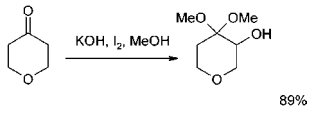
Organic Process Research & Development **2005**, *9*, 127–132

Highlights from the Literature

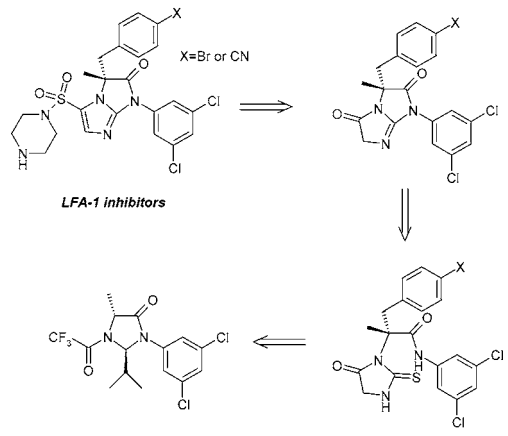
Some Items of Interest to Process R&D Chemists and Engineers

α-Hydroxylation



Zacuto and Cai from the department of process research at Merck report how aldehydes and ketones may be converted at the α-position to their corresponding hydroxyl derivatives using iodine (*Tetrahedron Lett.* **2005**, 447). Their reactions are run in basic methanol to furnish α-hydroxylated ketal products, and the publication describes how the method was developed. The group report that this method is superior to existing methodology for similar transformations (hypervalent iodine and electrochemical method) both in terms of practicality, cost, and waste. A variety of substrates are reported and the limitations, along with mechanistically expected side products, described.

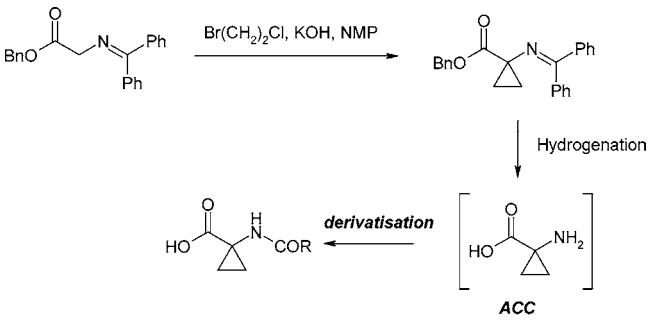
Practical Synthesis of LFA-1 Inhibitors



Wang and colleagues from Boehringer Ingelheim have recently disclosed (*Tetrahedron Lett.* **2005**, 273) a multikilogram route for the synthesis of LFA-1 inhibitors. These LFA-1 antagonists are reported to have potential therapeutic application for the treatment of inflammatory and immune disorders. Their approach has a pivotal step involving the conversion of thiohydantoins to a bicyclic guanidine using copper (I) chloride. The paper goes onto discuss the remainder of this chromatography-free synthesis through to the target compound from the bicyclic guanidine.

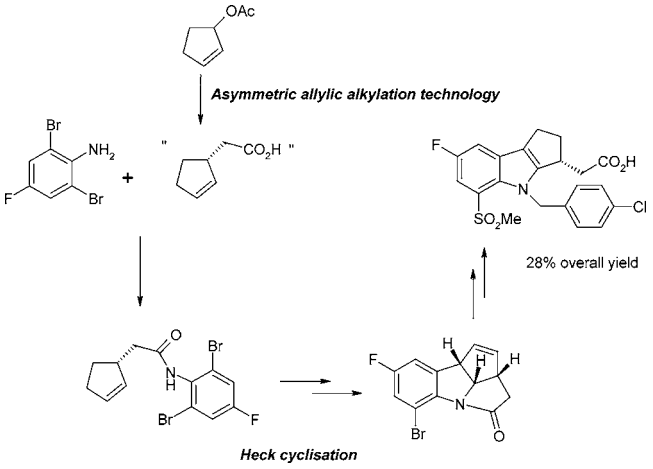
1-Aminocyclopropane-1-carboxylic Acid (ACC)

Allwein and colleagues at Merck describe (*Synlett* **2004**, 2489) in a recent letter how an expedient route to 1-aminocyclopropane-1-carboxylic acid (ACC) was developed. This naturally occurring amino acid and its derivatives have been previously synthesized using a number of methods owing to interest in its biological properties and potential in a number of therapeutic areas.



The Merck approach is outlined in the scheme. Direct isolation of ACC from a nonaqueous solution or direct derivatisation was found to be advantageous as isolation from aqueous media was found to be difficult.

Prostaglandin D2 Receptor Antagonist



Campos and colleagues from Merck have recently reported (*J. Org. Chem.* **2005**, *70*, 268) an asymmetric synthesis to prepare a prostaglandin D2 receptor antagonist for the treatment of allergic rhinitis. The stereogenic center was set initially using asymmetric allylic alkylation chemistry and the core built via Pd-catalysed N-cyclisation/Heck methodology. The group report some interesting chemistry for the isomerisation of the double bond to the final target molecule. One approach involves hydrogenation (using Crabtree's catalyst) to the saturated indoline followed by a late-stage MnO_2 oxidation without loss of chirality.

10.1021/op050016f CCC: $30.25
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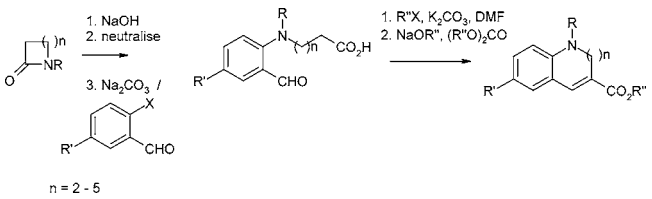
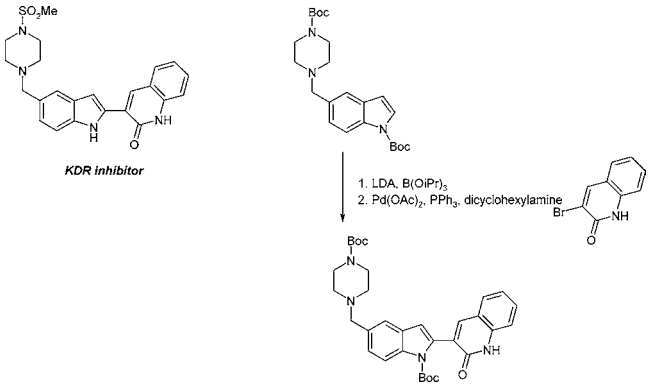
7−10-Membered Ring Formation



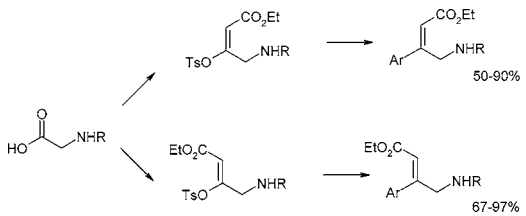
Ikemoto and colleagues from the Takeda Pharmaceutical company report how 7−10-membered rings may be prepared by the intramolecular condensation and subsequent dehydration as shown in the scheme (*Tetrahedron Lett.* **2004**, 9335). Their synthesis allows expedient access to 1-benzazepines ($n = 2$) which are important intermediates in oral HIV-1 therapy as CCR5 antagonists. Interestingly the dialkyl carbonate (final step) was used as solvent.

Antiangiogenic Tyrosine Kinase Inhibitor



An efficient synthesis of the potent KDR inhibitor (scheme) has been reported by Payack and co-workers at Merck (*J. Org. Chem.* **2005**, *70*, 175). The key step in their approach is the Suzuki−Miyaura coupling between the 2-boronic acid derivative of the indole and bromide as shown in the scheme. The lithiation and in situ quench with triisopropyl borate makes use of a noncryogenic protocol developed in the Merck laboratories. The chemistry outlined in their paper has been used on pilot plant, and experimental descriptions are described.

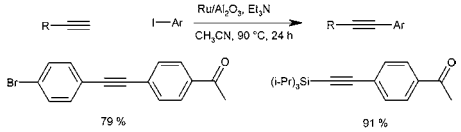
Stereoselective Enol Tosylation



γ-Aminobutyric acid (GABA) analogues are important target molecules in the pharmaceutical industry due to their profound effects on the various central nervous system functions. The common structural feature of these molecules is the γ-amino carbonyl group. To this end Baxter, Steinhuebel, and colleagues from Merck report (*Org. Lett.* **2005**, *7*, 215) how the stereoselective preparation of (*E*)- or (*Z*)-trisubstituted α,β-unsaturated esters can be achieved in three steps from *N*-protected glycine. The key step in their synthetic approach is the highly selective enol tosylation of γ-amino β-keto esters, and the group outline how this selectivity was achieved by variation of reaction conditions (solvent, base). The enol tosylates are stable, crystalline compounds that undergo smooth and effective Suzuki−Miyaura coupling reaction with a variety of aryl boronic acids.

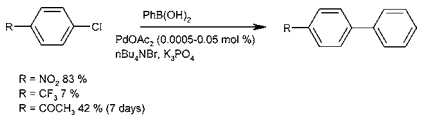
Ruthenium/Alumina as a Convenient Catalyst for Copper-Free Sonogashira Coupling Reactions

S. Chang et al. (*Adv. Synth. Catal.* **2004**, *346*, 1638) have found that ruthenium supported on alumina is a new practical catalyst for copper-free Sonogashira coupling reactions with high efficiency over a wide range of aryl iodides under mild conditions. The heterogeneous catalyst can be recovered and reused.



"Homeopathic" Ligand-Free Palladium Catalysis for Aryl−Aryl-coupling Reactions

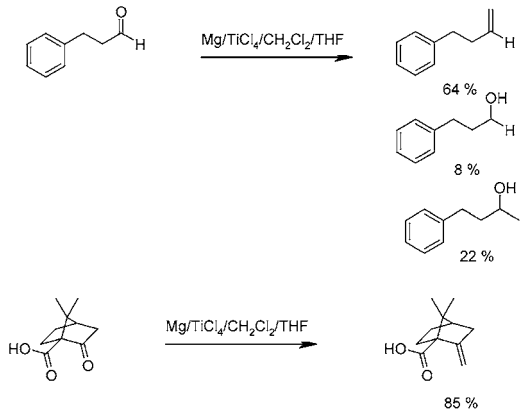
J. G. de Vries et al. (*Adv. Synth. Catal.* **2004**, *346*, 1812) have extended their investigation on the topic "homeopathic" palladium catalysis to aryl−aryl coupling using $Pd(OAc)_2$ for the Kumada, Negishi, and Suzuki cross-coupling reactions. The Suzuki reaction with aryl bromides, both activated and deactivated, is possible using 0.02−0.05 mol % palladium acetate although in some cases the reaction time is extremely long. The Negishi coupling was possible between arylzinc halides and strongly deactivated aryl bromides. The Kumada reaction only gave low yields of products under the chosen reaction conditions.



Dichloromethane Activation: Direct Methylation of Ketones and Aldehydes with CH_2Cl_2 Promoted by Mg/$TiCl_4$/THF

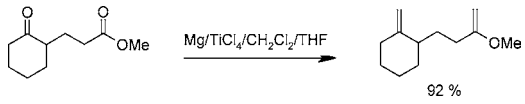
T.-H. Yan et al. (*Org. Lett.* **2004**, *6*, 4961) have developed a new Mg−$TiCl_4$-promoted CH_2-transfer reaction of dichloromethane to a variety of aldehydes and ketones. The method is simple, practical, and efficient especially in enolizable or sterically hindered systems. The reaction needs also the addition of THF, otherwise there is no reaction. If another

ether such as DME is used, the reaction is less specific with much more reduction of the substrate.



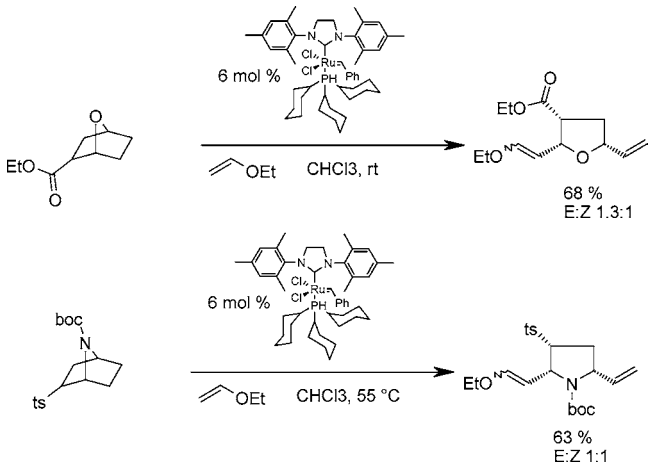
A New Entry of Selective Titanium−Methylene Complexes for Ester Methylation

The group also reports (T.-H. Yan et al. *Org. Lett*. **2004**, *6*, 4965) the successful application of $CH_2Cl_2-Mg-TiCl_4$ system-mediated methylation of various esters such as *tert*-butyl esters. The nonbasic nature of this methylene carbenoid makes it attractive for methylation of also easily enolizable substrates.



Regioselective Ring-Opening/Cross-Metathesis Reactions of Norbornene Derivatives with Electron-Rich Olefins

J. D. Rainier et al. (*Org. Lett*, **2005**, *7*,131) have demonstrated that electron-rich olefins undergo regioselective ring-opening/cross-metathesis reactions (ROCM) with unsymmetrical norbornene analogues in the presence of second-generation Grubbs' catalyst. These reactions result in the efficient and stereoselective synthesis of highly substituted furans and pyrrolidines having electronically distinct olefins suitable for selective manipulation. That the starting norbornenes are readily available from simple precursors makes the protocol attractive.

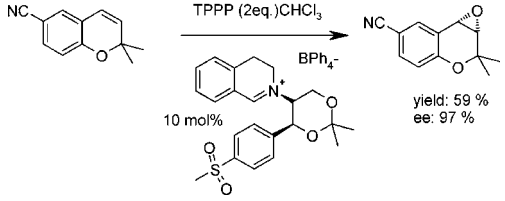


A Critical Review of Palladium Catalysts in Cross-Coupling and Heck Chemistry

V. Farina (*Adv. Synth. Catal*. **2004**, *346*, 1553) has reviewed the new development of high-turnover catalysts for the cross-coupling and Heck reactions. New development in the area is mainly palladacycles and coordinatively unsaturated Pd catalysts featuring bulky phosphanes. These catalysts have been reviewed from a mechanistic and synthetic standpoint and are compared with more traditional catalysts obtained from mono-and polydentate N- and P-based ligands, as well as Pd catalysts without strong ligands. Carbene ligands are also briefly discussed. Whereas a single, most promising approach to high-turnover catalysis cannot presently be defined, it is clear that the new "PdL1" catalysts, where the ligand is a bulky P ligand of high donicity, represents the latest, most important development in palladium research from the standpoint of scope and efficiency.

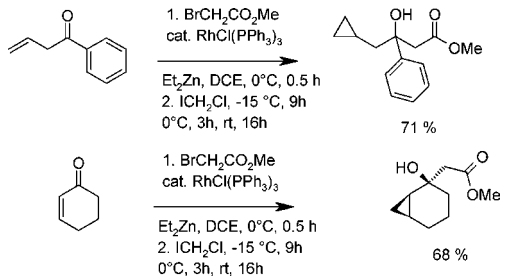
Asymmtric Epoxidation of *cis*-Alkenes Mediated by Iminium Salts

P. C. B. Page et al. (*Org. Lett*. **2005**, *7*, 375) have epoxidised a range of cis-substituted olefins with a new dihydroisoquinolinium salt catalyst, using tetraphenylphosphonium monoperoxysulfate as the stoichiometric oxidant giving ee's of 61−97% and yields between 52 and 89%. The reaction is performed under nonaqueous conditions in contrast to earlier iminium salt-catalysed methods where the need for oxone as a stoichiometric oxidant made water necessary due to solubility of the oxone.



One-Pot Reformatsky/Cyclopropanation Sequence Induced by Diethylzinc

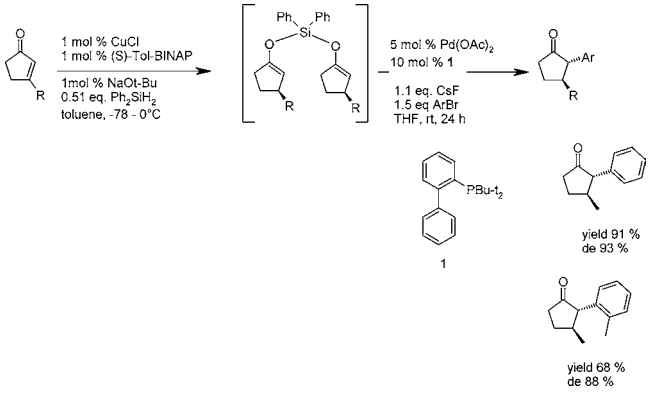
J. Cossy et al. (*Org. Lett*. **2005**, *7*, 171) have a one-pot Reformatsky/cyclopropanation sequence, which is induced by diethylzinc to allow the transformation of ω-unsaturated ketones and aldehydes to the corresponding cyclopropyl alcohols.



One-Pot Sequential Cu-Catalysed Reduction and Pd-Catalysed Arylation of Silyl Enol Ethers

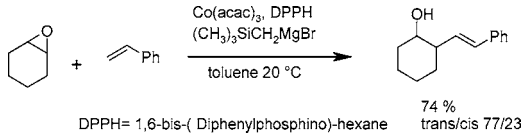
S. L. Buchwald et al. (*Org. Lett*. **2004**, *6*, 4809) have used enantiomerically enriched β-substituted diphenylsilyl enol

ethers, which can be prepared from Cu-catalysed asymmetric conjugate reduction in the Pd-catalysed arylation using various aryl bromides. The method provides a simple route to α-arylated cycloalkanones in high levels of enantiomeric and diastereomeric purity. There is no need to isolate the intermediate diphenyl enol ethers.



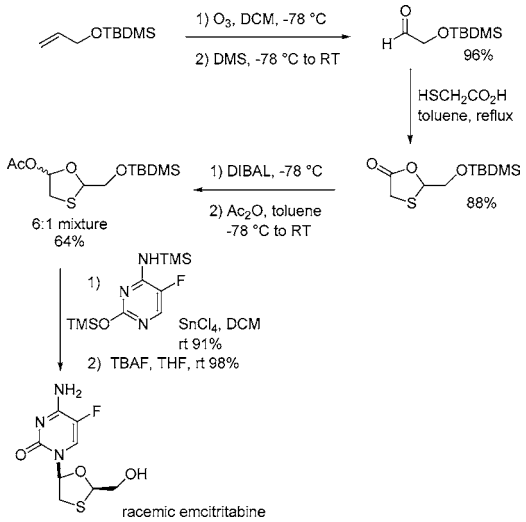
Cobalt-Mediated Mizoroki−Heck-Type Reaction of Epoxides with Styrenes

K. Oshima et al. (*Adv. Synth. Catal*. **2004**, *346*, 1631) have developed a cobalt-mediated synthesis of homocinnamyl alcohols from epoxides and styrene. The reaction proceeds via ring opening of the epoxides by means of magnesium bromide which generates a radical from an electron-rich cobalt complex through single electron transfer. The reaction is applicable to the synthesis of homocinnamylamines as well.

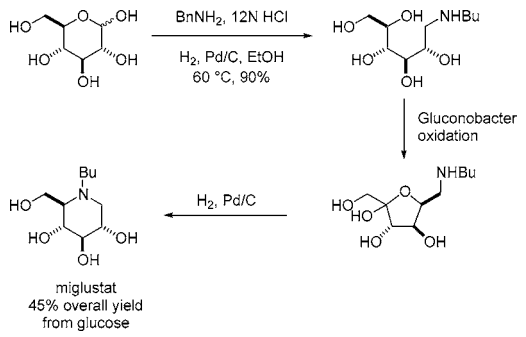


Synthetic Approaches to 2003 New Drugs

Last year we highlighted a review by chemists from Pfizer which analysed synthetic routes to all the new chemical entities (NCEs) marketed in 2002 (Li, J. and Liu, K. K.-C. *Mini-Rev., Med. Chem.* **2004**, *4*, 207) and expressed the wish that they would do the same each year. With the addition of a third author, they have obliged by publishing a second minireview covering the synthesis of 23 NCEs marketed in 2003 (Liu, K. K.-C.; Li, J.; Sakya, S. *Mini-Rev. Med. Chem.* **2004,** *4*, 1105). An example of a concise synthesis described in the review is that of emcitritabine, a drug discovered by researchers at Emory University and licensed to Triangle Pharmaceuticals (subsequently acquired by Gilead). The drug is a novel HIV nucleoside reverse transcriptase inhibitor marked under the trade name Emvitra. An efficient synthesis of the racemic drug from the group of Liotta is shown below. The drug is sold as a single enantiomer, and the resolution of key intermediates can be a key issue, as shown in the synthetic routes to GlaxoSmithKline's 3TC. In the patented synthesis, which may be the one used commercially, the resolution is carried out on the butyroyl ester rather than the TBDMS ether of the oxathiolinone, and the coupling is carried out with TMSI rather than a tin reagent.



Miglustat is a drug for the treatment of Gaucher's disease and was developed by Oxford Glyco Sciences (now part of UCB-Celltech) and Actelion Pharmaceuticals. One synthesis of the drug begins with D-glucose (see scheme).



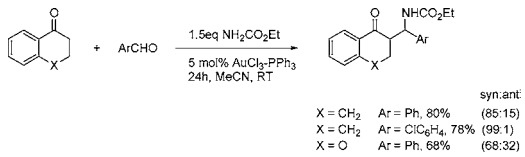
The review also covers the synthesis of tadalafil (Cialis) and vardenafil (Levitra) which are competitive products for Viagra. It is interesting to compare the synthetic analysis of the Pfizer workers at Groton with the views discussed in the last issue of *Organic Process Research & Development* by Peter Dunn of Pfizer, Sandwich (UK), where he compared syntheses of the same two drugs with the commercial Viagra synthesis (Dunn, P. *Org. Process Res. Dev.* **2004,** *9,* 88).

Transition Metal-Catalysed Direct Three-Component Mannich Reactions

Multicomponent reactions are useful in discovery of new molecules and in process R&D, where the atom efficiency and the rapid construction of complex molecules are attractive features. Whilst there has been renewed interest in the Mannich reaction as a useful multicomponent reaction, the scope has been limited to certain amines, particularly with organic catalysts.

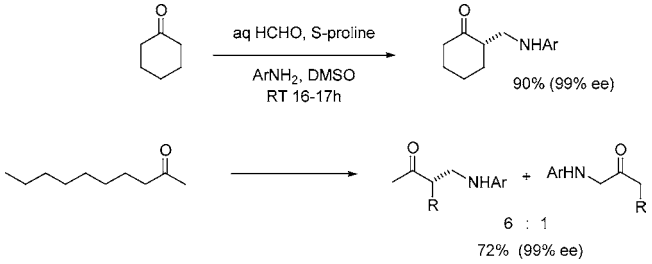
It has now been found (Xu, L.-W. et al. *J. Org. Chem.* **2004,** *69*, 8482) that certain transition metal salts ($RuCl_3 \cdot H_2O$; $AuCl_3$, $AuCl_3-PPh_3$) were effective in catalyzing the reaction of aromatic aldehydes and arylmethyl ketones with

carbamates. Catalysts which were ineffective were $Cu(OTf)_2$, $Pd(MeCN)_2Cl_2$, $RuCl_2(PPh_3)_2$, $NiCl_2 \cdot 6H_2O$, and $CuCl_2$.

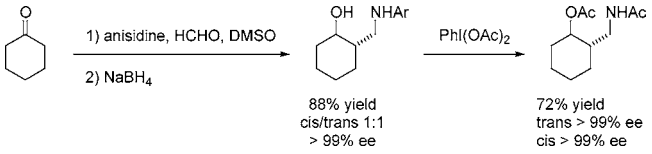


Catalytic Enantioselective Aminomethylation of Ketones

There has been renewed interest in Mannich-type reactions, particularly in asymmetric variants using organocatalysts. Now the group of Cordova at Stockholm University, Sweden, has reported an asymmetric Mannich reaction with very high enantiomeric excess (Ibrahem, I. et al. *Angew. Chem., Int. Ed.* **2004**, *43*, 6528). The reaction occurs between ketones, aqueous formaldehyde, and an aromatic amine, using amino acid catalysts in DMSO.



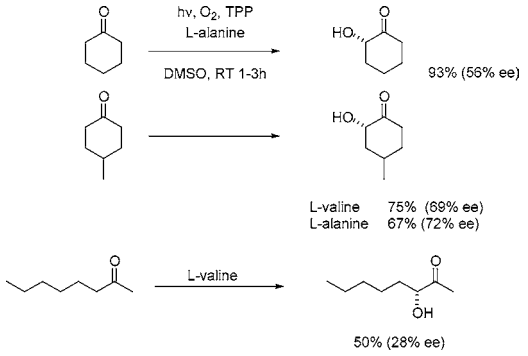
The reactions can be carried out in wet solvents and in the presence of air and can be readily scaled up. The disadvantage, however, is the need to use aromatic primary amines, whereas the Mannich reaction is normally carried out with aliphatic amines—an asymmetric variant with aliphatic amines would make the reaction so much more useful to industry, even if the enantioselectivity were only moderate. With aromatic amines, particularly anisidine, it is possible to deprotect by oxidation, but this adds another step.



Direct Amino Acid-Catalysed Asymmetric Oxidation with Molecular Oxygen

There have been a number of reports of oxidation of ketones to α-hydroxyketones, catalysed by amino acids in the past year, and some have been highlighted in these columns, The latest advance (Sundén, H. et al. *Angew. Chem., Int. Ed.* **2004,** *43*, 6532) uses air or molecular oxygen, but requires visible or UV light and tetraphenylporphine (TPP) as catalyst in addition to an amino acid. The α-hydroxy ketone product exists as a mixture of dimeric and oligomeric products and is best reduced in situ to the corresponding diol.

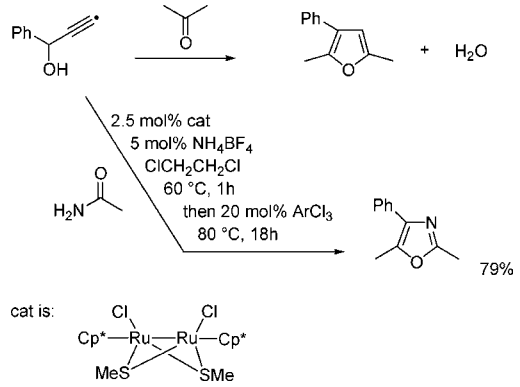
Unusually, alanine and valine give better results than proline, in terms of asymmetric induction. DMSO and other dipolar aprotic solvents such as DMF and NMP gave best results. whereas methanol and chloroform did not work. Surprisingly the reaction also worked in water, but lower ee was obtained.



It was also shown that acetone could be oxidized to α-hydroxyacetone and dihydroxyacetone using sunlight and these prebiotic conditions may have given rise to amino acid-catalysed synthesis of sugars (via α-hydroxyketones) in the beginnings of life on earth.

Oxazole, Furan, and Pyrrole Synthesis

The group of Uemura at the University of Kyoto, Japan, has recently disclosed a method of converting propargyl alcohols to heterocycles using ruthenium and gold catalysts (Nishibayashi, Y. et al. *Angew. Chem., Int. Ed.* **2003**, *42*, 2681). The original publication concerned reaction of ketones or anilines to give tetrasubstituted furans or pyrroles. It has now been reported (Milton, M. D. et al. *Chem. Commun.* **2004,** 2712) that reaction of acetylenic alcohols with amides can give oxazoles in moderate to good yield.

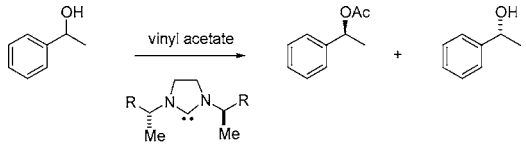


The reaction appears to proceed via ruthenium-catalysed displacement of the alcohol by the amide nitrogen, followed by a gold-catalysed isomerisation of acetylene to allene, and then cyclisation (see scheme on following page). The first step in the reaction has already been demonstrated in Uemura's group, and the intermediates have been isolated (Nishibayashi, Y. et al. *J. Am. Chem. Soc.* **2000,** *122*, 11019 and *Organometallics* **2004**, *23*, 26).

Chiral N-Heterocyclic Carbenes as Catalysts for Kinetic Resolution

N-Heterocyclic carbenes (NHCs) are efficient catalysts for a number of reactions, including the benzoin and Stetter reactions. It had been shown that NHCs will catalyse transesterification reactions and acylations, and it is now

reported that chiral NHCs will catalyse kinetic resolution of secondary alcohols in the presence of acylating agents. At present, ee's are moderate (up to 58%), and the process does not compete with enzyme methods. However, it is early days yet, and further design should lead to better catalysts (Suzuki, Y. et al. *Chem. Commun.* **2004,** 2770).

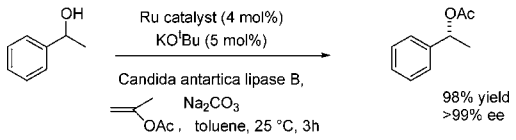


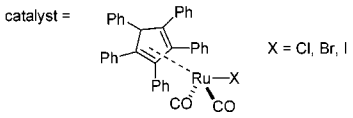
R = naphthyl, phenanthryl, anthryl, pyrenyl etc

Compatible Metal and Enzyme Catalysts for Efficient Dynamic Kinetic Resolution of Alcohols

Dynamic kinetic resolution is a powerful tool to transform a racemic mixture into a single enantiomer and is industrially applicable. The combination of an enzyme with a metal catalyst which performs in situ racemisation of the unreacted isomer has been widely reported, with the groups of Williams in the UK and Bäckvall in Sweden being prominent. The Swedish group have recently found that certain ruthenium complexes, after activation with potassium *tert*-butoxide catalyse the racemisation of chiral alcohols efficiently at room temperature (within 10 min in some cases). Initial attempts to combine these catalysts with enzymic resolution resulted in failure, but after fine-tuning and optimisation, reaction conditions were eventually found which gave good results. The dynamic kinetic resolution is 2 orders of magnitude faster than previously reported results (Martin-Matute, B. et al. *Angew. Chem., Int. Ed.* **2004,** *43*, 6535).

The system is, however, very sensitive to molecular oxygen and must be carried out under an inert atmosphere. The order of addition of reagents is also important—premixing the ruthenium complex with butoxide is required and presumably generates a new catalyst (the colour changes from yellow to dark red during this period). It is suggested that butoxide displaces halogen from the catalyst to form a new active species, and during the catalytic cycle the chiral alcohol displaces butoxide and itself becomes coordinated to the ruthenium. A β-elimination then gives the ketone and a ruthenium-hydride species which then reduces the ketone to racemic alcohol.





Microwave Technology

Several companies are involved in supplying microwave equipment for chemical synthesis, including Biotage (formerly Personal Chemistry) CEM, Milestone, and Anton Paar. An article in *Chemical Engineering News* (Marx, V. *Chem. Eng. News* **2004**, *82*, 14) discusses the latest advances in the technology, with views from users of equipment as well as the equipment manufacturers. For development chemists, scale-up is the key issue, and companies are now offering equipment which will operate on larger scale, using Raman spectroscopy to monitor progress, or using continuous flow technology.

An excellent review article on "Controlled Microwave Heating in Modern Organic Synthesis" has appeared recently (Kappe, C. O. *Angew. Chem., Int. Ed.* **2004,** *43*, 6250). The last section of this article is concerned with scale-up problems, and the author, who is from the Karl-Franzens University in Graz, Austria, cites a number of articles where scale-up has been carried out. However, this usually means up to one-litre scale. The preferred option for larger quantities appears to be continuous flow, although this may be because of equipment availability. At present, there does not appear to be any published example of the use of microwave technology for organic synthesis on a production scale, although I believe there are examples of microwave-induced depolymerisation of polystyrene waste which has been used commercially in South Africa.

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