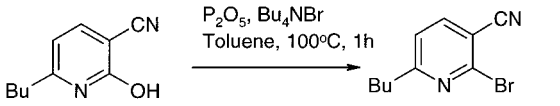
Organic Process Research & Development **2001**, *5*, 460–466

Highlights from the Literature

Some Items of Interest to Process R&D Chemists and Engineers as Selected by Trevor Laird and Stephen A. Hermitage

Halogenheteroarenes have been found to be of synthetic utility for the construction of both bioactive natural products and pharmaceutical drugs, owing to the wide range of cross coupling reactions they may undergo. Kato et al. from the Banyu pharmaceutical company have described a "facile bromination" reaction of hydroxyheteroarenes (*Tetrahedron Lett.* **2001**, *42*, 4849) using P_2O_5/Bu_4NBr to give the bromoheteroarene skeleton in good yields. In particular they have applied their method to the synthesis of 2-bromo-6-butyl-3-cyanopyridine on multikilogram scale with good control, avoiding hazardous gaseous by-products in 82% yield (Scheme 1). It is this substrate that is used as a key intermediate in an endothelin receptor antagonist programme.

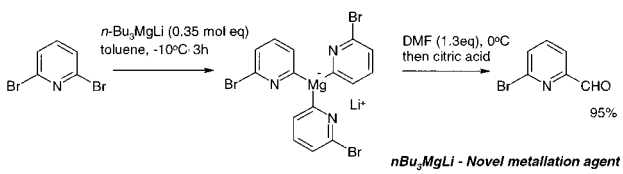
Scheme 1



Bromination

In a separate communication, also from the Banyu pharmaceutical company, Iida and co-workers describe (*Tetrahedron Lett.* **2001**, *42*, 4841) how lithium tributylmagnesate complex ($^nBu_3MgLi$) [readily prepared from ^{n}BuLi and ^{n}BuMgCl (2:1)] can be used as a novel metalation agent. This complex was found to be efficient for the *mono*-bromine−magnesium exchange of 2,6-dibromopyridine (Scheme 2) under noncryogenic conditions (−10 °C) to give a stable magnesate intermediate. Subsequent treatment with DMF gave 6-bromo-2-formylpyridine in excellent yield. The group have used this method on multikilogram scale and have produced 25 kg of 6-bromo-2-formylpyridine, using this chemistry as well as demonstrating the monometallation reaction on a variety of other substrates.

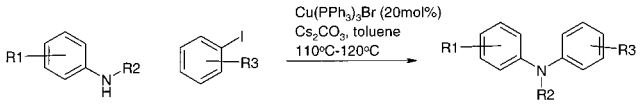
Scheme 2



nBu3MgLi - Novel metallation agent

Venkataraman and co-workers have recently described the formation of aryl-nitrogen bonds using a soluble copper(I) catalyst (*Tetrahedron Lett.* **2001**, *42*, 4791). In their method $Cu(PPh_3)_3Br$ was used as the air-stable catalyst with cesium carbonate as base to catalyse the combination of aryl iodides and amines (Scheme 3). The group describe a method for the preparation of $Cu(PPh_3)_3Br$ from triphenylphosphine and $CuBr_2$. Interestingly, they point out that copper provides economic attraction over noble metals such as palladium with the price of palladium rising from $100/ounce in 1995 to $800/ounce in 2001 and platinum costing $600/ounce compared to copper at $0.05/ounce.

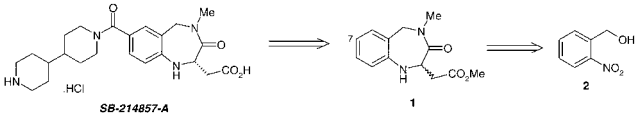
Scheme 3



Soluble copper catalyst

Carey and co-workers from GSK have reported their synthetic efforts towards the GPIIb/IIIa receptor antagonist SB-214857-A (*Tetrahedron Lett.* **2001**, *42*, 4915). The key steps involve the preparation of the racemic methyl ester **1** (Scheme 4) from 2-nitrobenzyl alcohol **2**, a resolution using an immobilised lipase enzyme and a palladium-catalysed amino carbonylation reaction.

Scheme 4



Scheme 5 outlines the preparation of the key racemic building block **1**, starting with conversion of amine **3** to the ene ester **4** by reaction with dimethyl acetylene dicarboxylate. Hydrogenation of **4** using Raney nickel as catalyst led to clean and selective nitro reduction to an intermediate aniline which was not isolated but was treated with mild acid, causing cyclisation to the tetrahydroquinazoline **5**. A variety of bases were screened for the conversion of **5** to **6**, but sodium methoxide in methanol provided the preferred conditions, giving **6** in excellent yield. Final hydrogenation of the single double-bond isomer of **6** using palladium on carbon as catalyst gave the racemic **1** in excellent overall yields. The group report resolution of **1** using *Candida antartica* lipase B. Iodination of the resolved acid in the 7 position and palladium-catalysed aminocarbonylation with 4,4′-pyridylpiperidine gave SB-214857-A after a final hydrogenation stage. This route has been scaled up to produce kilogram quantities of drug substance.

Neotame (*N*-[*N*-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester) is the next generation of nonnu-

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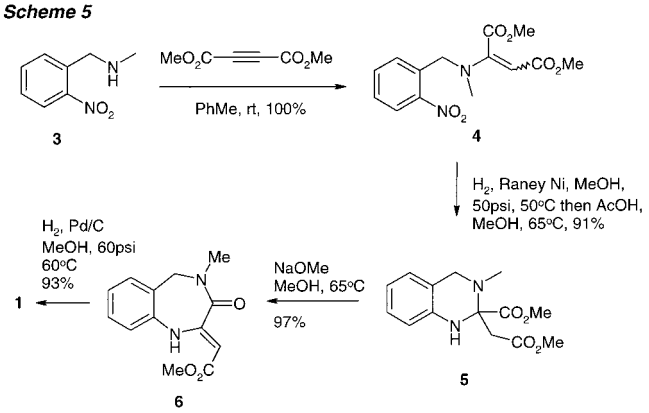
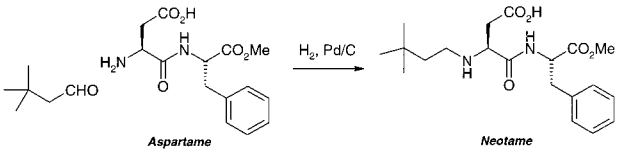
Scheme 5



tritive sweetners from the NutraSweet Company (*Synth. Commun.* **2001**, *31*, 667). Neotame is synthesised by the reductive alkylation of aspartame with 3,3-dimethylbutyraldehyde (Scheme 6).

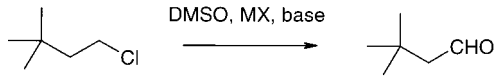
Scheme 6



Reductive amination

To explore economical synthetic routes to 3,3-dimethylbutyraldehyde the group at the NutraSweet Company have developed a process that involves oxidation of 1-chloro-3,3-dimethylbutane with DMSO in the presence of a base and substoichiometric amounts of MX (M = Na, K; X = Br, I) (Scheme 7). In addition they report the purification of the aldehyde via a bisulphite adduct.

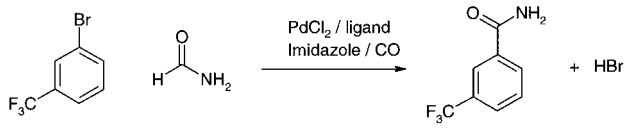
Scheme 7



Oxidation

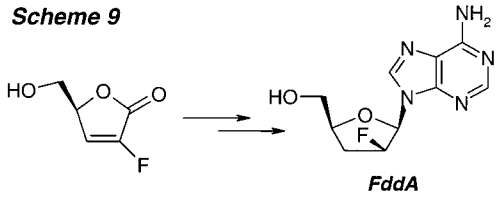
Primary aromatic amides have been synthesised by the aminocarbonylation of aryl halides using formamide as an ammonia synthon in high yield by Indolese and co-workers (*J. Org. Chem.* **2001**, *66*, 4311), Scheme 8. The reactions require a palladium catalyst in combination with a nucleophilic Lewis base such as imidazole or 4-(dimethylamino)pyridine (DMAP). The group have studied the influence of catalyst, base, solvent, pressure, and temperature and have clarified the mechanism.

Scheme 8



An efficient synthesis of FddA from (*S*)-(−)-2-fluoro-4-(hydroxymethyl)-2-buten-4-olide, a novel drug candidate for the treatment of AIDS, has been developed by Jin and colleagues at the DuPont pharmaceutical company (*Tetrahedron Lett.* **2001**, *42*, 4787) (Scheme 9). They report high efficiency for each chemical transformation and simplicity of purification of intermediates, rendering their approach applicable to larger-scale synthesis.

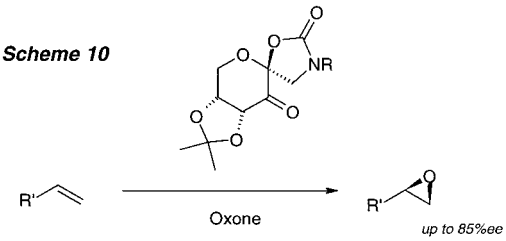
Scheme 9



FddA

Shi and co-workers make progress in the challenging problem concerning chiral epoxidation of terminal alkenes with good enantioselectivity in their recent paper (*Org. Lett.* **2001**, *3*, 1929). In their approach the chiral ketone (R = Boc, H, Me) is used (Scheme 10) as chiral catalyst, and Oxone is used as the oxidant with enantioselectivities of up to 85% being reported. The group indicate a precise understanding of the transition states for the epoxidation is difficult at the moment but clearly demonstrate the enormous potential for chiral dioxiranes (generated from the chiral ketone and Oxone) as enantioselective epoxidising agents. It is also worth noting, for new comers to this area, that this publication contains many excellent leading references.

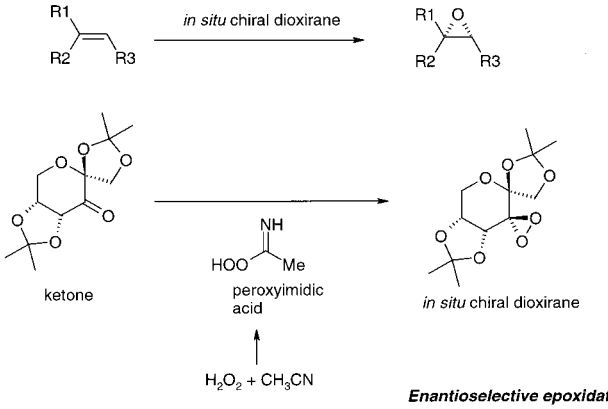
Scheme 10



Enantioselective epoxidation

In a separate publication (*Tetrahedron* **2001**, *57*, 5213) Shi and Shu also describe the epoxidation of alkenes using a fructose-derived chiral ketone (Scheme 11) as catalyst and hydrogen peroxide as the primary oxidant. Acetonitrile was used not only as solvent but as reagent to react with hydrogen peroxide to generate the dioxirane via the peroxyimidic acid. The group point out that these oxidations are performed under mild conditions. High yields and ee's are obtained for a number of olefins, using inexpensive H_2O_2 as the primary oxidant.

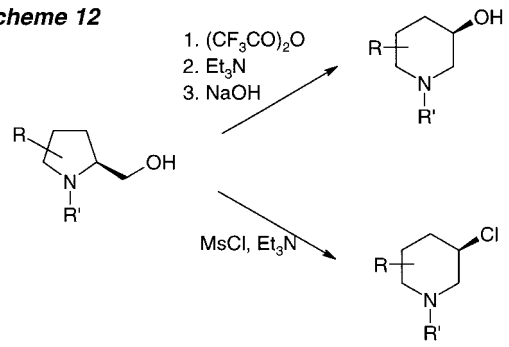
Scheme 11



Enantioselective epoxidation

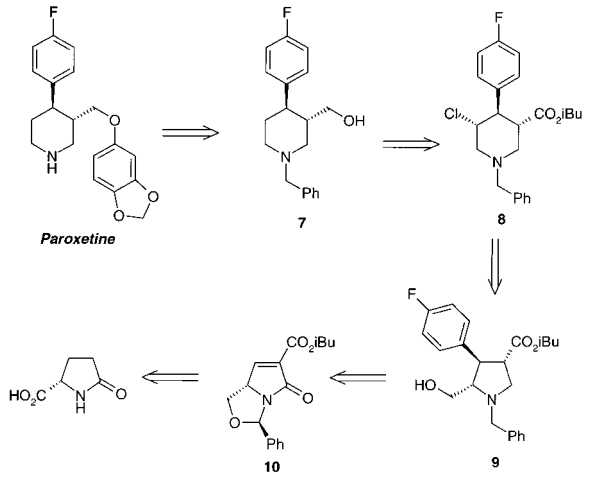
The ring expansion of enantiomerically pure substituted prolinols to enantiomerically pure substituted 3-hydroxypiperidines or substituted 3-chloropiperidines (Scheme 12) provides a useful synthetic tool to enable the construction of complex chiral heterocyles. In a publication from Cossy et al. (*Tetrahedron Lett.* **2001**, *42*, 5705) this reaction has been used as one of the key steps in the synthesis of the selective serotonin reuptake inhibitor (SSRI) paroxetine (Paxil).

Scheme 12



The disconnection of Paroxetine is shown in Scheme 13. Retrosynthesis back to the *N*-benzyl-protected chiral piperidine alcohol **7** allows for functional group manipulation to the ester **8**. The functionality contained within this key ester intermediate allows the rearrangement reaction of the chiral prolinol **9** to employed in the forward synthetic sequence. In a series of standard functional group manipulations (L)-pyroglutamic acid may be converted to the chiral template **10** which in turn can be manipulated to the chiral aryl compound **9** by cuprate chemistry.

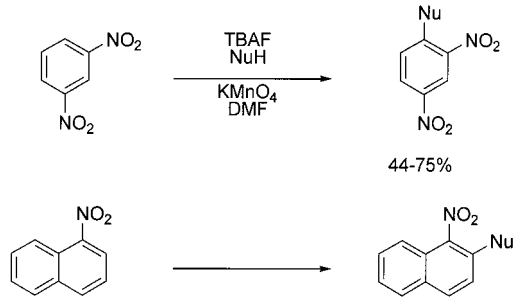
Scheme 13



A direct reaction between nucleophiles and *m*-dinitrobenzene takes place in the presence of $KMnO_4$ and fluoride ions (Huertas, I. et al. *Tetrahedron Lett*. **2001**, *42*, 3439). The reaction also proceeds with nitronaphthalenes. Nucleophiles include aliphatic amines, aromatic amines, amides, nitriles, and ketones. (Scheme 14).

A simple and effective method for removing Ph_3P and Ph_3PO from reaction mixtures has been described (Lipschutz, B. H. et al. *Org. Lett.* **2001**, *3*, 1869). Commercially available

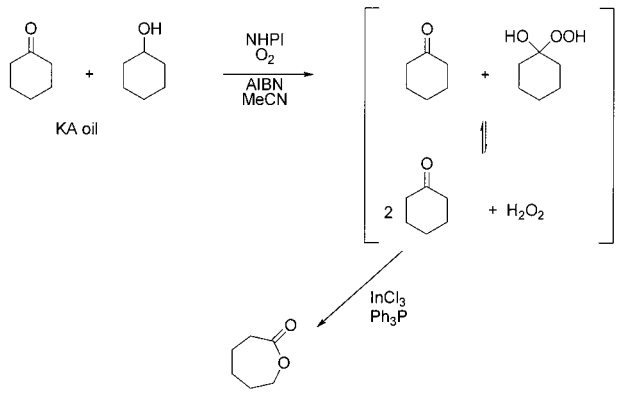
Scheme 14



high-loading chloromethylated polystyrene, modified in situ with NaI acts as a scavenger. In fact, the resin unsurprisingly reacts with Ph_3P and surprisingly with Ph_3PO to produce an oxophosphonium iodide. The effectiveness of the resin has been tested on various cross coupling reactions, a Staudinger (azide → amine) process but not a Wittig reaction.

KA oil is a mixture of cyclohexanone and cyclohexanol obtained by aerobic oxidation of cyclohexane and is an important intermediate in the production of adipic acid and caprolactam. Caprolactone is manufactured from cyclohexanone by peracetic acid Baeyer−Villager reaction, the peracid being generated from acetaldehyde and oxygen. A new method (Fukuda, O. et al. *Tetrahedron Lett.* **2001**, *42*, 3479) allows the catalytic B−V oxidation of KA oil directly to caprolactone using dioxygen in the presence of catalytic *N*-hydroxyphthalimide (NHPI) followed by treatment with indium trichloride. (Scheme 15). Yields are only moderate at present, but the idea has industrial potential if a more efficient and cheaper catalyst than indium can be found.

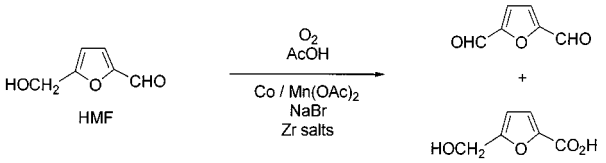
Scheme 15



Hydroxymethylfurfural (HMF) is one of the few compounds that can be prepared from various carbohydrates in high yield (up to 98%). Best yields are from fructose, but low-cost mono- and polysaccharides (glucose, sucrose, starch, etc.) can be used. HMF is therefore a useful building block for the fine chemicals industry. A group at DuPont (Partenheimer, W. et al. *Adv. Synth. Catal*. **2001**, *343*, 102) has studied the oxidation of HMF using O_2/metal/bromide catalysts, typically used for oxidising xylene to terephthalic acid on industrial scale. Surprisingly, HMF could be oxidised to diformylfuran or furan 2,5-dicarboxylic acid with high selectivity. (Scheme 16). This prompted the authors to examine the oxidation of benzyl alcohol, and it was found that under controlled conditions, benzaldehyde could be

produced in high yield. The paper contains a discussion of the mechanism of these selective oxidations.

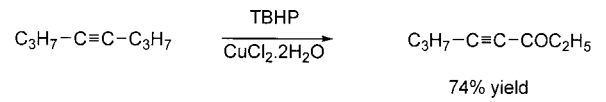
Scheme 16



Selective oxidation of alkanes remains a very difficult but highly desirable goal. Most reported systems convert alkanes to oxygenated derivatives such as alcohols, ketones, or further oxidised products. A recent publication, however, reports the oxidative dehydrogenation of alkanes to alkenes (Khenkin, A. M. et al. *J. Am. Chem. Soc.* **2001**, *123*, 6437). The oxidant is *tert*-butylhydroperoxide with a Keggin-type polyoxomolybdate ($H_3PMo_{12}O_{46}$) as catalyst in acetic acid. As yet, only moderate yields are obtained, but selectivity is high. Thus, cyclooctane and cycloheptane are converted to cyclooctene (30%) and cycloheptene (22%) in high selectivity 99%, whereas *cis*-decalin gives a 43% yield of a mixture of products of which tetralin (53%) is the major one. It is suggested that the mechanism is initial removal of one H via a radical process followed by conversion to a carbocation and loss of a proton from the adjacent carbon atom.

Another unusually selective oxidation is the *tert*-butylhydroperoxide-promoted oxidation of a methylene group adjacent to an acetylene (Li, P. et al. *J. Org. Chem*. **2001**, *66*, 4087)—the best catalyst is copper(II) chloride, although other catalysts do work as well. Without catalyst, the alcohol is produced, but with catalyst, the ketone is the major product. (Scheme 17).

Scheme 17



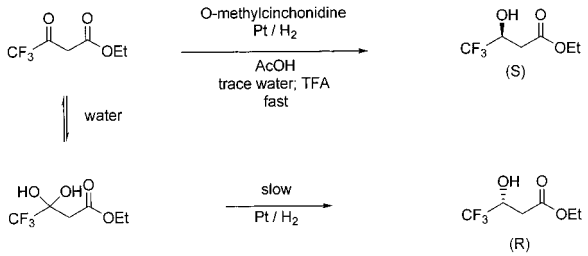
A review entitled "Practical Considerations in Kinetic Resolution Reactions" has appeared in the first issue of a new journal (Keith, J. M. et al. *Adv. Synth. Catal*. **2001**, *343*, 5). The journal is an updated version in English of the German publication *J. Prakt. Chem.*, which explains the 343 volume number! The review, from the group of Jacobsen at Harvard, analyses the conditions under which kinetic resolution can be the best option for synthesis of an optically active molecule. The review is not only of the author's work but also encompasses the whole literature.

When a kinetic resolution is performed under conditions where the substrate racemises, then high yields of single enantiomers can be obtained directly. The racemisation can be performed by an organometallic reagent (for an example see Persson, B. A. et al. *J. Am. Chem. Soc.* **1999**, *121*, 1645) or sometimes by a biocatalyst. A review on biocatalysis and its use in clean routes to making old and new products has appeared in a recent issue of *Chem. Eng. News* (**2001**, *79*(21), 27).

When a group at the University of Warwick were having difficulty with a resolution of enantiomers of metallic supramolecular helicates, they in desperation, turned to paper chromatography (Hannon, M. J. et al. *Chem Commun*. **2001**, 1078). Surprisingly, where most methods including HPLC had failed, paper chromatography worked. For preparative scale, cellulose column chromataography proved effective.

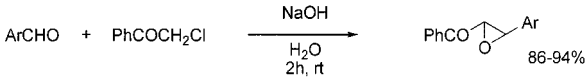
In the past few years there has been remarkable progress in the enantioselective hydrogenation of α-functionalised ketones over chirally modified Pt catalysts, with ee's of over 90% being achieved. Some understanding of how the modifiers work has helped with the design of new catalysts. The influence of reaction conditions, however, is less well understood. In a recent publication from the group of Baiker at ETH, Zurich (Baiker, A. et al. *Angew. Chem., Int. Ed.* **2001**, *40*, 2302), the ee in the reduction (See Scheme 18) varied when traces of water were present, and this variation was enhanced by catalytic amounts of strong acid. The ee varied with conversion and in some cases inverted to produce the R isomer after 50% conversion—this was not caused by racemisation of the product. As is typical of this type of behaviour, at least two reacting species are present which hydrogenate at different rates and in a different stereochemical sense—this was proved by NMR evidence. Although the CF_3 group encourages this behaviour (hydration), it is suggested that loss of ee at high conversions in previous publications may be explained by hydration when undried solvents such as acetic acid are used. This has obvious implications for scale-up, where time-dependent phenomena can be problematical. As always, better understanding of the mechanism can lead to effective control of the process.

Scheme 18



The Darzens reaction is an important C−C bond forming process and is usually carried out under dry conditions. A recent report (Tanaka, K. et al. *Green Chem.* **2001**, *3*, 135) indicates that Darzens condensations can take place in aqueous suspension. (See Scheme 19). If the product is a solid, it can easily be isolated by simple filtration. In the presence of a chiral phase-transfer catalyst a low selectivity (12% ee) was obtained.

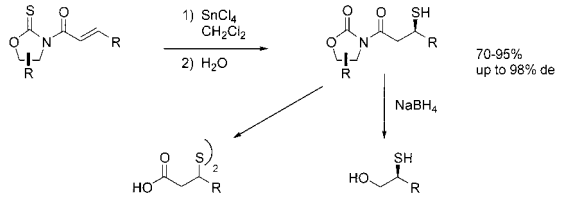
Scheme 19



β-mercapto carbonyl compounds are not easy to prepare since sulphur analogues of the Mannich reaction and the aldol condensation have limited use. The best procedure involves conjugate addition to double bonds but may involve difficult deprotection if thiols—rather than sulphides—are required.

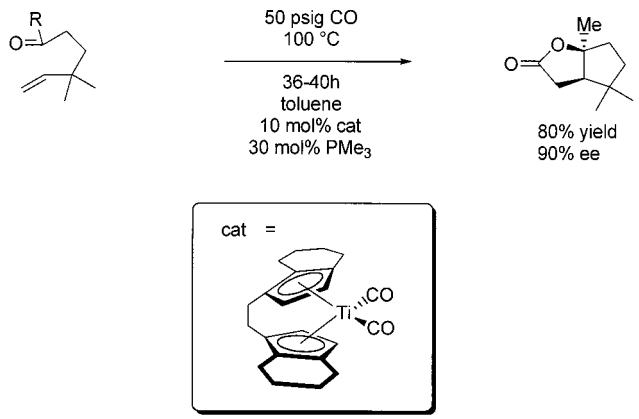
A new strategy for the asymmetric synthesis of β-mercapto carboxylic acid derivatives relies on intramolecular attack (Scheme 20), from a chiral auxiliary. Once reacted, the chiral auxiliary can be removed and recycled (Palomo, C. et al. *J. Am. Chem. Soc.* **2001**, *123*, 5602).

Scheme 20



Butyrolactones can be generated from an alkene, a carbonyl compound and carbon monoxide by a very atom-efficient hetero-Pauson−Khand-type process. A chiral version of this methodology has recently been announced by the group of Crowe at Louisiana (Mandal, S. K. et al. *J. Am. Chem. Soc.* **2001**, *1223*, 6457). The catalyst is a chiral titanocene.

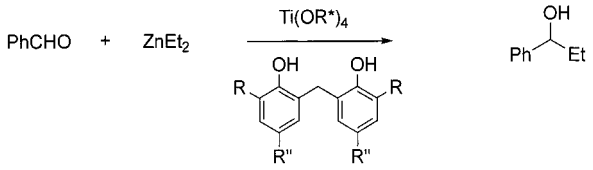
Scheme 21



I wonder how many publications there are on the asymmetric addition of diethyl zinc to aldehydes—possibly thousands. Hardly any report the addition of any other alkylzinc, the reason being that other alkyl or aryl zincs are difficult to remove from associated salts which affects the ee. As a result, I rarely read a new article on Et_2Zn additions to aldehydes. A recent communication, however, describes the optimisation of asymmetric catalysts using *achiral* ligands (Davis, T. J. et al. *Org. Lett.* **2001**, *3*, 2161). The principle—termed "metal geometry-induced ligand asymmetry"—is shown in Scheme 22, where a coordinated methylene-bisphenol reacts with a chiral titanium alkoxide to generate a chiral catalyst in situ. The ee depends on the R groups which affect the geometry of coordination. Although ee's of up to 83% were obtained in some cases, in others, the opposite enantiomer product was obtained. The principle may be extended to other reactions in the future.

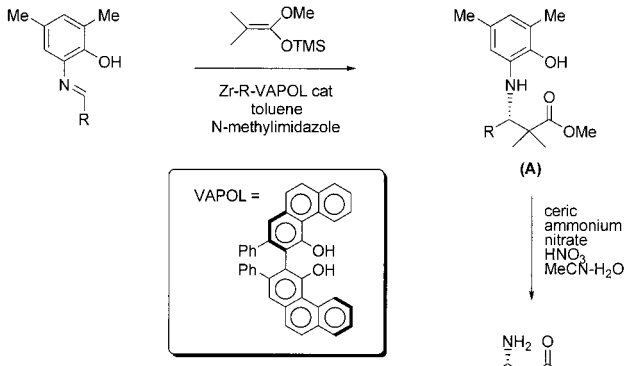
A highly asymmetric and remarkably temperature-independent catalyst for the imino-aldol reaction has been discovered by the group of Wulff at Michigan State University (Wulff, W. D. et al. *Angew. Chem., Int. Ed.* **2001**, *40*, 2271). Some typical results are shown in Scheme 23 for

Scheme 22



the synthesis of α-amino acids. On increasing the temperature, the amount of catalyst required can be reduced *and* the enantiomeric excess unchanged.

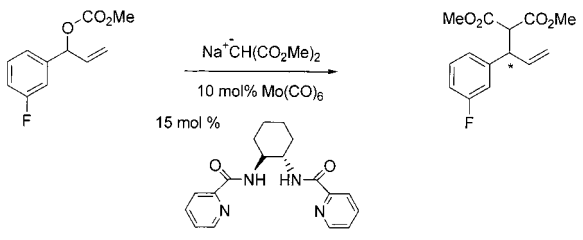
Scheme 23



mol % cat	T °C	Yield of **(A)** (R = Ph)	ee (%)
20	25	100	98.0
20	65	93	98.4
20	85	94	98.5
20	100	91	98.5
5	100	90	98.4
2	100	95	98.5

The molybdenum-catalysed asymmetric allylic alkylation reaction, originally developed by Trost has been modified by using the readily available $Mo(CO)_6$ in place of air-sensitive $(EtCN)_3Mo(CO)_3$. A group at Merck Process Research (Palucki, M. et al. *Adv. Synth. Catal*. **2001**, *343*, 46) have studied the reaction in Scheme 24 by in situ IR to ensure the proper activation time to maximize catalyst formation. Good yields and excellent ee's resulted—the reaction is used to prepare a key intermediate for a lead drug candidate on 2 kg scale.

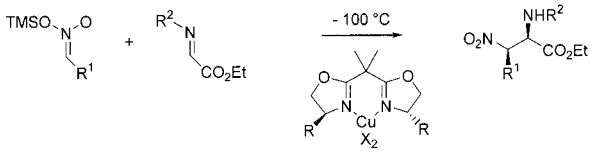
Scheme 24



Solvent	% ee	Branched : Linear	Assay Yield
Toluene	97	95 : 5	91
THF	92	92 : 8	86
DMF	87	86 : 14	55
DME	95	85 : 15	90

The first catalytic asymmetric aza-Henry reaction of nitronates with imines has been reported from the innovative group of Jorgensen in Denmark (Knudsen, K. R. et al. *J. Am. Chem. Soc.* **2001**, *1223*, 5843). Yields of 99% and ee's of up to 98% are obtained in some cases (See Scheme 25).

Scheme 25



A rapid inexpensive method for producing water-soluble enzyme-coated micro crystals has been announced (Kreiner, M. et al. *Chem. Comm*un. **2001**, 1096). These enzymes show much enhanced catalytic activity and stability in nonaqueous media and the authors have applied for a patent (WO OO/69877) on the invention. Purchased enzymes could be made more active by up to 200 times by this simple procedure which involved:

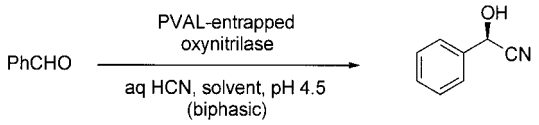
(1) mixing the aqueous solution of commercial enzyme and a solution of an excipient (e.g., K_2SO_4, sugar, amino acid), (2) slowly adding this solution into a water-miscible organic solvent (e.g., propanol) with rapid mixing—the solvent is chosen to precipitate the enzyme and excipient, (3) storing at room temperature until required or transferring to a different solvent.

During the process the organic solvent dehydrates the enzyme, minimising denaturation, and leaves most of the enzyme in an active conformation. The enzyme can be dried and resuspended in a different solvent.

Amongst industrial production of chiral building blocks, cyanohydrins play an important role. Although there are a wide variety of efficient asymmetric synthesis of these molecules, enzyme methods still seem popular, but oxynitrilase enzymes deactivate quickly. For large-scale work immobilisation is the preferred strategy and an important method, which avoids leaching and gives well-defined lens-shaped particles with high activity, has been reported previously (Jekel, M. et al. *Chem. Eng. Tecknol.* **1998**, *21*, 275). A recent report describes the use of these cross-linked and poly(vinyl alcohol)-entrapped enzymes in the synthesis of mandelonitrile (Gröger, H. et al. *Org. Lett.* **2001**, *3*, 1969). *R*-Mandelonitrile is obtained from benzaldehyde and excess HCN in 93% yield and 94% ee. The catalyst is easy to recycle and loses none of its activity—in fact after 20 cycles the ee slightly *increased.* The article also notes a small but important solvent effect on enantioselectivity (Scheme 26) with diisopropyl ether giving the best result. The process looks ideal for commercialisation—some of the authors are from Degussa AG in Germany. *R*-Mandelonitrile is already produced on a multihundred-tonne scale.

A review on the use of protein crystals as novel catalytic materials has appeared from the group at Altus Biologics (Margolin, A. I. et al. *Angew. Chem., Int. Ed.* **2001**, *40*, 2205). Chemically cross-linked protein crystals are much more stable against denaturation by heat, organic solvents, and so forth than soluble proteins and the review classes them as bioinorganic zeolites.

Scheme 26

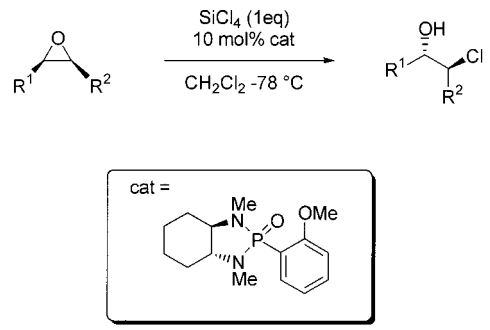


	% yield	% ee
MTBE-hexane	93	94
EtOAc	62	93
MTBE	70	92
$^{i}Pr_2O$	84	99

A review of chemical reaction engineering in the fine chemical industry has appeared (Carpenter, K. J. *Chem. Eng. Sci.* **2001**, *56*, 305). The review covers topics such as impurity generation (choice of conditions to minimise this), development costs, and time scales, batch-agitated vessels (which he calls "a cheap and flexible friend"), reactor selection, reactor design, and the future.

Process chemists are always concerned about reproducibility of their results, but often, at the early stage of a project, it may be difficult to reproduce a literature preparation or even a synthetic step that a colleague has carried out. The reason may be a slight change in the quality of the reagents or that a minor process change has occurred. It is rare that the failure to reproduce a published procedure is mentioned in print. Recent correspondence from the group of Denmark at Illinois (Denmark, S.E. *Angew. Chem., Int. Ed.* **2001**, *40*, 2255), however, mentions the inability of workers in his group and at MIT to reproduce the high enantiomeric excesses reported by the group of Buono (Brunel, J. M. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 2554) in the catalysed ring-opening of epoxides (Scheme 27). The speculation is that the analytical method of measuring the ee may have been flawed. In the hands of Denmark's group, the ee's were in the range 1−8%, not up to 99% as reported earlier. The message is clear—always read the Experimental Section to see how the data was established.

Scheme 27



And continuing the theme of reproduction problems, the editor wishes to apologise to authors in last month's

Highlights whose names were incorrectly spelled—poor proof reading by the editor was to blame. My thanks to Roger Sheldon for pointing these errors out!

Trevor Laird
Editor

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