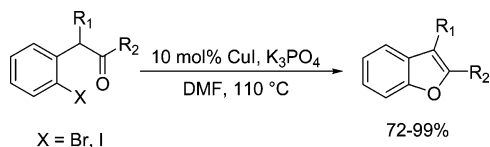


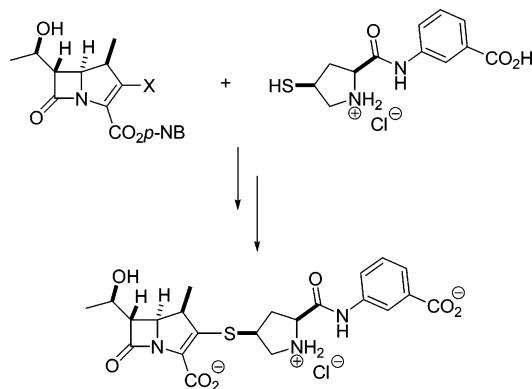
Some Items of Interest to Process R&D Chemists and Engineers

Cu-Catalyzed Synthesis of Benzo[*b*]furans



Having set out to prepare an indole derivative by a two-step amine arylation/ring-closure sequence, Chen and co-workers at Merck instead isolated a benzo[*b*]furan from the attempted Cu-catalyzed amination reaction. Further investigation of this unexpected result led to an optimized process in which a wide variety of benzo[*b*]furans can be efficiently synthesized via a CuI-catalyzed ring closure of 2-haloaromatic ketones (*J. Org. Chem.* **2005**, *70*, 6964–6967). The methodology is tolerant of various functional groups and affords benzo[*b*]furans in 72–99% yields. The method features a straightforward isolation by direct precipitation from the reaction mixture.

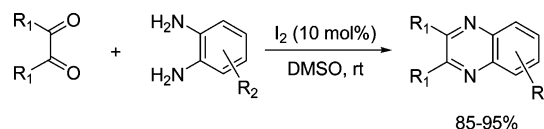
Practical Carbapenem Synthesis



Williams and co-workers at Merck report on the development of a practical procedure for the large-scale production of the new carbapenem antibiotic, ertapenem sodium (*J. Org. Chem.* **2005**, *70*, 7479–7487). A detailed and interesting discussion provides numerous insights into the subtle reactivity issues frequently encountered with this class of molecules. A highlight from this work is the novel use of 1,1,3,3-tetramethylguanidine as the base for the low-temperature reaction of a thiol with the carbapenem nucleus, activated as the enol phosphate. The use of bicarbonate in a hydrolysis was key in providing protection of the pyrrolidine amine as the sodium carbamate, improving both the performance of the reaction and the stability of the product. This discovery made processing at manufacturing scale possible. Also described is an expedient process for the simultaneous

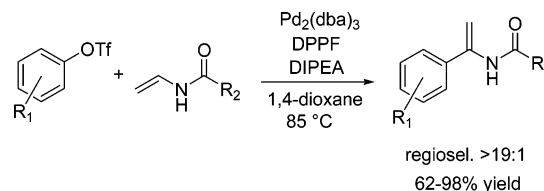
purification and concentration of the aqueous product stream, relying on ion-pairing extraction for the removal of the water-soluble 1,1,3,3-tetramethylguanidine.

Iodine-Catalyzed Quinoxaline Synthesis



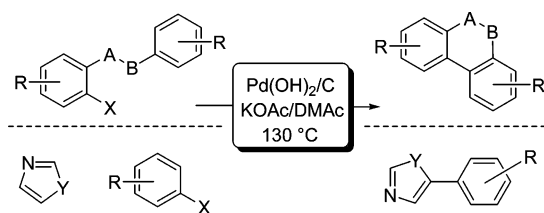
An efficient and mild procedure for the synthesis of substituted quinoxalines is described by Pawar and co-workers (*Tetrahedron Lett.* **2005**, *46*, 7183–7186). The condensation of 1,2-dicarbonyl compounds with different substituted *o*-phenylenediamines proceeds at room temperature in DMSO using a catalytic amount of molecular iodine.

Regioselective Heck Coupling of Enamides with Aryl Triflates



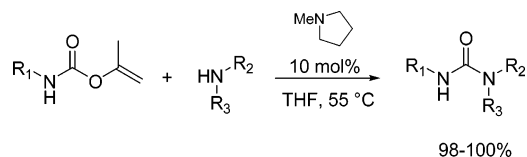
Highly regioselective Heck couplings of aryl triflates with *N*-acyl-*N*-vinylamines lacking an *N*-alkyl substituent are reported by Skydstrup and co-workers (*J. Org. Chem.* **2005**, *70*, 5997–6003). Several *N*-vinylamides, an *N*-vinylcarbamate, and an *N*-vinylurea were shown to participate efficiently in the title reaction. The Heck-coupled products easily underwent acidic hydrolysis to the corresponding aryl methyl ketone or in situ hydrogenation in the presence of (Ph₃P)₃RhCl under a hydrogen atmosphere to provide the *N*-acyl derivatives of pharmaceutically relevant benzylic amines. Additionally, a vinyl triflate and a vinyl tosylate afforded a 2-acylamino-1,3-butadiene with the same high regioselectivity in preference for the *R* isomer.

Direct Arylation Reactions Catalyzed by Pd(OH)₂/C



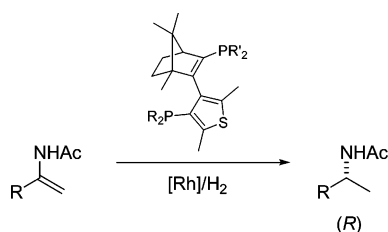
While direct arylation reactions have been known for 20 years, their general application in organic synthesis has been slow to appear. Recently, these transformations have been successfully applied in a variety of settings, and now Fagnou and co-workers report on the use of Pearlman's as a catalyst for these reactions (*J. Org. Chem.* **2005**, *70*, 7578–7584). Excellent arylation-to-hydrodehalogenation ratios (>30:1) are observed, and the process has scope for both intra- and intermolecular arylation processes. Studies aimed at determining the nature of the active catalyst (three-phase tests) indicated that an active homogeneous palladium species is produced under the reaction conditions.

Practical Synthesis of Unsymmetrical Ureas from Isopropenyl Carbamates



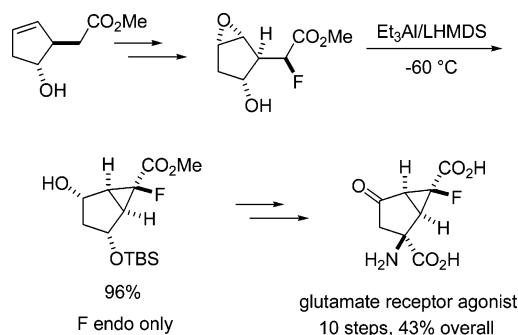
A convenient method for the synthesis of unsymmetrical ureas from isopropenyl carbamates is described by Gallou and co-workers at Boehringer Ingelheim (*J. Org. Chem.* **2005**, *70*, 6960–6963). The authors comment that the synthetic efficiency of traditional methods for urea formation, such as the use of phosgene or alkyl and aryl carbamates, can be limited by the formation of symmetrical urea side products or reaction reversibility. Isopropenyl carbamates, which react with amines cleanly and irreversibly to give unsymmetrical ureas in high yield/purity, are readily prepared from amines and isopropenyl chloroformate under Schotten–Bauman conditions. Isolation of the ureas from these reactions is straightforward since all byproducts are volatile. However, following a brief scan of commercial suppliers, it would appear that isopropenyl chloroformate is a relatively expensive reagent, perhaps detracting from its utility on scale.

Chiral Diphosphine Ligands Based on Camphor



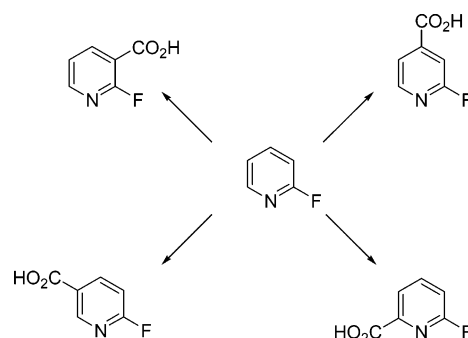
Researchers at Degussa have described their approach to a series of novel atropisomer chiral diphosphine ligands containing a bornene backbone (*Tetrahedron Lett.* **2005**, *46*, 7397–7400). The new ligands, which are commercially available under the trade name catASium T, were tested in a series of asymmetric hydrogenation reactions of enamides. The authors point out that the reduction of electron-deficient α -aryl enamides in the presence of the novel ligand (S/C 1000, 1 h 95% conversion, 99% ee) represents the highest reported enantioselectivity/activity for a substrate known to be challenging.

Stereoselective Syntheses of Highly Functionalized Bicyclo[3.1.0]hexanes



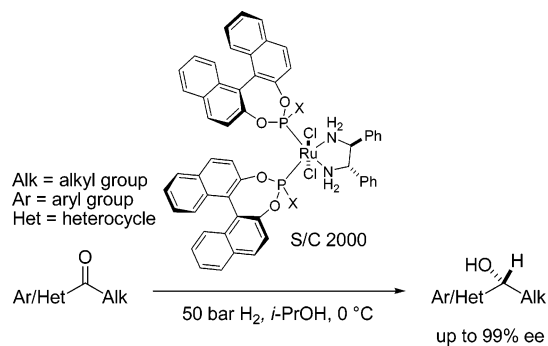
An efficient synthesis of a densely functionalized glutamate receptor agonist is described by Tan, Yasuda, and co-workers at Merck (*J. Org. Chem.* **2005**, *70*, 8027–8034). A highlight from this work is a Lewis acid-mediated intramolecular epoxide opening–cyclopropanation reaction, which efficiently delivers the bicyclo[3.1.0]hexane system with excellent stereoselectivity. Due to the instability of the required fluorinated enolate, the developed conditions involve pre-complexation of the epoxide with the Lewis acid (Et_3Al) at low temperature, followed by treatment with strong base. Application of this reaction to the synthesis of the target compound (43% overall yield) and a few intermediates suitable for the synthesis of other bicyclo[3.1.0]hexane glutamate receptor agonists is discussed. Multikilogram-scale experimental details are provided.

Regio-Exhaustive Functionalization of Fluorinated Pyridine Derivatives



The concept of “regio-exhaustive substitution” is described by Schlosser (*J. Org. Chem.* **2005**, *70*, 3039–3045) and has been successfully applied to the functionalization of 2-fluoro-, 2,3-difluoro-, and 2,5-difluoropyridine. All vacant positions were amenable to regioselective metalation and subsequent carboxylation by employing either chlorine as a neighboring site, activating protective group or trimethylsilyl as a neighboring site, screening protective group. In this way, approximately half a dozen fluorinated pyridinecarboxylic acids were derived from each starting material.

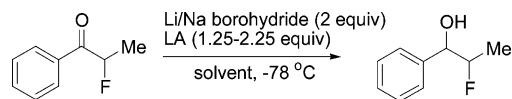
Ruthenium(II) Complexes of Monodonor Ligands: Efficient Reagents for Asymmetric Ketone Hydrogenation



Having released a previous communication of their studies on asymmetric hydrogenation of ketones, the group of Wills and collaborators at Rhodia now present the extended results from this research (*J. Org. Chem.* **2005**, *70*, 8079–8087). A series of BINOL-derived ligands were prepared and incorporated into ruthenium(II) complexes containing a diamine ligand. The complexes have proven to be excellent catalysts for the asymmetric hydrogenation of ketones, giving reduction products with enantiomeric excesses of up to 99%. The developed catalytic system represents a viable and practical alternative to the well-established analogous complexes that contain a bi-dentate diphosphine ligand. A potential advantage is that the novel ligands can be prepared in one step from BINOL, compared to the usual multistep syntheses of diphosphine ligands. The enantiocontrol appears to depend on steric differentiation between the groups on either side of the ketone. A mechanistic rationale for the absolute control of the reduction has been forwarded, in which a close analogy to the BINAP/Ru/DPEN catalyst system is highlighted.

Diastereoselective Reduction of α -Fluoroketones

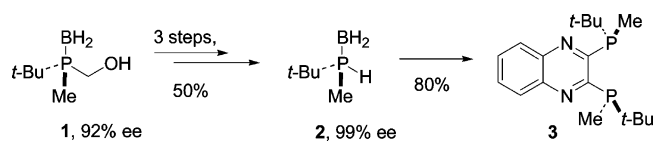
Demand is currently high for the development of methods to obtain optically pure α -fluoro alcohols that are relevant for numerous drug targets. Flowers and co-workers (*J. Am. Chem. Soc.* **2005**, *127*, 11896–11897) reported an innovative methodology that uses chelation with Ti(IV) Lewis acids (LA) to control the relative stereochemistry of the newly formed chiral center. The desired fluoro alcohol was obtained in moderate stereoselectivity and excellent yields (76–100%). Chelation was evidenced by ¹H, ¹³C, and ¹⁹F NMR studies of 2-fluoropropiophenone before and after the addition of LA and the preferred *syn* relative stereochemistry of the OH and F groups. Selected examples showed the inversion of selectivity from *anti* to *syn* when TiCl₄ was used, as well as an 8-fold increase in selectivity by using LiBH₄ and Et₂O. The optimized protocol has been successfully expanded to a series of α -fluoroketones.



LA	Li/Na hydride	Solvent	<i>syn:anti</i>
none	NaBH ₄	CH ₂ Cl ₂	1:4
TiCl ₄	NaBH ₄	CH ₂ Cl ₂	6:1
none	LiBH ₄	Et ₂ O	3:1
TiCl ₄	LiBH ₄	Et ₂ O	24:1

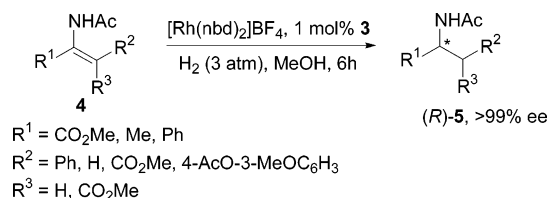
Air-Stable Catalysts for Transition Metal Promoted Reactions

Imamoto, Sugita, and Yoshida (Chiba University) have developed an air-stable phosphine ligand that can be used in a variety of transition-metal catalyzed reactions (*J. Am. Chem. Soc.* **2005**, *127*, 11934–11935). Air sensitivity of commonly used ligands (BisP*, MiniPHOS, see *Adv. Synth. Catal.* **2001**, *343*, 118–136) is due to the high electron density at the phosphorus atoms. The designer ligand **3** contains an electron-withdrawing quinoxaline backbone that renders the phosphine moiety less susceptible to air oxidation. Ligand **3** was readily prepared from (*R*)-methylphosphine borane **1** and showed no degradation or epimerization at the stereogenic phosphorus atoms on standing in air at room temperature for 8 months.

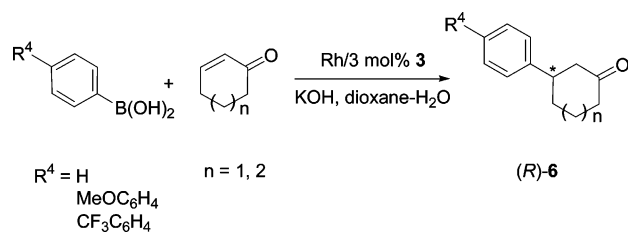


The enantioinduction ability of ligand **3** was probed in the Rh-catalyzed asymmetric hydrogenation of dehydramino acids and α -enamides to yield amino acids and acetylated primary amines. Products with the *R* configuration were obtained with excellent ee's. Notably, (*E*)- and (*Z*)-acetyl(amino)acrylates were reduced with high enantioselectivities.

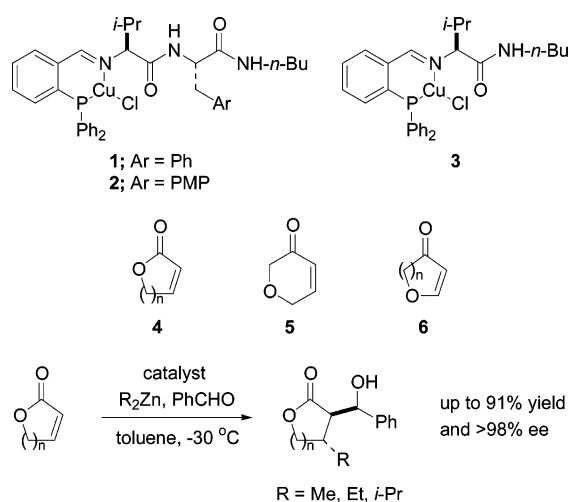
In the case of C–C-forming reactions, **3** was successfully



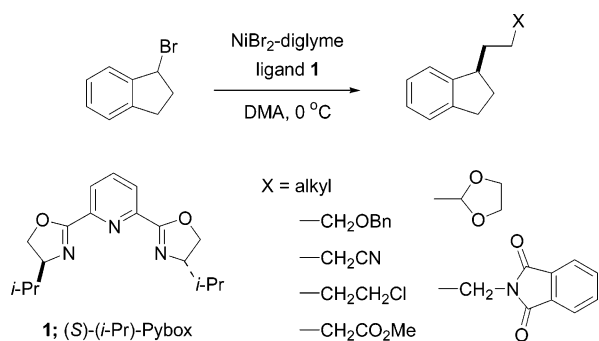
used for the Rh-catalyzed asymmetric 1,4-addition of arylboronic acids to α,β -unsaturated carbonyl compounds. The reactions proceeded at 40–50 °C to give the addition products in high yields with excellent ee's.



The Hoveyda group has developed a catalytic asymmetric conjugate addition of dialkylzinc nucleophiles to furanones and pyranones (*Angew. Chem., Int. Ed.* **2005**, *44*, 5306–5310). The method uses air-stable Cu-peptide catalysts (**1–3**, typically <5 mol %) that can be stored for at least a week to afford β -alkyl carbonyls in excellent yields and enantioselectivities. Generic substrates **4–6** react with a variety of dialkylzinc reagents, including hindered (*i*-Pr)₂Zn and the less reactive Me₂Zn. The additions must occur in the presence of an aldehyde with the purpose of trapping the intermediate adduct and prevent ketene formation and intermolecular reactions. The aldol products can be transformed into simple β -alkyl carbonyls by an effective retro-aldol process (K₂CO₃ in refluxing toluene, >83% yield) or can be oxidized to afford the corresponding 1,3-diketones (PCC-NaOAc, >85% yield). Marked solvent effects upon yields and ee's (e.g., THF versus Et₂O or toluene) are related to alterations in the substrate–catalyst binding.



The first catalytic enantioselective version of a Negishi cross-coupling has been developed by Arp and Fu (*J. Am. Chem. Soc.* **2005**, *127*, 10482–10483). Thus, racemic

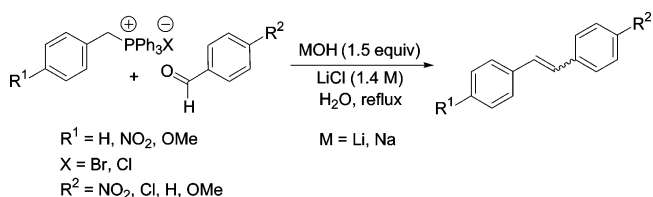


1-bromo- and 1-chloroindanes can be coupled with organozinc reagents in the presence of NiBr₂–diglyme complex (10 mol %) and Pybox ligand **1** at 0 °C in *N,N*-dimethylacetamide (DMA) with yields up to 89% and 99% ee. The transformation is stereoconvergent since both haloindane enantiomers afford the same enantiomer of the product. Moreover, the reaction occurs selectively at the benzylic position in the presence of an aryl chloride moiety and is effective with a variety of functionalized organozinc reagents,

including nitriles, chlorides, ketals, ethers, esters, and imides. Interestingly, the active catalyst is prepared in situ from commercially available reagents, and the reactions show no moisture or air sensitivity. The synthetic utility of the asymmetric cross-coupling is illustrated with the preparation of two intermediates of pharmaceutical interest.

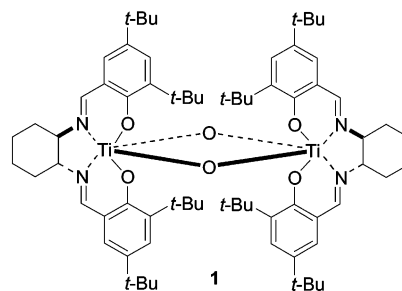
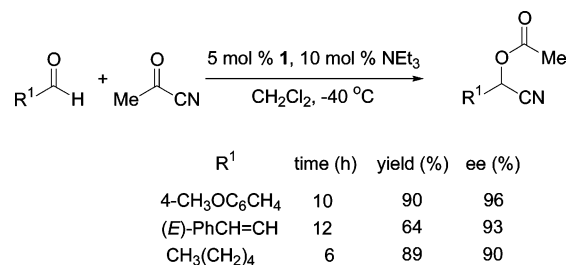
Wittig Reactions in Water

Wu, Li, and Zhang reported heterogeneous aqueous Wittig reactions without using any organic cosolvent (*Synth. Commun.* **2005**, *35*, 2543–2551). Ylides were generated in situ from benzyltriphenylphosphonium halides and LiOH or NaOH, and reacted with aromatic aldehydes in refluxing water in the presence of LiCl. Most of the reactions proceeded to completion in less than 5 h to afford the desired olefins in 60–100% yields. Moderate to good *E:Z* selectivity was obtained, depending on the substitution pattern on the aromatic rings of both species. The authors propose that LiCl promotes the aqueous Wittig reactions and suppresses decomposition of the ylide or the corresponding phosphonium salt in water.



Enantioselective Cyanation of Aldehydes: Dual Lewis Acid–Lewis Base Activation

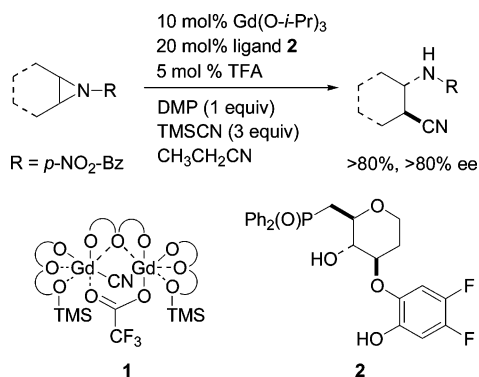
Among the methods to obtain enantiomerically pure cyanohydrins, of particular importance are those that provide direct access to *O*-functionalized derivatives. The group of Christina Moberg at the Royal Institute of Technology in Sweden reported a protocol to access enantioenriched *O*-acetylated and *O*-alkoxycarbonylated cyanohydrins by dual Lewis acid–Lewis base activation (*J. Am. Chem. Soc.* **2005**, *127*, 11592–11593). The reaction uses pyruvonnitrile or ethyl



cyanofornate as the source of cyanide and the Ti-salen catalyst system **1**. An assortment of tertiary amines (DMPA, DABCO, DIPEA) have been successfully employed to afford the *S*-enantiomer in high selectivity (81–94% ee). The use of chiral bases (quinine, sparteine, cinchonidine) did not result in enhanced selectivities. The optimized conditions use a combination of **1** (5 mol %) and Et₃N (10 mol %) and were successfully applied to a variety of aromatic and aliphatic aldehydes.

Desymmetrization of *meso*-*N*-Acylaziridines using Gd Complexes and TMSCN

The catalytic desymmetrization of *meso*-aziridines constitutes an enormous challenge despite the existence of successful desymmetrizations for their cousin epoxides. Kanai and Shibasaki reported the enantioselective opening of *meso*-aziridines promoted by the carbon nucleophile TMSCN, and catalyzed by Gd complexes (*J. Am. Chem. Soc.* **2005**, *127*, 11252–11253). The transformation generates chiral β -amino nitriles that can be transformed in β -amino acids upon acidic hydrolysis. The proposed active catalyst (**1**, 10 mol %) contains two Gd metal centers, three units of chelating ligand **2**, and one molecule of trifluoroacetate. The best results were obtained with *N*-*p*-nitrobenzoyl aziridines in the presence of 1 equiv of 2,6-dimethylphenol (DMP) as additive.



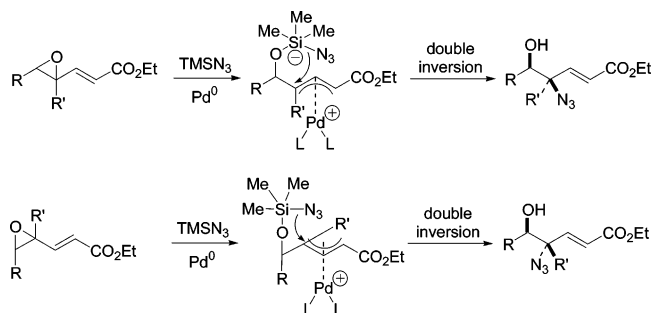
Properties, Synthesis and Reactivity of Organic Azides

Despite their explosive properties, organic azides continue to be a subject of interest to the chemical community. Bräse and co-workers have meticulously reviewed many of the most relevant aspects of these energy-rich and flexible compounds (*Angew. Chem., Int. Ed.* **2005**, *44*, 5188–5240). The physical properties and safety considerations for azides are enumerated. The review compiles synthetic methods to prepare alkyl and aryl azides, as well as its numerous reactions such as Curtius rearrangement, Staudinger ligation, and the synthesis of heterocycles (triazoles and tetrazoles). Of particular interest are the new applications of traditional reactions in the interface between chemistry and biology, as well as the use of azides as intermediates in the preparation of a variety of natural products.

Pd-Catalyzed Azide Substitution of α,β -Unsaturated γ,δ -Epoxy Esters

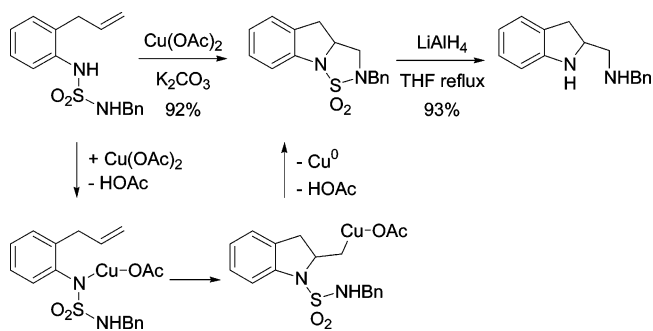
Recent investigations on Pd-catalyzed substitutions of unsaturated γ,δ -epoxy esters by Miyashita and co-workers

triggered the development of a new methodology to prepare azido alcohols (*Angew. Chem., Int. Ed.* **2005**, *44*, 5094–5097). The reaction of γ,δ -epoxy esters with TMSN₃ in the presence of a Pd catalyst occurs with complete stereoselectivity at the position γ to give β -azido alcohols in excellent yields. The transformation involves an intermediate π -allyl palladium complex, and the stereospecificity arises from a double inversion of configuration throughout two consecutive S_N2 reactions. Whereas the stereochemical outcome is independent of the structure of the epoxide, yields are substrate-dependent and rely on the phosphine ligand. For example, P(2-furyl)₃ accelerates dramatically the reaction of cyclic substrates. Representative conditions involve the addition of TMSN₃ (2 equiv) to a solution of the substrate in THF at room temperature followed by the Pd catalyst (5–10 mol %).



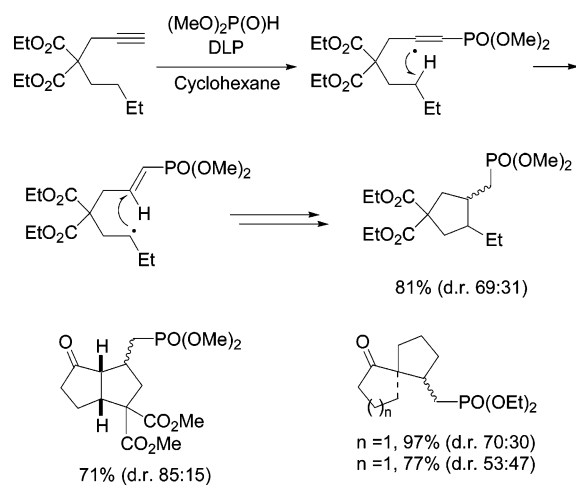
Cu(II) Acetate-Mediated Diamination of Alkenes

A new methodology for the intramolecular diamination of unactivated alkenes has been communicated by Chemler and co-workers (*J. Am. Chem. Soc.* **2005**, *127*, 11250–11251). The reaction of sulfamides with terminal olefins occurs in the presence of 1.2 equiv of Cu(OAc)₂ and 2 equiv of K₂CO₃ at 90 °C to give the desired heterocycles in good yields. Reduction of these adducts with LiAlH₄ affords the unprotected diamines. During the optimization of reaction conditions, the authors found that DMF/DMSO mixtures are superior to THF and CH₃CN, probably due to the improved solubility of Cu(OAc)₂. Moreover, different Cu(II) halides did not mediate diamination, and excess CuOAc affords incomplete transformation via disproportionation to active Cu(OAc)₂ and inactive Cu⁰. A mechanistic proposal considers the formation of an N–Cu intermediate that undergoes migratory insertion followed by ligand exchange and reductive elimination.



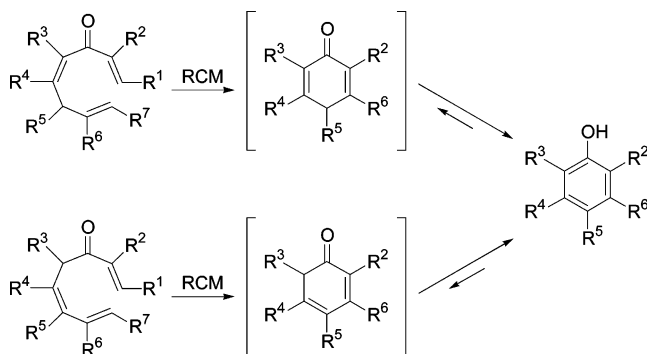
Tin-Free Radical Cyclizations Using Dimethyl Phosphite

The addition of a phosphorus radical onto a terminal alkyne followed by 1,5-hydrogen transfer and cyclization affords cyclopentane derivatives in good to excellent yields. The reaction developed by Renaud and co-workers (*Angew. Chem., Int. Ed.* **2005**, *44*, 5273–5275) offers an environmentally benign alternative to prior methods based on tin or sulfur initiators. In a typical experiment, the radical cascade uses dimethyl phosphite (5 equiv) and dilauroyl peroxide (DLP, 1 equiv) in cyclohexane at 80 °C for approximately 6 h. The excess of dimethyl phosphite is removed by evaporation, and a short-pad filtration affords clean products. Elegant variations on the theme allow the rapid assembly of fused and spiro bicyclic ketones.



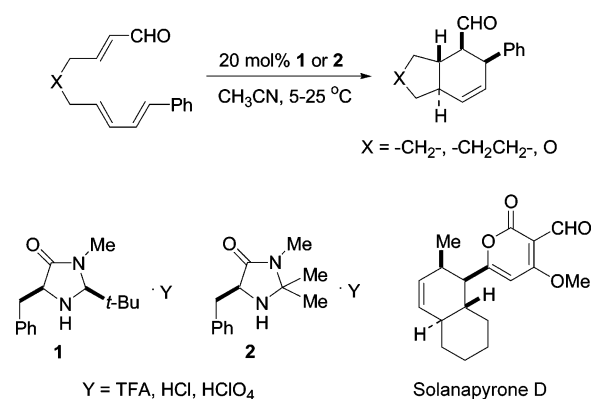
Synthesis of Phenol Derivatives via Ring-Closing Olefin Metathesis

To overcome the inherent limitations of the direct functionalization of phenols, Yoshida and Imamoto prepared functionalized phenols from linear precursors using the Ru-catalyzed ring-closing olefin metathesis reaction (*J. Am. Chem. Soc.* **2005**, *127*, 10470–10471). Two types of ketonic tautomers of phenol were identified and prepared from their corresponding trien-3-one precursors via ring-closing metathesis. Typically, the use of Grubb's second-generation catalyst (7.5 mol %) at room temperature for 2 h afforded highly substituted phenols in excellent yields. The success of this approach relies on its mildness and tolerance to a variety of functional groups such as hydroxy, acetoxy, silyloxy, silyl, chloro, and aryl substituents.



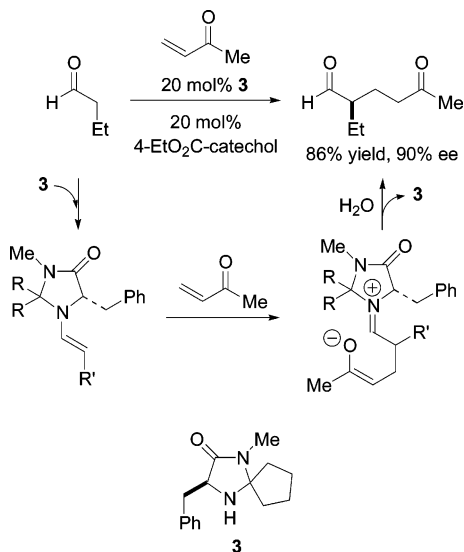
Enantioselective Organocatalytic Reactions

The growth of organocatalytic methods based on the reversible formation of iminium ions evolves relentlessly. MacMillan and co-workers described the first instance of an organocatalytic intramolecular Diels–Alder reaction (*J. Am. Chem. Soc.* **2005**, *127*, 11616–11617). Thus, imidazolidinone catalysts **1** and **2** activate α,β -unsaturated aldehydes toward cycloisomerization to provide [4.3.0] bicyclic aldehyde adducts in good yields (70–85%) and stereoselectivities (typically >20:1 *endo:exo* and 77–97% ee). The reaction conditions are mild and tolerate substrates containing oxygen tethers. Variations of the cycloaddition open an asymmetric entry to decalin [4.4.0] ring systems as well as cycloadducts incorporating a quaternary carbon moiety. The authors demonstrated the power of this methodology in a straightforward synthesis of Solanapyrone D.

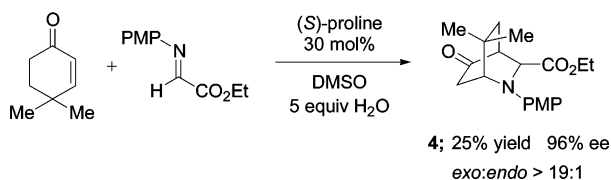
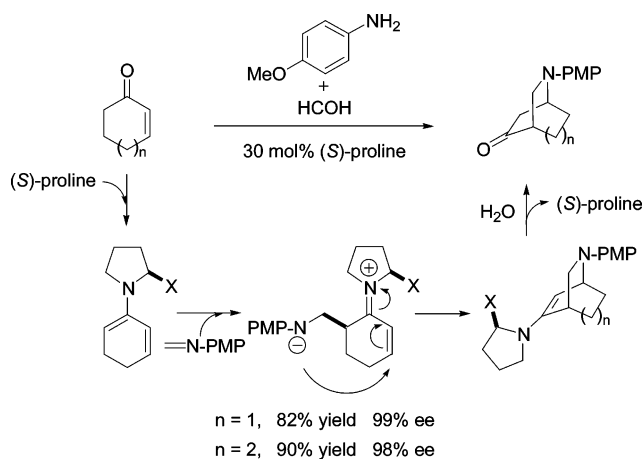


Imidazolidinones were also the catalysts used by researchers in the group of Gellman to mediate enantioselective organocatalytic Michael additions of aldehydes to enones (*J. Am. Chem. Soc.* **2005**, *127*, 11598–11599). The emblematic addition of butyraldehyde to methyl vinyl ketone using 20 mol % of catalyst occurs with good yields and enantioselectivities in the presence of 4-EtO₂C–catechol as cocatalyst. Mechanistic investigations of the addition indicate that the catalyst reacts with the aldehyde to generate a nucleophilic enamine, which in turn attacks the enone that is activated by the catechol hydrogen donor. The zwitterionic intermediate resulting from the addition regenerates the catalyst upon hydrolysis. Inspection of different imidazolidinone structures led to **3** as the most effective species. Screening of different cocatalysts showed that structures with two adjacent hydrogen bond donors (i.e. catechols) are superior to single hydrogen bond donors of similar acidity (i.e. phenols), and that increased acidity correlates with improved yields.

The group of Córdoba at Stockholm University exploited the concept of organocatalysis in the development of enantioselective aza-Diels–Alder reactions (*Angew. Chem., Int. Ed.* **2005**, *44*, 4877–4880). Catalysts derived from (*S*)-proline (X = CO₂H, 30 mol %) promote the one-pot three-component cycloaddition of a cyclic α,β -unsaturated ketone, aqueous formaldehyde, and *p*-anisidine in wet DMSO to furnish the desired aza-Diels–Alder adducts in good yields



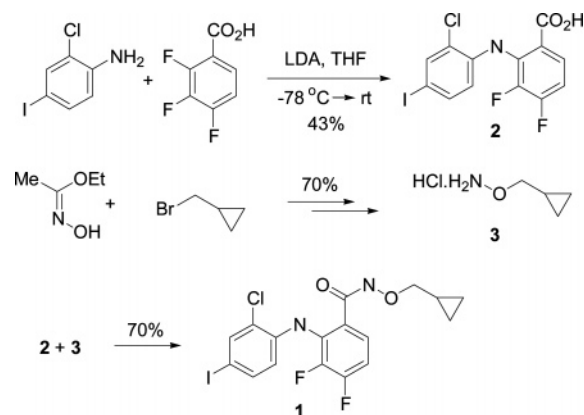
with excellent chemo- and enantioselectivities (up to >99% ee). The stepwise mechanism proposed is based on the detection of Mannich base intermediates. In general, different α,β -unsaturated ketones and amine components react successfully, indicating the broad scope of the process. Furthermore, proline derivatives catalyze aza-Diels–Alder reactions with preformed imines. As an example, the condensation of 4,4-dimethylcyclohexenone and ethyl *N*-PMP- α -imino glyoxylate yields azabicyclic amino acid **4** with excellent diastereo- and enantioselectivity.



Improved Synthesis of MEK Inhibitor PD184352

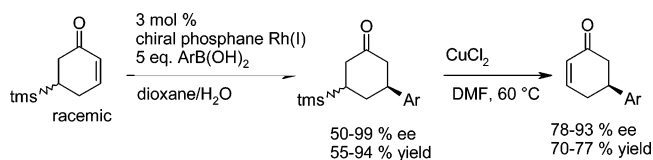
Shapiro and Marquez reported a novel synthesis of PD184352, **1**, a potent MEK/ERK kinase cascade inhibitor that can be used for the treatment of septic shock (*Synth. Commun.* **2005**, 35, 2265–2269). Biarylamine **2** was prepared by substitution of 2,3,4-trifluorobenzoic acid with

4-iodo-2-chloroaniline in the presence of LDA and isolated by crystallization. The cyclopropylmethyl hydroxylamine portion **3** was synthesized from ethyl *N*-hydroxyacetimidate in two steps and 70% overall yield. Coupling of the two subunits was performed using a DCC–HOBt protocol that afforded the desired compound in 70% yield. The synthesis provided multigram quantities of PD184352.



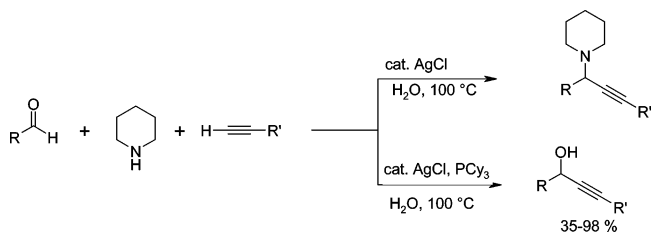
Rhodium (I)-Catalyzed Asymmetric Synthesis of 5-Arylcyclohexenones

Tomioka, K. et al. (*Org. Lett.* **2005**, 7, 4439) have developed a catalytic asymmetric conjugate arylation of racemic 5-(trimethylsilyl)cyclohex-2-one with arylboronic acids catalyzed by 3 mol % chiral amidophosphane- or BINAP-Rh(I) in dioxane–water (10:1) to afford *trans*- and *cis*-3-aryl-5-(trimethylsilyl)cyclohexanones in high enantioselectivity. Dehydrosilylation with cupric chloride in DMF affords 5-arylcyclohex-2-enones with up to 93% ee in good yields.



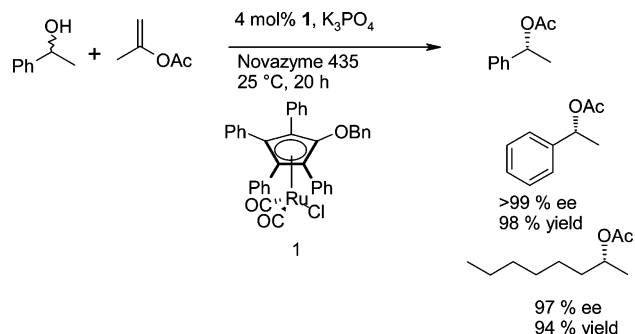
Phosphine-Triggered Complete Chemo-Switch

Li, C.-J. and Yao, X. (*Org. Lett.* **2005**, 7, 4395) have found that a phosphine ligand serves as a remarkable chemo-switch for the silver-catalyzed reaction of alkynes with aldehydes in the presence of amines in water. Exclusive aldehyde–amine–alkyne coupling was observed in the absence of phosphine, whereas in the presence of phosphine, exclusive aldehyde–alkyne coupling was observed.



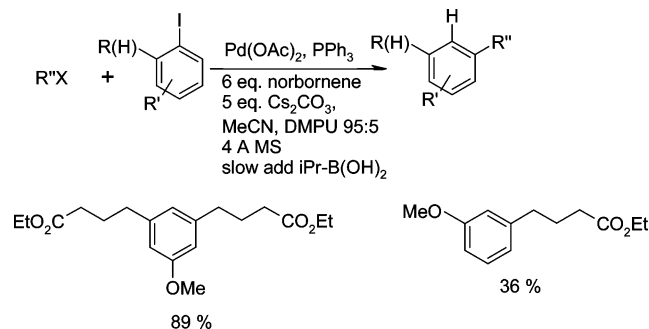
Air-Stable Racemization Catalyst for Dynamic Kinetic Resolution of Secondary Alcohols

Kim, N. et al. (*Org. Lett.* **2005**, *7*, 4523) have developed a novel air-stable reusable racemization catalyst for the dynamic kinetic resolution of secondary alcohols in connection with a lipase at room temperature. Excellent enantioselectivities (up to 99%) and good to excellent yields were obtained.



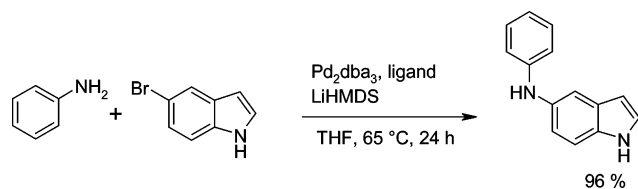
Synthesis of Meta-Substituted Arenes

Lautens, M. et al. (*Org. Lett.* **2005**, *7*, 4053) have developed a new three-component, palladium-catalyzed domino reaction which gives access to meta-substituted arenes using aryl iodides and primary alkyl halides. The reaction tolerates various functional groups both on the aryl iodide and the alkyl halide.



Efficient Pd-Catalyzed Amination of Heteroaryl Halides

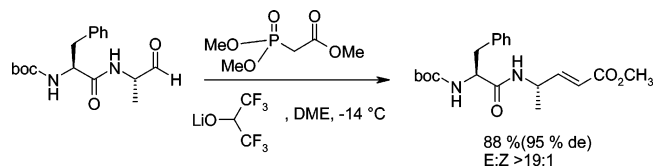
The Pd-catalyzed amination of a variety of heteroaryl halides has been accomplished by utilizing bulky electron-rich biaryl phosphine ligands (Buchwald, S. et al. *Org. Lett.* **2005**, *7*, 3965). The group reports the first couplings of amines with chloro- and bromoindoles bearing a free NH.



Use of Lithium Hexafluoroisopropoxide as a Mild Base for the Horner–Wadsworth–Emmons Olefination of Epimerizable Aldehydes

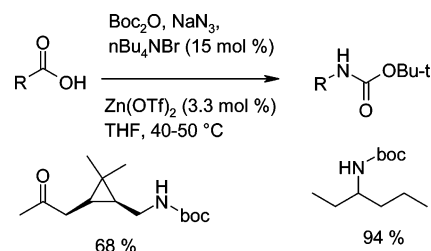
The weak base, lithium hexafluoroisopropoxide (LiHFI), has been found (Blasdel, L. K. and Myers, A. G. *Org. Lett.*

2005, *7*, 4281) to be highly effective as a reagent for intermolecular Horner–Wadsworth–Emmons olefination of epimerizable aldehydes with trimethyl phosphonoacetate, affording products with little or no epimerization and high E-selectivity.



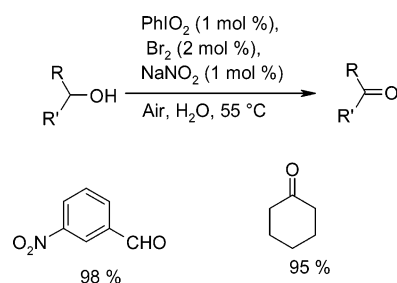
Boc-Protected Amines via a Mild and Efficient One-Pot Curtius Rearrangement

The reaction of carboxylic acids with Boc-anhydride and sodium azide allows for the in situ formation of an acyl azide intermediate, which undergoes a Curtius rearrangement in the presence of tetrabutylammonium bromide and zinc(II) triflate. The trapping of the isocyanate derivative in the reaction mixture leads to the Boc-protected amine in high yields at low temperature (Lebel, H. et al. *Org. Lett.* **2005**, *7*, 4107).



An Efficient Catalytic Aerobic Oxidation of Alcohols in Water

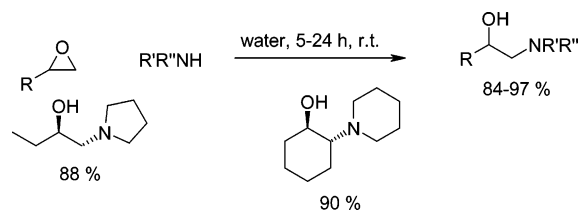
Liu, Z.-L. et al. (*Adv. Synth. Catal.* **2005**, *347*, 1333) have developed a transition metal-free aerobic oxidation of alcohols to the corresponding aldehydes or ketones using iodoxybenzene, bromine, and sodium nitrite as catalysts in water. The corresponding aldehydes and ketones are obtained in excellent yields; only in a few cases with long-chain primary alcohols does the reaction stop before completion, giving a lower yield.



Highly Chemoselective Addition of Amines to Epoxides in Water

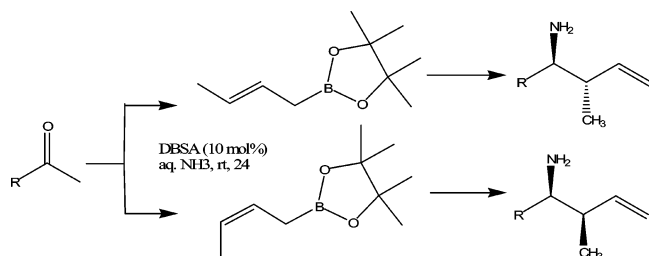
Aminolysis of a variety of epoxides by aliphatic and aromatic amines in water gives the corresponding product as a result of attack at the terminal carbon, giving the corresponding amino alcohols in good to excellent yields

without any catalyst. Only in the case of styrene is a mixture of products observed. Aromatic amines preferably attack at the benzylic position aliphatic amines in contrary attacks preferably at the β -carbon. Saidi, M. R. et al. (*Org. Lett.* **2005**, *7*, 3649).



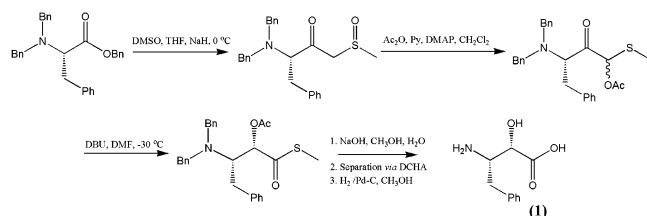
α -Aminoallylation of Aldehydes in Aqueous Ammonia

Although ammonia is a readily available nitrogen source, use of aqueous ammonia has often been avoided due to incompatibility with substrates and reagents. In the presence of surfactants such as dodecylbenzenesulfonic acid (DBSA), (S. Kobayashi et al. *Chem. Commun.* **2005**, 104–106) aldehydes, with allylboronate in 25% aqueous ammonia at room temperature, give good to moderate yields of homoallylamines in regio- and chemoselective manner. Although structural variations in aldehydes play some role in chemoselectivity, the overall yields in most cases were good, and in some cases stereospecificity is remarkably high.



Optically Active β -Amino α -Hydroxy Carboxylic Acids

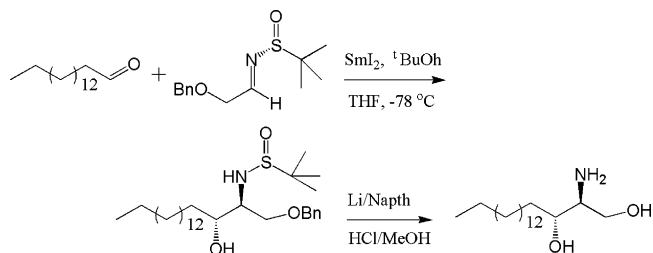
Optically active β -amino α -hydroxy carboxylic acids such as AHPBA (**1**) are important building blocks for variety of biologically active compound. (T. Suzuki et al. *J. Org. Chem.* **2005**, *70*, 7317–7323) devised a practical synthetic route to such compounds from L-phenylalanine. The key step involves highly stereoselective acyl migration of α -acyloxy β -keto-sulfide to an α -acyloxy thioester. This facile rearrangement is dependent on the protecting groups on the amine nitrogen. This procedure is general and suitable for the preparation of a variety of β -amino α -hydroxy acids.



Enantiopure β -Amino Alcohols

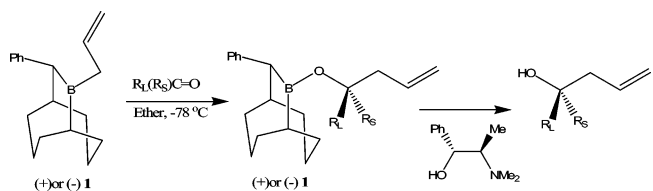
Enantiopure β -amino alcohols are synthesized by asymmetric pinacol-type coupling of chiral *N-tert*-butenesulfinyl

imines with aldehydes. (Yu Zhong et al. *J. Am. Chem. Soc.* **2005**, *127*, 11956–11957). When aliphatic aldehydes are coupled with optically active *N*-sulfinyl imines derived from aliphatic aldehydes in the presence of 2 equiv of SmI_2 , β -amino alcohols are produced in high yields with high enantiomeric purity. Aromatic aldehydes are not suitable for this coupling. ^tButyl alcohol is necessary for obtaining high yields. The stereochemistry of the *N*-sulfinyl group, rather than the electronic effects of substituents of aldehydes with which imines are prepared controls the diastereoselectivity.



Asymmetric Allylboration of Ketones

For asymmetric allylation of aldehydes several procedures and reagents are known, but relatively few methods are available for such allylations with ketones. Soderquist and co-workers (E. Canales et al. *J. Am. Chem. Soc.* **2005**, *127*, 11572–11573) prepared the reagent (**1**) from readily available starting materials and found that it gives high yields of enantiomerically pure tertiary homoallyl alcohols when reacted with a variety of ketones. The stereoselectivities are equal or exceed the selectivities observed with known procedures even when groups on the ketones are similar in size. The reagent is stable in an inert atmosphere, environmentally stable, and recyclable.

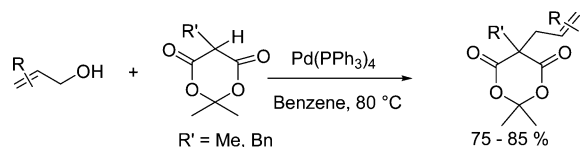


Palladium-Catalyzed Allylation of Meldrum's Acid Using Allyl Alcohol

Meldrum's acid and its derivatives are known to be very useful synthons in the synthesis of a number of interesting entities. The methods of synthesis include direct alkylation, Michael addition of Meldrum's acid to an electrophile, Mitsunobu C-allylation, and Pd-catalyzed coupling with allyl esters and allyl halides. Hou (Chung Hwa College of Medical Technology, Tainan, Taiwan, R.O.C.), Chen (Kaohsiung Medical University, Taiwan, R.O.C.), and others have described [*Heterocycles* **2005**, *65*, 1917] the reaction of substituted allyl alcohol with Meldrum's acid in the presence of tetrakis(triphenylphosphine)palladium(0) in refluxing benzene to afford the 5-allyl-substituted Meldrum's acid in good

yields (Scheme 1). In most of the cases involving allylation using allyl alcohol, presence of a Lewis acid is necessary because of the poor leaving ability of the OH group. However in this paper, the authors were able to accomplish this without employing any Lewis acid catalysis. The method has some drawbacks from the process and ecological point of views. The method uses benzene as the solvent. Also this method does not work with unsubstituted Meldrum's acid to synthesize the mono allylated product—it resulted in diallylated species.

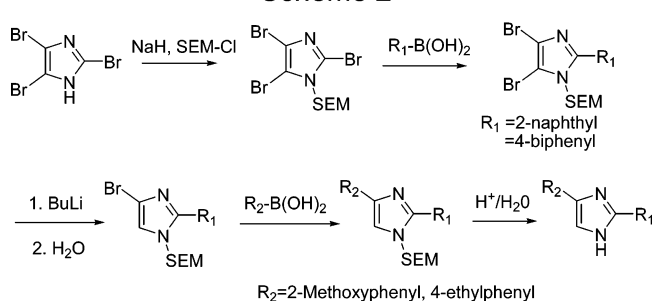
Scheme 1



Synthesis of 2,4-Diarylimidazoles through Suzuki Cross-Coupling Reactions of Imidazole Halides with Arylboronic Acids

Diaryl imidazoles are compounds with interesting pharmacological activity. For example, 2,4-diarylimidazoles showed NPY5 receptor antagonist activity as well as anti-inflammatory activity. The usual synthesis of these compounds involves the condensation of amidines with α -halogenated ketones or by the condensation of α -aminoketones with KSCN. However, these reactions usually are low yielding and not always successful. Langhammer and Erker at the University of Vienna, Austria, have reported [*Heterocycles* **2005**, 65, 1975] the transformation of 2,4,5-tribromo-1-[(trimethylsilyloxy)methyl]-1H-imidazole to diaryl imidazole as illustrated in Scheme 2.

Scheme 2

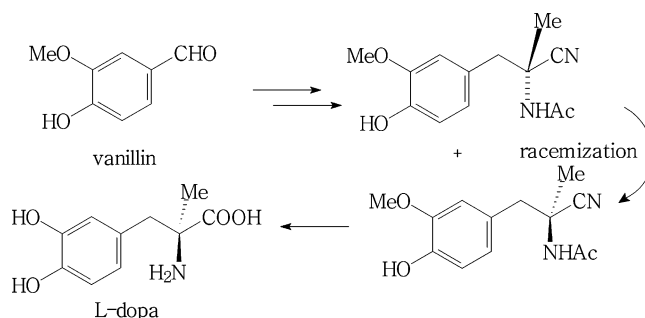


Merck on Blockbuster Chirality

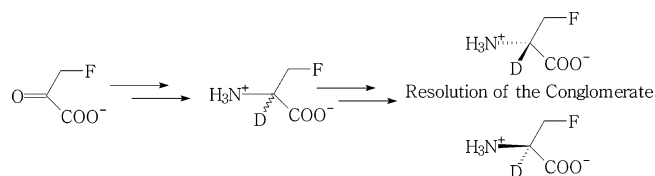
In a recent article Edward J. J. Grabowski (*Chirality* **2005**, 17, S249–S259) from Merck, reviewed Merck's achievements on chiral resolution/synthesis.

At first, the L-methyldopa process was discussed. The key step in the production of this API was the continuous fluidized-bed crystallization resolution–racemization process of the D,L-precursor.

Dominium of this technology allowed Merck to apply it



on the resolution of the benzene sulfonate salt of D,L-3-fluoroalanine-2-d. Optical purities as high as 99.8% were achieved.

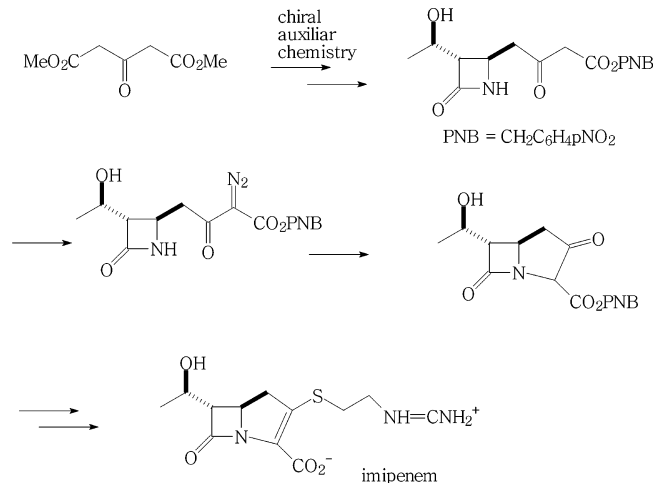


Interestingly, an enzymatic process of production of D-fluoroalanine is also available (Gonçalves et al. *J. Fluorine Chem.* **2003**, 124, 219–227)

Following his account, process development of the drug imipenem was described.

Imipenem is the formimidyl derivative of thienamycin, the world's first carbapenem. To produce this antibiotic the method of choice would be fermentation. However, since the titer of the fermentation was never above 100 mg/L, a synthetic plan was outlined and successfully executed.

The first process involved, after the use of a chiral amine as chiral auxiliary, the production of a β -lactam and, as the key step, a diazo transfer and cyclization.



Following the development of this process a new one based on the condensation of a commercially available diazo intermediate afforded the suitable intermediate for imipenem production.

The use of tetrabutyl hydroxide as base instead of KOH or Na₂CO₃ and heptylammonium bromide was needed for the Suzuki reaction. Tetraheptylammonium bromide proved to be a better solvent in these reactions than tetrabutylammonium bromide, perhaps due to better hydrophobic interactions.

Recycling was proved to be possible although reaction yields dropped from around 90% to around ~70% after the fourth cycle.

This reaction system, making use of Pd nanoclusters stabilized in melted tetraalkylammonium salts, proved also to be useful for the Stille reaction.

Biocatalytic Reduction

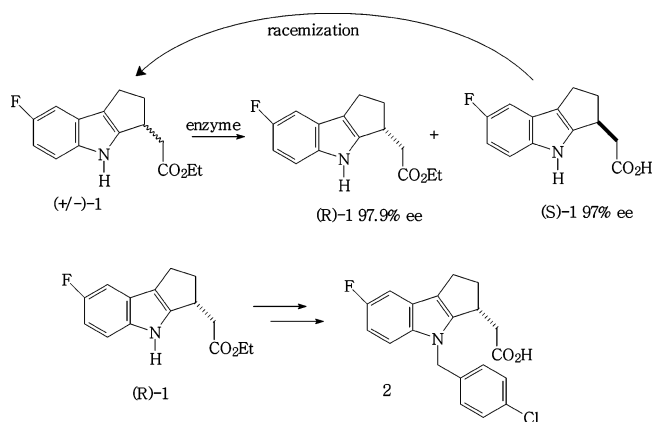
Kamble, Soni, and Banerjee (*J. Mol. Catal. B: Enzym.* **2005**, *35*, 1), from the National Institute of Pharmaceutical Education (India), reported their results on the microbial reduction of acetophenone to *S*-(-)-1-(1-naphthyl)ethanol. This compound is claimed to be an important synthetic intermediate to mevinic acid analogues.

The authors used a new yeast strain, *Candida viswanathii* MTCC 5158. Acetophenone was proved to be the best inducer at 2 mM. Maximum enzyme activity was found after 36 h of growth. A broad pH range of enzyme activity was found for this enzyme, exhibiting a maximum at pH 10. Glucose was the best carbon source for microorganism growth, while mannitol led to maximum enzymatic activity. Calcium addition (2 mM) to the reaction media also increased the carbonyl reductase production.

The best compromise between conversion (83%) and enantiomeric excess, ee, (99%) was found after 18 h. The best conversion was achieved at pH 7–8 and did not influence the ee which was kept at over 99%.

Merck on Lipase Resolution

Shafiee et al. (*Tetrahedron: Asymmetry* **2005**, *16*, 3094), from Merck, reported an efficient, large-scale, enzyme-catalyzed kinetic resolution. In this work an enantiomerically pure indole-ethyl ester, (*R*)-1, derivative was obtained.



(*R*)-1 is the key intermediate for the production of **2**, a claimed prostaglandin D₂ receptor antagonist, an anti-allergic rhinitis drug candidate.

Enzymatic resolution proved to be feasible using the lipase from *Pseudomonas fluorescens*.

After several buffer, solvent, and/or detergent combinations, it was found that an aqueous 0.5 M phosphate buffer/DMF/hexane (36:4:10) triphasic solvent system was the best compromise in running this reaction.

Batches of over 1 kg were carried out using this process.

Of industrial importance is the fact that (*S*)-1 is racemized during esterification in EtOH, in the presence of a catalytic (substoichiometric) amount of H₂SO₄.

Fragrances via Lipase Resolution

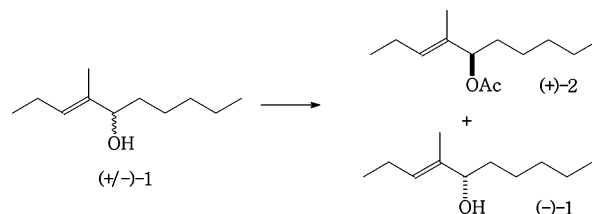
Undecavertol, (\pm)-1, is described as having a powerful green-floral character, related to lily of-the-valley aroma. The commercial product is a 98.5:1.5 mixture of trans/cis isomers.

Abate, Brenna and Fregosi (*Tetrahedron: Asymmetry* **2005**, *16*, 1997) described the use of lipases to produce both enantiomers of this alcohol which were subjected to odor evaluation.

(\pm)-1, as a trans/cis 97.3:2.6 mixture, was subjected to acetylation by using lipases from different sources.

Lipase PS, *Burkholderia cepacia* (Amano), -mediated acetylation (six days) of (\pm)-1 gave the acetate (+)-2 as 93.5:2.5 (trans/cis mixture). The enantiomeric excess of the corresponding (+)-1 alcohol was determined as 93% via lanthanide chiral shift reagents.

The unreacted (-)-1 alcohol was treated with the same enzyme, in the same conditions for an additional 10 days to obtain an enantioenriched sample of this compound (75% ee).



Absolute stereochemistry of (-)-1 was proved to be *S* by chemical means.

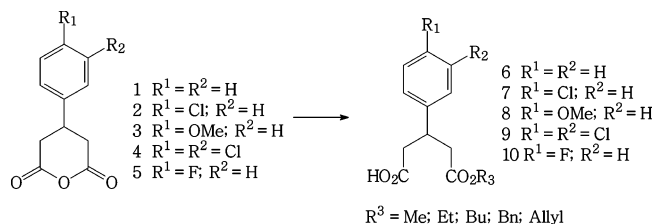
These samples were submitted to odor evaluation, and it was proved that (*R*)-(+)-1 has a typical Undecavertol odors, floral, green, fresh, violet leaves, stronger and greener than the racemic commercial material. Since the corresponding (*S*)-(-)-1 enantiomer does not contribute to Undecavertol odor, pure (*R*)-(+)-1 isomer can be used at least in half dosage in perfumery.

As stated in this article, it is important to point out that following the proposed 7th Amendment of European Cosmetic Directive (effective on March 11, 2005) the identity of compounds in products intended to remain on the skin should be labeled. Therefore, it is expected that products commonly used in perfumery have to be tested in pure chiral form to evaluate their potential allergic skin reactions.

Enzymatic Desymmetrization

Meso substrates are attractive starting materials for fine chemicals as APIs since they can be **desymmetrized**; that is, upon a chemical transformation (e.g., hydrolysis or ethanolysis), they can be converted to a enantioenriched or enantiopure compound.

Fryszkowske et al. (*Tetrahedron: Asymmetry* **2005**, *16*, 2475) reported the lipase-mediated desymmetrization of 3-arylgutamic anhydrides.



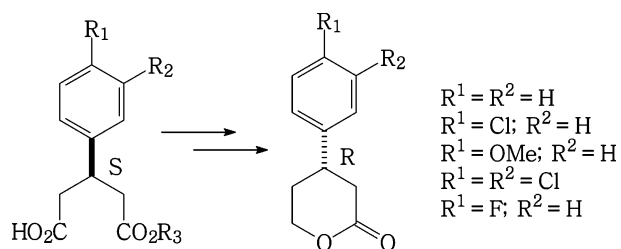
Preliminary enzymatic screening using **1** and EtOH (in *iso*-propyl ether) as substrates showed that only immobilized lipases (e.g., Amano PS-C and Novozyme 435, CALB) showed activity on desymmetrization.

Using Novozyme 435, CALB, as catalyst, it was found that, among a series of solvents tested, *iso*-propyl ether and TBME afforded better ees in reasonable reaction times.

Testing substrates **1–4** with a series of enzymes showed that *Candida cepacia* type B lipases, Novozyme 435, CALB, and Chirazyme L-2, c.f., C3, Iyo. CALB have superior performance in ethanolysis, thus yielding **6 to 9** ($R^3 = Et$) in ees ranging between 60 and 83%. Ethanolysis of **1** occurred in 61 h with Novozyme 435, CALB, and in **19** with Chirazyme L-2, c.-f., **C3**, Iyo. CALB, while ethanolysis of **2 to 4** required 4–13 days.

Pseudomonas sp. lipases led to (*R*)-**6** from **1** but, surprisingly, to the *S* enantiomers for the other substrates (**2–4 to 7–9**).

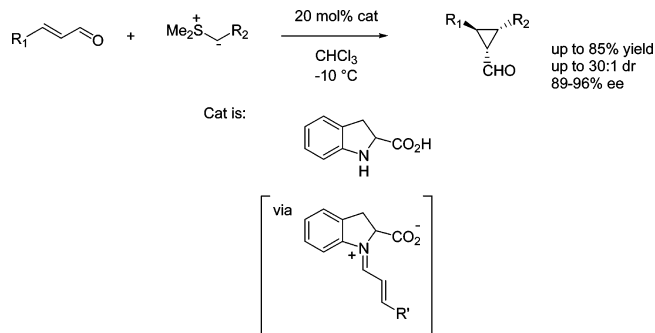
Different alcohols were tested in this desymmetrization using Novozyme 435, CALB. In general very good chemical yields were obtained. Reaction products were converted to the respective lactones, and ee's were measured. In general, methanol afforded the best ees.



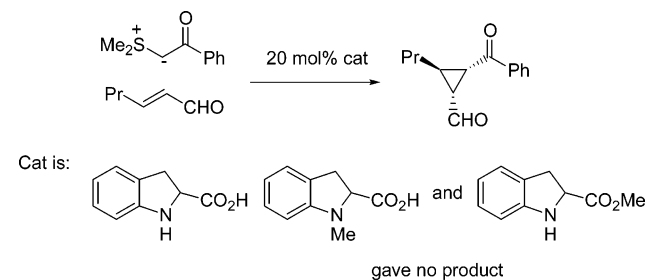
Enantioselective Organocatalytic Cyclopropanation

Cyclopropane ring formation continues to fascinate organic chemists (for a review, see Lebel, H. et al. *Chem. Rev.* **2003**, *103*, 977). The group of MacMillan at CalTech has recently reported (Kunz, R. K. et al. *J. Am. Chem. Soc.* **2005**, *127*, 3240) that a new class of iminium salt gives good yields and excellent enantioselectivities in cyclopropane formation using sulphur ylides.

Electrostatic interaction between the iminium ion and the ylide is suggested to account for the high selectivity.



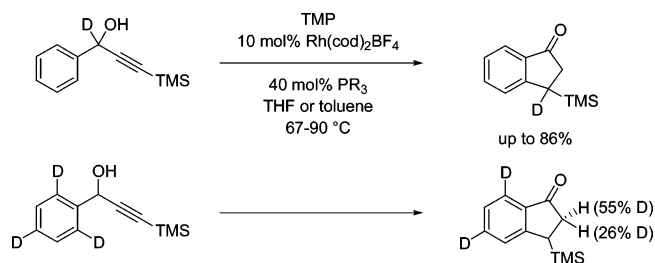
Solvent effects are quite pronounced. In one series of experiments, conversion and ee varied widely when the solvent was changed. When the catalyst cannot form a zwitterion, no product is obtained.



Solvent	%	ee
DMF	20	-30
Acetone	16	28
THF	25	77
CHCl ₃	85	95

Rhodium-Catalyzed Cyclization of Arylprop-2-yn-1-ols

Construction of a cyclopentanone ring onto aromatic compounds can be a problem if the appropriate arylpropionic acid is unavailable. A new method involves treating acetylenic alcohol derivatives with a rhodium catalyst in the presence of base, when excellent yields of cyclized products are obtained (Yamabe, H. et al. *J. Am. Chem. Soc.* **2005**, *127*, 3248).

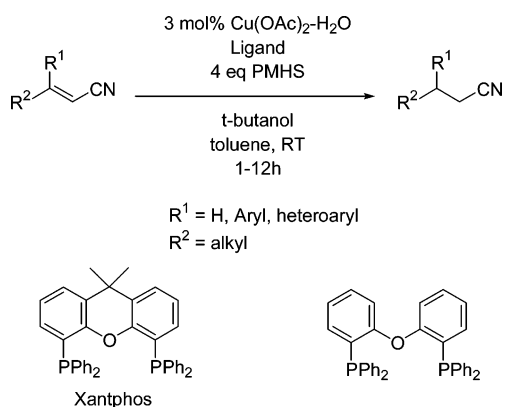


The deuterium-labeling study provides the reader with an intriguing mechanistic problem to solve. Have fun!

Conjugate Reduction of α,β -Unsaturated Nitriles

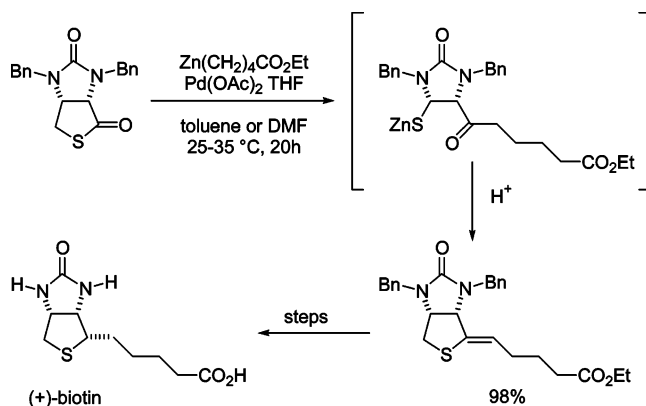
Selective reduction of α,β -unsaturated nitriles can be problematic and low-yielding, especially if there are two

β -substituted. It has now been reported that chemoselective reduction using polymethyl hydrosiloxanes (PMHS) in the presence of *tert*-butyl alcohol can be carried out if copper-DPEphos or Xantphos is the catalyst. The latter catalyst usually gives the best yields (84–94%) (Kim, D. et al. *Chem. Commun.* **2005**, 1755).



Phosphine-Free Fukuyama Coupling for Biotin Synthesis

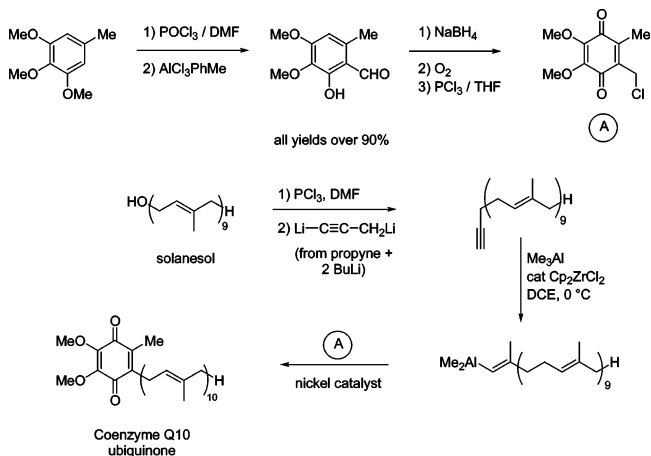
A group at Tanabe Seiyaku in Japan has found a very efficient way to complete the synthesis of biotin. Coupling of ethyl iodopentanoate with a thiolactone proceeds with zinc dust and zinc bromide in the presence of very low levels of palladium acetate (up to 0.01%) but in the absence of any phosphine ligands. (Mori, Y. et al. *SynLett* **2005**, 2233). This should permit an alternative practical synthesis of (+)-biotin.



Coenzyme Q₁₀ Synthesis

Coenzyme Q₁₀, also known as ubiquinone or CoQ₁₀ is a vital human nutrient, responsible for shuttling electrons through the respiratory chain. It is an antioxidant, quenching free radicals, and assists in fighting aging. The demand for CoQ₁₀ as a dietary supplement already exceeds supply, and there is a need to find an efficient synthesis. The group of Lipshutz at Santa Barbara, in conjunction with BASF, have recently published some results which have scale-up possibilities (Lipshutz, B. H. et al. *Org. Lett.* **2005**, 7, 4095). One part of the molecule derives from trimethoxytoluene,

the other half, from solanesol, a waste product from the tobacco industry. The route is shown below.



New Heterogeneous Catalysts for Hydrogenation

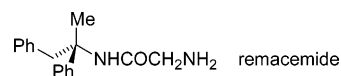
New DeLink catalysts, which are palladium on carbon powder support and are available as 3, 5, or 10% loading, are superior to conventional Pd/C catalysts. They are much more active and have better filtration properties, allowing shorter reaction and work-up times and improved space-time-yields. In certain cases, such as debenzoylation in the presence of aromatic halogen, selectivity is improved (Chen, J. J. et al. *Catalysis of Organic Reactions*; CRC Press: Boca Raton, 2005; pp 111–122).

Crystal Structures of Drug Salt Forms

Remacemide was developed as a potential agonist for epilepsy, Parkinson's disease, and Huntington's disease. A number of salt forms of the drug were investigated during the preformulation programme, partly for solubility reasons, but also because the HCl salt was unpleasant tasting. The crystal structure of the free base and several salt forms have now been determined (Lewis, G. R. et al. *Cryst. Growth Des.* **2005**, 5, 427) as the racemates. Whereas the free base, hydrochloride, nitrate, acetate, hydrogenfumarate, and xinafoate (1-hydroxynaphthalene-2-carboxylate) are all anhydrous, the napsilate (naphthalene-2-sulphonate) salt incorporates 0.5 mol of water and also, more unusually, 0.4 mol of ethanol in the crystal lattice.

All the crystalline salts were racemates with four molecules in the unit cell, except the napsilate salt, which was a conglomerate—the crystal solved was the S enantiomer, with only two molecules in the unit cell.

The study was undertaken to examine the conformation of the active molecule in the crystal and to see how this changed with salt form. It is concluded that hydrogen-bonding interactions dominate the crystal packing, with few hydrophobic interactions between the aromatic rings.



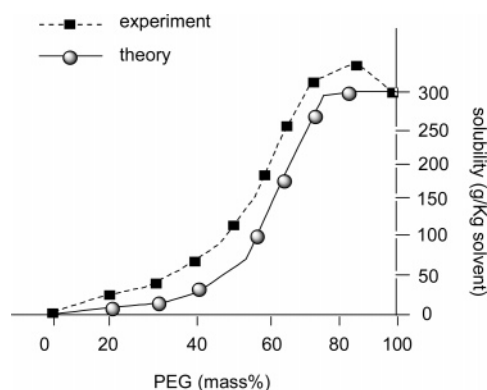
Low Molecular Weight Poly(ethylene glycol) as an Environmentally Benign Solvent for Pharmaceutical Crystallization and Precipitation

Low molecular weight (200–500) poly(ethylene glycol), PEG, is nonvolatile and nontoxic, being certified as safe for ingestion. It is used in various food products, medicines, and cosmetics. It is completely miscible with water, and aqueous mixtures can vary in hydrophobicity, making it a “tunable” solvent for dissolving organic compounds.

A new report (Wang, X. et al. *Cryst. Growth Des.* **2005**, *5*, 85) examines the potential for its use in antisolvent crystallization of drugs, by dissolving the drug in PEG and adding water, and compares the results with those in methanol and 2-propanol. In the absence of seeds, induction time for crystallization was longer in PEG–water, but crystal growth rates were slightly lower, and it was shown that this was not due to transport limitations in the higher viscosity PEG system. Crystal habit and structure were identical in PEG and in methanol systems.

No measurement of residual solvent was made, and this may be a potential issue for such a high-boiling solvent for use in pharmaceutical products.

A comparison of the actual solubility of the drugs in the aqueous organic system with that predicted by the computer programme UNIFAC was provided in the paper. For salicylic acid the UNIFAC programme is reasonably consistent with practice but fails to predict the maximum solubility of the drug in an 85:15 mixture of PEG–water salicylic acid solubility curves.



Occurrence of Pharmaceutically Acceptable Anions and Cations in the Cambridge Structural Database

An estimated one-half of all drug molecules used in medicine are administered as salts (cf. Stahl, P. H.). A team from Pfizer and the Cambridge Crystallographic Data Center (Haynes, D. A. et al. *J. Pharm. Sci.* **2005**, *94*(10), 2111) answers a few interesting questions regarding pharmaceutically acceptable salts: (a) how many unique structures containing pharmaceutically acceptable anions (69 acids) and cations (21 bases) occur in the Cambridge Structural Database (CSD)? (b) How many, and what proportion of those structures can exist as hydrates? (c) How many, and what proportion of those structures can form polymorphs;

how many polymorphs? (d) How many, and what proportion of those structures can form cocrystals? Not surprisingly, chloride salts were found to be the most numerous of all salts in both groups. Twenty of the 69 anions investigated accounted for 94% of the anionic search hits. Only five of the 21 cations investigated make up almost 80% of the cationic search hits (the ammonium cation tops this list). Pharmaceutically acceptable salts were found to be more prone to form hydrates than was seen in the CSD. Relatively smaller ions, such as acetate, oxalate, and phosphate show a higher tendency to form polymorphs. Interestingly, polymorph incidence was correlated with the ratio [number of O atoms:total number of non-H atoms]: the higher this ratio, the more polymorphs were observed. The number of cocrystals formed by the anions and cations investigated was counted. An interesting correlation between the pK_a of the acid and the number of cocrystals formed was discovered: the higher the pK_a , the more cocrystals counted. Future work includes analysis of the contribution of functional groups present in the drug substance on hydrate and polymorph formation.

Surface Feed with Minimum Byproduct Formation for Competitive Reactions

The typical recommendation of subsurface feed for the scale-up of fast competitive reaction systems requires solving mechanical, metallurgical, and/or operational challenges (such as vibrations, plugging, back-mixing, etc). A group from Prof. Kresta's laboratory (Bhattacharya, S. et al. *Trans. Ind. Chem. Eng., Part A, (Chem. Eng. Res. Des.)* **2005**, *82*(A9), 1153) demonstrates that the use of an up-pumping, pitched-blade turbine (PBTU), located in the upper third of a reactor, can give selectivity results comparable to those obtained with subsurface feed and a down-pumping pitched-blade turbine (PBTD). The test reactive system used was the Third Bourne “reaction” wherein the impact of mixing is assessed on two fast competitive reactions: the neutralization of HCl with NaOH, and the NaOH hydrolysis of ethylchloroacetate. The amount of ethanol formed is an indication of mixing efficiency, with relatively lower yields of ethanol produced under relatively better mixing conditions.

When surface feed was used, the yield of ethanol byproduct formation was decreased from 0.25 (down-pumping pitched blade) to 0.13 (up-pumping pitched blade). Interestingly, in the micromixing control region, the byproduct yield is unchanged whether a PBTU is used alone or in conjunction with a PBTD. Nevertheless, the authors do indicate that, for difficult processes, the use of a second impeller, down-pumping and located towards the bottom of the reactor, may improve processing results and add operational flexibility. A high agitation speed limit was identified, above which gas bubbles are entrained and trapped in the tank. Further work is planned to better characterize this agitation limit and its corresponding critical Froude number.

Interaction between Mixing, Chemical Reactions and Precipitation

The Third Bourne reactive system was also used to verify a micromixing model describing mixing effects on chemical selectivity. The fast precipitation of barium sulfate, resulting from the reaction of aqueous solutions of sodium sulfate and barium chloride, was used to test the predictions of computational fluid dynamics (CFD) and conditional moment closure calculations. Prof. Baldyga's group (Baldyga, J. et al. *Ind. Eng. Chem. Res.* **2005**, *44*, 5342) analyzed mixing effects on fast, competitive reactions and precipitations using a multiple-time-scale turbulent mixer model. Good agreement was observed between experiment and micromixing-based mixing models for the Bourne III reactive system. For the case of average particle size prediction for barium sulfate precipitation, better predictions are obtained at higher concentrations. A possible explanation for the less well predicted average particle size of BaSO₄ at lower concentrations may be an insufficient knowledge of nucleation kinetics. Better understanding of the kinetics and thermodynamics of the precipitation process is expected to improve predictions more than a refinement of the mixing model could accomplish.

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