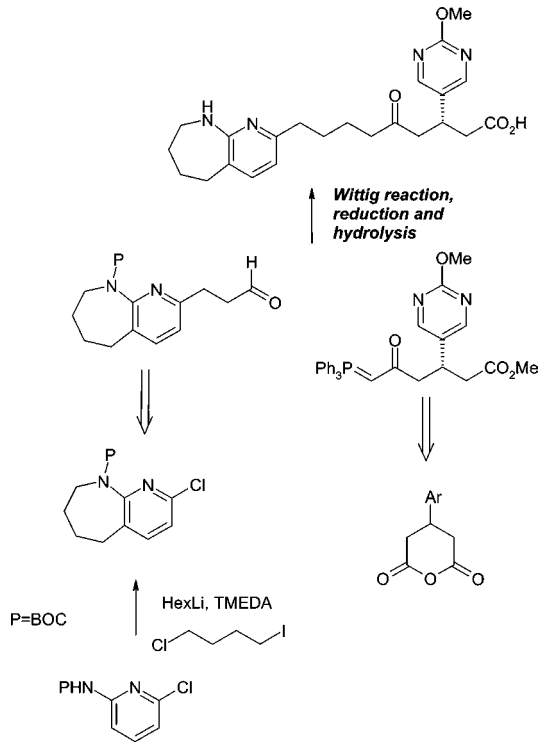
Organic Process Research & Development **2005**, *9*, 228–234

Highlights from the Literature

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

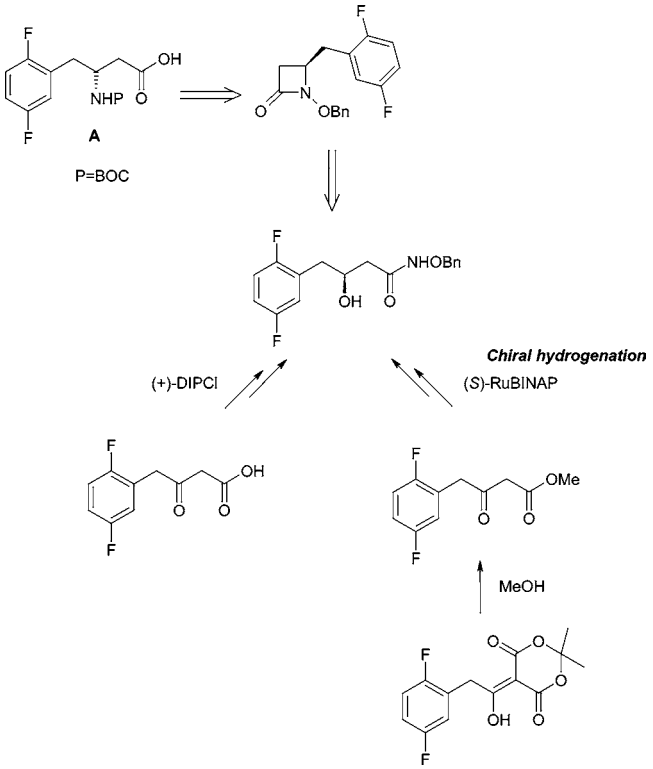
Nonpeptidic $\alpha_v\beta_3$ Antagonist Synthesis

Keen, Cowden, and colleagues from Merck report (*J. Org. Chem.* **2005**, *70*, 1771) how the synthesis of a nonpeptidic $\alpha_v\beta_3$ antagonist was developed and performed on multikilogram scale. The retrosynthetic analysis is shown in the following scheme whereby two key fragments were prepared and coupled in a convergent late-stage Wittig olefination reaction. Manipulation to the desired product involved reduction of the product enone from the Wittig coupling followed by hydrolysis of the ester. The pyridoazepine fragment was prepared from *N*-Boc 6-chloro-2-aminopyridine via directed ortho-metalation/alkylation followed by in situ cyclization. A Suzuki reaction was then used to attach the propionaldehyde side chain. The chiral β-keto phosphorane was prepared from asymmetric methanolysis of a 3-substituted glutaric anhydride using quinidine followed by functional group manipulation. The drug substance was prepared in 17% yield (longest linear sequence) and multikilogram methods are described in the paper.

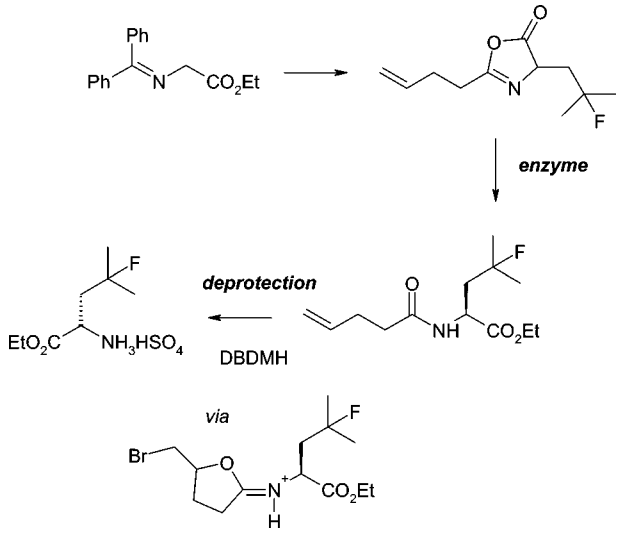


Chiral β-Amino Acid Synthesis

In a further "process paper" from the Merck group (*J. Org. Chem.* **2005**, *70*, 1949) a stereoselective synthesis of an (*R*)-β-amino acid **A** is described. The preparation involves methanolysis of a key β-lactam (followed by hydrogenation and saponification). In turn the chirality of the β-lactam was installed via enantioselective reduction of the β-ketoacid (scheme) using diisopinocampheyl chloroborane or more efficiently via chiral hydrogenation of the methyl ester using Noyori conditions.



(*S*)-γ-Fluoroleucine Ethyl Ester



Continuing the amino acid (and Merck!) theme, an asymmetric synthesis of (*S*)-γ-fluoroleucine ethyl ester has been reported by their process group (*J. Org. Chem.* **2005**,

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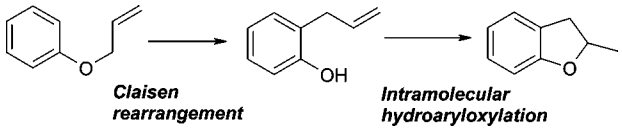
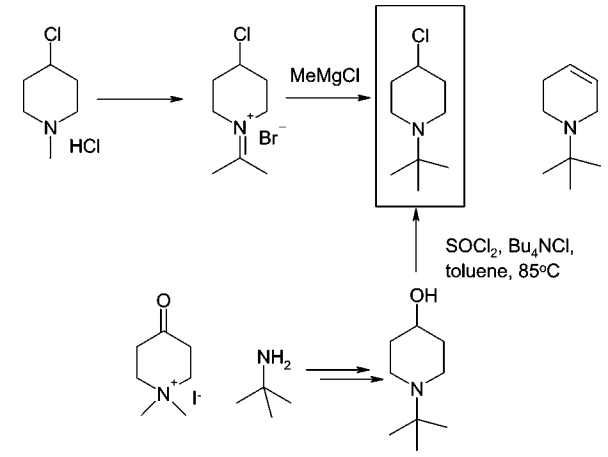
70, 2372). The key transformation involves an immobilized lipase-catalyzed (Novozyme-435) dynamic ring-opening of 2-(3-butenyl)azlactone with EtOH to give an amide ester in 84% enantiomeric excess. Removal of the *N*-pentenoyl group with commercially available and inexpensive *N*,*N*′-dibromodimethylhydantoin (DBDMH) in the presence of trifluoroacetic acid gives the target product which could be crystallized from solution as its hydrogen sulfate salt in 75% yield and >97% ee. The paper is a great read and again outlines the power of enzymatic transformations in synthetic organic chemistry.

Tandem Claisen Rearrangement/Intramolecular Hydroaryloxylation



Grant and Liu from GSK describe their synthetic efforts (*Tetrahedron Lett.* **2005**, *46*, 1237) towards the preparation of dihydrobenzofurans through iridium(III)-catalyzed tandem Claisen rearrangement and intramolecular hydroaryloxylation of ally aryl ethers. In their communication the range of conditions (additives, catalysts) used to screen the reaction are described along with a variety of substrates that were subjected to the protocol.

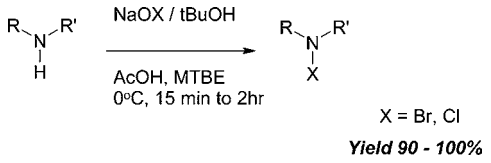
Addition of Methylmagnesium Chloride to a Dimethyliminium Salt



With a need to synthesize multikilogram quantities of 1-*tert*-butyl-4-chloropiperidine, McLaughlin and co-workers from Merck (*J. Org. Chem.* **2005**, *70*, 1930) describe two methods to access the material in a recent note. In the first approach, the key thionyl chloride reaction makes use of tetrabutylammonium chloride as an additive to suppress the formation of an elimination-derived side product (see scheme). In the group's second approach the tertiary *N*-butyl group is built through addition of methylmagnesium chloride to a dimethyliminium salt in 71% overall yield.

N-Halo Compounds

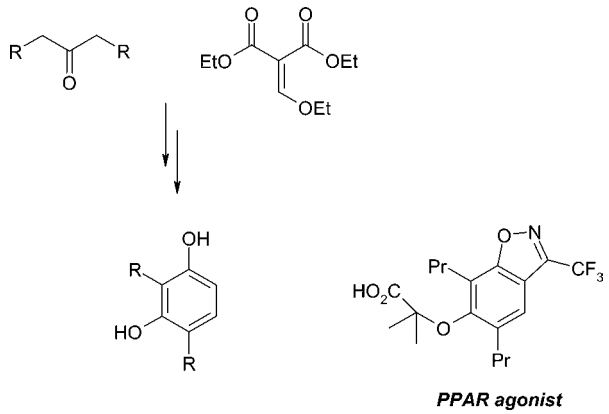
A simple procedure to prepare *N*-halo compounds has been reported by Zhong and colleagues from Merck



(*Tetrahedron Lett.* **2005**, *46*, 1099). Reaction of primary and secondary amines or amides with sodium hypohalite in the presence of *tert*-butyl alcohol and acetic acid (safely generating *tert*-butyl hypohalite in situ) affords the *N*-halo derivatives in excellent yields.

Regioselective 2,4-Dialkyl Resorcinol Synthesis

The regioselective synthesis of 2,4-dialkyl resorcinols has been described by Ceglia and colleagues from Merck (*Tetrahedron Lett.* **2005**, *46*, 1731) and finds applicability towards the synthesis of PPAR agonists. Their preparation begins from EMME (2-ethoxymethylenemalonate ethyl ester) and a range of dialkyl ketones (see scheme). The publication covers the intricacies of the reaction and describes conditions whereby efficient conversions can be achieved.

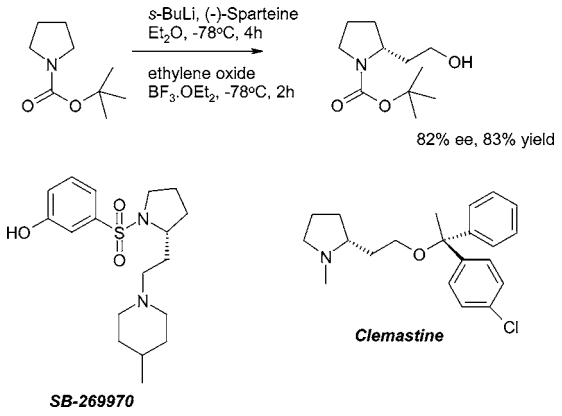


(*R*)-*N*-Boc-2-(2-hydroxyethyl)pyrrolidine

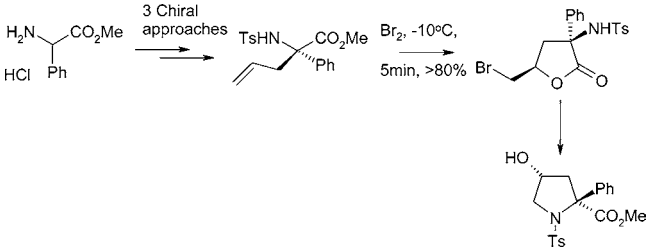
Asymmetric lithiation using (−)-sparteine is a commanding technology to install new chiral centres and generate compounds of value which would otherwise be hard to prepare. Deng and Mani from Johnson and Johnson Pharmaceutical Research and Development report a practical synthesis of (*R*)-*N*-Boc-2-(2-hydroxyethyl)pyrrolidine with good chiral purity (*Tetrahedron Asymmetry* **2005**, 661). In their method the homochiral carbanion obtained from sparteine-mediated asymmetric lithiation of *N*-Boc-pyrrolidine is trapped with ethylene oxide/BF_3·Et_2O. This chiral molecule finds application in syntheses en route to a variety of bioactive molecules (see scheme).

4-Hydroxy-2-phenylproline Framework

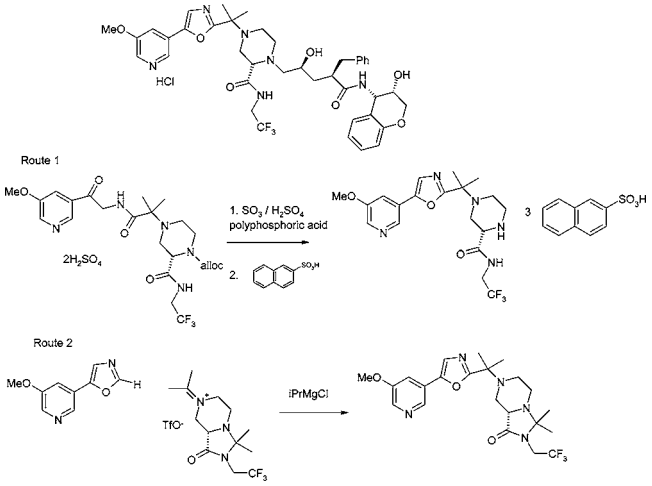
In a recent publication from the Banyu pharmaceutical company and Merck (*Tetrahedron Lett.* **2005**, *46*, 1545) the diastereoselective (>20:1) bromolactonization of *N*-sulfonyl-2-allyl-2-phenylglycine methyl ester is described (see scheme). Subsequent conversion of the chiral lactone to the (2*S*,4*R*)-4-hydroxy-2-phenylproline derivative in high yield was achieved without loss of diastereoselectivity using sodium



methoxide in methanol. This route provides an expedient approach to this complex chiral building block.



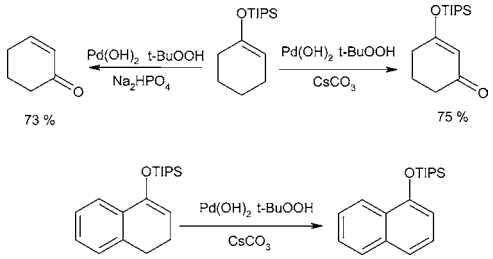
Second-Generation HIV Protease Inhibitors



The synthesis of a "second-generation" HIV protease inhibitor (see scheme) has been disclosed by workers at Merck (*Tetrahedron Lett.* **2005**, *46*, 1867) in their quest to identify new and better molecules to treat patients. In particular the group have examined two approaches for construction of the oxazole ring moiety, route one via formation and dehydration of a ketoamide and then route two via an oxazolyl anion/iminium coupling reaction.

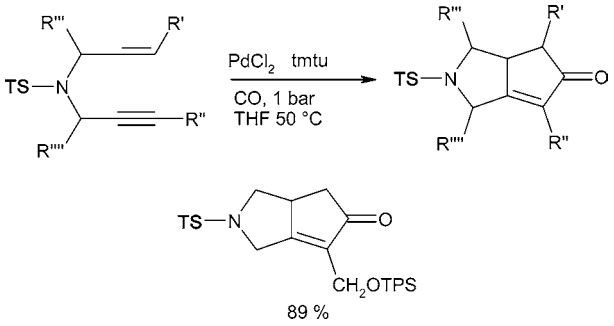
$Pd(OH)_2$-/C-Mediated Selective Oxidation of Silyl Enol Ethers by *tert*-Butylhydroperoxide

E. J. Corey et al. (*Org. Lett.* **2005**, *7*, 1415) have reported a useful method for the conversion of ketones to α,β-enones or β-silyloxy-α,β-enones dependent on which base is used. If disodiumphosphate is used α,β-enones are obtained; on the other hand, if cesium carbonate is used, the product is a β-silyloxy-α,β-enone. Yields are good with all of tested substrates. The present methodology can also be applied to aromatization of dihydroaromatic substrates.



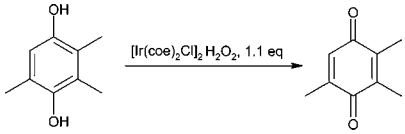
Thioureas as Ligands in the Pd-Catalyzed Intramolecular Pauson−Khand Reaction

Tang, Y. et al. (*Org Lett.* **2005**, *7*, 1657) have found that a thiourea−Pd complex can be a useful catalyst for the Pd-catalyzed Pauson−Khand reaction. Various ratios between Pd(II) and different thioureas were investigated on different allylpropargylamines. The best results were obtained with tetramethylthiourea and $PdCl_2$ in a 1:1 complex. Yields obtained were low-to-good, depending on the substrate.



A Rapid and Efficient Synthesis of Quinones

Iwasa, S. et al. (*Adv. Synth. Catal.* **2005**, *347*, 517) have found that hydroquinone and methoxybenzenes are catalytically oxidized easily to the corresponding quinones using a Ru(II)- or Ir(I)-catalyst and hydrogen peroxide as the primary oxidant in high-to-excellent yields with low catalyst loading (0.01−1 mol %).



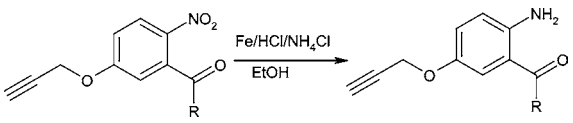
Transition Metal-Catalyzed Asymmetric Hydroamination of Alkenes

K. C. Hultzch (*Adv. Synth. Catal.* **2005**, *347*, 367) has reviewed hydroaminations promoted by chiral catalysts, in which a new chiral center is generated or chiral substrates are kinetically resolved.

A Practical and Chemoselective Reduction of Nitroarenes to Anilines Using Activated Iron

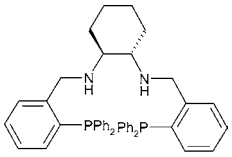
The group around O. Repic (*Adv. Synth. Catal.* **2005**, *347*, 217) has found that the reduction of nitroarenes to anilines

using activated iron generated from Fe/HCl or Zn/$FeSO_4$ is a practical and chemoselective method. A variety of functional groups such as alkyne, ketone, enone, nitrile, lactone, and aromatic halide are well tolerated under these conditions.



Highly Efficient Iridium Catalyst for Asymmetric Transfer Hydrogenation of Aromatic Ketones under Base-Free Conditions

Catalytic systems generated in situ from chiral PNNP ligands with iridium or rhodium hydride complexes exhibit excellent catalytic activity and good enantioselectivity in asymmetric transfer hydrogenation of aromatic ketones without added base (Dong, Z.-R. et al. *Org. Lett.* **2005**, *7*, 1043). $IrH(CO)(PPh_3)_3$−**1** was found to be the best system with up to 99% yield and 97% ee. The yield is in all cases excellent, but the ee varies (70−97%).



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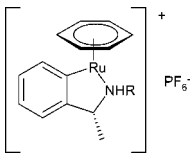
Cycloruthenated Primary and Secondary Amines as Efficient Catalyst Precursors for Asymmetric Transfer Hydrogenation

Ruthenacycles obtained by cyclometalation of enantiopure aromatic primary or secondary amines with $[(\eta^6\text{-benzene})RuCl_2]_2$ or with $[(\eta^6\text{-cymene})RuCl_2]_2$ are efficient catalysts for asymmetric transfer hydrogenation with potassium *tert*-butoxide as base (Sortais, J.-B. *Org. Lett.* **2005**, *7*, 1247). Enantioselectivities in the transfer hydrogenation of acetophenone ranged from 38 to 89%. It is possible to prepare the catalysts in situ, which simplifies the use on large scale.



Palladium-Catalyzed C−N and C−O Coupling: A Practical Guide from an Industrial Vantage Point

Scholz, U. and Schlummer, B. (*Adv. Synth. Catal.* **2004**, *346*, 1599) have reviewed the palladium-catalyzed C−N and C−O coupling reactions from an industrial standpoint. This review focus on the practical problems arising during implementing the methodology in an industrial environment and gives also practical hints to this end.

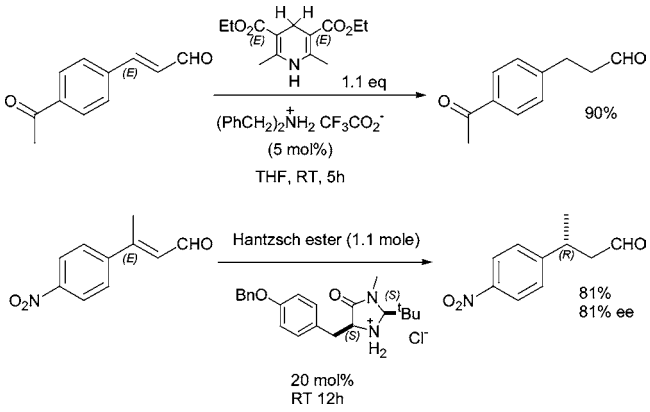
Industrial R&D on Catalytic C−C and C−N Coupling Reactions

The group at Solvias AG (Blaser, H.-U. et al. *Adv. Synth. Catal.* **2004**, *346*, 1583) has reviewed R&D issues for the application of Pd- and Ni-catalyzed C−C and C−N coupling reactions in the fine chemicals industry.

Metal-Free Transfer Hydrogenation

Organocatalytic conjugate reduction of α,β-unsaturated aldehydes can be achieved by treating the aldehyde with a Hantzsch ester in the presence of a catalyst such as an ammonium salt. Dibenzylammonium triflate, originally introduced by Corey as a catalyst for intramolecular aldol reactions, gives the best results in the reduction, but other ammonium triflate salts also work well. An asymmetric variant of the reaction has also been carried out (Yang, J. W. et al. *Angew. Chem., Int. Ed.* **2005**, *44*, 108−110).

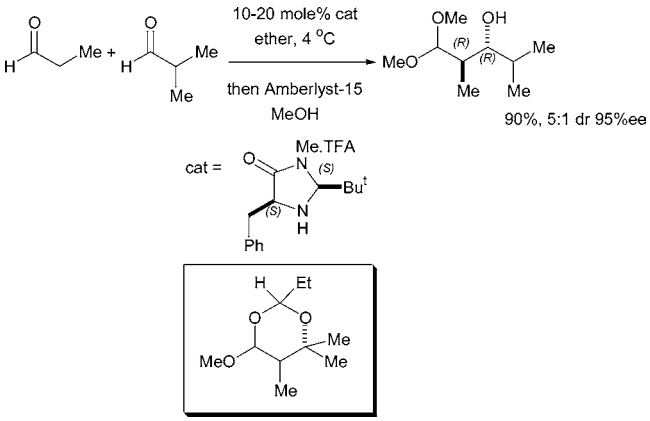
Of course, the Hantzsch ester is an expensive reducing agent, and maybe in the future other processes can be developed which are more atom efficient. The advantage of the reduction is that it is chemoselective, and nitro, nitrile, benzyloxy, and alkenyl functionalities are all tolerated.



Aldehyde−Aldehyde Coupling Reactions

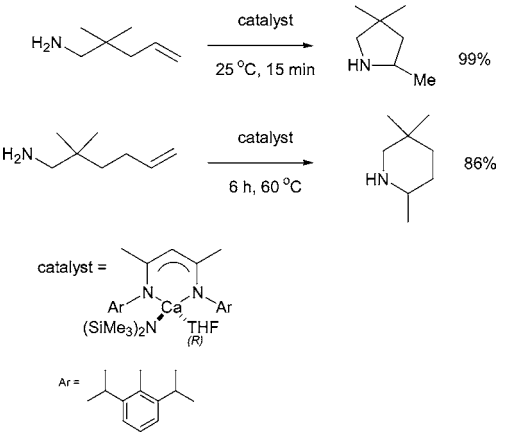
In a further advance on the organocatalytic asymmetric aldol reaction, the group of MacMillan at CalTech has found that mixed aldol reactions can be efficiently carried out. In contrast to reactions using proline, reactions catalyzed by chiral imidazolinones work in solvents of low dielectric constant such as hexane, dioxane, and ether. (Manglion, I. K. et al. *Angew. Chem., Int. Ed.* **2004**, *43*, 6722)

The reaction proceeds to an aldol product which is rapidly transformed to a hemiacetal—the latter is cleaved in the presence of a resin.



Calcium-Mediated Intramolecular Hydroamination Catalysts

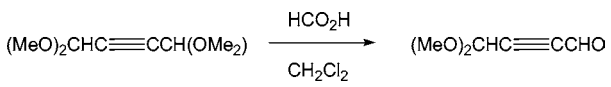
The heavier group 2 metals, calcium, strontium, and barium are underexploited in catalysis, yet they are inexpensive, and on account if their large radii and electropositive character, possess a number of characteristics of 4f transition metals (for a review see Hong, S. et al. *Acc. Chem. Res.* **2004**, *37*, 673). It has now been shown (Crimmin, M. R. et al. *J. Am. Chem. Soc.* **2005**, *127*, 2042) that a calcium complex of a bisimine of a β-diketone will catalyze the intramolecular addition of an amine across the double bond of amino alkenes. The catalytic activities of the calcium complexes are broadly similar to those of scandium species reported earlier (Lauterwasser, F. et al. *Organometallics* **2004**, *23*, 2234).



Large-Scale Synthesis of Acetylene Carboxaldehyde Mono Acetal

A paper which appeared last year on this topic (Akué-Gédu, R. et al. *Tetrahedron Lett.* **2004**, *45*, 1829) has now been found to be difficult to reproduce, and an interesting correction has been published (*Tetrahedron Lett.* **2005**, *46*, 1947). The yield in the reaction of 1,1,4,4-tetramethoxybut-2-yne with formic acid in dichloromethane, the last step in the synthesis, has been found to depend on the quality of the formic acid. Formic acid (99%) from Acros Organics only worked if the bottle was old and had previously been opened—a new bottle gave poor results. Formic acid (98%) from Lancaster or from Avocado also gave poor results. Aldrich material (95−97%) gave good and reproducible results.

Presumably it is the water content of the formic acid which is critical. A process chemist would therefore develop the formic acid specification and use a Karl Fischer titration to ensure any formic acid was within the desired limits or simply add the desired amount of water to the reaction.

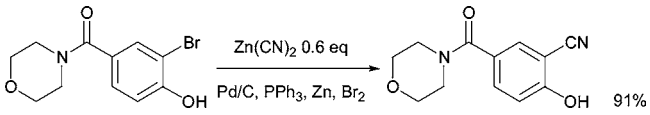


Cyanation of Aryl Bromides Catalyzed by Pd/C

Palladium-catalyzed cyanation of aryl halides has attracted much attention recently in the synthesis of intermediates and drug substances. The usual methods involving homogeneous Pd may have disadvantages when applied on scale, namely:

- the requirement for expensive phosphine ligands
- the difficulty in removing Pd from the drug substance/product
- the difficulty in recovering and recycling Pd
- poor reproducibility

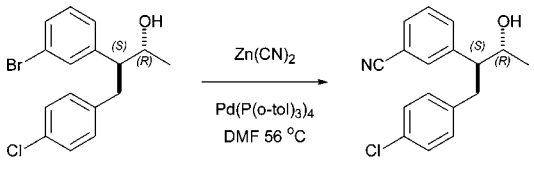
Initial results in the reaction of 4-bromobenzoate with zinc cyanide in the presence of Pd/C, Ph_3P, and zinc dust in DMA gave variable results, and the reaction often stopped before completion (Hatsuda, M. et al. *Tetrahedron Lett.* **2005**, *46*, 1849). This was ascribed to insufficient activation of the Zn surface and/or formation of Pd black. The well-known deactivation of Pd by coordination with CN may also be a problem, but this can be overcome by addition of bromine, which leads to formation of more soluble BrZnCN from insoluble $Zn(CN)_2$. This preactivation of the zinc with bromine leads to high and reproducible results, and the Pd can easily be recovered from the reaction mixture, after dilution, by filtration.



A previous investigation into the sensitivity of palladium-catalyzed processes to dissolved cyanide had been carried out by workers at Merck (Marcantonio, K. M. et al. *Org. Lett.* **2004**, *6*, 3723). They were concerned that simple reagents, carried over from previous steps, could affect the solubility of cyanide.

Even simple reagents such as NaCl, NaOH, dimethylamine (present in DMF) adversely affected the homogeneous palladium-catalyzed cyanation reaction. Excess cyanide also inactivates the catalyst. The Merck solution was to ensure that the catalytic cycle initiates before the cyanide has a chance to deactivate the catalyst. Practically, this was achieved by adding a slurry of $Zn(CN)_2$ slowly to the catalyst (prepared from $Pd(OAc)_2$ and $P(O\text{-tol})_3$ in DMF, followed by addition of $Zn(Et)_2$.

When reactions fail, usually owing to high soluble CN levels, increasing the amount of catalyst usually leads to an excellent result.



CN level	cat (mol%)	addn method	conversion
617	1	A	0
617	1	B	100
2000	1	B	0
2070	3	B	99

A: cat added to $Zn(CN)_2$
B: $Zn(CN)_2$ added to cat

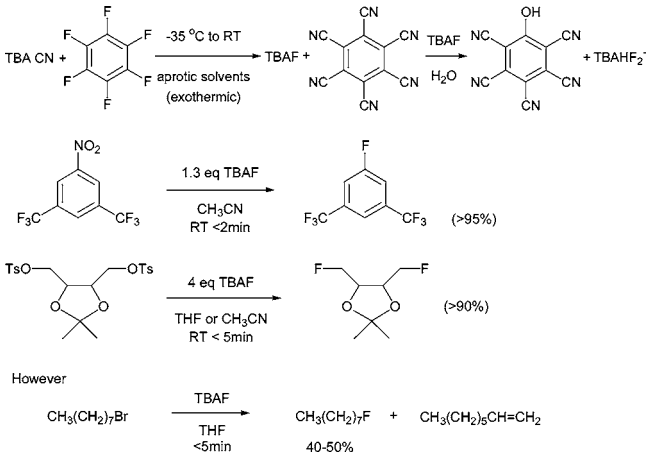
Anhydrous Tetrabutylammonium Fluoride (TBAF)

Replacement of various groups by fluorine is a common industrial procedure. The simplest and most effective reagents are often "naked" organic fluoride salts such as tetraalkylammonium fluorides in an anhydrous state. They are usually prepared hydrated and then dried, but the aggressive drying

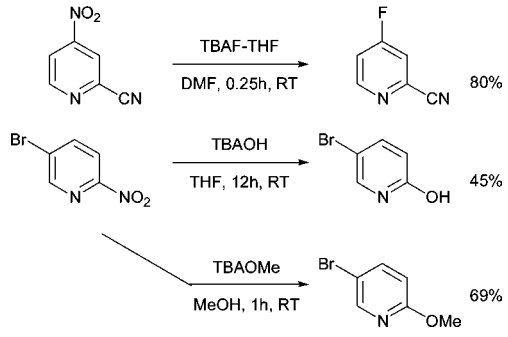
conditions may also lead to decomposition (e.g., Hofmann elimination).

It has now been shown that reaction of hexafluorobenzene with tetrabutylammonium cyanide in dipolar aprotic solvents is an excellent way of generating anhydrous TBAF. If THF is used as solvent, the anhydrous TBAF can be crystallized at low temperature, although it is usually sufficient to use a solution. (Sun, H. et al. *J. Am. Chem. Soc.* **2005**, *127*, 2050).

It has been shown that the reaction byproduct is an excellent scavenger for water, and this helps to keep the solution anhydrous. TBAF prepared in this way is superior to vacuum-dried "anhydrous" TBAF and to other fluorinating agents in nucleophilic fluorination.

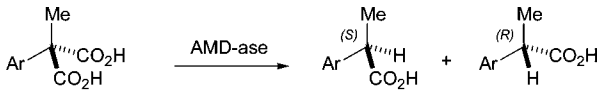


On the other hand, the group of Kuduk at Merck, West Point, indicate that fluorodenitrations can be carried out with a solution of TBAF in THF, which contains approx 5% water. In some cases they found that use of anhydrous TBAF proved deleterious, giving some hydroxy product rather than fluoro. This was exploited to obtain hydroxypyridines or methoxypyridines from nitropyridines using TBAOH or TBAOMe (Kuduk, S. D. et al. *Org. Lett.* **2005**, *7*, 577).



Asymmetric Biocatalytic Decarboxylation

The asymmetric decarboxylation of aryl- and heteroaryl-malonates to give optically active α-arylpropionates is catalyzed by an enzyme, arylmalonate decarboxylase, and yields and ee are generally high. Surprisingly, it has been found that the introduction of only two mutations into the wild-type enzyme leads to a reversal of enantioselectivity (Ijima, Y. et al. *Chem. Commun.* **2005**, 877). However, the hydrolysis is much slower (e.g. 60% yield after 72 h compared to complete conversion after 1 h with wild-type enzyme) so further mutations are needed to improve biocatalyst turnover before this can be practically useful.



Ar = Ph	wild type	99.5	:	0.5
	mutant G74C/C1885	3.0	:	97.0
Ar = 2-thienyl	wild type	98.5	:	1.5
	mutant G74C/C1885	2.0	:	98.0

Hazards of Lithium 2,6-Difluoroanilide

The title compound, prepared from 2,6,-difluoroaniline and *n*-butyllithium in diethyl ether solution has been shown to be a touch-sensitive explosion hazard (letter to *Chem. Eng. News* **2005**, February 28, 8). During transfer of the vacuum-dried solid, a sudden violent explosion occurred. This emphasizes that any compound containing both a C−F bond and highly reactive metal−nonmetal bonds should not be isolated (see advice given by P. Urben (*Chem. Eng. News* **1996**, July 8, 3).

Polymorph Transformation via Solvent Drop Grinding

Last year it was reported that solid-state grinding in the presence of a solvent increased the kinetics of cocrystallization and directed a solid-state cocrystallization to a specific polymorph (*Chem. Commun.* **2004**, 890; **2002**, 2372). The group of Jones at the Pfizer Institute for Pharmaceutical Material Science at Cambridge, UK, has now found that their solvent drop grinding method is useful for carrying out several polymorph interconversions that could not be achieved with neat grinding.

Thus, form I of anthranilic acid is stable when ground with acetonitrile present, but when dry, it converts partly to polymorph III. When ground with heptane, form II is obtained from form I. Form II, which was stable to neat grinding, could be converted to form III by grinding with chloroform present. (Trask, A. V. et al. *Chem. Commun.* **2005**, 880).

Whilst the grinding does generate heat, the temperature of the bulk remains below the transition temperature. The reason for the effect of solvents is not yet clear (simply slurrying crystals in the solvent does not work!), but selective adsorption of solvent onto one particular face is a possible rationale. The adsorption may promote defect production which is known to assist with propagation of metastable forms.

Unusual Stoichiometry in Hydrates of Sodium Saccharin

The artificial sweetener, sodium saccharinate, exists as a hydrate and in catalogues is usually listed as a dihydrate, Na(sac)·$2H_2O$. A recent determination of the crystal structure of this molecule reveals that the crystal contains 1.87 mol of water per mole of saccharin, and this corresponds to 15 molecules of water for 8 mol of saccharin. Dehydration of this hydrate leads to Na(sac)·$^9/_8H_2O$.

Whereas the above $^{15}/_{8}$ hydrate is obtained from water, recrystallisation of sodium saccharinate from 95% ethanol yields another hydrate, Na(sac)·$^{2}/_{3}H_2O$. This dehydrates to an intermediate Na(sac)·$^{4}/_{9}H_2O$ before becoming anhydrous.

The crystal structures of the monoclinic Na(sac)·$^{15}/_{8}H_2O$ and triclinic Na(sac)·$^{2}/_{3}H_2O$ have both been determined. The monoclinic crystal corresponds to $Na_{64}(C_7H_4NO_3S)_{64}$·$120H_2O$, with 64 molecules in the unit cell (Naumor, P. et al. *Angew. Chem., Int. Ed.* **2005**, *44*, 1251).

Unusual hydrates can occur with drug substances, too. I remember a presentation at a conference where it was shown that one polymorph of a drug substance contained 6 mol of drug substance and only 1 molecule of water.

Cocrystals and Salts

The physical properties of APIs, particularly aqueous solubility and dissolution rate, can be enhanced by the formation of a cocrystals with pharmaceutically acceptable substances. This is often an advantage for APIs which do not form salts, but a recent paper has shown that amine hydrochloride salts can form cocrystals with simple carboxylic acids such as benzoic acid, succinic acid, and fumaric acid. (Childs, S. L. et al. *J. Am. Chem. Soc.* **2004**, *126*, 13335).

Thus, fluoxetine hydrochloride, which does not exist in other polymorphic forms or hydrates, forms cocrystals with carboxylic acids, the driving force being hydrogen bonding between the chloride ion and the hydrogen of the carboxylic acid. The 1:1 salt with benzoic acid is approximately half as soluble as the API itself and is stable in aqueous solution. The 2:1 adduct with fumaric acid is more soluble than the API itself, whereas the 1:2 adduct with succinic acid is unstable in water, resulting in crystallization of the API.

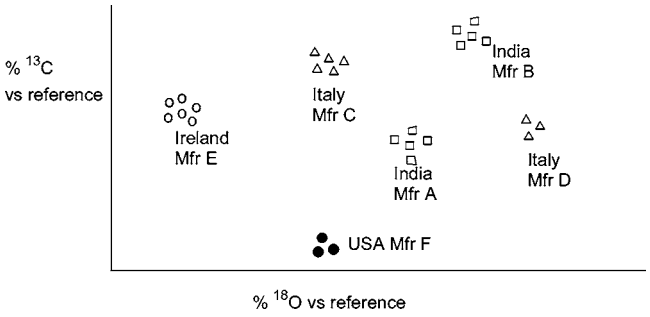
The adducts are simply prepared by evaporation of a mixture of the API and carboxylic acid dissolved in acetonitrile. Other API amine hydrochlorides can also form cocrystals with simple molecules.

Saccharin is a strong hydrogen bonder and has been shown to form cocrystals with APIs such as carbemazepine. However, saccharin (being a weak acid) can also form salts with APIs, such as haloperidol, mirtazapine, and quinine, and these salts have much enhanced water solubility. With piroxicam, however, a cocrystal was formed which had only low solubility (Bhatt, P. M. et al. *Chem Commun* **2005**, 1073). Saccharin has the advantage that it is generally recognized as safe (GRAS), and the high water solubility of saccharinates means that they can be used in liquid formulations. The sweet taste also masks any bitter taste in the API. The pH of saccharinate solutions is generally in the 5−6 range compared to hydrochlorides in the 2−3 range.

Isotopic Analysis of Batch Products

A novel method of characterization of products, particularly APIs, has been developed as a way of divining the provenance of these materials. Different synthetic pathways to the same substance will yield different isotopic composition in the final product, and this may be used to prove infringement or counterfeiting. (Jasper, J. P. et al. *J. Pharm BioMed. Anal.* **2004**, *35*, 21; see also www.molecularisotopes.com).

For example, batches of Naproxen from different sources can be characterized by the differences in the ^{13}C and ^{18}O content as shown below. Each manufacturer's product appears in a different region of the graph, allowing determination of the provenance of each sample. Presumably this depends on the source of raw materials and the synthetic route used.



Note Added after ASAP Publication: In the version published on the Internet May 4, 2005, the reference was omitted for one of the literature highlights. The final version, published May 13, 2005, and the print version are correct.

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