of NaN_3 addition. Bn = benzyl.

the investigation of this reaction we noticed that **1** was transformed with excess NaN_3 very rapidly into a variety of products of which many had, according to mass spectrometry, one to three hydrogen atoms replaced with azido groups. When the analogous reaction was carried out on benzyl ethyl ether **3** [Eq. (1), light substituted with heat to avoid decomposition of azides] the monoazido derivative **4** was isolated in 65% yield together with small amounts of the by-products **5** and **6**.^[2]

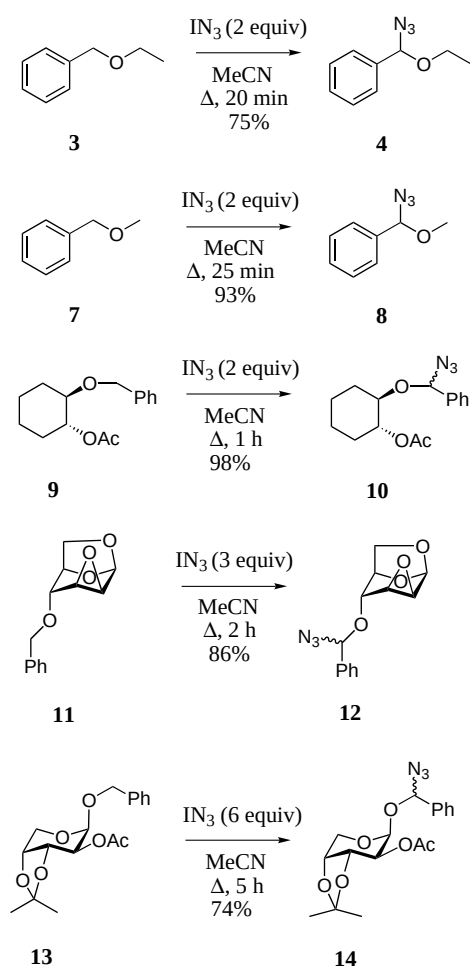


Since this azidonation reaction appeared faster than the benzylidene derivative formation promoted by NIS alone and since the red color of the reaction mixture indicated that IN_3 was present, it was suggested that iodine azide was the reagent

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causing the reaction. Indeed if IN_3 was used, **3** could be transformed to **4** in 75% yield (Scheme 2).



Scheme 2. Reaction of various benzyl ethers with IN_3 in MeCN.

Some related chemistry has been reported in a series of papers by Magnus et al. They used $\text{PhIO}/\text{trimethylsilylazide}$ (TMSN_3) at low temperature to azidonate a carbon atom α to amino and enol ether functionalities.^[3] It has also been reported that $\text{PhI}(\text{OAc})_2/\text{NaN}_3$ can be used to generate carbon-centered radicals.^[4] Hassner et al. have pioneered and extensively studied the addition of IN_3 and other haloazides to alkenes.^[5] They found that though the addition of haloazides to alkenes normally follows an ionic mechanism, in certain cases, in particular when ClN_3 or BrN_3 is the reagent, the products of a radical addition to the alkene are obtained.^[5b] However, substitution of activated hydrogens by azido groups with IN_3 has not been carried out nor has the introduction of an azido group in a benzylic position.

As can be seen from Scheme 2 the reaction is highly efficient^[6] when carried out in refluxing acetonitrile: The yields of azides (Table 1) were 74–98%. The transformations **9** $\rightarrow$ **10**, **11** $\rightarrow$ **12**, and **13** $\rightarrow$ **14** show that the reaction tolerates other functionalities such as ester, epoxide, or acetal units. The reaction of **13** is more sluggish than the others requiring more reagent and time. The reason is presumably that the acetal functionality makes the benzylic position less reactive

Table 1. Analytical data of the azido compounds **4**, **8**, **10**, **12**, and **14**.^[a]

4 :	$^1\text{H NMR}$: δ = 7.25–7.41 (m, 5H), 5.38 (s, 1H), 3.85 (dq, 1H, J = 7.0, 9.5 Hz), 3.58 (dq, 1H, J = 7.0, 9.5 Hz), 1.19–1.24 (t, 3H, J = 7.0 Hz)
8 :	$^1\text{H NMR}$: δ = 7.22–7.38 (m, 5H), 5.24 (s, 1H), 3.43 (s, 3H)
10 :	$^1\text{H NMR}$ (diastereomeric ratio 1:1): δ = 7.25–7.50 (m, 10H), 5.59 (s, 1H), 5.42 (s, 1H), 4.93 (m, 2H), 3.82 (m, 2H), 2.11 (s, 3H), 2.30–1.90 (m, 4H), 1.82 (s, 3H), 1.68–1.84 (m, 4H), 1.25–1.49 (m, 8H); MS (EI): m/z : calcd ($\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_3 + \text{Na}$) 312.1324, found 312.1322
12 :	$^1\text{H NMR}$ (diastereomeric ratio 1:1): δ = 7.39–7.53 (m, 10H), 5.72 (s, 1H), 5.70 (s, 1H), 5.68 (s, 1H), 5.67 (s, 1H), 4.51 (t, 1H, J = 4.4 Hz), 4.49 (t, 1H, J = 4.4 Hz), 4.05 (br s, 2H), 3.72 (d, 2H, J = 4.4), 3.70 (d, 2H, J = 4.4), 3.48 (dd, 2H, J = 3.7), 3.28 (br d, 1H, J = 3.7), 3.16 (br d, 1H, J = 3.7); MS (EI): calcd ($\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_4 + \text{Na}$) 298.0804, found 298.0804
14 :	$^1\text{H NMR}$ (diastereomeric ratio 1:1): ^[b] δ = 7.40–7.50 (m, 5H, 5H'), 5.64 (s, 1H'), 5.55 (s, 1H), 5.47 (d, 1H, J = 3.50 Hz), 5.08 (d, 1H', J = 3.50 Hz), 5.01 (dd, 1H, J = 3.50, J = 8.1 Hz), 4.91 (dd, 1H', J = 3.50 Hz, J = 7.7 Hz), 4.31–4.46 (m, 1H, 2H'), 4.17–4.25 (m, 1H, 1H'), 4.09 (d, 1H'), 3.99 (d, 1H, J = 13.6 Hz), 3.83 (dd, 1H, J = 13.6, 2.9 Hz), 2.15 (s, 3H), 2.03 (s, 3H'), 1.56 (s, 3H), 1.53 (s, 3H'), 1.37 (s, 3H'), 1.20 (s, 3H); MS (EI): m/z : calcd ($\text{C}_{17}\text{H}_{21}\text{N}_3\text{O}_6 + \text{Na}$) 386.1328, found 386.1329

[a] 200 MHz for all $^1\text{H NMR}$ spectra, in CDCl_3 . [b] Primed protons refer to the second diastereomer.

because it is more electron withdrawing than a regular ether unit.

Strong support was found for the reaction to follow a radical mechanism: Compound **8** was not formed when **7** was allowed to react in the presence of the radical trap *N*-tert-butyl- α -phenylnitron (Scheme 2).^[8] Substrate **7** and most of the radical trap (2 equiv) were recovered unconverted, which shows that capture of a small amount of radicals prevented the reaction. A certain electron-donating capacity is necessary at the benzylic position for the reaction to occur: When an ester is attached to this position as in benzyl benzoate no reaction is observed. Benzyl alcohol, on the other hand, is oxidized to benzaldehyde under the reaction conditions. Based on these results we suggest the following reaction course: Homolysis of IN_3 results in an azide radical that abstracts a hydrogen atom from the substrate to form a benzylic radical. This radical is oxidized by IN_3 or I_2 to a benzylic cation that combines with the azide ion to form the product.^[9]

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1.4 mmol) in MeCN (3 mL) at -10°C .^[5c] After 15 min the cooling bath was removed, and the ether compound (0.3 mmol) was added. The mixture was refluxed for between 0.4 and 5 h. Then CH_2Cl_2 (25 mL) was added, and the mixture was washed with 5% $\text{Na}_2\text{S}_2\text{O}_3$ solution (20 mL). The dried (MgSO_4) and evaporated organic phase was purified by flash chromatography.

[7] IN_3 is an explosive substance, particularly as a solid (see ref. [5a]). We encountered no problems, but took care to remove IN_3 after the reaction by washing with $\text{Na}_2\text{S}_2\text{O}_3$ solution.

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[9] We have also investigated some amine substrates in order to compare IN_3 with the Magnus reagent PhIO/TMSN_3 . Reaction of *N,N*-dimethylaniline with IN_3 gave several products, the major one being 4-iodo-*N,N*-dimethylaniline, while benzyldimethylamine led to a number of very labile products that on decomposition gave benzaldehyde and benzyldimethylamine. This is in agreement with the formation of α -azidoamines like those obtained in the Magnus reaction. Magnus et al. could isolate such α -azidoamines by using nonaqueous work-up, but they are clearly much less stable than the α -azidoethers.

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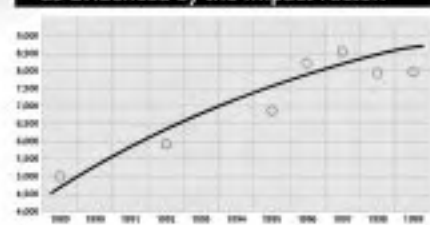
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