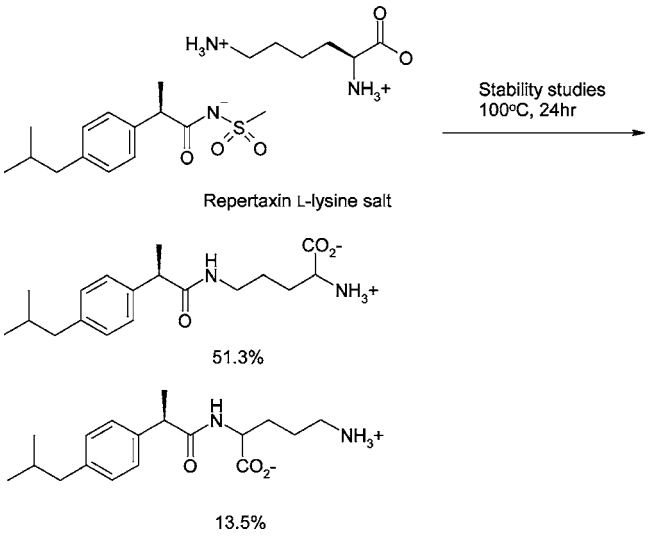
Organic Process Research & Development **2004**, *8,* 816–822

Highlights from the Literature

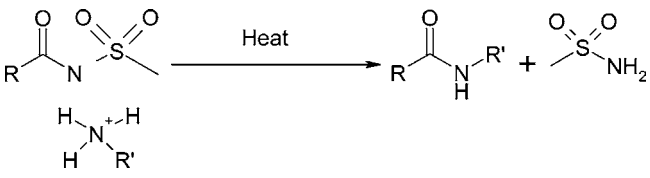
Some Items of Interest to Process R&D Chemists and Engineers

Acylmethanesulfonamides as New Acylating Agents

Coniglio, Allegretti, and colleagues from Dompé Research and Development describe (*Tetrahedron Lett.* **2004**, *45*, 5375) a novel method for the highly chemoselective acylation of primary amino groups in molecules possessing both primary and secondary amino functionalities. Their method has been inspired by the results of stability studies on Repertaxin L-lysine salt, a compound under clinical investigation for the prevention of delayed graft function during organ transplant. Under stressed conditions the Repertaxin L-lysine salt showed enhanced amounts of amide byproducts (see scheme below) resulting from internal condensation in the solid or melted state.

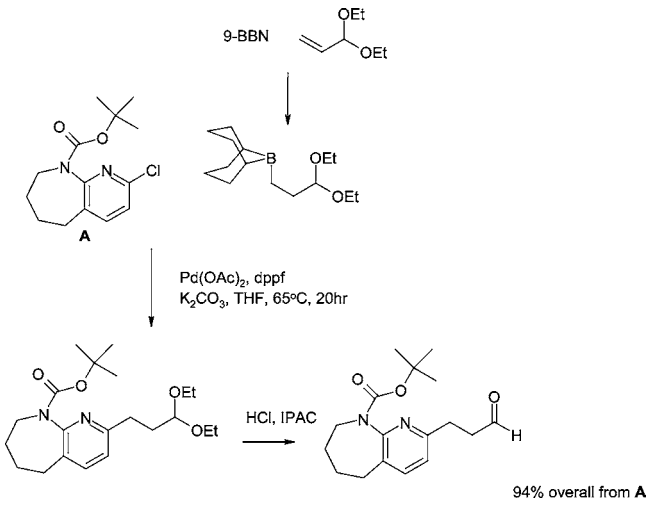


In their method a variety of ammonium salts have been prepared by mixing acylmethanesulfonamides with the desired amine in dichloromethane followed by evaporation. The crude mixtures are then heated at 120 °C for 3 h in a drying oven to give amide products. For diamine substrates primary amino acylation was observed in high yields.



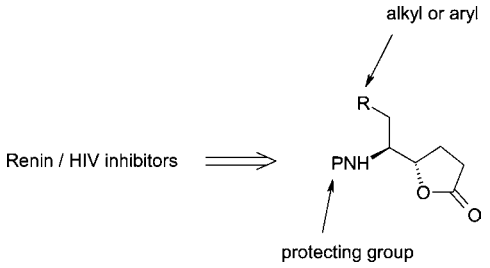
Synthesis of 3-Substituted Propionaldehydes

Cowden, Hammond, and colleagues at Merck required a synthesis of the propionaldehyde derivative (shown in the scheme above) as part of synthetic efforts towards $\alpha_v\beta_3$ integrin antagonists. In a recent publication (*Tetrahedron Lett.* **2004**, *45*, 6125) the group disclose an efficient method to prepare these 3-substituted propionaldehyde derivatives using a Suzuki−Miyaura coupling. The reaction has been demonstrated on a range of substrates including several where the Heck reaction with allyl alcohol failed to give the desired aldehyde product.



5-[(1*S*)-*N*-Boc-amino-(2*S*)-(3-fluorophenyl)ethyl]-dihydrofuran-2-one

Compounds that possess the γ-hydroxy-δ-amino moiety (see scheme below) are important precursors to hydroxyethylene dipeptide isosteres, a class of compound that have shown therapeutic potential as HIV and renin inhibitors.



Li and colleagues at Pfizer report (*Tetrahedron Lett.* **2004**, *45*, 6887) a short, efficient, and highly diastereoselective synthesis of 5-[(1*S*)-*N*-Boc-amino-(2*S*)-(3-fluorophenyl)ethyl]-dihydrofuran-2-one. The thioester starting material (see scheme below) can be prepared from commercially available Boc-L-3-(fluorophenyl)alanine and is crystalline and nearly odourless. When reacted with the organozincate reagent with palladium catalysis, the product α-amino ketone was found to be racemised. The group attribute this loss of chirality to

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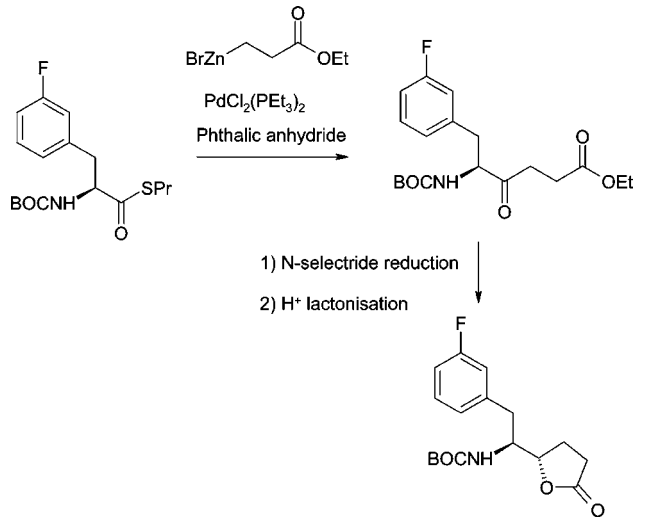
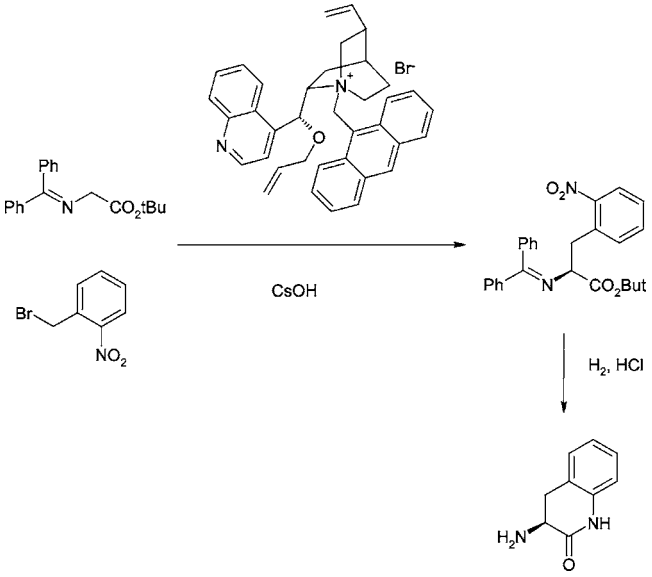
amounts of ethoxide being produced through thiolate displacement of the ethyl esters and subsequent deprotonation. To eliminate this issue the group used phthalic anhydride as a thiolate scavenger to effectively preserve the chiral integrity of the α-aminoketone product.



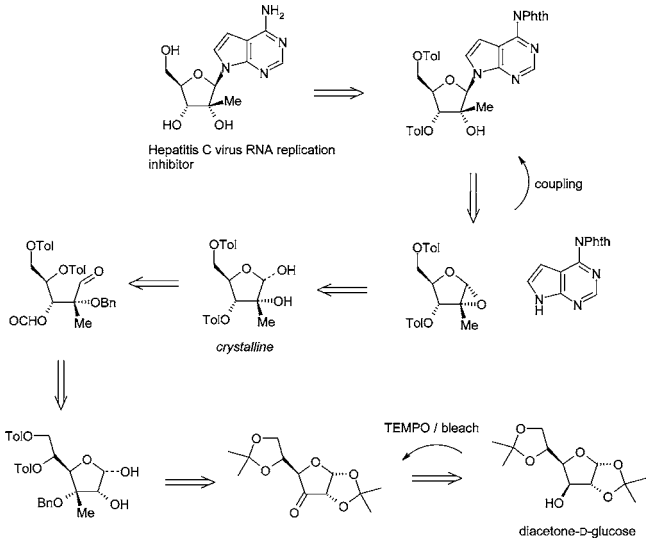
(*R*)- and (*S*)-3-Amino-3,4-dihydro-1H-quinolin-2-one



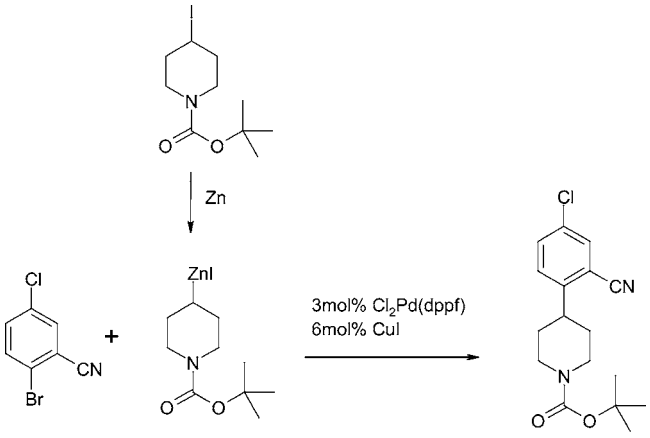
The 3-amino-3,4-dihydro-1H-quinolin-2-one motif has been incorporated in a variety of interesting biological molecules. In a recent paper, Hulin and Lopaze from Pfizer report (*Tetrahedron Asymmetry* **2004**, 1957) the asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester with 2-nitrobenzyl bromide followed by reductive cyclization to provide either enantiomer, (*R*)- or (*S*)-3-amino-3,4-dihydro-1H-quinolin-2-one, in high yield and with high enantiomeric excess. In their method either enantiomer of the chiral tetraalkylammonium salt can be used in the phase transfer alkylation.

Hepatitis C Virus RNA Replication Inhibitor: Synthesis

A practical and efficient synthesis of a hepatitis C virus RNA replication inhibitor has been reported by Bio and colleagues from the process research department at Merck (*J. Org. Chem.* **2004**, *69*, 6257). Starting with the inexpensive diacetone glucose, the 12-step synthesis features an environmentally friendly catalytic TEMPO/bleach oxidation and a novel stereoselective rearrangement to prepare a key crystalline furanose diol intermediate. This is followed by a highly selective glycosidation to couple the C-2 branched furanose epoxide with deazapurine. Multikilogram experimental details are described in the article.



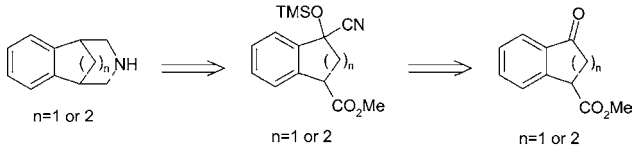
Pd/Cu(I)-Cocatalysed Negishi Coupling



A general procedure for the synthesis of 4-arylpiperidines via the coupling of 4-(*N*-BOC-piperidyl)zinc iodide with aryl halides and triflates has been reported by Corley and colleagues from Merck (*J. Org. Chem.* **2004**, *69*, 5120). The reaction requires cocatalysis with both $Cl_2Pd(dppf)$ and a copper(I) species. In addition the group have developed an improved, safer procedure for the activation of zinc dust by a modified Knochel procedure. In their method (experimental details are outlined in the paper) chlorotrimethylsilane and 1,2-dibromoethane are premixed and then added to a slurry of zinc dust in dimethylacetamide. In this way the exotherm can be controlled.

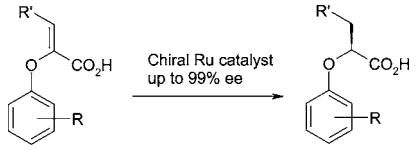
1,5-Methano- and 1,5-Ethano-2,3,4,5-tetrahydro-1H-3-benzazepines

A general approach to the preparation of 1,5-methano- and 1,5-ethano-2,3,4,5-tetrahydro-1H-3-benzazepines has



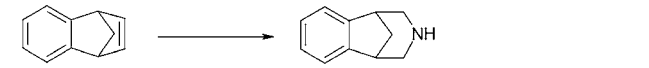
been reported by O'Donnell and co-workers from Pfizer (*J. Org. Chem.* **2004**, *69*, 5756). Their strategy involves converting an indanone or tetralone to a cyanohydrin which is subjected to hydrogenolysis followed by lactamization and reduction to provide the bicyclic aryl piperidine and bicyclic aryl homopiperidine structures. Previous synthetic approaches to these compounds have utilized chemistry that has either been problematic or low yielding.

Enantioselective Hydrogenation of α-Aryloxy α,β-Unsaturated Acids



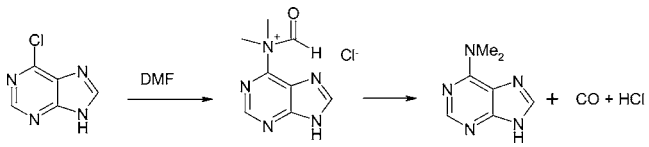
A facile preparation of chiral α-aryloxy carboxylic acids via asymmetric hydrogenation of the corresponding unsaturated acids has been published by Maligres, Krska, and Humphrey at Merck (*Org. Lett.* **2004**, *6*, 3147). A number of catalysts have been identified that give high product enantioselectivity, and the scope of the reaction has been examined with respect to substitution on the aromatic ring and olefin.

2,3,4,5-Tetrahydro-1,5-methano-1H-3-benzazepine



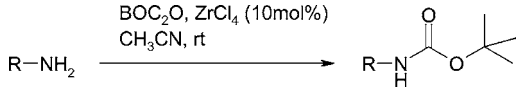
Coe, Singer, and colleagues from Pfizer report (*Synthesis* **2004**, 1755) two preparations of 2,3,4,5-tetrahydro-1,5-methano-1H-3-benzazepine from benzonorbornadiene. In different synthetic routes the use of oxidative cleavage and reductive amination sequences were investigated. Osmium-mediated dihydroxylation of benzonorbornadiene followed by $NaIO_4$ cleavage, reductive amination, and debenzylation provided the desired product in 64−73% yield overall from the three operations. A second method involving a tandem ozonolysis−reductive amination procedure gave the benzazepine derivative as the tosylate salt from benzonorbornadiene with no isolation of intermediates in 28% yield. In their publication, multigramme methods are described.

Use of DMF in Dimethylamino Amination of Heterocycles and Aromatics



A convenient dimethylamino amination of various heterocyclic and aromatic compounds having an activated chloro group has been achieved in good yields using dimethyl formamide (DMF) by Chauhan and Agarwal (*Synth. Commun.* **2004**, 2925).

Lewis Acid-Catalyzed BOC Protection of Amines

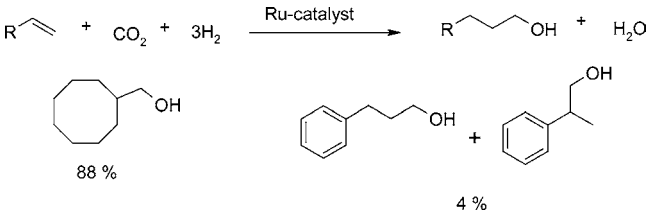


Sharma and colleagues report (*Tetrahedron Lett.* **2004**, *45*, 6963) how efficient BOC protection of amines can be performed using BOC_2O in the presence of a catalytic amount of the Lewis acid $ZrCl_4$ (10 mol %) in acetonitrile at room temperature. The reaction times are very short, and the yields are generally high.

The Art of Meeting Palladium Specifications in API Produced by Pd-Catalyzed Reactions

The use of palladium-derived catalysts in the synthesis of fine chemicals and pharmaceutical ingredients has become quite common in the last few decades. The number of these reactions available to chemists has provided access to more complex structures in fewer steps and with less waste. An unfortunate side effect of using palladium is the potential for palladium-containing impurities to remain in the desired compound after isolation. This is an especially significant problem for the pharmaceutical industry as there is a low limit for heavy metal impurities allowed in drug substance. C. Garrett and K. Prasad *(Adv. Synth. Catal*. **2004**, *346*, 889) have summarized the methods developed for the art of meeting the palladium specifications in active pharmaceutical ingredients. Over the years various methods for the removal of palladium impurities have been developed. Trial and error seems to be the norm when determining the optimal conditions for the removal of the palladium. Most of the methods described are very specific with respect to the physical characteristics of both the compound being purified and the form of palladium to be removed. The solvent conditions and intended work-up also play a large part in determining the most effective purification method.

Ruthenium-Catalyzed One-Pot Hydroformylation of Alkenes Using Carbon Dioxide as Reactant

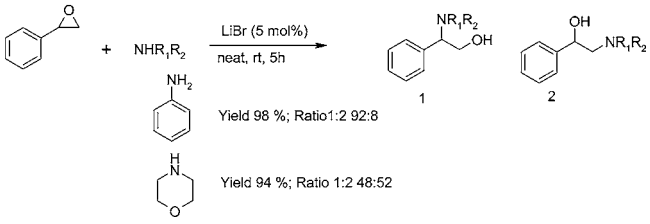


A new hydroformylation of alkenes using carbon dioxide as a reactant has been shown by K. Tominaga and Y. Sasaki (*J. Mol. Catal. A: Chem.* **2004**, *220*, 159) to take place in the presence of ruthenium cluster complexes and halide salts. Similar and in some cases better yields of alcohols were formed as compared to the conventional hydroformylation

with CO under the same reaction conditions. The reaction proceeds in three steps: CO_2 is converted to CO; then it is used as a reagent for hydroformylation to give the corresponding aldehyde; subsequently, it is hydrogenated to alcohol. The most effective ruthenium catalysts were found to be $H_4Ru_4(CO)_{12}$, $Ru_3(CO)_{12}$, and $[(Ph_3P)_2N][RuCl_3(CO)_3]$. LiCl was found to be the best salt. The reaction works well with aliphatic alkenes; aromatic alkenes are mostly merely reduced by the new system.

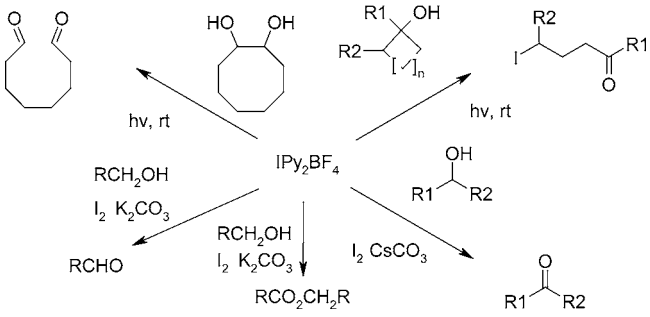
LiBr, an Inexpensive and Efficient Catalyst for Opening of Epoxides by Amines at Room Temperature

LiBr (5 mol %) has been found to be an inexpensive and efficient catalyst for the ring opening of epoxides by amines (Chakraborti, A. et al. *Eur. J. Org. Chem*. **2004**, 3597). Aromatic and aliphatic amines react with cycloalkene oxides to exclusively form *trans*-2-(aryl/alkylamino)cycloalkanols I high yields. Aromatic amines attack styrene epoxides preferably at the benzylic carbon. However, aliphatic amines exhibit a marginal preference for the reaction at the terminal carbon atom. Unsymmetrical alkene oxides undergo selective attack at the sterically less hindered carbon by aniline.



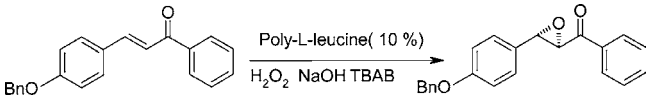
Bis(pyridine)iodonium Tetrafluoroborate: A Versatile Oxidizing Reagent

The use of bis(pyridine)iodonium tetrafluoroborate (IPy2-BF4) has been reported by Barluenga, J. et al. (*Chem.—Eur. J.* **2004**, *10*, 4206) as an oxidizing agent towards different types of alcohols. The observed reactivity involves different reaction pathways dependent on the substrates and the reaction conditions. For instance a general β-scission process of secondary and tertiary cycloalkanols which gives rise to ω-iodofunctionalized systems has been developed. The reactions are done under photochemical conditions at room temperature.



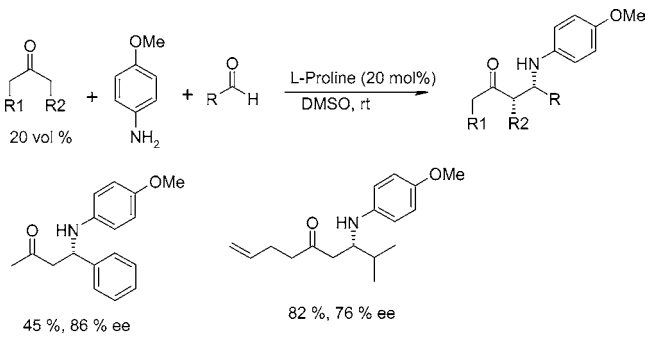
Scale-Up Studies for the Asymmetric Juliá–Colonna Epoxidation

Gerlach, A. et al. *(Adv. Synth. Catal*. **2004**, *346*, 1247) have scaled up the poly-α-amino acid-catalyzed asymmetric Juliá–Colonna epoxidation using tetrabutylammonium bromide (TBAB) as phase transfer catalyst to improve the reaction kinetics. The scale-up of the reaction lead to a significant increase in reaction time. To overcome this the reaction was run in a sealed glass autoclave with efficient stirring. It was possible to reduce the reaction time to 12 h on a 100-g scale.



The Scope of Proline-Catalyzed Asymmetric Addition of Ketones to Imines

The amino acid-catalyzed additions of unmodified ketones to imines are performed under very mild, operationally simple, environmentally friendly, and benign conditions employing a one-pot, three-component protocol as well as with preformed imines. Typically, products are obtained with high regio- and diastereoselectivities and excellent enantioselectivities. Notz, W. et al. *(Adv. Synth. Catal*. **2004**, *346*, 1131) have reported their results on the application of this methodology toward the synthesis of α-amino acids, γ-lactones, oxime-functionalized amino acids, and other pharmacologically important targets.



Transition-Metal-Catalyzed Addition of Heteroatom–Hydrogen Bonds to Alkynes

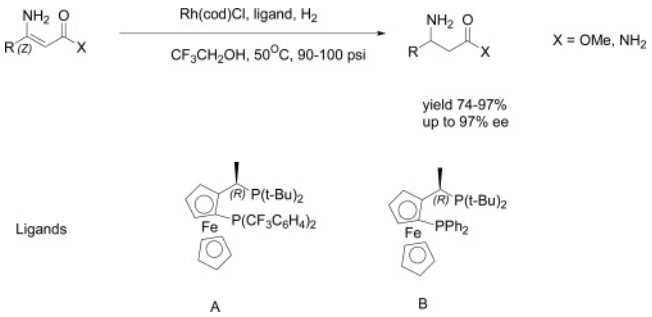
Alonso, F. et al. (*Chem. Rev*. **2004**, *104*, 3079) have reviewed the transition-metal-catalyzed addition of heteroatom–hydrogen bonds to alkynes. These reactions include the addition of N–H, O–H, S–H, Se–H, and P–H. All these processes are very important from the synthetic point of view because, in principle, the addition reactions can be performed with almost 100% atom efficiency. They fulfill the requirements for green chemistry better than the substitution reactions leading to the same products.

Synthesis of β-Amino Acid Derivatives by Asymmetric Hydrogenation of Unprotected Enamines

Much research is devoted to the synthesis of β-amino acids. For large-scale work, catalytic asymmetric hydrogenation is the ideal approach, yet most current methods rely on resolution of racemates or use of auxiliaries. The reason is the need for the protection of nitrogen by an acyl group in the asymmetric hydrogenation methods; synthesis of the enamides is not straightforward, and the subsequent removal of the acyl group requires strong acidic or basic conditions, which may cause racemisation or incompatibility with other func-

tionalities in the molecule. It has been suggested that an acyl group is required for good enantioselectivity, since chelation to the metal leads to enhanced reactivity and selectivity.

Now, the process R&D group at Merck, Rahway, in conjunction with Solvias, Basel, have discovered by catalyst screening that some catalysts are effective in the asymmetric hydrogenation of *unprotected* β enaminoesters and amides. Best results were with the Josiphos-type ligands and rhodium catalysts (Hsiao, Y. et al. *J. Am. Chem. Soc.* **2004**, *126*, 9918).

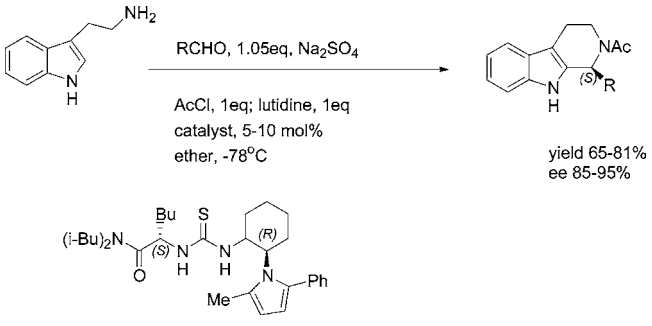


For the hydrogenation of esters, ligand A gave the best results; in methanol the reaction is inhibited but in CF_3CH_2OH there is high reactivity. For amides catalyst B is best with selectivity better in methanol than in CF_3CH_2OH. It is believed that solvent acidity is important.

Preliminary deuterium studies suggest that the reaction may proceed through the imine tautomer. Reductions with D_2 lead to incorporation of only one D in the β position. This discovery should lead to simpler, improved processes for the larger-scale preparation of β-amino acids and their derivatives.

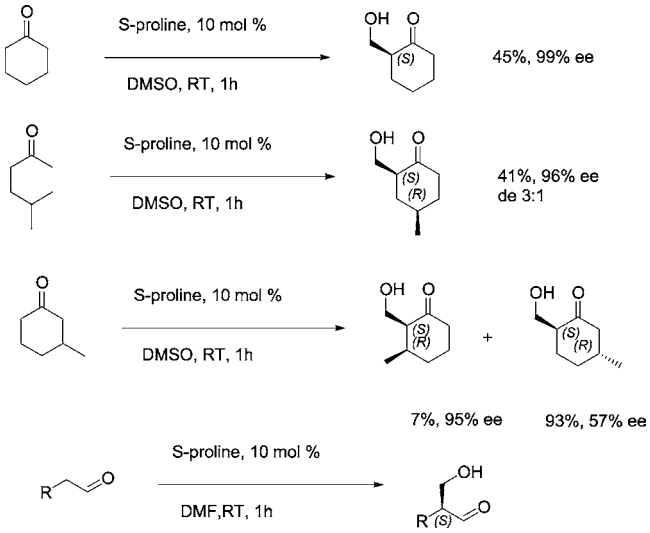
Highly Enantioselective Pictet−Spengler Reactions

Tetrahydroisoquinoline and tetrahydro-β-carboline ring systems occur in many pharmaceuticals; many are made via the Pictet−Spingler reaction. This involves the cyclisation of an imine or immonium salt to the aromatic or heteroaromatic nucleus. Now the group of Jacobsen has found that chiral thiourea catalysts, previously used in other highly enantioselective reactions, work well in the Pictet−Spingler reaction. (Taylor, M. S. et al. *J. Am. Chem. Soc.* **2004**, *126*, 10558).



Asymmetric Hydroxymethylation

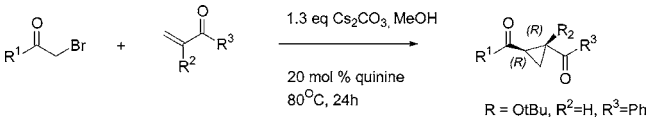
Using standard organocatalysis conditions (proline, DMSO) gaseous or aqueous formaldehyde can be induced to react with cyclohexanones to give high enantioselectivities; yields, however, are only moderate (Casas, J. et al. *Tetrahedron Lett.* **2004,** *45*, 6117). Other substituted prolines also give similar results. The hydroxymethylation reaction also works with aldehydes rather than ketones.



Enantioselective Organo Catalytic Cyclopropanation via Ammonium Ylides

Some of the earlier work in this area from the group of Matthew Gaunt at Cambridge has already been described in previous highlights (*Angew. Chem., Int. Ed.* **2003**, *42*, 328; **2004**, *43*, 2681). The latest report (Papageorgiu, C. D. et al. *Angew. Chem., Int. Ed.* **2004**, *43*, 4641) describes an optimized process for reacting an α-bromo carbonyl derivative with an unsaturated carbonyl component in the presence of base and a quinine derivative. Best results are obtained when an α-bromoester is added to a phenyl enone in the presence of 0.2 equiv each of alkaloid and cesium carbonate.

By changing the cinchona alkaloid, the opposite enantiomer can be obtained. Slow addition of a mixture of the two reagents to the alkaloid and the base often results in higher yields. Presumably the bromo carbonyl reacts with the alkaloid and base to give a quaternary ammonium ylide which performs the cyclopropanation reaction, releasing the alkaloid for further catalytic cycles. The catalyst loading can be reduced to 1 mol %, but the yield (conversion?) drops to 53%; the enantioselectivity, however remains high. Use of bromomethyl alkyl ketones is problematical, but the desired cyclopropane can be made from the alkyl enone and a bromomethyl Weinreb amide.



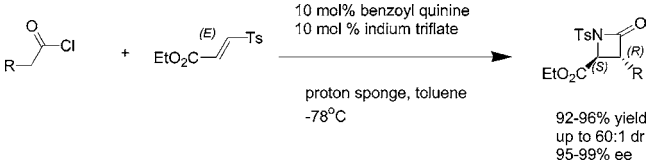
Towards Perfect Catalytic Asymmetric Synthesis

A recent review (Ma, J.-A. et al. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566) describes how dual activation of the electrophile and the nucleophile, often using a combination of a Lewis acid and a Lewis base working in concert, can lead to excellent results in catalytic asymmetric synthesis. High reaction rates occur, leading to excellent transfer of

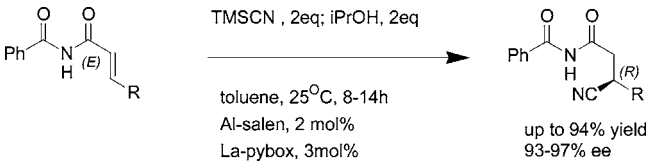
stereochemical information in many processes. The review discusses the following:

- boron-mediated asymmetric reduction of carbonyl compounds
- catalytic asymmetric additions to carbonyl compounds
- catalytic asymmetric 1,4 additions
- catalytic asymmetric aldol and Mannich reactions
- catalytic ring opening of epoxides

Other reactions are also described, such as the synthesis of β-lactams.

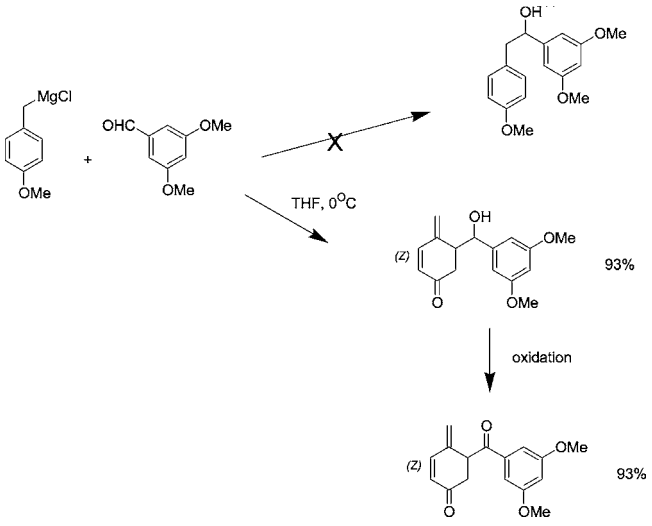


The enantioselective conjugate addition of cyanide to unsaturated imides, recently reported by the group of Jacobsen at Harvard (Sammis, G. M. et al. *J. Am. Chem. Soc.* **2004**, *126*, 9928) is another example of cooperative dual catalysis. In this case a combination of an aluminium (salen) with a pybox−lanthanide complex activates the process.



Surprising Reaction of a Benzyl Grignard Reagent with an Aromatic Aldehyde

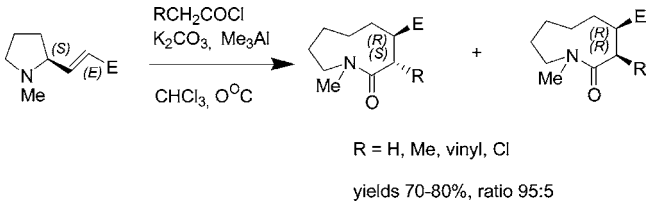
The reaction of 4-methoxybenzylmagnesium chloride with 3,5-demethoxylbenzaldehyde gives a high yield of the product where attack on the aromatic ring has taken place (Kraus, G. A. et al. *Tetrahedron Lett.* **2004**, *45*, 6839). The ortho attack suggests that coordination of the aldehyde carbonyl with the magnesium is a key factor in the production of the unusual product.



The resultant "dearomatised" alcohols were unstable but could be oxidised to the corresponding ketones. Surprisingly, aromatisation of these products does not occur.

The Bellus−Claisen Rearrangement

A review on this interesting variant of the Claisen rearrangement has appeared (Gonda, J. *Angew. Chem., Int. Ed.* **2004,** *43*, 3516). It is the reaction of an allylic ether, thioether, or amine with a ketene leading to a rearranged E-unsaturated ester, thioester or amide. When applied to cyclic substrates, ring enlargement occurs.



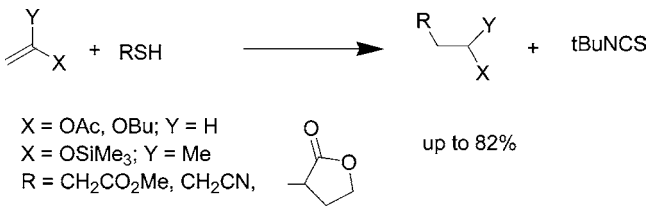
Dihydrogen Trioxide Generation from H_2O_2 and O_3

The reactivity of ozone is markedly increased by the presence of hydrogen peroxide, and this has fascinated scientists for almost 100 years. Recently, the reaction has aroused biological interest since it has been discovered that all antibodies have the ability to catalyse the oxidation of water by singlet oxygen. It is suggested that HOOOH is an intermediate which breaks down to H_2O_2 and O_3.

It has now been shown (Nyffeler, P. T. et al. *Angew. Chem., Int. Ed.* **2004**, *43*, 4656) that passage of a stream of ozone/oxygen through aqueous hydrogen peroxide (96% w/w) dissolved in acetone or THF at −78 °C generates HOOOH. A better method is via the reduction of ozone using a polymer-supported diphenylhydrazine. No safety information was provided in the paper, but one can imagine that there are certain hazards involved in reacting ozone with H_2O_2, and possibly with HOOOH. Generation of solutions of HOOOH may allow further chemistry, possibly of interest to those already accustomed to handling ozone, to be explored.

Novel Tin-Free Procedure for Alkyl Radical Generation

Radical reactions are very powerful methods in synthetic organic chemistry and would be used more on large scale if better alternatives to tin catalysis were available. An Italian group, based in Bologna, has recently published work on generation of alkyl radicals (Benati, L. et al. *Angew. Chem., Int. Ed.* **2004**, *43*, 3598). The method involves reaction of an isocyanate with a thiol in the presence of a radical trap.



In contrast, it is surprising to see papers such as the reduction of nitroarenes with $SnCl_2$ in ionic liquids being described as "green" and "eco friendly" (De, P. *Synth. Lett.* **2004,** 1835), when no attempt to reuse the tin is described.

Handling of NaSH on Large Scale

Recent bulletins from the U.S. Chemical Safety and Hazard Investigation Board (see http://www.csb.gov) note that 32 workers have died and 176 have been injured since 1971 in sodium hydrosulphide (NaSH) caused incidents. Many of these relate to acidfication or heating resulting in release of hydrogen sulphide. Safe use and design of installations as well as emergency response measures are proposed.

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