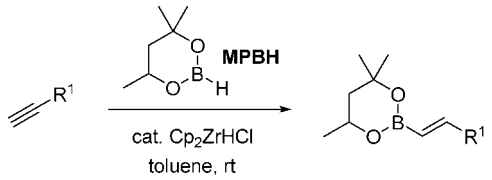
Organic Process Research & Development **2007,** *11,* 784–796

Highlights from the Literature

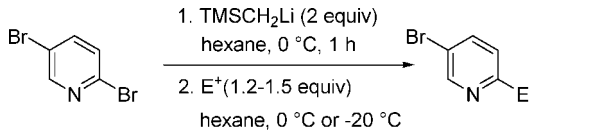
Some Items of Interest to Process R&D Chemists and Engineers

Easy Access to Highly Functionalized Vinylboronates



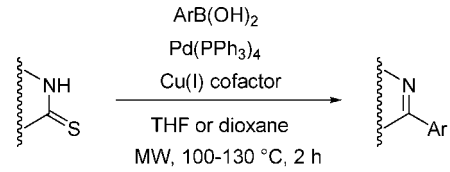
The Chavant group reports on the preparation and use of methylpentanediolborane (MPBH) as a reagent for the synthesis of functionalized vinylboronates (*J. Org. Chem.* **2007**, *72*, 4510–4514). Although both the preparation of MPBH and its use in the hydroboration of alkynes have been known for decades, this chemistry has been under utilized. MPBH is prepared from inexpensive hexyleneglycol (2-methyl-2,4-pentanediol) by reaction with either commercial $BH_3 \cdot SMe_2$ or in situ generated B_2H_6 (from $NaBH_4$ and I_2), and the authors note that the reagent is stable for months when stored at or below 4 °C. The hydroborating ability of MPBH was studied using 15 alkynes and the Schwartz zirconium complex as the catalyst. Yields ranged from 0% to 93%, and for certain substrates (e.g., propargyl bromide) MPBH provided acceptable yields (73% isolated) where the more commonly used pinacolborane failed to react.

Lithium–Halogen Exchange in Bromopyridines



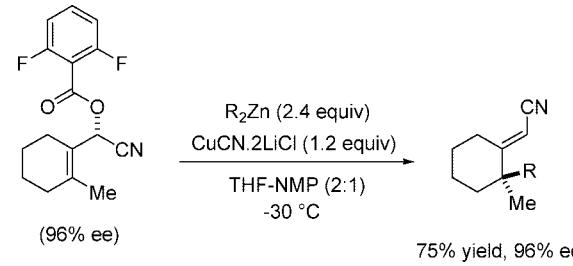
The selective metal–halogen exchange of 2,5-dibromopyridine has been investigated by various researchers over the years. Originally, Parham established that treatment with *n*-butyllithium at low temperature yielded the 5-lithiated species. Subsequently, workers at Merck found that adjustment of reaction conditions could lead to selectivity for the 2-lithiated species, although at the expense of material throughput (high dilution). Later still, researchers at Boehringer demonstrated selectivity for the 2-metallated species when 2-iodo-5-bromopyridine was subjected to Mg–I exchange, but this method required prior synthesis of the iodo-derivative. Now, Gros and coworkers report on a new method for the direct lithation of 2,5-dibromopyridine that selectively yields the 2-lithiated species at temperatures and reaction concentrations that are more amenable to large-scale synthesis (*J. Org. Chem.* **2007**, *72*, 4978–4980). Under the optimized conditions, treatment of 2,5-dibromopyridine with $TMSCH_2Li$ (2 equiv) and lithium 2-dimethylaminoethanol as an additive (1 equiv) in toluene at 0 °C gives good yields of 2-substituted products after quenching with various electrophiles.

Pd-Catalyzed, Cu-Mediated Coupling of Boronic Acids with Cyclic Thioamides



The Pd-catalyzed cross-coupling of cyclic thioamides with arylboronic acids in the presence of stoichiometric amounts of a Cu(I) cofactor is described by the Kappe group (*J. Org. Chem.* **2007**, *72*, 4440–4448). This desulfative carbon–carbon cross-coupling protocol is performed under neutral conditions and can be applied to a range of heterocyclic structures with embedded thioamide fragments. Successful carbon–carbon bond formation is independent of the ring size, aromaticity/nonaromaticity, the presence of additional heteroatoms, or other functional groups in the starting thioamide structure. Employing controlled microwave irradiation at 100 °C, most cross-couplings can be completed within 2 h and proceed in high yields. An advantage of using thioamides as starting materials is the fact that the system can be tuned to an alternative carbon–sulfur cross-coupling pathway by changing to stoichiometric Cu(II) under oxidative conditions. Both types of thioamide cross-couplings are orthogonal to Suzuki–Miyaura cross-coupling of aryl halides with boronic acids.

Diastereoselective Cu(I)-Mediated S_N2' Allylic Substitutions



In a recent communication, the Knochel group describes a method for the construction of unsaturated nitriles bearing a quaternary chiral center at the γ-position (*Synlett* **2007**, 1047–1050). Enantiomerically enriched cyanohydrins were synthesized from the corresponding carbaldehydes via (*S*)-

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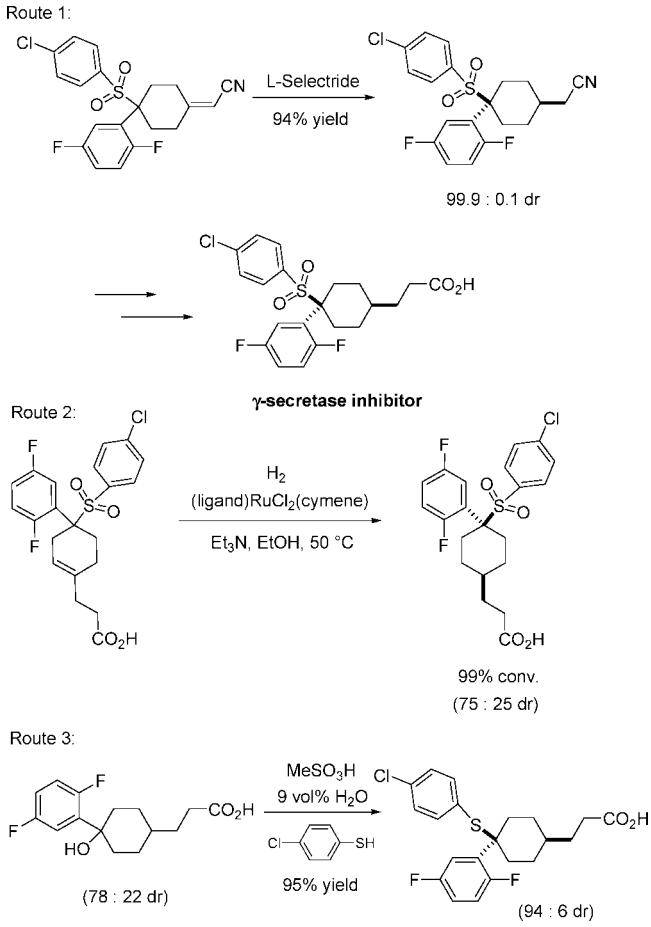
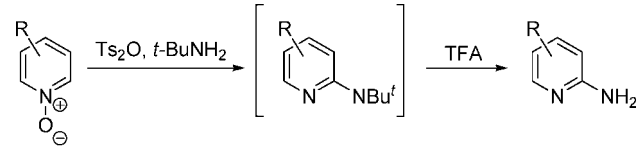
oxynitrilase-catalyzed addition of KCN (2 equiv) in a citrate buffer. Subsequent esterification with 2,6-difluorobenzoyl chloride afforded the allylic substitution substrates in good yield without racemization. Reaction of the allylic cyanohydrin derivatives with diorganozinc reagents (2.4 equiv) in the presence of CuCN·2LiCl (1.2 equiv) in THF–NMP (2:1) at −30 to 0 °C afforded γ-substituted unsaturated nitriles as a single regioisomers in good yields and ee. No traces of S_N2 products were detected, and the substitution afforded only the *E*-isomers.

Practical Syntheses of a γ-Secretase Inhibitor



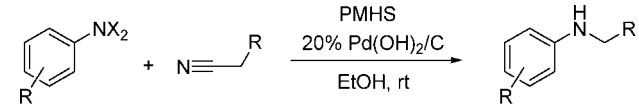
Scott, Davies, Lieberman and co-workers at Merck describe various aspects of the process development work done around a γ-sectretase inhibitor, which consists of a central trisubstituted cyclohexane core with appended propionic acid, 2,5-difluorophenyl, and 4-chlorophenylsulfonyl moieties (*J. Org. Chem.* **2007**, *72*, 4149–4155 and *J. Org. Chem.* **2007**, *72*, 4864–4871). In the first paper, early development routes are discussed, and two distinct approaches are presented in detail. In one route, conjugate reduction of an acrylonitrile derivative with L-Selectride configures the desired relative stereochemistry of the cyclohexane core with >99.9:0.1 dr. The second route, based on catalyst-controlled hydrogenation of a racemic cyclohexene derivative, is more convergent but less diastereoselective (up to 75:25 dr). The cyclohexanone intermediate common to both these routes was constructed by a regioselective Diels–Alder condensation of a 1,1-disubstituted vinyl sulfone with 2-trimethylsiloxybutadiene. The second paper describes an alternative strategy, which represents the basis for a manufacturing synthesis for the target γ-secretase inhibitor. The target is synthesized in only five steps with an overall yield of 58%. The key operation is a highly selective and practical, crystallization-driven transformation for the conversion of a mixture of tertiary benzylic alcohols into the desired sulfide diastereomer with 94:6 dr. This unprecedented process is based upon a reversible carbon–sulfur bond formation under acidic conditions. A detailed account of the optimization of this novel crystallization-induced diastereomeric transformation is provided.

Amination of Pyridines and Quinolines



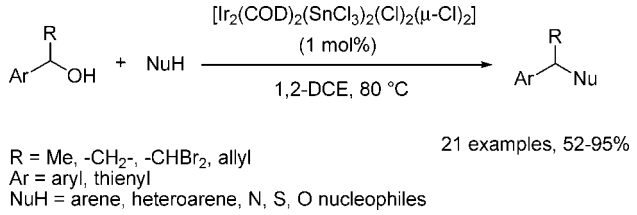
Installation of an unsubstituted amino-group in the 2-position of pyridine rings is often a less trivial synthetic transformation than one might initially predict. Use of the direct Chichibabin reaction is restricted by the need for forcing conditions. The other commonly used technique requires preparation of a pyridine *N*-oxide followed by conversion to the halide before reaction with a nitrogen nucleophile and is frequently plagued by low overall yields and poor 2- versus 4-regioselectivity for the sequence. Now an alternative method is reported by Yin, Xiang and co-workers at Merck in which pyridine *N*-oxides are converted to 2-aminopyridines in a one-pot fashion using Ts_2O–*t*-$BuNH_2$ followed by in situ deprotection with TFA (*J. Org. Chem.* **2007**, *72*, 4554–4557). The amination proceeds in good yield and with 2-/4-selectivity, and various functional groups are tolerated. 2-Amino (iso)quinolines were also obtained in the same manner.

Reductive Alkylation Between Amines and Nitriles Using PMHS



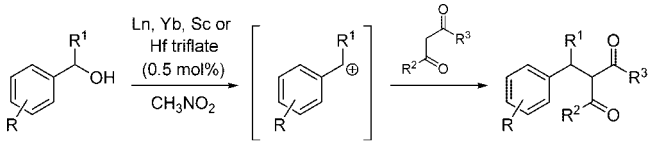
Reddy and co-workers describe a procedure for the reductive alkylation of aromatic amines and nitro-compounds with nitriles using polymethylhydrosiloxane (PMHS) as the reductant (*Tetrahedron Lett.* **2007**, *48*, 2765–2768). Application of this method, in an intramolecular sense, to the synthesis of 3,4-dihydro-2*H*-1,4-benzoxazines and dihydroquinolines is also presented.

Catalytic Secondary Benzylation Using Benzyl Alcohols



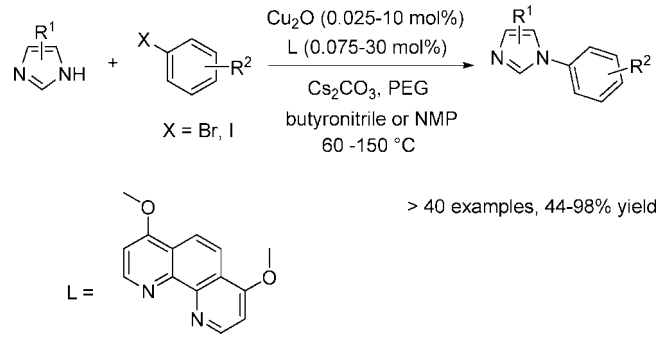
An efficient secondary benzylation procedure using a high-valent heterobimetallic complex $[Ir_2(COD)_2(SnCl_3)_2(Cl)_2(\mu\text{-}Cl)_2]$ as the catalyst has been developed by the group of Roy (*J. Org. Chem.* **2007**, *72*, 3129–3132). The researchers studied the reaction between 1-phenylethanol (1 equiv) and *o*-xylene (5 equiv) in 1,2-dichloroethane in the presence of the aforementioned catalyst and observed mainly dehydration of the alcohol to the symmetric ether at room temperature and also at 50 °C. However, when the reaction was conducted at 80 °C, the alcohol was 100% converted and an isolated yield of 89% of the targeted benzylated arene was obtained. The authors note that this particular example gave an isolated yield of 85% even when the stoichiometry was adjusted to only 20% excess of the arene but all other examples reported used a 5-fold excess. The reaction was also performed with oxygen (alcohol), nitrogen (amide and sulfonamide), and sulfur (thiol) nucleophiles. Mechanistic investigation showed the intermediacy of the symmetric ether, which itself proved to be a competent reaction partner in separate experiments. An electrophilic mechanism is proposed from Hammett correlation studies.

Metal Triflate Catalyzed Benzylation and Allylation of 1,3-Dicarbonyl Compounds



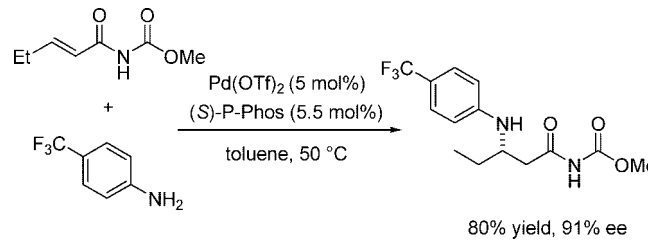
Rare earth metal and hafnium triflate catalyzed secondary benzylation and allylation of 1,3-diketones, ketoesters, and ketoamides is reported by the Ishii group (*J. Org. Chem.* **2007**, *72*, 5161–5167). Various 1-phenylethyl cations can be generated from substituted 1-phenylethanols using 0.5 mol % of the metal triflates in CH_3NO_2 (1,2-DCE was the only other solvent investigated and appeared to give lower yields). The cations react with 1,3-diketones and ketoesters to give benzylated products in high yields. Following a detailed study, the researchers demonstrated that the optimal Lewis acid catalyst varied depending upon the particular substrate type. The ketoamide reactions required stronger Lewis acids than those used in the diketone and ketoester reactions. A tertiary-alkylated diketone and a corresponding ketoester were also benzylated to afford products with a quaternary carbon atom in 57–84% yield. It was also possible to use allylic alcohols directly for the allylation of diketone. The catalyst can be recovered by water extraction and reused up to five times.

General Cu-Catalyzed *N*-Arylation of Imidazoles and Benzimidazoles



Following up on a recent communication, the Buchwald group now provides a full account of their efforts towards the development of a general copper-based catalytic system for the N-arylation of imidazoles and benzimidazoles (*J. Org. Chem.* **2007**, *72*, 6190–6199). 4,7-Dimethoxy-1,10-phenanthroline (L) was found to be an efficient ligand for this process, with both aryl iodides and bromides functioning well under mild conditions. Further optimization of the system has revealed that the addition of poly(ethylene glycol) (PEG) accelerates this reaction. A variety of hindered and functionalized imidazoles, benzimidazoles, and aryl halides were transformed in good to excellent yields. Heteroaryl halides were also coupled in moderate to good yields. The authors also present the results obtained from a series of coupling reactions, which directly compare the use of L with other recently reported ligands.

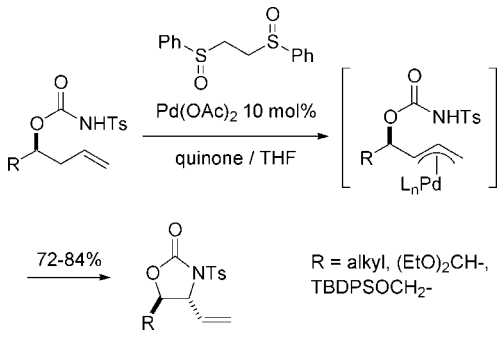
Asymmetric Synthesis of Torcetrapib



A novel asymmetric synthesis of torcetrapib, the cholesteryl ester transfer protein (CETP) inhibitor pulled from further development during late stages of clinical development last year, has been demonstrated by Hii and co-workers at Imperial College (*J. Org. Chem.* **2007**, *72*, 6290–6293). Starting from achiral precursors, the route features a Pd-catalyzed enantioselective aza-Michael reaction as the key step, does not involve the use of protecting groups, and occurs in seven steps overall from chloroacetyl chloride. All of the synthetic intermediates are crystalline solids that can be purified by crystallization. The authors note that the convergent nature of their approach allows for structural modifications to be made in straightforward fashion.

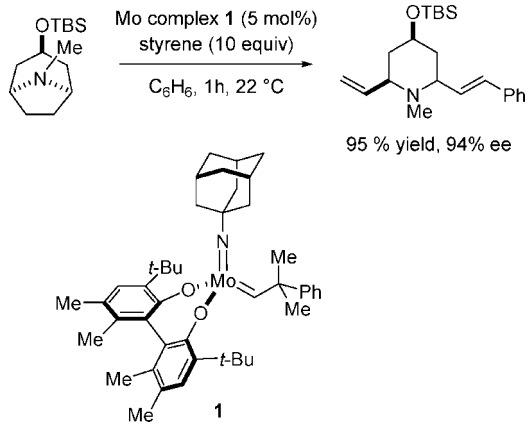
syn-1,2-Amino Alcohols via Allylic C-H Amination

Fraunhoffer and White at the University of Illinois reported an original route for synthesizing chiral *syn*-1,2-amino alcohols (*J. Am. Chem. Soc.* **2007**, *129*, 7274–7276). The transformation, which is promoted by a mixture of $Pd(OAc)_2$/bis-sulfoxide catalyst and stoichiometric benzoquinone, involves the allylic C-H amination of chiral homoallylic *N*-tosyl carbamates. Remarkably, the resulting oxazolidinones can be further elaborated into valuable 1,2-amino alcohols, amino acids, or intermediates in the synthesis of amino sugars. Mechanistic studies support the formation of a π-allylPd intermediate via allylic C-H cleavage, followed by acetate-mediated intramolecular functionalization with the weak nucleophilic nitrogen of the carbamate. A key factor for the success of the amination is the ability of the acetate counterion to deprotonate the carbamate nitrogen without inhibiting the reactivity of the electrophilic Pd(II) catalyst.



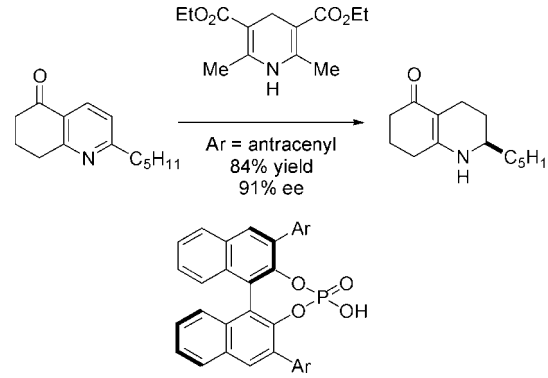
Catalytic Enantioselective Synthesis of Piperidines

Chiral adamantylimido Mo complex **1** mediates the asymmetric ring-opening/cross-metathesis of unsaturated *N*-methyl- and *N*-carbamate-protected azabicycles to give 2,4,6-trisubstituted piperidines in good yields and enantioselectivities (Cortez, G. A.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4534–4538). The success of the reaction relies on the use of an excess of cross-partner such as styrene that generates intermediate Mo-benzylidenes, which in turn minimize the competitive homodimerization of the initial azabicycles and continue the catalytic cycle. In contrast to Mo complexes, Ru carbenes are ineffective probably due to undesired nitrogen-Ru coordination. In addition, the authors report a series of representative functionalizations of the resulting enantiomerically enriched piperidines.



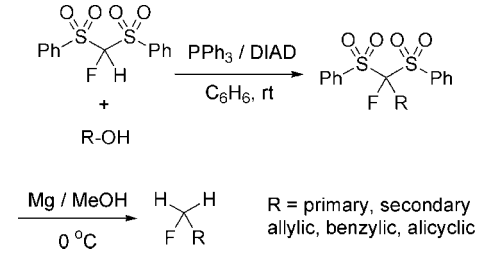
Enantioselective Reduction of Pyridines

Rueping and Antonchick at University of Frankfurt developed an enantioselective reduction of pyridines catalyzed by chiral binol phosphates as Brønsted acids (*Angew. Chem., Int. Ed.* **2007**, *46*, 4562–4565). The methodology constitutes an innovative alternative to metal-catalyzed enantioselective hydrogenations. Under optimized conditions, pyridines can be reduced by treatment with 5% acid catalyst and 4 equiv of a Hantzsch dihydropyridine in benzene at 50 °C to give the corresponding tetrahydropyridines in good isolated yields and with excellent enantioselectivities (up to 92% ee). The postulated mechanism involves the following sequence: (1) activation of the pyridine via protonation to give a chiral ion pair, (2) first hydride transfer from the Hantzsch ester, (3) acid-catalyzed isomerization to give an iminium ion, and (4) a second hydride transfer to afford the desired product and regenerate the binol phosphate catalyst.



Stereoselective Fluoromethylation of Alcohols

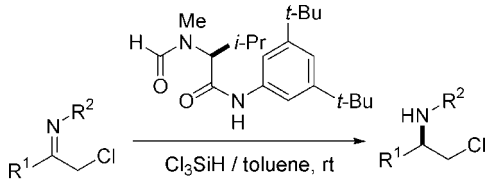
Finding methods to stereoselectively fluoroalkylate a substrate constitutes a pressing challenge in the field of Medicinal Chemistry since fluoroalkyl substituents impart unique pharmacological and pharmacokinetic properties to bioactive molecules. Prakash, Olah and co-workers accomplished the stereoselective monofluoromethylation of primary and secondary alcohols by using a fluorocarbon nucleophile in a Mitsunobu reaction (*Angew. Chem., Int. Ed.* **2007**, *46*, 4933–4936). Thus, the reactions of 1-fluoro bis(phenylsulfonyl)methane with a variety of primary and secondary alcohols afford the corresponding 1-fluoro-bis(phenylsulfonyl) derivatives with excellent stereospecificity from chiral alcohols. The products were subsequently subjected to reductive desulfonation using activated magnesium in MeOH at 0 °C to stereoselectively yield the desulfonated monofluoromethyl derivatives.

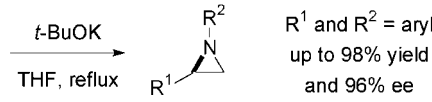


Enantioselective Synthesis of 1, 2-Diarylaziridines

Arguably, current methodologies for the enantioselective preparation of aziridines lag far behind those em-

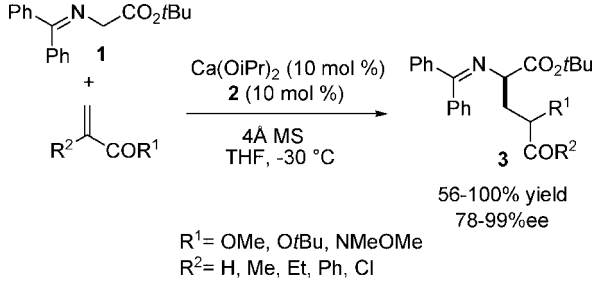
ployed in the synthesis of their epoxide counterparts. Malkov, Stoncius, and Kocovsky (University of Glasgow) report a convenient protocol to prepare 1,2-diaryl aziridines as pure enantiomers in *Angew. Chem., Int. Ed.* **2007**, *46*, 3722–3724. The final step of the sequence involves the base-mediated ring closure of enantiopure α-chloroamines with preservation of chirality using *t*-BuOK in THF at reflux. The key intermediate *β*-chloroamines can be obtained in good yields and high enantioselectivity by organocatalytic reductive amination of α-chloroacetophenones. Thus, their readily available *β*-chloroimines can be enantioselectively reduced with Cl_3SiH in the presence of 5 mol % valine-derived formamide. This is an elegant, metal-free methodology that uses toluene as an environmentally friendly solvent in the key steps.

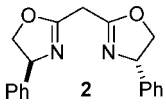




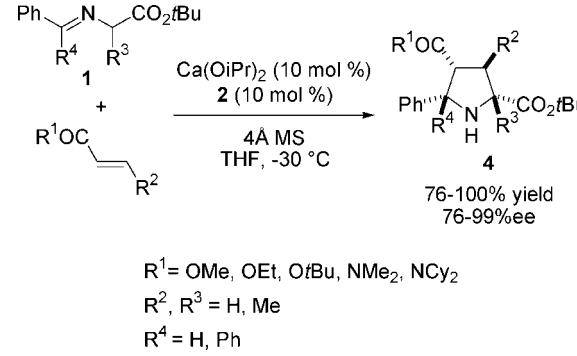
Chiral Calcium Complexes as Brønsted-Base Catalysts

With exception of the widespread use of Mg, in organic synthesis there are scarce examples on the synthetic utility of the remaining elements in Group 2, Ca, Sr, and Ba. These metals have large coordination numbers and low electronegativities and, therefore, can be used as Brønsted base catalysts. Saito, Tsubogo and Kobayashi at the University of Tokyo reported two reactions of α-amino acids derivatives with *β*-unsaturated carbonyl compounds catalyzed by Ca complexes: a chiral asymmetric addition and a [3 + 2] cycloaddition (*J. Am. Chem. Soc.* **2007**, *129*, 5364–5365). The reaction of glycine derivatives





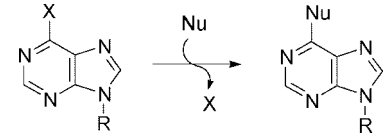
1 (1.2 equiv) with methyl acrylate in the presence of $Ca(OiPr)_2$ and a chiral bisoxazoline **2** in THF at −30 °C provides an efficient method to obtain chiral glutamic acid derivatives in high yields (56–100%) and ee's (78–99%). In cases where 2,4-*syn/anti* diastereomers were generated, the selectivity ranged from 61:39 to 91:9.



Interestingly, when methyl crotonate or acrylic acid amides reacted with **1**, the corresponding pyrrolidine derivative **4** was obtained as a single diastereomer, with excellent yield and enantioselectivity via a formal [3 + 2] cycloaddition. The authors postulate an anionic chiral Ca-bisoxazoline complex as the catalytic species. In contrast with phase transfer methods, the reaction system does not require excess electrophile or addition of a base.

S_NAr of 6-Halopurine Nucleosides

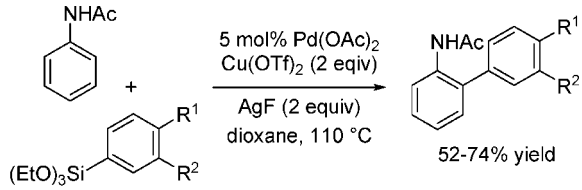
Liu and Robins published the results of a systematic study on the S_NAr reactivities of 6-(fluoro-, chloro-, bromo-, iodo-, and alkylsufonyl)purine nucleosides in a contribution from Brigham Young University, Utah (*J. Am. Chem. Soc.* **2007**, *129*, 5962–5968). Detailed mechanistic investigations demonstrate that 6-fluoropurine nucleosides are the fastest reacting substrates for S_NAr transformations involving *n*-buylamine, aniline/TFA, MeOH/DBU, and $MeCOS^-K^+$/DMSO as nucleophiles. In contrast, a 6-iodopurine reacts faster than its 6-halopurine counterparts in the presence of aniline without external acid catalyst as a rresult of the generation of catalytic HI during the reaction. Finally, a 6-alkylsulfonylpurine nucleoside reacted even faster than a 6-fluoropurine nucleoside with oxygen and sulfur nucleophiles. The study sets the foundations to understand structure–reactivity relationships within a group of substrates of indisputable biological interest.



Ortho-Arylation of Acetanilides

Shi and co-workers at Peking University reported a method for the formation of biaryls by coupling (trialkyloxyl)phenylsilanes with acetanilides via Pd(II)-catalyzed C–H functionalization (*J. Am. Chem. Soc.* **2007**, *129*, 6066–6067). Two equivalents of $Cu(OTf)_2$ as the oxidant of choice brought Pd^0 to Pd^{II} and inhibited the homocoupling of phenylsilane. Trialkoxyarylsilanes with different electronic patterns produced biaryls in good yields (52–74%) when the reaction was carried out in the presence of AgF (dioxane, 110 °C, 48 h). However, the transformation was less efficient using benzoyl anilines and

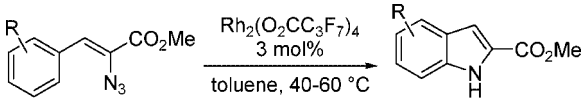
formyl anilines, whereas *N*-alkylated and unprotected anilines were not fit for this transformation.



R^1= H, OMe, Me, F, Cl
R^2= H, OMe

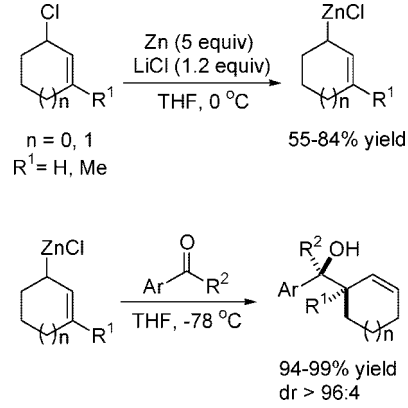
Intramolecular C–N Amination Reactions

Azides are readily available and key intermediates in benchmark processes (i.e., in the Roche synthesis of Tamiflu, *Org. Process Res. Dev.* **1999**, *3*, 266–274), but the high temperatures required to promote the formation of nitrenes from azides cause safety concerns. Scientists at the University of Illinois at Chicago developed a novel, mild way to generate Rh(II) nitrenoids from azides (*J. Am. Chem. Soc.* **2007**, *129*, 7500–7501). Using this methodology, indoles and other functionalized heterocycles can be prepared in two steps from commercially available starting materials. The activity of the rhodium catalyst is enhanced by the use of electron-deficient carboxylate, with optimal results obtained by using Rh(II) perfluorobutyrate in toluene at 40–60 °C. When a deuterium *ortho*-labeled vinyl azide was used, no H/D exchange occurred, and the product isotope effect was 1.0, indicating that the C-N bond formation occurs after the irreversible loss of N_2.



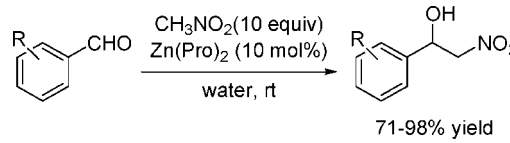
Sterically Encumbered Homoallylic Alcohols via Allyl Zinc Reagents

The group of Paul Knochel continues making strides in the field of organozinc reagents. They applied the LiCl-mediated insertion of Zn dust for the preparation of allyl zinc reagents using the corresponding allylic chlorides as starting materials (*J. Am. Chem. Soc.* **2007**, *129*, 5376–5377). The resulting organozinc compounds add with remarkable diastereoselectivity to various aldehydes and ketones, affording homoallylic alcohols bearing quaternary centers. The reaction is highly chemoselective, with α-chloro ketones and α-azido ketones yielding exclusively the corresponding tertiary homoallylic alcohols. When 3-methyl-2-cyclohexenyl chloride (n = 1; R^1 = Me) reacted with an aromatic ketone, the new C-C bond was formed exclusively on the most substituted end of the allylic system, yielding an alcohol bearing two adjacent quaternary centers.



Aqueous Henry Reaction Using a Zn-Proline Complex

Reddy and co-workers from the Indian Institute of Chemical Technology in Hyderabad reported the synthesis of 2-nitro alcohols catalyzed by a Zn–proline complex using water as the solvent (*Synth. Commun.* **2007**, *37*, 1971–1976). The $Zn(proline)_2$ complex was prepared by reaction of $Zn(OAc)_2$ with proline in the presence of Et_3N. The product precipitated from MeOH and was isolated by filtration. Nitro aldol reactions were performed in water at room temperature, using a mixture of nitromethane and aldehyde in 10:1 ratio. Conversion was faster and the product was obtained in better yields when using aldehydes with electron-withdrawing substituents. After extractive workup, the aqueous phase containing the catalyst can be recycled and used in subsequent Henry reactions with minimal impact on the yield. The catalyst can also be precipitated from the aqueous phase by simple addition of acetone.

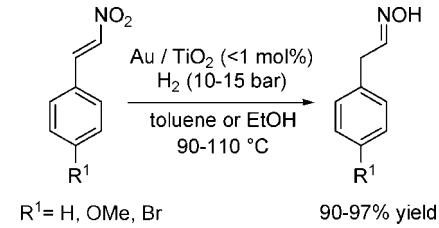


R= H, 4-NO_2, 2-NO_2, 4-CN, 4-CF_3, 2-Br, 2-OMe

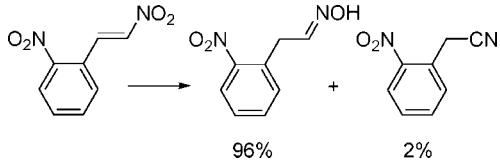
Gold-Catalyzed Synthesis of Oximes from α,β-Unsaturated Nitro Compounds

Oximes are traditionally prepared by condensation of an aldehyde or ketone with hydroxylamine. Nevertheless, the intrinsic toxicity and instability of hydroxylamine makes it objectionable for large-scale processes. Corma, Serna and Garcia from the Universitat Politecnica de Valencia-CSIC (Spain) reported a general chemoselective process for the hydrogenation of α,β-unsaturated nitro compounds into oximes using 1.5% Au on TiO_2 as the catalyst (*J. Am. Chem. Soc.* **2007**, *129*, 6358–6359). Whereas hydrogenations using Pd or Pt catalysts yielded mixtures of the desired product with saturated nitro

compounds, the gold catalyst showed remarkable selectivity towards the formation of the oxime.

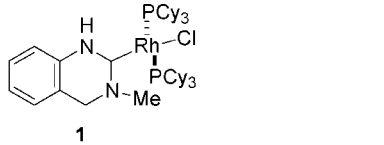


The methodology was validated by the reduction of β-dinitrostyrene. In the case of the Pd- or Pt-catalyzed hydrogenation, competing reactions (reduction of the nitro group to aniline, reductive cyclizations) led to extensive formation of byproducts. The use of the gold catalyst selectively afforded the aromatic oxime in excellent yields

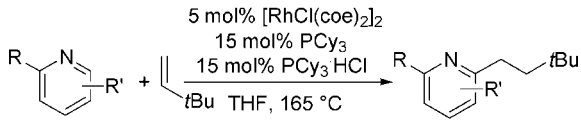


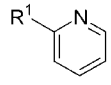
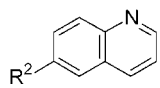
Rh(I)-Catalyzed Alkylation of Quinolines and Pyridines

Alkylation of pyridines and quinolines generally requires directing groups or electron-rich heteroarenes and proceeds via electrophilic metalation. In the case of the *ortho*-alkylation of nitrogen-containing heterocycles with olefins, Lewis, Bergman and Ellman had gathered extensive evidence supporting the intermediacy of a substrate-based *N*-heterocyclic carbene (NHC, **1**) arising from coordination of the heterocycle to the catalytically active $RhCl(PCy_3)_2$ fragment. On this basis, they employed the Rh/PCy_3 catalyst system not only to activate but to alkylate these heterocycles (*J. Am. Chem. Soc.* **2007**, *129*, 5332–5333). Several 2-substituted pyridines and 6-substituted quinolines reacted with 3,3-dimethylbutene under the optimized conditions (5 mol % $[RhCl(coe)_2]_2$, 15 mol % PCy_3, 15 mol % $PCy_3 \cdot HCl$, 0.8 M) to provide the desired *ortho*-alkylated product. Of particular interest is the TIPS-substituted pyridine, as the silyl group blocks the ortho position and can be removed to provide



1

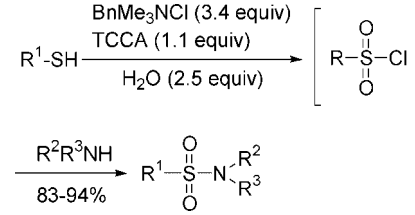


	R^1	R_2	yield (%)
	Me		59
	*i*Pr		83
	TIPS		64
		OMe	96
		H	98
		CO_2Me	96

monoalkyl pyridines. Olefins suitable to undergo the transformation include *n*-hexene, cyclohexene, 2-methylpropene and camphene.

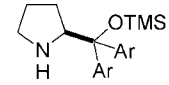
One-Pot Synthesis of Sulfonamides from Thiols

The sulfonamide group is an illustrious pharmacophore most frequently prepared by reaction of a sulfonyl chloride with primary or secondary amines. Bonk, Amos, and Olson at 3M Pharmaceuticals (St. Paul, Minnesota) communicated a convenient synthesis of sulfonamides from thiols by oxidation with a mixture of trichloroisocyanuric acid (TCCA), benzyltrimethylammonium chloride and water using acetonitrile as solvent (*Synth. Commun.* **2007**, *37*, 2039–2050). The combination of these reagents in nonprotic solvents generates chlorine gas in a controlled manner. Exposure of the resulting sulfonyl chlorides to excess amine in the same pot affords the desired sulfonamides with excellent yields. The reactions are general for a variety of sulfides and can be carried out at 0 °C under open atmosphere.

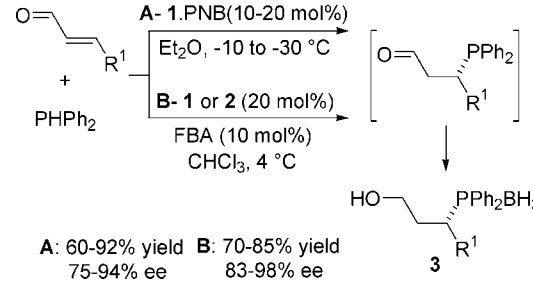


Hydrophosphination of α,β-Unsaturated Aldehydes en Route to Chiral Ligands

In back-to-back papers, two independent groups reported the asymmetric hydrophosphination of α,β-unsaturated aldehydes using an organocatalytic approach. The products are highly enentioenriched β-phosphine aldehydes, which can be further elaborated into bidentate P ligands for metal-catalyzed enantioselective transformations. The group of Melchiore at the Università di Bologna exploited the known capability of iminium catalysts to lower the LUMO of the electrophile and impart high chemo- and enantioselectivity in conjugate additions (*Angew. Chem., Int. Ed.* **2007**, *46*, 4504–4506). The best enantiocontrol was obtained when using a combination of the proline derivative **1** and *p*-nitrobenzoic acid (PNB) as the catalyst. Due to the instability of the target aldehydes, they were converted in situ in the corresponding alcohol **3** without erosion



1, Ar = 3,5-$(CF_3)_2C_6H_3$
2, Ar = Ph

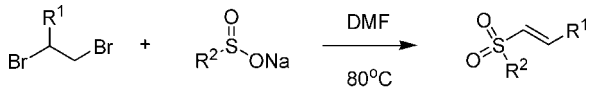


of the enantiomeric excess. Cordova and co-workers at Stockholm University followed a similar strategy using catalysts **1** and **2** along with 2-fluorobenzoic acid (FBA) (*Angew. Chem., Int. Ed.* **2007**, *46*, 4507–4510). Complementary DFT calculations showed that the lowest energy transition state led to the *S*-products.

How Green and Efficient Are Organocatalytic Reactions in the Presence of Water?

The title question was posed by Prof. Donna G. Blackmond and her collaborators from industry and academia (*Angew. Chem., Int. Ed.* **2007**, *46*, 3798–3800). In the essay, topics overshadowed by the virtues of water as a solvent are given a second glance. The limitation of performing organocatalytic reactions in water is how to get the products out of the water, resulting in aqueous streams containing organic remnants. "*Water is only a truly green solvent if it can be directly discharged to a biological effluent treatment plant.*" The problem worsens when large amounts of solvents (30-fold) are added to recover the product: the solvents used in the whole process, and not only as the reaction media, have to be considered in the "*greenness*" equation. Removal of residual solvents from water (incineration, carbon treatment, and stripping) is energy-costly, and the authors encourage an overall analysis of the process that may conclude that "*... an organic-solvent-based process is cheaper, easier, and ultimately environmentally more sound than a water-based organic reaction*". Whereas the essay does not provide solutions to the problems posed, it is a determining piece for scientists aiming at proper environmentally friendly processes.

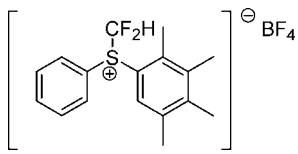
A Practical Synthesis of Vinyl Sulfones



R^1 = $CONH_2$, CO_2Me, CN, CO_2H, Me, Ph, etc
R^2 = Ph or Me

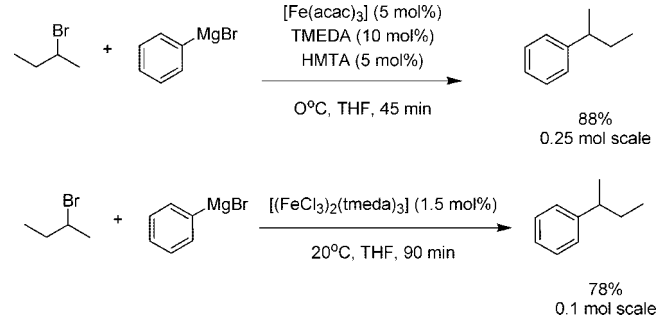
A practical process for the synthesis of vinyl sulfones from dibromides and commercially available sulfinic acid sodium salts in DMF has been developed by Liang and co-workers (*Synthesis* **2007**, *10*, 1465–1470). A broad spectrum of dibromides was shown to react with either sodium phenylsulfinate dihydrate or methanesulfinic acid sodium salt (65–88% yields, 12 examples). Functional group tolerance includes amides, ketones, esters, acids and nitriles. Addition of small amount water to DMF improved yields in the case of methylvinyl sulfones, which the authors attribute to the increased solubility of the methanesulfinic acid sodium salt. Alternative solvents were investigated but failed to improve yields.

A New Electrophilic Difluoromethylating Reagent



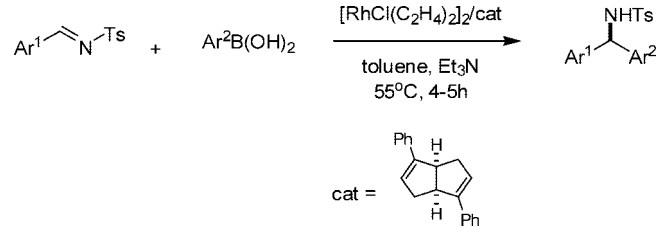
A new method for introducing a difluoromethyl group to heteroatom nucleophiles has been described by Olah and co-workers (*Org. Lett.* **2007**, *9*, 1863–1866). The *S*-difluoromethyl)diarylsulfonioum tetrafluoroborate reagent, synthesized in 5 steps from 2-bromothiophenol, transfers the difluoromethyl group, known to be isosteric and isopolar to the carbinol (CH_2OH) moiety, in moderate to good yields (54–89%, 8 examples) onto sulfonic acids, tertiary amines, imidazole derivatives and phosphines. The reagent failed to transfer the difluoromethyl group to phenols, carbon nucleophiles, and primary and secondary amines.

Iron-Catalyzed Alkylations of Aromatic Grignard Reagents



In an effort to advance the field of cost-effective and environmentally friendly catalytic cross-coupling reactions, new reaction methodology based on iron catalysts has been reported by Cahiez and co-workers (*Angew. Chem., Int. Ed.* **2007**, *46*, 4364–4366). Past systems have suffered from either low chemical yield, large excesses of Grignard reagent, or solvents that are not suitable for large scale applications (Et_2O). Two catalytic systems, [$Fe(acac)_3$]/HMTA/TMEDA (1:1:2) and [$(FeCl_3)_2(tmeda)_3$], have been demonstrated for efficient coupling of primary and secondary alkyl halides with aromatic Grignard reagents. Also noteworthy is the first use of hexamethylenetetramine (HMTA) as a ligand in transition-metal-catalyzed cross-coupling reactions. The ligand also has the added advantage of being inexpensive, readily eliminated, and then degraded during the treatment of the effluents.

New Chiral Ligands for Rh-Catalyzed Arylation



New C_2-symmetric tetrahydropentalenes have been synthesized for use as chiral diene ligands for the Rh-catalyzed aryation of *N*-tosylarylimines with arylboronic acids (*J. Am Chem. Soc.* **2007**, *129*, 5336–5337). Excellent yields and enantioselectivities were observed despite variation of sterics and electronics on either the *N*-tosylarylimines or the arylboronic acids (20 examples). The final step in the ligand synthesis allows for introduction of various aromatic groups, which should allow for individual reactions to be optimized on a case-by-case basis. The authors also disclose preliminary results for their diene

ligands in 1,4-additions to α,β-unsaturated ketones and arylations of *N*-nosylimines.

Innovations and Green Chemistry

Chemical Reviews has dedicated one of the latest issues (*Chem. Rev.* **2007**, *107*, no. 6) to innovations and green chemistry. The guest editors for this special issue are István T. Horvath and Paul T. Anastas. As we look over the field of green chemistry since its emergence as a cohesive field of study, beginning with the development of environmentally friendly processes in the early 1990s, it is possible to identify certain trends where much research has focused and where significant advances have been made. The area of environmentally benign solvents has been one of the leading areas, with biphasic aqueous catalysis and the use of supercritical fluids. The greenness of ionic liquids and fluorous media will ultimately depend on their individual properties with respect to health and environment. There has been renewed focus on the design of the ideal synthesis in terms of atom efficiency and step economy as a major goal. Techniques such as microwave and ultrasonic synthesis as well as in situ spectroscopic methods have been used extensively, leading to some spectacular results.

The success of green chemistry will depend on the practicing chemists who will use the same brilliance and creativity that is a long tradition of chemistry and use it with the new perspective for transformative innovations for sustainability.

Design of Sustainable Chemical Products–The Example of Ionic Liquids

Since the pioneering work of Wilkes and co-workers, ionic liquids have not only become increasingly popular as reaction and extraction media in research and development, they have also widely been promoted as "green solvents". The rationale for calling them green generally consists of three arguments; their vapor pressure is generally negligible, they have been shown to be nonflammable, they are claimed to be relatively nontoxic. Ranke et al. (*Chem. Rev.* **2007**, *107*, 2183) have reviewed in more detail the pros and cons of the use of ionic liquids from an environmental standpoint.

Greener Approaches to Organic Synthesis Using Microreactor Technology

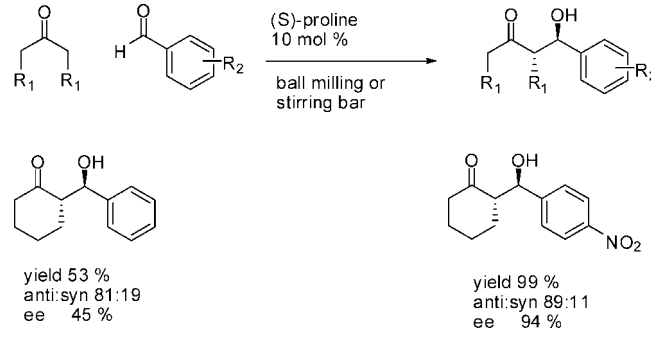
McQuade et al. have reviewed (*Chem. Rev.* **2007**, *107*, 2300) the unique aspects of microreactors that make them efficient tools for organic chemistry on both small and large scale. The types of reactions that have been run in microreactors have also been surveyed. In this review the authors have limited their discussion to those reactions they thought would be of interest to organic chemists; they have not reviewed bulk chemical processes performed in microreactors and have kept the discussion of engineering aspects to a minimum. Also, although the term "microreactor" has been loosely defined in dimensional terms, the authors have tried to limit the discussion to reactors using 10–1000 μm channels. The authors summarizes their findings that the burgeoning field of microreactor technology can have a significant impact when applied to organic synthesis not only for industrial chemists but also for the bench chemist designing new methodologies. The advantages inherent to microreactors, increased safety, decreased inputs and waste, the potential for catalyst recycling, and the opportunity for low volume optimization, make them ideal for doing more environmentally benign chemistry. Moreover, the increased control over reactions in microreactors, in the form of thermal stability and mixing control, means that new reactions can be made more reproducible from inception and may offer better regioselectivity and chemical selectivity than traditional batch synthesis.

A Green Approach to Asymmetric Catalysis: Solvent-Free and Highly Concentrated Reactions

Walsh, P. J. et al. (*Chem. Rev.* **2007**, *107*, 2503) have reviewed the development of asymmetric catalysis under solvent-free or highly concentrated reaction conditions. The results of these studies have been mixed. In some cases catalysts that demonstrate excellent enantioselectivity and activity under standard solvent conditions exhibit lower selectivity in the absence of solvent. In contrast, other catalysts react with excellent levels of enantioselectivity and greatly increased activity, enabling significant reduction in catalyst loading under solvent-free conditions. The review covers the literature up to the end of 2006. The authors define solvent-free conditions as those employing less than 5 equiv of one reagent with respect to the starting material. Highly concentrated are conditions that employ less than 5 equiv of solvent with respect to the substrate.

A Highly Efficient Asymmetric Organocatalytic Aldol Reaction in a Ball Mill

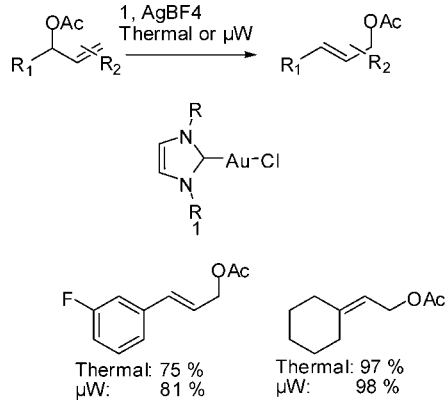
Anti-aldol products with up to >99% enantiomeric excess (ee) have been obtained by proline catalysis in good to excellent yields under experimentally simple solvent-free conditions (Bolm, C. et al. *Chem. Eur. J.* **2007**, *13*, 4710). Efficient mixing of all of the components is accomplished by applying a mechano–chemical technique (ball milling). The catalysis is air- and moisture-tolerant and can be performed with nonpurified starting materials. Even mixtures of solely solid compounds react giving (mostly solid) products through a partially homogeneous intermediate melt. When only solid components are used, the reaction time is pronouncedly longer. Since the reactant ratio is almost 1:1 (avoiding the common excess of ketone), the product isolation is easy, leading to good to excellent yields of 20 different products.



{(NHC)Au^{I}}-Catalyzed Rearrangement of Allylic Acetates

{(NHC)AuCl} complexes (NHC = *N*-heterocyclic carbene), in conjunction with a silver salt, were found to efficiently catalyze the rearrangement of allylic acetates under conventional and microwave-assisted heating. The optimization of several

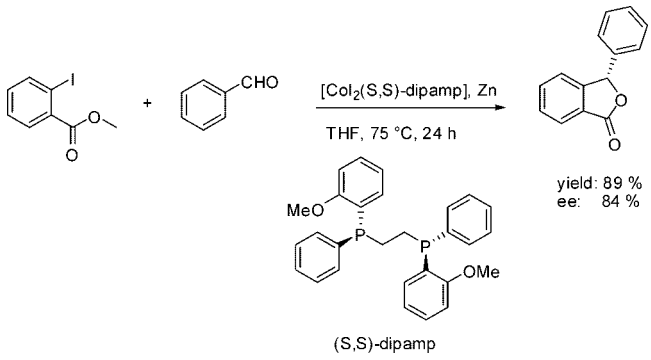
reaction parameters (solvent, silver salt, and ligand) as well as a study of the reaction scope has been studied by Nolan et al. (*Org. Lett.* **2007**, *9*, 2653). The steric hindrance of the ligand bound to gold was found to be crucial for the outcome of the reaction as only extremely bulky ligands permitted the isomerization.



Highly Efficient Cyclization of *o*-Iodobenzoates with Aldehydes Catalyzed by Cobalt Bidentate Phosphine Complexes: A Novel Entry to Chiral Phthalides

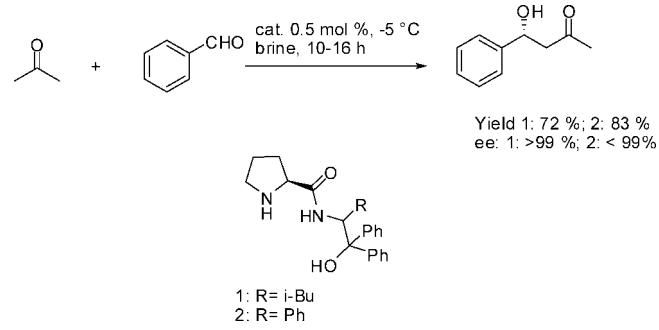
Methyl 2-iodobenzoates undergo cyclization reactions with various aromatic aldehydes in the presence of {CoI_2(dppe)} and Zn powder in dry THF at 75 °C for 24 h to give the corresponding phthalide derivatives in good to excellent yields (Chang, H.-T. et al. *Chem. Eur. J.* **2007**, *13*, 4356). Under similar conditions the less reactive aliphatic aldehydes also undergo cyclization to the corresponding phthalide derivatives in fair to good yields.

In addition, high enantioselectivity was obtained from the cyclization by employing cobalt complexes with a suitable bidentate chiral ligand. This new cobalt-catalyzed reaction highlights the potential of using cobalt as an inexpensive and efficient catalyst for coupling of carbon–carbon bonds and for catalytic asymmetric synthesis.



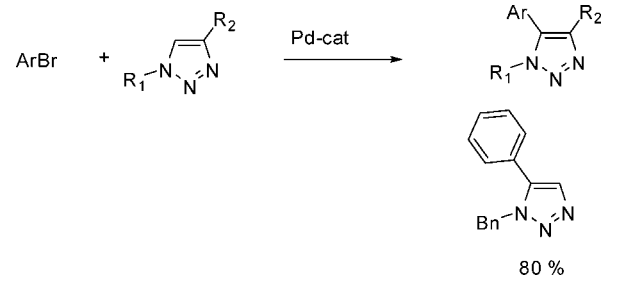
Highly Enantioselective Organocatalytic Direct Aldol Reaction in an Aqueous Media

The enantioselective aldol reaction catalyzed by small organic molecules is an important C–C bond formation reaction for which excellent enantioselectivities have been achieved. The reaction is presumed to proceed via an enamine intermediate, mimicking nature, where the type I aldolase enzyme catalyzes the aldol reaction in water. Recently the groups of Barbas and Hayashi have shown independently that efficient proline derived catalysts give high enantiocontrol in water. Now Singh, V. K. et al. (*Org. Lett.* **2007**, *9*, 2593) have also demonstrated that two different small proline derivatives catalyze the direct aldol reaction of both acyclic and cyclic ketones with various aldehydes in an excess of water/brine. Excellent enantioselectivities up to >99% and diastereoselectivities up to 99% with good to high yields were obtained with a low catalyst loading (0.5 mol %).



Direct Pd-Catalyzed Arylation of 1,2,3-Triazoles

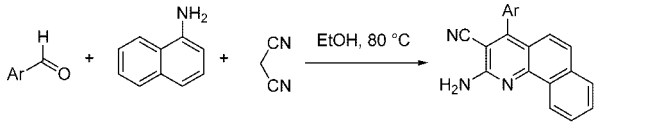
1,2,3-Triazoles, because of their unique chemical and structural properties, have received much attention over the past decades and have found wide application in medicinal chemistry and material science. Known methods for the regioselective synthesis of fully substituted 1,2,3-triazoles include reactions of azides with active methylene compunds or bromo-magnesium acetylides, with subsequent addition of electrophile, metalation of the existing triazole ring followed by reaction with electrophile and cross-coupling reactions of 5-halo-1,2,3-triazoles. However, these methods have their limitations as they require employment of organometallic reagents or halotriazoles. Now Gevorgyan, V. et al. (*Org. Lett.* **2007**, *9*, 2333) have developed a highly efficient method for the synthesis of multisubstituted 1,2,3-triazoles via a direct Pd-catalyzed C-5 arylation. The scope of the reaction has been shown with 19 examples with yields from 61% to 99%.



Catalyst-Free One-Pot Synthesis of Substituted Benzoquinolines

Benzoquinolines are found in a number of interesting compounds. Tu (Xuzhou Normal University, China) and others have reported [*J. Heterocycl. Chem.* **2007**, *44*, 735] the novel catalyst-free one-pot synthesis of 2-amino-4-arylbenzo[*h*]quinoline-3-carbonitriles by an interesting multiple-component reaction. An ethanolic solution of equimolar amounts of aromatic aldehyde, α-naphthylamine and malononitrile was heated to 80 °C to give the product after workup and recrystallization in 80–96% yields. Among glycol, acetic acid, DMF and ethanol, ethanol was found to be the best solvent for this synthesis. The

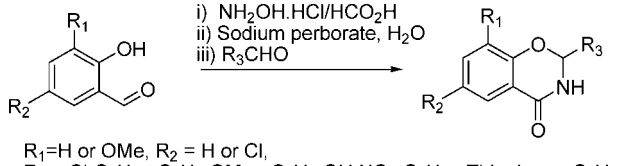
advantages of this reaction are short route, convenient operation, lack of chromatography and high yields. However, this reaction has been found to work only with aldehydes containing electron-withdrawing groups.



Ar = Cl-C_6H_4-, NO_2-C_6H_4-,F-C_6H_4-, $Cl_2C_6H_3$-

One-Pot Sodium Perborate Catalyzed Synthesis of Benzoxazinone Derivatives

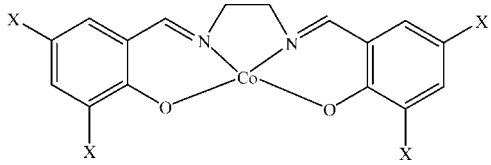
Benzoxazinone derivatives are known to possess a number of biological activities and therefore are compounds of great interest. Efavirenz, a benzoxazinone derivative, is used as part of highly active antiretroviral therapy (HAART) for the treatment of human immunodeficiency virus (HIV) type 1. Kidwai (University of Delhi, India) and others have recently reported (*Heterocycles* **2007**, *71*, 1615) a one-pot heterocondensation of *o*-hydroxy aromatic aldehyde, hydroxylamine hydrochloride and aromatic (or heteroaromatic) aldehydes in the presence of formic acid and aqueous sodium perborate to give 2-substituted-2,3-dihydrobenzo[*e*][1,3]oxazinones in 75–95% yields. This replaces a three-step procedure where all the intermediates were isolated. The reaction works well with electron-rich as well as electron-deficient aldehydes. The key advantages are (i) the reaction is done in an aqueous media, and (ii) the catalyst is very cheap. However, the product is isolated after a chromatography, which could be an issue on scale-up.



R_1=H or OMe, R_2 = H or Cl,
R_3 = Cl-C_6H_4, -C_6H_4-OMe, -C_6H_4-OH,NO_2-C_6H_4-, Thiophene, C_6H_5-

Epoxidation of Styrene with Molecular Oxygen

Zhang, Yang and Lu (*Asian J. Chem.* **2007**, *19*, 2083) reported the epoxidation of styrene with molecular oxygen catalyzed by cobalt(II) salen complexes at atmospheric pressure. They showed that conversions and selectivities depend on the nature of the substituents on salen (X = Br > H > *t*-Bu).

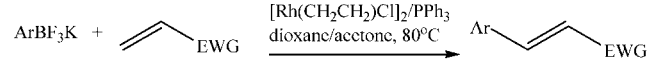


Temperature does influence conversions and selectivities. Temperatures lower than 90 °C favor not only styrene conversion (from 11.8% at 60 °C to 89.1% at 90 °C) but also styrene oxide selectivity (from 6% at 60 °C to 57.8% at 90 °C) in dioxane. This solvent proved to be the best solvent in this reaction, although *N*-methylpyrrolidone also led to good conversion (71%) but poor selectivity (38%). Contrary to many previous reports using manganese salen complexes, imidazole (im), pyridine (py) and acetic acid (AcOH) addition decreased (AcOH, py) conversion or suppressed reaction (im).

The use of molecular oxygen as terminal oxidant makes this system attractive for further investigation and industrial use.

Base-Free Mizoroki–Heck Reaction

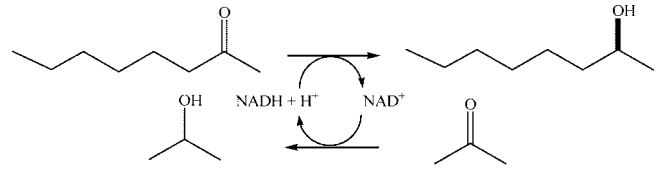
Genet's group (*Org. Lett.* **2007**, *9*, 3213–3216) has recently reported an elegant protocol to carry out Mizoroki–Heck reactions in the absence of bases using $ArBF_3K$ derivatives as arene sources. Remarkably, reaction takes place in acetone/dioxane in absence of base under Rh(I) catalysis (yields between 71% and 94%). Several acrylate derivatives and related olefins were successfully used. Since the reaction conditions are mild, catalyst loading is not prohibitive (1.5% mol), and different arenes (electron-donating or -withdrawing groups at *ortho*, *meta* or *para* positions) can be used. This reaction can be regarded of general use.



EWG = CO_2Et, CO_2tBu, $P(O)(OEt)_2$, CONHtBu, COC_3H_7

Enzymatic Reduction of Ketones in "Microaqueous" Media

Considering the fact that the use of enzymes and microorganisms in organic synthesis has a rather restricted use due to the low solubility of organic compounds in aqueous media, the University of Graz group (*Org. Lett.* **2007**, *9*, 2163) devoted to the development of new enzymatic processes showed an elegant protocol for the reduction of ketones using alcohol dehydrogenase from *Rhodococcus ruber* DSM 445419 overexpressed in *E. coli* (ADH-A) and lyophilized whole cells of *E. coli* harboring the overexpressed protein (*E. coli*/ADH-A) in two different solvent mixtures, 50% (v v^{-1}) organic cosolvent and 90% (v v^{-1}) microaqueous–organic solvent. The model system was 2-octanone (**1a**) to (*S*)-2-octanol in the presence of 2-propanol, to recycle NAD^+.



Mono- or biphasic aqueous–organic solvents showed good performance; in general, conversions were high and whole cells showed better conversions. A moderate decrease of conversion after 24 h was observed for recombinant ADH-A. In all cases, however, enantioselectivity was kept. Microaqueous–organic solvent systems behave differently; water-miscible solvents (DMSO, acetonitrile, 1,4-dioxane, EtOH) led to complete inactivation of either recombinant enzyme or whole cells. The influence of substrate concentration was studied in 99% v v^{-1} hexane. Conversions dropped, as expected. However, space–time yield (expressed as g of 2-octanone consumed per L of solution per hour) increased up to 120 g L^{-1} (whole cells) or 180 g L^{-1} for recombinant enzyme.

One advantage of the use of microaqueous–organic solvents is that recycle of the enzyme is possible and was proved to be feasible in this work. Other substrates were successfully tested, including isopropyl chloroacetylacetate, an intermediate to

several APIs, and showed good conversions and high enantiomeric excesses.

Solvent-Free Production of 1,3-Diglyceride

Diacylglycerols have increasing importance as nutraceutical agents due to their claimed properties to reduced blood levels of cholesterol and triglycerides. The production of these agents has become, therefore, very important. In this arena Guo and Sun (*Food Chem.* **2007**, *100*, 1076) have disclosed their results concerning the use of Novozyme 435 in the production of conjugated linoleic acid (CLA) 1,3-glycerol derivatives. Vacuum-driven N_2 bubbling proved to be the best operation mode. It eliminated mass transfer resistance, created effective interaction for a multiple-phase reaction system, eliminated water from reaction medium, and provided faster reaction rate. Yields up to 96% are obtained using 5 mmol of glycerol and 10–12 mmol of CLA. No 1,3 to 1,2 acyl migration was noticed, and the product was obtained free of impurities. The enzyme load is satisfactory (70 g L^{-1}), and little activity loss of enzyme was observed after 10 consecutive batch reactions. A smart experimental design of the apparatus provides efficient product removal.

Stereoselective Hybrid Catalysts

A brief review from the Vienna University of Technology (Mihovilovic, M. D. *J. Chem. Technol. Biotechnol.* **2007**, in press; http://dx.doi.org/10.1002/jctb.1752) provides a perspective on recent developments for hybrid catalysts applications. There seems to exist a renewed interest in this field, given that the synergy between enzyme- and metal-based catalysts was considered first over 3 decades ago. This review focuses on the preparation of biopolymers having stereoselective catalytic properties. The design principle of such metal-containing hybrid catalysts containing biomacromolecules is based on the modification of a suitable functionality on the biopolymer, with the goal of incorporating a metal ligand. The ligand can be inserted in the biopolymer either via a covalent bond or via a supramolecular assembly. Variation of the "anchor" and/or the "spacer" allow for building of catalyst libraries. After complexation of the catalytically active metal, stereoselctive transformations are possible because of the chiral environment of the biomacromolecule.

Examples of both types are presented, as well as their corresponding catalytic applications. More attractive results appear to be possible using the supramolecular assembly approach. For example, in stereoselective hydrogenations of α-amino acrylic acid derivatives, using biotinylated phosphine ligands carrying a Rhodium center, depending on the spacer used, optical purity of up to 92% ee was obtained. Nevertheless, this field is still considered to be an emerging one, and the chiral transformations discussed have not been scaled up yet. Recent advances in chemical optimization and molecular biology are expected to make hybrid biocatalysts competitive and suitable for large scale production.

The Path Ahead for Ionic Liquids

The science of ionic liquids as solvent replacements has been rapidly developing for the past 10 years. Nevertheless, commercial applications of ionic liquids used as solvents are fewer than expected. One of the very few reported cases of ionic liquid industrial applications is the use of *N*-methylimidazolium chloride by BASF in the manufacture of alkoxyphenyl phosphines for use in the fabrication of printing inks, glass fiber and wood coatings. A review from the National Chemical Laboratory in Pune, India (Joglekar, H. G. et al. *Chem. Eng. Technol.* **2007**, *30*, 819) addresses the commercialization challenges of ionic liquids. First, the authors present an overview of physical properties and applications of ionic liquids, used as reaction solvents, separation solvents, catalysts, cocatalysts, and even as heat transfer fluids. Second, the authors identify some of the apparent obstacles that prevent extensive commercialization of ionic liquids. This list contains nine such obstacles, including the lack of suitable analytical methods; the lack of data for physical properties, reaction mechanisms (for the formation of ionic liquid materials), ecotoxicity, lifetime and recyclability; and the insufficient process knowledge about the scale-up behavior of ionic liquids. As expected, due to the lack of extended commercialization, the cost of ionic liquids is relatively high (ca. $1,000 per kilogram). Several suggestions are offered to overcome some of those challenges, including the need for chemical engineers, working in close collaboration with research chemists, to execute process engineering studies to evaluate the commercial viability of ionic liquids, especially as reaction solvent replacements.

Improved Selectivity in Heterogeneous Catalytic Hydrogenation: Solid Catalyst with Ionic Liquid Layer (SCILL)

A promising catalytic application of ionic liquids is summarized in a report from Bayreuth University in Germany (Kernchen, U. *Chem. Eng. Technol.* **2007**, *30*, 985). An older concept of supported ionic liquid phase (SILP), involves a thin film of an ionic liquid with a homogeneous catalyst dissolved therein, applied to the internal surface of a porous inert solid. A new concept, solid catalyst with ionic liquid layer (SCILL) is based on SILP technology, with the key difference that the solid support is a heterogeneous catalyst. To verify this concept, the authors used the hydrogenation of cyclooctadiene in the presence of commercial nickel catalyst on SiO_2, coated with up to 20% ionic liquid [BMIM] [n-$C_8H_{17}OSO_3$], where BMIM = 1-butyl-3-methylimidazolium. The catalyst thus prepared was shown through electron microscopy to contain all of the ionic liquid fixed on the internal surface of the nickel catalyst, with no ionic liquid detected on the catalyst surface. The hydrogenations were typically carried in *n*-dodecane, at 50 °C and at a constant H_2 pressure of 50 bar. Suitable mixing was provided by a magnetic rotor and a multistage agitator. For larger particles catalyst, because of undesired grinding effects of the typical agitation system. a modified mixing approach had to be used. A detailed physical characterization of the system was executed and so were kinetic and mechanistic investigations. The stability of the ionic liquid coating was also confirmed. For the case of the SCILL procedure the yield of cyclooctene was 70%, compared with 40% yield in the case of the same catalyst, but uncoated. Two obvious limitations of such catalysts are the maximum tem-

perature of operation (dictated by the decomposition temperature of the ionic liquid, 120 °C in this example) and the requirement of insolubility of the ionic liquid in the organic phase. A more unexpected finding that deserves further investigations is the apparent interaction between the ionic liquid and the nickel catalyst in the absence of H_2 (even in the presence of argon).

Industrial Implementation of Online Multivariate Quality Control

Numerous impressive accomplishments were reported in the field of pharmaceutical process analytical technology (PAT) in the past 5 years. A few industrial applications, in particular in drug product manufacturing, have been reported. However, extremely few, if any, API manufacturing processes seem to benefit from high level PAT. By high level PAT we understand a process that is not only monitored but also controlled, based on a model preferably developed using a multivariate approach. Online multivariate quality control is more common in the manufacture of specialty chemicals. A recent report from the Dow Chemical Company (Chiang, L. H. et al. *Chemom. Intell. Lab. Syst.* **2007**, *6*, 616) provides an up-to-date insight into a successful implementation of high level PAT. This quality control approach was used for the production of epoxy resins. The quality variables monitored were epoxy equivalent weight (EEW), viscosity, and softening point. All of these quality variables are reflective of the molecular weight and/or architecture of the epoxy resin. Even though direct measurements of the molecular weight of a polymer are available, such methods can be cost-prohibitive in a manufacturing setting. Robust (rather than standard) principal component analysis had to be used to exclude outliers, and T^2 statistic was employed for fault detection. A model for one specific product was developed based on historical data from 1,602 lots. The model was used successfully, at another site, for another product. Over 2,800 lots of the second product, passing all specifications, were manufactured at the new site. In addition to interesting statistical insights, this account may also help us understand why so few high level PAT applications are practiced in API manufacturing, such as the availability of far fewer batch data for model development and optimization.

Mark McLaughlin
Merck & Co. Inc.,
Rahway, New Jersey 07065, U.S.A.
E-mail: mark_mclaughlin@merck.com

Silvina García Rubio
Sapphire Therapeutics, Inc.,
Bridgewater, New Jersey 08807, U.S.A.
E-mail: sgarciarubio@sapphirethera.com

Matthew Pfeiffer
Process R&D, PTD, Exelixis Inc.,
South San Francisco, California 94080, U.S.A.
E-mail: mpfeiffe@exelixis.com

Ulf Tilstam
CMC-Solutions, Belgium.
E-mail: tilstam@skynet.be

Joseph Swaroop Mathen
Pharmacore Inc.,
High Point, North Carolina 27265, U.S.A.
E-mail: jsmathen@pharmacore.com

Octavio Augusto Ceva Antunes
Departamento de Quimica Inorganica,
Instituto de Quimica, UFRJ, Cidade Universitaria,
Rio de Janeiro, RJ 21949-900, Brazil
E-mail: octavio@iq.ufrj.br

Trevor Laird*
Editor

Andrei A. Zlota
The Zlota Company,
Sharon, Massachusetts 02067-2858, U.S.A.
E-mail: andrei.zlota@thezlotacompany.com

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