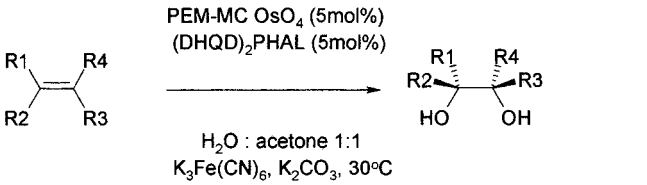
Organic Process Research & Development **2001**, *5*, 544–556

Highlights from the Literature

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

Osmium-catalysed dihydroxylation of olefins is one of the most efficient methods for the preparation of vicinal diols. In particular, catalytic asymmetric dihydroxylation of olefins using a catalytic amount of osmium tetroxide in the presence of chiral ligands allows access to a wide variety of enantiomerically pure vicinal diols. Kobayashi and co-workers have addressed the issue of OsO_4 being highly toxic and

Scheme 1

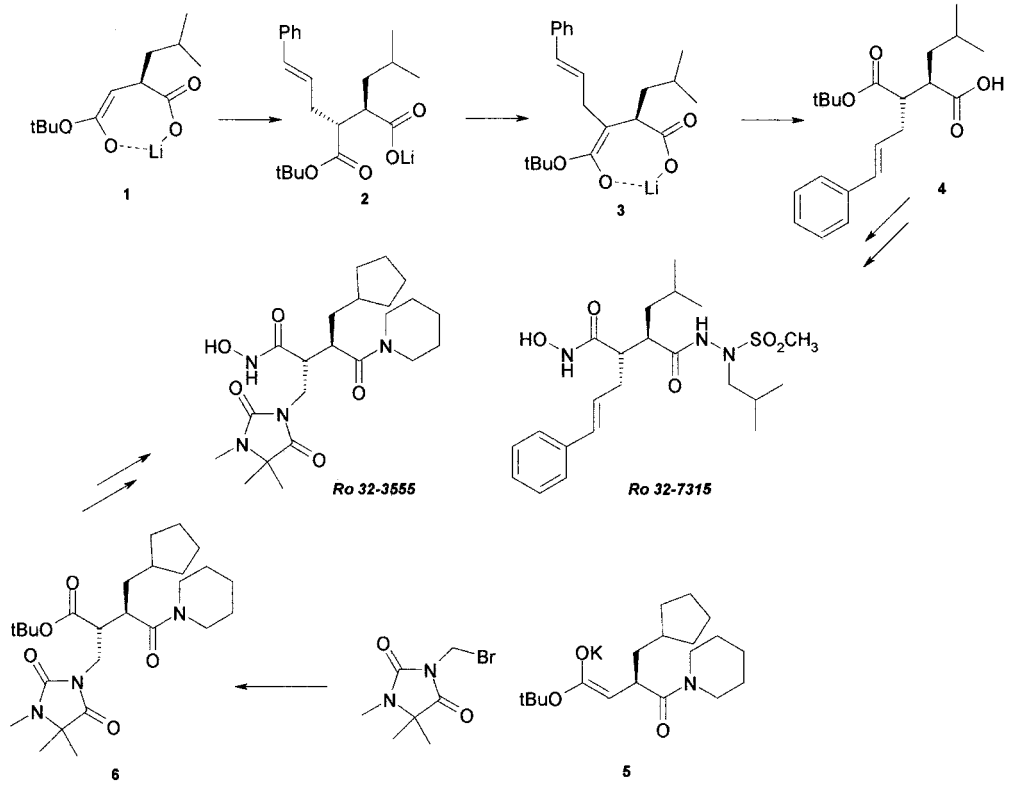


Microencapsulated osmium tetroxide

volatile by microencapsulating OsO_4 onto a polymer support, thus providing a more readily handled material with the potential for recycling. In particular they have developed a phenoxyethoxymethyl-polystyrene (PEM)-based novel polymer-supported osmium catalyst (*Org. Lett.* **2001**, *3*, 2649) using microencapsulation, a new method for immobilising catalysts onto polymers. Microencapsulation is based on the physical envelopment of the polymers by electron interactions between aromatic π electrons of the polystyrene-based polymers and vacant orbitals of the catalysts. This catalyst was successfully used in asymmetric dihydroxylations of alkenes using $(DHQD)_2PHAL$ as the chiral ligand and $K_3Fe(CN)_6$ as a cooxidant in H_2O/acetone. The catalyst was recovered quantitatively by simple filtration and reused several times without loss of activity (Scheme 1).

Hydroxamic acid derivatives have been reported as potent inhibitors of matrix metalloproteinases (MMPs) and for the recently characterised TNF-α converting enzyme (TACE); both enzymes are involved in degrading all components of the extracellular matrix. This process has been implicated in rheumatoid arthritis and osteoarthritis, chronic inflammatory diseases leading to loss of normal joint function. Hilpert from Hoffmann-La Roche Pharmaceuticals has reported (*Tetrahedron* **2001**, *57*, 7675) two methods for the synthesis of *anti* configured 2- and 3-alkylated succinates. Two linear six-step syntheses were developed to efficiently prepare Trocade (Ro 32-3555) and the TACE inhibitor (Ro 32-7315) (Scheme 2) on multiton and multikilogram scale avoiding

Scheme 2



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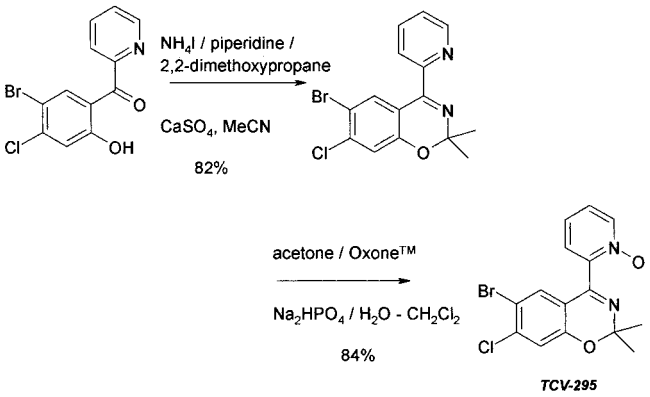
chromatographic purifications. In particular the *anti* configuration of Ro 32-3555 was set up by alkylation of the nonchelated potassium enolate **5** with bromomethyl hydantoin to give a 92:8 mixture favouring the 2,3-*anti* configured succinate **6**. The preparation of Ro 32-7315 was accomplished by highly stereoselective protonation of the dialkylated enolate **3** (prepared via **2** from enolate **1**) using CF_3CONH_2 affording a 98:2 mixture in favour of the 2,3-*anti* configured succinate **4**.

An efficient process for the synthesis of the potassium channel opener TCV-295, based on a novel and convenient 4-(2-pyridyl)-2*H*-1,3-benzoxazine ring formation from *o*-hydroxybenzoylpyridine by the NH_4I/piperidine/2,2-dimethoxypropane system and the subsequent pyridine-*N*-oxidation using dimethyldioxirane (generated in situ by reaction of acetone and Oxone), has been developed by Mizufune and co-workers (*Tetrahedron* **2001**, *57*, 7501) (Scheme 3). The

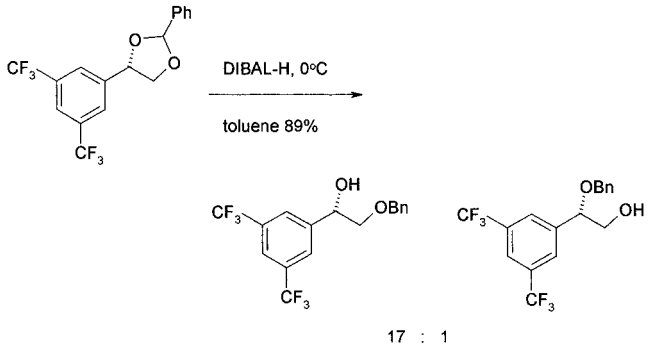
Scheme 3



group describes this chemistry to be superior to the original chemistry where ammonia gas and acetone under sealed-tube conditions were used and resulted in a lack of selectivity of *N*-oxidation of the pyridyl moiety. They have used this chemistry on a multikilogram scale, and experimental procedures are described in the paper.

Gauthier, Jr., and co-workers at Merck describe (*Tetrahedron Lett.* **2001**, *42*, 7011) how the DIBAL reduction of benzylidene acetal (Scheme 4) gave the primary benzyl-

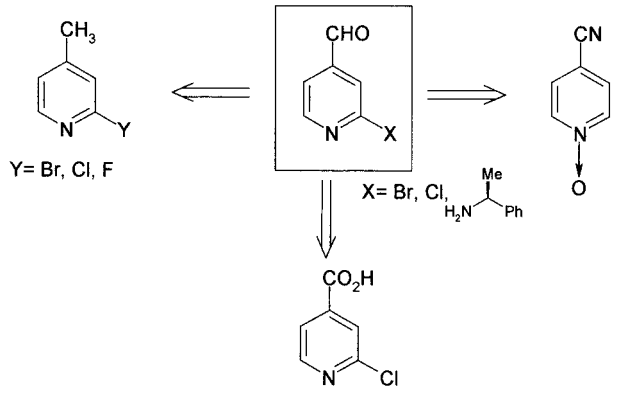
Scheme 4



protected alcohol in a 17:1 ratio over the secondary protected alcohol. A plausible mechanistic rationale to explain this unusual regioselectivity of benzylidene acetal reduction is proposed in their paper in which the stereoelectronic effects are discussed. Needless to say this reaction provided the group with a convenient method for the monoprotection of a diol as part of their NK-1 receptor antagonist programme.

Frey and co-workers, also at Merck, have reported (*Tetrahedron Lett.* **2001**, *42*, 6815) several routes to 2-substituted-4-pyridine carboxaldehydes from commercially available starting materials as shown in Scheme 5. In particular

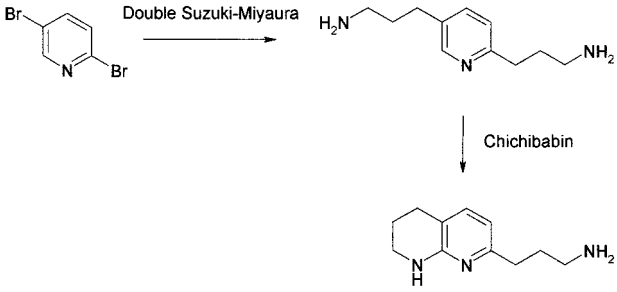
Scheme 5



the group has prepared 2-chloro-4-pyridine-carboxaldehyde from 4-cyanopyridine *N*-oxide in 55% yield (using $POCl_3$ 100 °C followed by DIBAL reduction) and 2-bromo-4-pyridinecarboxaldehyde from 2-bromo-4-methylpyridine in 64% yield (using ^tBuONO, KO^tBu, THF followed by HCl/CH_2O). Interestingly, when the final step is a DIBAL reduction of a nitrile to the aldehyde, isolation of the bisulphite adduct allows for ease of purification and improved long-term stability and handling.

The synthesis of 2-[3-aminopropyl]-5,6,7,8-tetrahydronaphthyridine has been accomplished by Palucki et al. (*Tetrahedron Lett.* **2001**, *42*, 6811) in four chemical steps with an overall yield of 76% (Scheme 6). The key steps of

Scheme 6

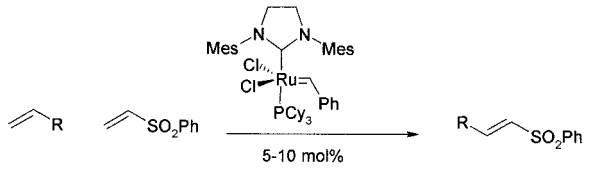


the synthesis included a double Suzuki reaction of 2,5-dibromopyridine with phthalimide-protected amine to form two C−C bonds in one pot and an intramolecular Chichibabin reaction. The Chichibabin reaction was optimised and afforded the desired product in high yield with excellent regioselectivity and a significant reduction in reaction times compared to those in literature precedence.

During the past few years olefin metathesis has gained a position of increasing significance in synthetic organic chemistry. Grela and Bieniek from the Institute of Organic Chemistry, Polish Academy of Sciences in Poland have

reported (*Tetrahedron Lett.* **2001**, *42*, 6425) a highly selective cross-metathesis reaction between functionalised terminal olefins and phenyl vinyl sulphone using the commercially available Grubbs catalyst (Scheme 7). The cross-metathesis

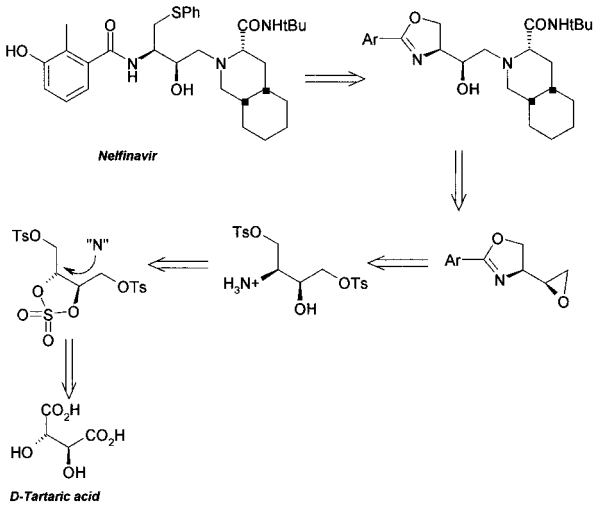
Scheme 7



products were isolated in moderate-to-good yield with excellent (*E*)-stereoselectivity.

HIV protease inhibitors, as a class, possess a fairly complex structure and are a synthetic challenge to produce economically on the metric ton scale. Nelfinavir (Scheme 8) contains five chiral centres with a core four-carbon

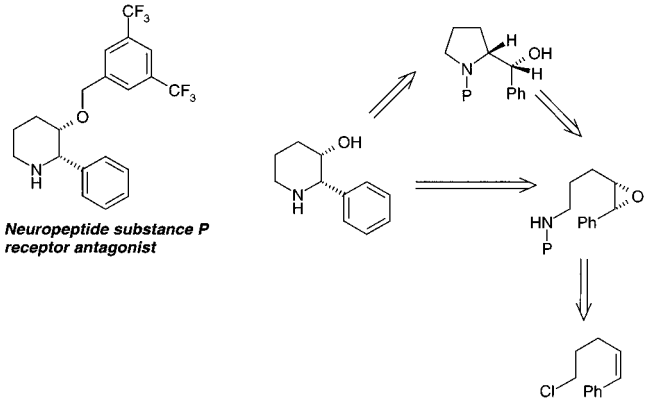
Scheme 8



backbone in which each carbon atom is attached to a heteroatom. Borer and co-workers report (*Tetrahedron Lett.* **2001**, *42*, 6481) a new synthesis of nelfinavir from D-tartaric acid. The group describes how the cyclic sulphate (Scheme 8) can be opened in the key step by using potassium phthalimide which serves in a dual role to act as protecting group and oxazoline precursor prior to reaction with thiophenol. The sequence avoids the use of azide as a nitrogen nucleophile and has been operated on multikilogram scale.

In the last Highlights we reported how the ring expansion of enantiomerically pure substituted prolinols can give rise to enantiomerically pure substituted 3-hydroxypiperidines or substituted 3-chloropiperidines. Indeed, functionalised piperidines have attracted increasing attention as pharmacaphores in medicinally active compounds. Lee and co-workers from Merck have reported (*Tetrahedron Lett.* **2001**, *42*, 6223) a catalytic highly enantioselective (>99% ee) preparation of *N*-*tert*-butyloxycarbonyl-(2*S*,3*S*)-3-hydroxy-2-phenylpiperidine and *N*-*tert*-butyloxycarbonyl-(2*S*)-2-phenyl-piperidin-3-one using an intramolecular epoxide opening followed by ring expansion (Scheme 9). The *cis*-epoxide starting

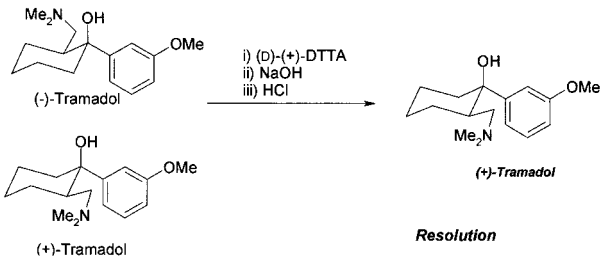
Scheme 9



material was available in high ee via a Jacobsen epoxidation. The method is particularly suitable for the preparation of a key chiral building block of a neuropeptide substance-P (neurokinin-1) receptor antagonist.

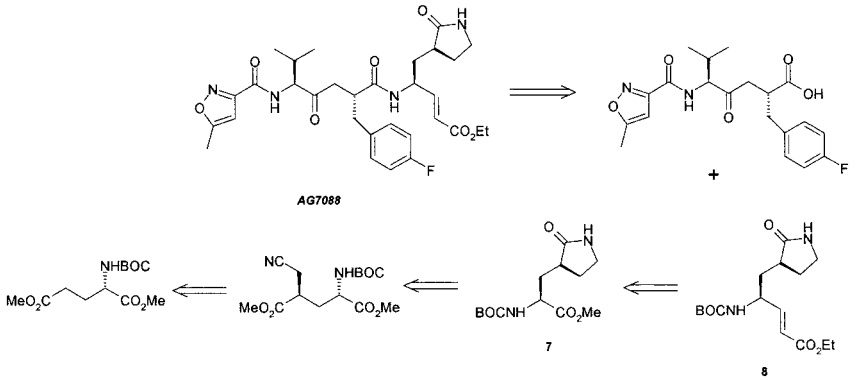
Tramadol is a chiral drug substance which is used as a high-potency analgesic agent. Although it is currently marketed as the racemate, there has been considerable interest in the physiological properties associated with its individual enantiomers. Evans and co-workers have recently reported (*Tetrahedron Asymmetry* **2001**, *12*, 1663) a robust and efficient resolution of (±)-tramadol using di-*p*-toluoyl-tartaric acid (DTTA). Both enantiomers have been efficiently separated and isolated in high chemical and optical purities requiring both antipodes of DTTA. The resolving agent was found to be highly selective for the desired *trans*-tramadol enantiomers, enabling isolation of a single isomer from a crude mixture of all four possible isomers. It has also been shown that less than one equivalent of resolving agent is effective in separating the enantiomers and that the resolving agent may be recovered and reused. The paper gives experimental details on multikilogram scale (Scheme 10).

Scheme 10



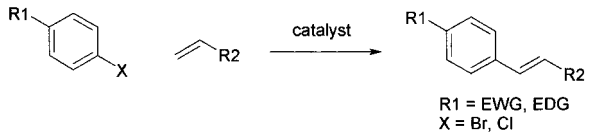
An efficient synthetic route to a key intermediate of AG7088 (a rhinovirus protease inhibitor) has been described by Tian, Nayyar, and co-workers (*Tetrahedron Lett.* **2001**, *42*, 6807). Disconnection is shown in Scheme 11 to two fragments. The chiral lactam unit was prepared via an asymmetric dianionic cyanomethylation reaction of *N*-BOC-L-(+)-glutamic acid dimethyl ester using 2.16 equiv of LiHMDS and 1.07 equiv of bromoacetonitrile in excellent yield and stereoselectivity. Reduction (by high-pressure hydrogenation) of the nitrile followed by lactam formation gave the lactam ester **7** which was manipulated to **8** in a number of simple transformations.

Scheme 11



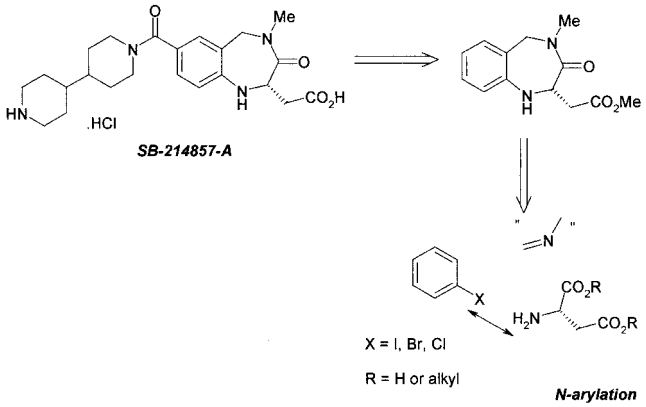
Advances in the Heck olefination reaction (Scheme 12) of activated and unactivated aryl chlorides have been reviewed by Gibson et al. (*Tetrahedron* **2001**, *57*, 7449).

Scheme 12



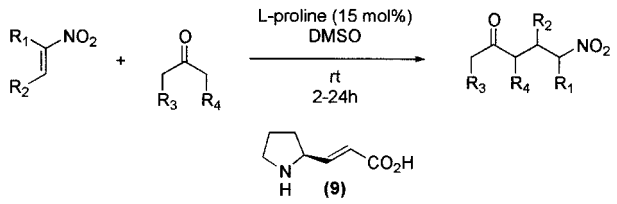
In the last highlights we reviewed the synthetic efforts of workers at GSK towards the synthesis of SB-214857. In another publication Hayes and co-workers report the synthesis of SB-214857 using a copper-catalysed amination of an aryl bromide with L-aspartic acid (*Synlett* **2001**, *9*, 1423). In this approach they have shown that amino acids containing hydrophilic substituents can be *N*-arylated under mild conditions using copper catalysis once solubilised as their tetrabutylammonium salts. Raney copper containing 5% copper (I) oxide is a very effective catalyst but causes significant racemisation of the aspartic acid. Copper (I) iodide is a less efficient catalyst but does not cause racemisation to the same extent (Scheme 13).

Scheme 13



A fascinating trend over the last couple of years has been the use of organic—rather than organometallic—catalysts for many reactions. Since generally these catalysts are amines or amino acids (which are easier to remove from product (and recycle?) than organometallic species), the potential for large-scale use is apparent. We have previously mentioned the work of MacMillan (see *J. Am. Chem. Soc*. **2000**, *122*, 4243; 9874), List (*J. Am. Chem. Soc*. **2000**, *122*, 2395; 7386; 9336), and Fu (*Acc. Chem. Res.* **2000**, *33*, 412, *J. Am. Chem. Soc*. **2001**, *123*, 353) in these Highlights columns on the use of organic catalysts for Diels—Alder reactions, 1,3-dipolar cycloadditions, aldol, and Mannich reactions. Now the group of List has extended its work to the Michael addition of ketones to nitrolefins (List, B. et al. *Org. Lett*. **2001**, *3*, 2423). Proline catalyses the addition of cyclohexanone to nitrostyrene in good yield and regio- and diastereoselectivity, although the ee's could at best be described as modest (up to 23%)—see Scheme 14. Use of a "vinologous" proline **(9)**

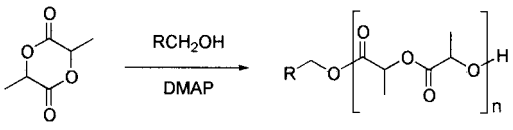
Scheme 14



improved ee's to 40% in one case. No doubt future publications will report improved asymmetric catalysts. For a recent review of the asymmetric Michael reaction see Krause, N. et al. (*Synthesis* **2001**, 171).

Organocatalysis has now been applied by a group at IBM (Nederberg, F. et al. *Angew. Chem., Int. Ed.* **2001**, *40*, 2712) to the preparation of polymers using ring-opening polymerisation of lactide. Using DMAP as catalyst and an alcohol as initiator, polylactides with narrow dispersities are produced, presumably because termination and side reactions are minimised. These polyesters combine biocompatibility and biodegradability with high thermal stability at typical processing temperature and have remarkable physical properties (Scheme 15).

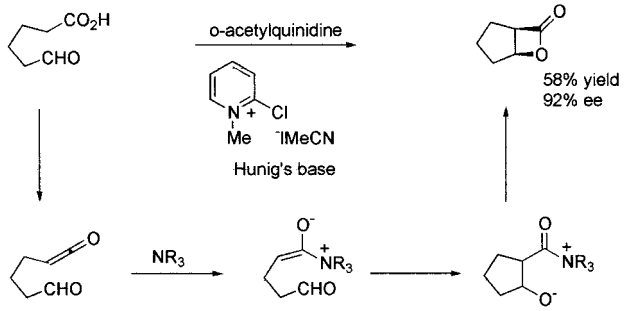
Scheme 15



β-Lactones are normally prepared using the Wynberg procedure—addition of a ketene to an aldehyde in the

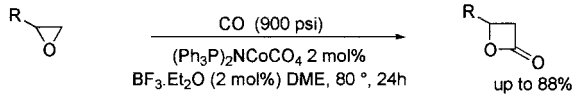
presence of a chiral catalyst (e.g., quinine), and this process has been commercialised by Lonza for the manufauture of optically active malic and citromalic acids. An intramolecular variant of this methodology has now been demonstrated but is shown to proceed via a nucleophile-catalysed aldol-lactonisation mechanism rather than the possible 2 + 2 cycloaddition (Cortez, G. S. et al. *J. Am. Chem. Soc.* **2001**, *123*, 7945). The ketone is generated "in-situ" (Scheme 16) using Mukaiyama's reagent.

Scheme 16



An improved method for the synthesis of β-lactones by the atom-efficient carbon monoxide insertion into epoxides has been published (Lee, J. T. et al. *J. Org. Chem.* **2001**, *66*, 5424). When the researchers at University of Ottawa and Dow Chemical tried to repeat a 1993 patent describing carbonyl insertion, they obtained mostly polyester, not lactone, when the reported $Co_2(CO)_8$/3-hydroxypyridine catalyst was used—this catalyst usually works well for the carbomethoxylation of epoxides. After a number of failures, they eventually came up with bis(triphenylphosphine) iminium $Co(CO)_4$ in conjunction with a Lewis acid ($BF_3{\cdot}Et_20$ or $SnCl_4$) in DME or THF which gave β-lactones in excellent yields (Scheme 17).

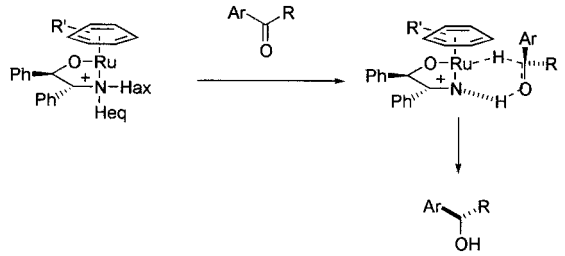
Scheme 17



A recent paper examines the origin of enantioselectivity in transfer hydrogenation of aromatic carbonyl compounds (using 2-propanol as reducing agent) catalysed by chiral-arene−ruthenium complexes. Professor Noyori's group at Nagoya (Japan) suggests that the previously unrecognised attraction between the arene ligand on ruthenium and the π system of the carbonylaryl substituent contributes to the enantioselectivity, (Yamakama, M. et al. *Angew. Chem., Int. Ed.* **2001**, *40*, 2819). This explains the role of aryl substituents in asymmetric transfer hydrogenation (See Scheme 18).

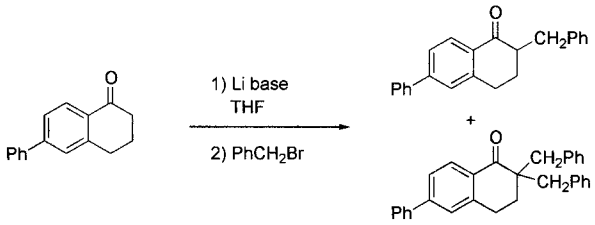
One of the problems of alkylation of an enolate in ethereal solvents is the relatively large amount of bis- and, if feasible, polyalkylation that takes place. For example even after 10% of reaction of the lithium enolate of α-tetralone with benzyl bromide, >30% of the product is dibenzyl product. On scale-up, this would probably get worse! Thirty years ago House, in his book *Modern Synthetic Reactions* (surely one of the best books on mechanistic organic chemistry ever published), suggested that the less substituted enolate will be more highly

Scheme 18



aggregated in ethereal solvents, hence less reactive. Surprisingly, this hypothesis has never been thoroughly tested but a recent publication from the group of Streitwieser (Streitwieser, A. et al. *Org. Lett.* **2001**, *3*, 2599) has proved that House's conjecture was essentially correct. Thus, at 10% reaction, dialkylation proceeds at 24 times the rate of monoalkylation, though other factors may work to affect the mono:dialkyl product ratio. Presumably by changing from lithum to another cation and moving to a non-ethereal solvent, aggregration can be disrupted and higher levels of monoalkyl product will be achieved (Scheme 19).

Scheme 19



The study of the detailed basis for enantioselectivity in terms of transition-state structure is an important aspect of research into catalysis. An understanding of the origin of enantioselectivity not only aids in catalyst design but also helps with design of reaction conditions and scale-up of the process. In a feature article, E. J. Corey examines the formyl C−H···O hydrogen bond as a critical factor in enantioselective Lewis-acid-catalyzed reactions of aldehydes (Corey, E. J. et al. *Chem. Commun.* **2001**, 1321). He suggests, and provides evidence for using X-ray crystallography, that intramolecular formyl C−H hydrogen bonds to O or F ligands in complexes of aldehydes with boron Lewis acids provide an additional organising element which helps to understand the basis for selectivity in aldol, allylation, ene, and Diels−Alder reactions. (Figure 1).

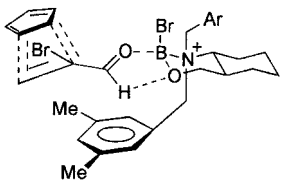
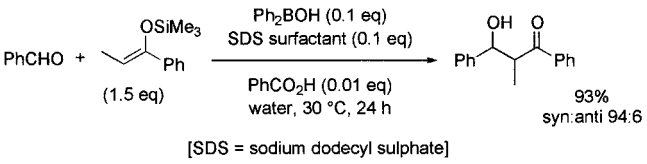


Figure 1.

One of the factors hindering the use of boron enolate chemistry on large scale for the synthesis of aldols is the stoichiometric amount of dialkylboron triflates required. The group of Kobayashi in Tokyo has now reported that a stereoselective aldol reaction can be carried out in water with

a catalytic amount of boron reagent (Mori, Y. et al. *Angew. Chem., Int. Ed.* **2001**, *40*, 2816). Scheme 20 shows the

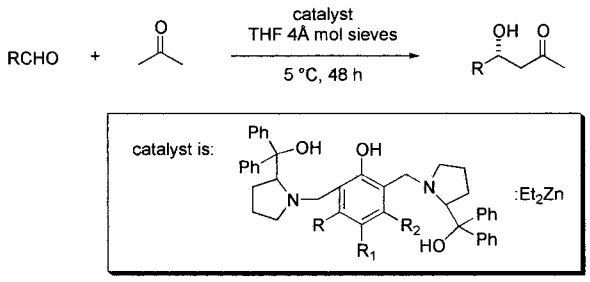
Scheme 20



conditions used. The yields are in the range 61−92% for a number of aldehydes and silylenol ethers. Yields are better than those for the Lewis acid−surfactant-combined catalysts (LASCs) reported recently (Manabe, K. et al. *J. Am. Chem. Soc.* **2000**, *122*, 7202).

There has been a lot of recent interest in the catalytic asymmetric aldol reaction from the groups of Shibasaki (see Yoshikawa, N. et al. *J. Am. Chem. Soc*. **2001**, *123*, 2466), List (see Notz, W. et al. *J. Am. Chem. Soc*. **2000**, *122*, 7386) and Trost (*J. Am. Chem. Soc*. **2001**, *123*, 3367; **2000**, *122*, 12033). Trost's group has now extended the reaction to the use of acetone as well as unbranched aldehydes using a novel zinc binuclear catalyst (Trost, B. M. et al. *Org. Lett.* **2001**, *16*, 2497). Yields of 62−89% and ee's of 76−92% are obtained (Scheme 21). In some cases the elimination product

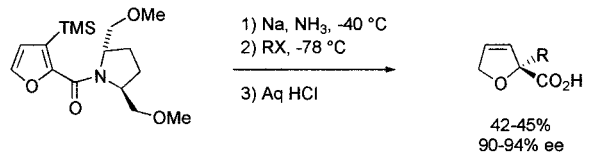
Scheme 21



competes. Enantiomeric excesses are not as good as when acetophenone is the ketone when branched aldehydes are used. The active catalyst is believed to involve two zinc atoms each coordinated to two of the three oxygen atoms of the ligand. One zinc binds to the enol of acetone, the other to the aldehyde, the conformational and steric interactions accounting for the high selectivity.

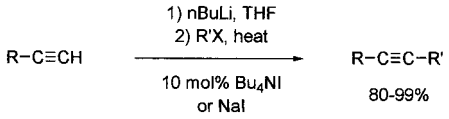
Asymmetric Birch reductions have attracted a lot of interest in the past few years (for a review see Schultz, A. G. *Chem. Commun*. **1999**, 1263). The group of Donohue at Manchester has now found that in the reduction of furans higher enantioselectivity can be achieved by attaching a silyl group to the nucleus (Donohoe, T. J. et al. *Tetrahedron Lett.* **2001**, *42*, 5841). Conditions can be tailored so that the silyl protection is lost during work-up (Scheme 22).

Scheme 22



The alkylation of acetylenes is another traditional reaction carried out in liquid ammonia, though other solvents such as the carcinogenic HMPA and the alternative DMPU have also worked well. It has now been found, after all these years, that THF can be used (Buck, M. et al. *Tetrahedron Lett.* **2001**, *42*, 5825). This is in contrast to previous reports that alkynyllithiums react "sluggishly with most alkyl halides in ether or THF". The trick is to enhance the reactivity of the halide by adding a catalytic amount of Bu_4NI or NaI and to carry out the reaction at reflux (Scheme 23). Protecting

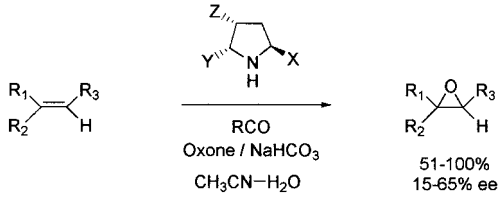
Scheme 23



groups such as THP are well tolerated. The reaction is limited, however, to primary halides.

The epoxidation of olefins using Oxone as oxidising agent and iminium salts as the catalyst continues to attract interest. Last year the group of Aggarwal (Adamo, M. F. A. et al. *J. Am. Chem. Soc.* **2000**, *122*, 8317) reported the use of amines directly to catalyse the reaction, and now the group of Yang in Hong Kong (Wong, M.-K. et al. *Org. Lett.* **2001**, *3*, 2587) has reported similar results where the iminium salt is generated from an amine and aldehyde "in situ". Yields are generally high using 20 mol % of amine/aldehyde. With chiral amines, enantioselectivities of up to 65% are obtained (Scheme 24). One interesting result is the effect of amine:

Scheme 24



aldehyde ratio on conversion of *trans*-stilbene to stilbene oxide, with the maximum conversion at a 1:1 ratio of amine: aldehyde (Figure 2). Excess of either compound decreases

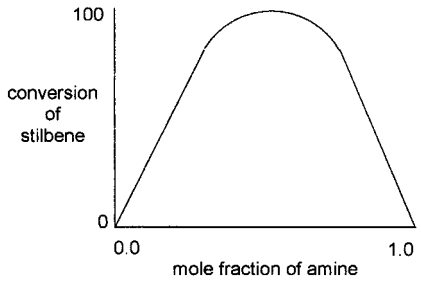


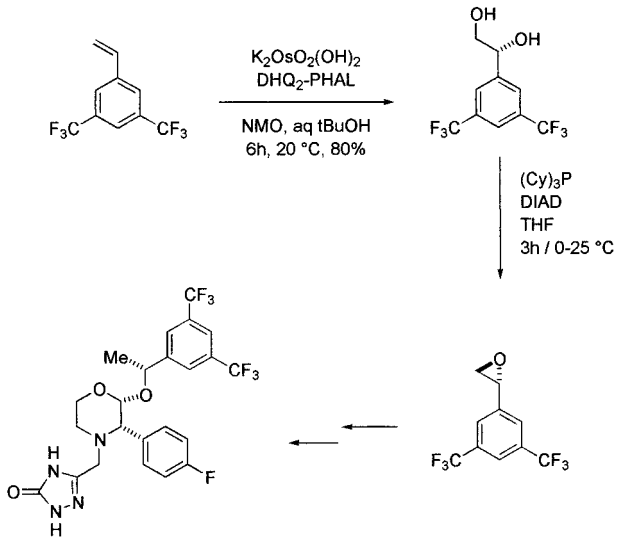
Figure 2.

the rate (the enantioselectivity is not, however, affected). This shows that the iminium salt is the most likely catalyst responsible for epoxidation.

Chiral epoxides can also be generated from diols prepared using the Sharpless asymmetric dihydroxylation reaction (for scale-up conditions see Ahgren, L. et al. *Org. Process Res.*

Dev. **1997**, *1*, 425). A report from a group at Merck Process Research uses the Mitsunobu reaction for cyclodehydration of diols to epoxides (Weissman, S. A. et al. *Org. Lett.* **2001**, *3*, 2513). The group screened solvents (THF best), phosphine (tricyclohexyl and tricyclopentylphosphine best), and azodicarboxylate (diisopropyl best) to give epoxides in high yield and ee on a variety of diols derived from substituted styrenes. The epoxides were required for the synthesis of a substance P inhibitor, NK_1 antagonist (Scheme 25).

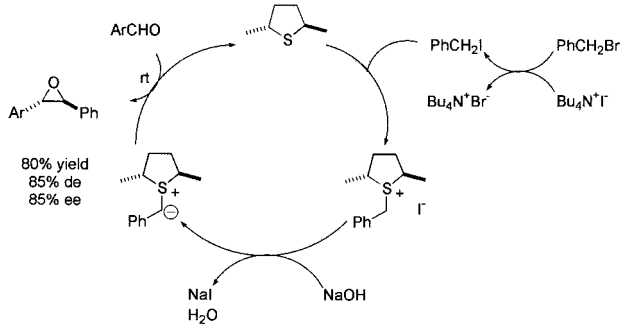
Scheme 25



Enantiopure epoxides are versatile intermediates for organic synthesis and one method of synthesising them, which has attracted increasing interest over the past decade, has been the reaction of sulphur ylides with aldehydes. The choice of chiral sulphur compound can be critical. (For recent of examples of use of sulphur ylides see Aggarwal, V. K. et al. *Angew. Chem., Int. Ed.* **2001**, *40*, 1430; Miliymaki, V. et al. *Tetrahedron* **2001**, *57*, 4629). A new study suggests that a chiral thiolane derivative can be quaternised and reacted with base/aldehyde in a one-pot process (Zanardi, J. et al. *J. Org. Chem.* **2001**, *66*, 5620). The reaction works well with aromatic and heteroaromatic aldehydes and benzyl bromide, but with heterocycles the epoxide products are extremely acid sensitive, so careful work-up is essential. From a practical viewpoint, the reaction can be made catalytic in the expensive chiral sulphide (0.1 mol %), but reactions are very slow (2−4 days) and increasing the temperature lowers the enantioselectivity. The chiral thiolane is made from the appropriate enantiomer of 2, 5-hexanediol, which is commercially available, via the dimesylate using sodium sulphide (Scheme 26).

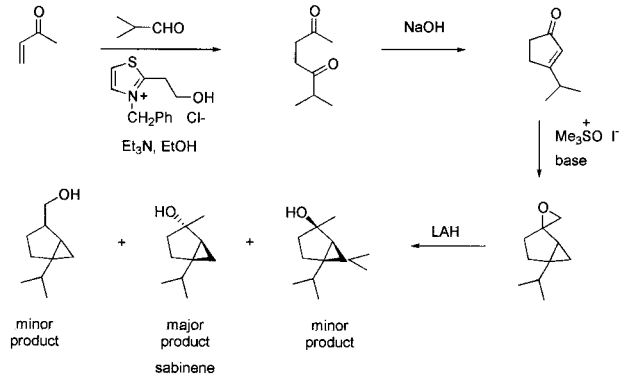
A new synthesis, suitable for scale-up and large-scale production, of the important flavour chemical *trans*-sabinene hydrate has been published. Sabinene is expensive ($1200−1800/kg) which limits its use in flavours. The new synthesis from the R&D department at Givaudan (Cincinnati) promises to change that (Galopin, C. C. *Tetrahedron Lett.* **2001**, *42*, 5589). The process uses a Stetter reaction followed by dehydrative cyclisation to a cyclopentenone. A Corey−Chaykovsky sulphonium ylide process introduces two carbon

Scheme 26



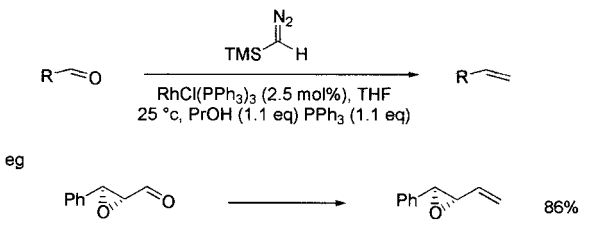
atoms selectively, and the resultant product can be reduced to *trans*-sabinene with some selectivity. A 28% overall yield has been obtained (Scheme 27).

Scheme 27



The main drawbacks with the Wittig methylenation of carbonyl derivatives include the low reactivity of the Wittig reagent with sterically hindered carbonyls as well as the possible epimerisation of base-sensitive substances. To overcome these problems a variety of reagents, such as the Tebbe/Petasis titanium compounds and Oshima/Lombardo zinc compound (see Wirth, T. *Synthesis* **1998**, *2*, 162) have been invented. However, many of these reagents also have disadvantages such as cost, pyrophoricity, and competing processes (reductive coupling of aldehydes). A new report shows that in an analogous manner to the generation of sulphur ylides from diazo compounds, followed by reaction with aldehydes to give epoxides, a similar one-pot process can be used to generate and react phosphorus ylides. (Lebel, H. et al. *Angew. Chem. Int. Ed*. **2001**, *40*, 2887). Best results are achieved with TMS−diazomethane, Wilkinson's catalyst, in THF at room temperature with 2-propanol added to aid desilylation (Scheme 28). The reaction can be performed in the presence of secondary amides, enolisable ketones, and epoxides, and a number of protecting groups are compatible.

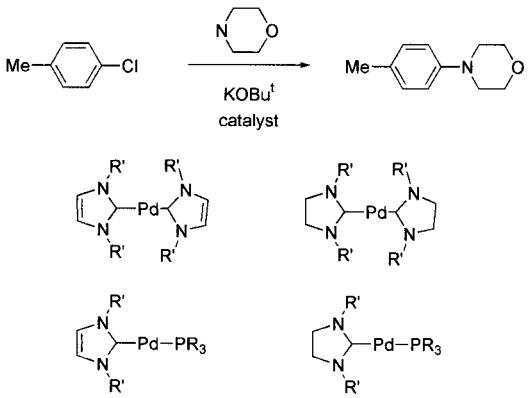
Scheme 28



Yields are much higher with this system than when the ylide is generated from a phosphonium salt plus base. In contrast to the sulphur system, the authors have evidence that a metal carbene mechanism is *not* involved—they suspect that the rhodium catalyst complexes with the nitrogen of the diazo compound and activates it to nucleophilic attack by Ph_3P, followed by desilylation (mediated by 2-propanol) and nitrogen extrusion.

It has recently become apparent that stable N-heterocyclic carbenes can offer an interesting alternative class of ligand to phosphines for catalytic applications (for recent reviews, see Bourissou, D. et al. *Chem. Rev.* **2000**, *100*, 39; Arduengo, A. J. *Acc. Chem. Res.* **1999**, *32*, 913). There have been many examples which we have highlighted in these pages of the use of these catalysts in a variety of processes such as metathesis (for reviews see Jafarpour, L. et al. *Adv. Org. Chem*. **2001**, *46*, 181; Trnka, T. A. et al. *Acc. Chem. Res.* **2001**, *34*, 18) and various coupling reactions (for examples see Grasa, G. A. et al. *Org. Lett.* **2001**, *3*, 119). A report from a group at the University of Sussex UK, has recently shown that saturated heterocyclic carbene complexes are effective as unsaturated heterocyclics in the amination of chloroarenes and that the metal carbene bond may be more labile than originally thought—this may be important in the design of new palladium—carbene catalysts for organic synthesis (Titcomb, L. R. et al. *Chem. Commun*. **2001**, 1388)—see Scheme 29.

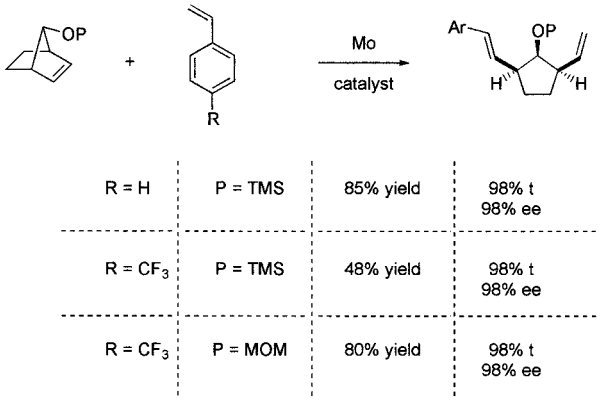
Scheme 29



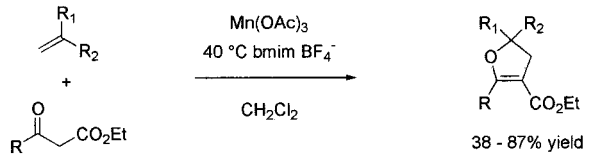
The full paper on the catalytic asymmetric ring-opening metathesis/cross-metathesis reactions (AROM/CM) originally reported by the groups of Schrock and Hoveyda at Boston College in 1999, has now appeared (La, D. S. et al. *J. Am. Chem. Soc.* **2001**, *123*, 7767). A typical example of this process is shown in Scheme 30.

Manganese acetate can be a useful oxidising agent for radical generation but often requires acetic acid as solvent and high temperatures, owing to its poor solubility in most organic solvents. A group at the University of York, UK, has found that addition of a small amount of an ionic liquid to an organic solvent allows reaction to take place at much lower temperatures, and the manganese acetate can be recovered by precipitation at the end of the reaction (as Mn(II), which needs reoxidising to Mn(II)). The ionic liquid can be recovered and recycled (Bar, G. et al. *Chem. Commun.* **2001**, 1350). See Scheme 31.

Scheme 30

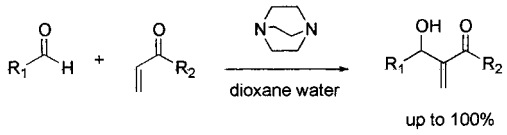


Scheme 31



The main disadvantages of the atom-efficient Baylis—Hillman reaction of aldehydes with unsaturated esters or nitriles are the long reaction times and moderate yields. By using aqueous conditions, with a stoichiometric amount of DABCO as base catalyst, however, high yields of products can be achieved in a few hours, rather than days (Yu, C. et al. *J. Org. Chem.* **2001**, *66*, 5413). Choice of solvent was critical—the reaction works best in a mixture of dioxane and water, but amazingly no product is obtained in either of the pure solvents (Scheme 32).

Scheme 32

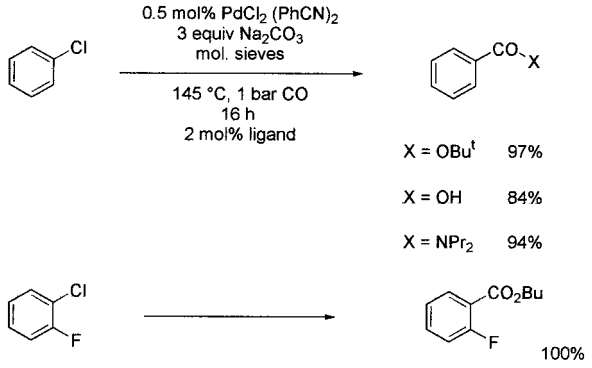


solvent ratio dioxane : water		yield (R_1 = $NO_2C_6H_4$, R_2 = OMe)
100	0	0%
4	1	21%
1.5	1	57%
1	1	68%
1	1.5	27%
1	4	10%
0	100	0%

Whereas the use of aryl chlorides in the Heck, Suzuki, and other reactions has been the subject of many recent papers, the carbonylation of aryl chlorides has remained a problem; the use of sterically demanding monodentate ligands, successfully used in the above named reactions, does not work for carbonylation. Use of the ligand, 1,3-bis(di-isopropylphosphanyl) propane with Pd was successful (Ben-

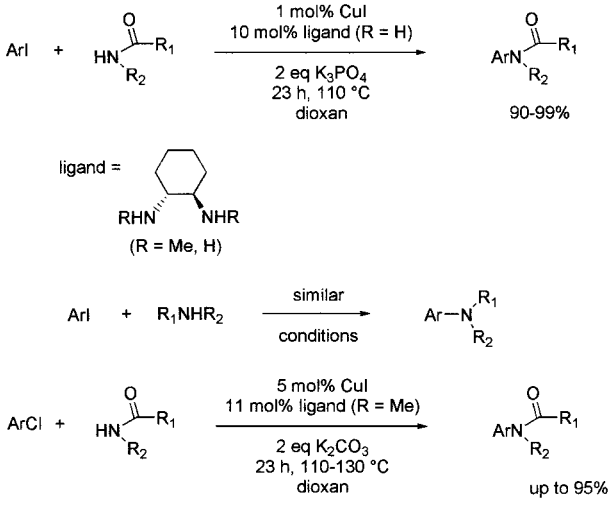
David, Y. et al. *J. Am. Chem. Soc.* **1989**, *111*, 8742; *Chem. Commun.* **1989**, 1816; *Organometallics* **1993**, *12*, 1655), but this ligand is said to be difficult to make, is pyrophoric, and has low turnover number (<100). A new catalyst system has been developed (Mägerlein, W. et al. *Angew. Chem. Int. Ed.* **2001**, *40*, 2856) which allows conversion of chloroarenes to esters, acids, or amides in good yield and selectivity and with turnover numbers in the region of 1650 and a catalytic activity (turnover frequency) of 100 h^{-1}. See Scheme 33.

Scheme 33



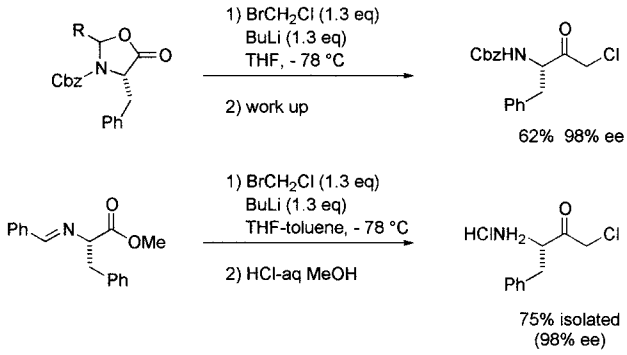
One of the problems with the Ullmann arylation reaction and the related Goldberg reaction—the copper-catalysed amidation of aryl halides—is the use of high reaction temperatures and often large amounts of copper catalysts. The latest publication from Buchwald's group at MIT (Klapars, A. et al. *J. Am. Chem. Soc.* **2001**, *123*, 7723) indicates that these problems with the Goldberg reaction have largely been overcome. Thus lactams, primary amides, and formamides derived from primary amines and acetanilide can be coupled to aryl halides at 90−110 °C using a copper iodide catalyst with a diaminocyclohexane ligand. The paper also reports progress on arylation of nitrogen heterocycles. (See Scheme 34.)

Scheme 34



A relatively simple way of generating protected α-amino α′chloromethyl ketones, useful in the synthesis of HIV protease inhibitors has been reported (Onishi, T. et al. *Tetrahedron Lett.* **2001**, *42*, 5883). For example, reaction of phenylalanine with anisaldehyde followed by Cbz protection gave an oxazolinone, which readily reacted with chloromethyllithium at low temperature. Simple work-up gave the desired product (Scheme 35). In the following paper (p 5887),

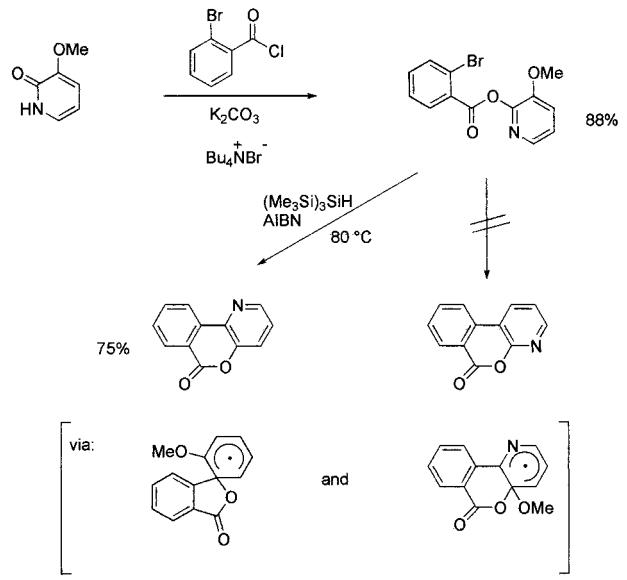
Scheme 35



the use of imine protection allows synthesis of the free amino, α-chloroketone hydrochlorides.

An unusual heterocyclisation involving a double "ipso" substitution is reported in a paper from scientists at DuPont (Zhang, W. et al. *Tetrahedron Lett.* **2001**, *42*, 5613). Radical cyclisation of the benzoate (Scheme 36) yielded only the

Scheme 36

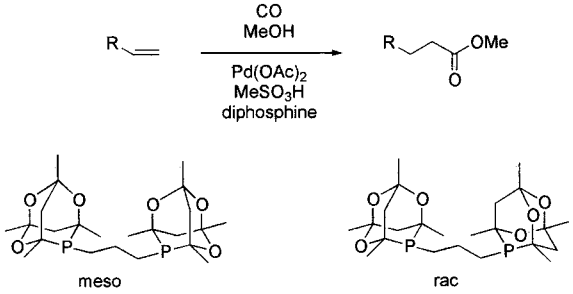


azocoumarin shown and not the expected product. The methoxy group seems to be required for this reaction; otherwise, simple reduction of the C−Br bond occurs.

Fast and selective conversion of internal olefins to linear esters is catalysed by Pd(II) complexes of bulky phospha-adamantyl bis-phosphines (Pugh, R. I. et al. *Chem. Commun.* **2001**, 1476). The reaction is extremely sensitive to the ligand backbone and diastereomer used. This discovery has potential use in the synthesis of detergents and nylon intermediates (Scheme 37).

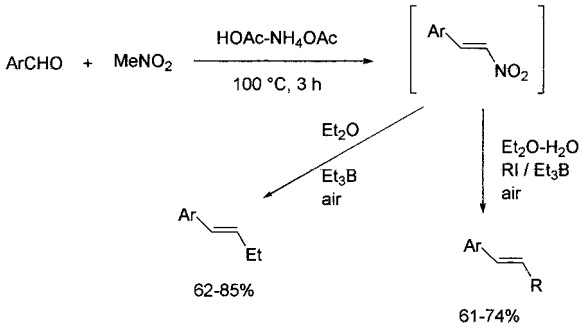
The Henry reaction of nitroalkanes with aldehydes is a useful synthetic procedure for the synthesis of nitroaldols or nitro alkenes (Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915). Nitrostyrenes now been shown to react with Et_3B to generate

Scheme 37



olefins, and the procedure can be combined with the Henry reaction in a one-pot olefination methodology (Liu, J.-T. et al. *Tetrahedron Lett.* **2001**, *42*, 6147). If alkyl iodides are added, groups other than Et can be introduced (Scheme 38).

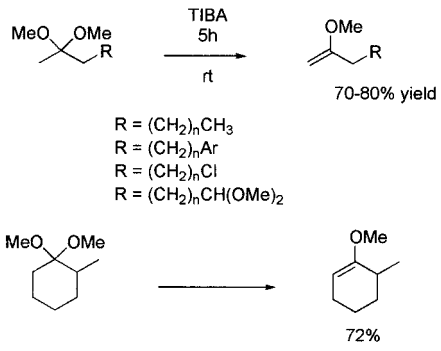
Scheme 38



The mechanism of the reaction is via radical species so primary iodides have not been used—best yields are with secondary or tertiary iodides

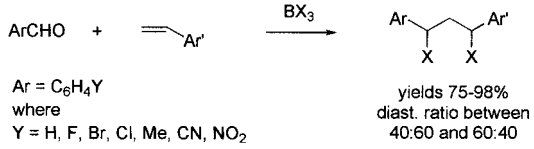
A convenient way of converting ketals into vinyl ethers is to treat them with triisobutylaluminium, TIBA (Cabrera, G. et al. *Tetrahedron Lett.* **2001**, *42*, 5687). Unfortunately an excess of TIBA is required to drive the process to completion at room temperature. The product is generally the less substituted olefin. Perhaps a catalytic process could be developed by removing the methanol as it is formed (reaction at reflux, under vacuum, or both?). Some examples are shown in Scheme 39.

Scheme 39



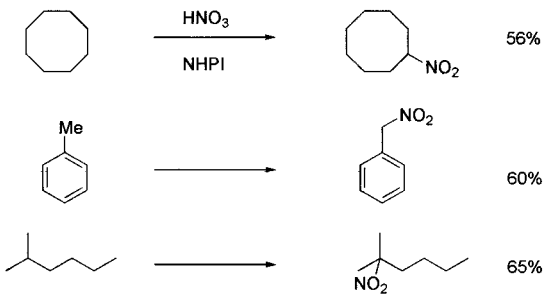
Boron trichloride and boron tribromide have been found to be very effective promoters for the addition of aromatic aldehydes to olefins to give diastereomeric mixtures of 1,3-dihalo compounds (Kabalka, G. W. et al. *Tetrahedron Lett.* **2001**, *42*, 5793). Interestingly, the reaction only works if commercial quality olefins, containing stabilisers such as *tert*-butylcatechol, are used; distilling the olefin followed by addition of BCl_3 only resulted in polymerisation. The reaction must be carried out at low temperature, otherwise chlorination of the aromatic aldehyde can occur. With BBr_3, this bromination is extremely fast, but by slowly adding BBr_3 to a 1:1 mixture of olefin:aldehyde, high yields of dibromo compounds can be obtained (Scheme 40).

Scheme 40



Nitration of hydrocarbons using nitric acid is usually carried out at very high temperature (250−400 °C) because of the difficult of generating NO_2 from HNO_3, but the reaction is, as a consequence, messy, difficult to control, and of little practical value. Using *N*-hydroxyphthalimide (NHPI) as catalyst, the group of Ishii in Osaka has shown that aliphatic hydrocarbons can be nitrated not only with NO_2 but also with nitric acid in moderate yields (Isozaki, S. et al. *Chem. Commun.* **2001**, 1352)—See Scheme 41.

Scheme 41

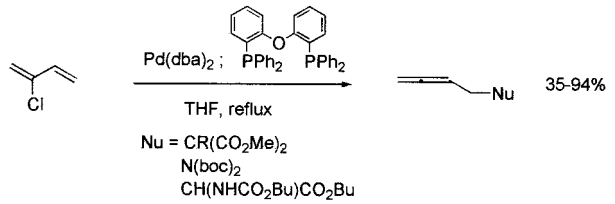


In the past decade, in situ MAS NMR spectroscopy has developed as a powerful tool for investigating heterogeneously catalysed reactions, often under continuous flow conditions. The method has been used to detect the imine intermediate in the methylation of aniline with methanol on a CsOH/Cs NaY zeolite (Wang, W. et al., *Chem. Commun.* **2001**, 1362).

A short highlight on the recent reactions of the hypervalent iodine reagent IBX has appeared with 24 references (Wirth, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 2812). As well as the traditional selective oxidation of alcohols, dehydrogenation of ketones to α,β unsaturated ketones, oxidation of benzylic CH_2 groups to CO, and oxidative cyclisations are covered.

Chloroprene is one of the few conjugated dienes that is made on an industrial scale, but its use is mostly for polymerisation. Its use as a raw material for other organic compounds is limited, partly because the chemistry has not been widely explored (Diels Alder reactions and reaction with Grignards being the chemistry that is occasionally used). A Japanese group has now shown that allenes can be easily prepared by reaction of soft nucleophiles with dienes in the presence of a palladium catalyst (Ogasawara, M. et al. *Org. Lett.* **2001**, *3*, 2615)—See Scheme 42.

Scheme 42



Living polymerisation of olefins is important in the preparation of precisely controlled polymers which are expected to display novel physical properties. Generally these processes are carried out at low temperature but provide low activity with insufficient molecular weight value. A group at Mitsui chemicals in Chiba, Japan, has now reported that group 4 transition-metal complexes bearing fluorinated phenoxyimine ligands (Figure 3) display high catalytic

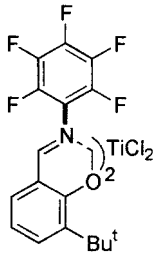
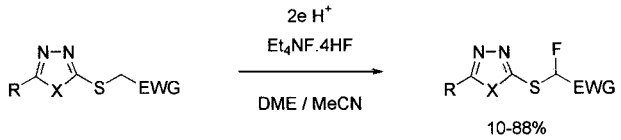


Figure 3.

performance for the polymerisation of ethylene, ethylene–propylene, or l-hexene at room temperature (Fukita, T. et al. *Angew. Chem., Int. Ed.* **2001**, *40*, 2918). At the end of the article it is implied that polymerisation of other olefins has been successful.

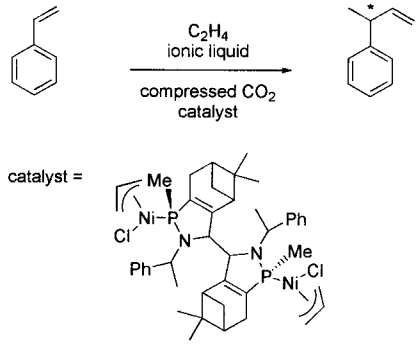
Organofluorine compounds often have unique properties and have captured intense attention of chemists in the agrochemical, pharmaceutical, colour, and specialty chemical industries. Fluorinated heterocyclics are often difficult to make by direct fluorination, which may give poor regioselectivity. Many of the new fluorinating reagents are expensive, whereas electrochemical fluorination using fluoride ion as F source is likely to be much cheaper. A recent paper (Shaaban, M. R. et al. *J. Org. Chem.* **2001**, *66*, 5633) describes the selective side-chain monofluorination of heterocyclic compounds (Scheme 43)—best results are with thiadiazoles and oxadiazoles.

Scheme 43



There has been a lot of activity in the past decade in the areas of ionic liquids (IL) and in supercritical fluids. A number of recent publications emphasise that using a combination of IL and supercritical CO_2 ($SECO_2$) can confer additional advantages (see, for example, Brown, R. A. et al. *J. Am. Chem. Soc.* **2001**, *123*, 1254). A recent report from the groups of Wasserschied at Aachen and Leitner at Max Plank Institute, Mulheim, Germany, demonstrates the use of a continuous process for hydrovinylation of styrene (Scheme 44). This allowed the activation and tuning of an

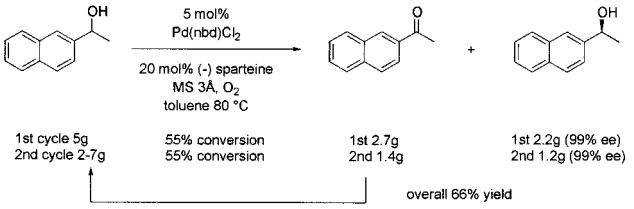
Scheme 44



immobilised nickel catalyst—the recycling of the catalyst in a batch system led to progressive loss of activity so that a continuous flow system was preferred. Product separation from the catalyst can be achieved without exposing the catalyst to conditions which cause loss of activity (Bösmann, A. et al. *Angew. Chem. Int. Ed.* **2001**, *40*, 2697). In contrast to the use of IL systems, the compressed CO_2 decreases the viscosity of the solution, facilitating mass transfer.

A simple kinetic resolution of secondary alcohols uses a palladium catalyst in the presence of sparteine (Ferreira, E. M. et al. *J. Am. Chem. Soc.* **2001**, *123*, 7725). The reaction at present is limited to activated alcohols, particularly benzylic and allylic systems. Reduction of the oxidised product (ketone) can be carried out by borohydride, to the racemic alcohol, giving an opportunity for coupling the two processes to give high yield and enantioselectivity (Scheme 45).

Scheme 45

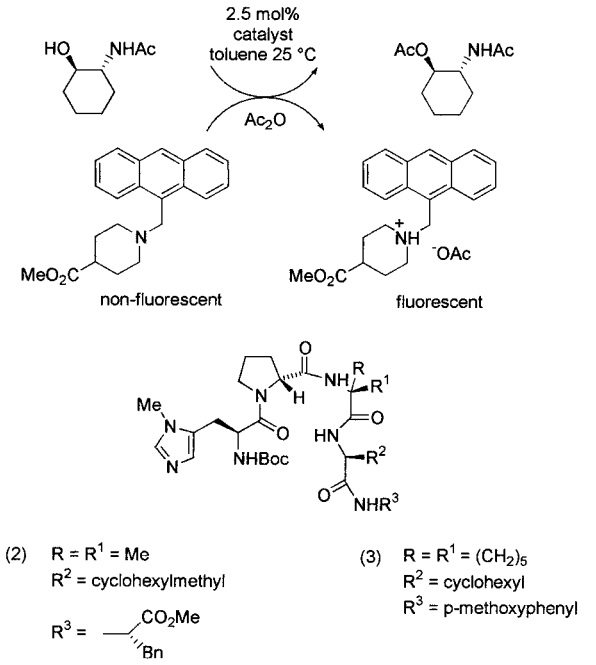


Despite the preponderance of examples in the academic literature—as shown above—readers are reminded that the use of methanol as a solvent for borohydride reductions is not recommended (particularly on-scale) owing to the relatively fast reaction of borohydride with this solvent, generating large amounts of hydrogen—as well as being wasteful of borohydride. Ethanol, higher alcohols, and even water (at the appropriate pH) react much more slowly and are preferred solvents.

A fluorescence-based screening technique for evaluation, using high-throughput screening, of enantioselective acylation catalysts has allowed the identification of a catalyst for tertiary alcohol resolution (Jarvo, E. R. et al. *J. Org. Chem.* **2001**, *66*, 5522). Previously the group had used Chiral GC to assay the results of kinetic resolution of secondary alcohols using low-molecular weight peptides (to mimic enzymes)

but found that the slow separation of enantiomers (30 min per reaction) limited the fast screening. A fluorescent sensor can now be used to detect the acetic acid byproduct in an acylation (Scheme 46), but each enantiomer must be

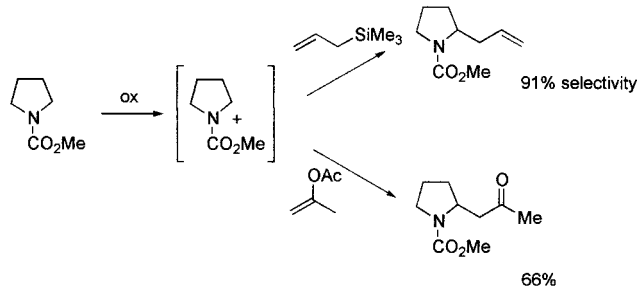
Scheme 46



examined in a separate reaction-well of the automated equipment. For secondary alcohols, a highly selective (k_{rel} = 46) pentapeptide (**4**) was the most enantioselective, whereas for tertiary alcohols the peptide (**9a**−**9f**) was best (k_{rel} > 20).

Microreactors have received a lot of attention in the past 2 years and are expected to make an innovative and revolutionary change in the way organic synthesis is carried out. The possibility of generating highly reactive species and controlling their reactions at short residence times is appealing. Using low-temperature electrolysis, a "cation pool" can be created, and the resultant cation, in a microflow reactor, can react with various nucleophiles (Suga, S. et al. *J. Am. Chem. Soc.* **2001**, *123*, 7941). As yet, yields and conversions are moderate, but in some cases good selectivity is achieved (Scheme 47).

Scheme 47



Although phase-transfer catalysis is a useful synthetic method for manufacture of organic molecules, separation and recycling of the catalyst can be problematical. Nanofiltration (NF) is suggested as the solution (Luthra, S. S. et al. *Chem. Commun*. **2001**, 1468). NF is a membrane process with a MW cut off in the 200−1000 range. Recently NF membranes which perform well in organic solvents have been introduced (White, L. S. *J. Membr. Sci.* **2000**, *179*, 267; Ahu, J. A. *J. Membr. Sci.* **2000**, *179*, 159). Efficient separation of the lipophilic tetraoctylammonium bromide from products was achieved using these NF membranes, and the catalyst was recycled. Membrane fouling occurs during filtration but is reversed when the membrane is washed with solvent.

Chemical and Engineering News (**2001**, *July 30*, 14) highlights a paper from the group of Corma in Spain published recently in *Nature* (Corma, A. et al. *Nature* **2001**, *412*, 423). The paper describes a new tin-infused zeolite for catalysis of the Baeyer−Villager oxidation of cyclohexanone with hydrogen peroxide. The reaction can be extended to other ketones with high selectivity. It is said that this route is more environmentally friendly than traditional manufacturing methods for caprolactone and other lactones; however, the report tends to compare the new method with *m*-CPBA-induced oxidations, which I do not believe are used commercially. It is important for "green" chemists to compare their results with real processes—*m*-CPBA would be far too expensive to use for cyclohexanone oxidation, and cheaper peracids (in which the acid can be recycled) are preferred (see Cotarca, L. et al. *Org. Process. Res. Dev.* **2001**, *5*, 69 for use of cyclohexaneperoxycarboxylic acid in a Baeyer−Villager reaction).

The 16−22th July edition of *European Chemical News* contained a supplement devoted to Process Technology, in which the first article is from Tony Bishop and Luca Raffellini of Arthur D. Little (UK) entitled "Getting a blast from process R & D". It explains how innovation can increase shareholder return if managed correctly and concludes that the chemical companies that will thrive in the next 20 years will be those that learn how to make radical innovations regularly. Attracting the best scientists and engineers by creating an innovative multi disciplinary, idea-sharing environment is a key part of this.

I came across an older reference which may be of interest to those involved in crystallisation and polymorphism of organic compounds (Caira, M. R. *Top. Curr. Chem.* **1998**, *198*, 163). This is one of the best reviews I have seen on the subject, and with 45 pages and 169 references, is a more manageable length than many monographs on the subject.

A recent article suggests that, if you were to ask five chemical engineers what they mean by the term "mixing", you would get five different answers—and they may all be correct. Generally, mixing involves dispersion (the breaking down of particles or droplets into smaller elements) and distribution (the rearranging of the material for greater uniformity, or blending). However, whereas dispersion is primarily a function of the energy input, distribution is usually a function of mixer and vessel geometry, viscosity, density, and the rheological characteristics of the system. To assist with choice of appropriate equipment for batch and for continuous processes, a list of types of mixers, with advantages and disadvantages, has been produced (Brown, P. *The Chemical Engineer* **2001**, *August*, 33).

The physical properties of polymers—particularly conductivity—has been of importance in new materials applications ever since the pioneering work of Heeger, MacDiarmid, and Shirakawa in the 1970s. This year they won the Nobel prize for Chemistry, and Heeger's Nobel Lecture contains predictions that we are on the verge of a revolution in what he calls "Plastic Electronics", where devices currently made from inorganic materials will, in future, be made from organics (particularly polymers)—see Heeger, A. J. (*Angew. Chem. Int. Ed.* **2001**, *40*, 2591). The lectures by Shirakawa and MacDiarmid are also published in the same issue (pp 2575 and 2581). The discovery of the conducting polymer, "doped" polyacetylene, came after an error made in a Japanese experiment produced a metallic sheen, which was soon recognised as an important—if serendipitous-discovery. The lectures are interesting in describing how discoveries are made, recognised and applied. The importance of a multidisciplinary approach is emphasised.

Readers will enjoy an article on "Management and Creativity in Research", written by Ray Firestone (formerly with Merck, BMS, and other pharmaceutical companies) which appears in the August edition of *Chemical Innovation* (**2001**, *August*, 43). The theme is innovation and risk and how the modern management gurus are averse to risk, thereby stifling anything which is truly innovative. He suggests that the only true way to encourage innovation is to allow chemists up to 15% of their time for "doing their own thing"—rather on the lines of the 3M approach. Has any company the courage to allow this? This is an article to photocopy and send to your VP of R&D or to pin on the notice board.

A second article you may wish to pin to your notice board describes a new element, administratium. It is the heaviest element yet discovered, has no protons or electrons, but has one neutron, 125 assistant neutrons, 75 vice neutrons, and 111 assistant vice neutrons. Although the element is inert, it does impede all known reactions. It has a half-life of approx 3 years, but does not decay—it just restructures itself. It is toxic at any concentration (for more details see *The Chemical Engineer* **2001**, *September*, 64).

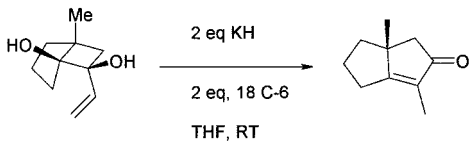
There is also one correction to last issue's highlights. It has been pointed out that the patent referred to re: water-soluble enzyme-coated microcrystals was WO 00/69887, not 69877 as published.

Information on important typos—particularly to references—is always gratefully received.

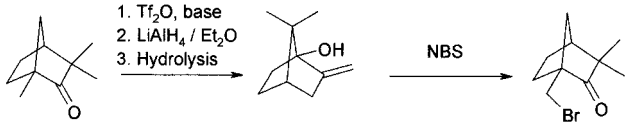
Puzzles and problems

In this new section to the highlights we have selected three papers that use rearrangements as key transformations to construct complex molecular skeletons. We have left it to you to think about the mechanism, rationalisation of the stereoselectivity and potential scalability issues. (*If you need any help we've given the references!!*)

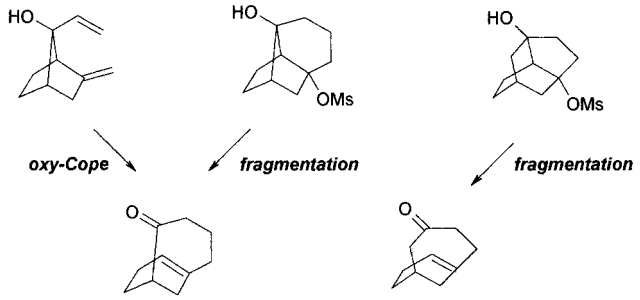
Problem 1. The first reported anionic oxy retro-ene reaction (Jung and Davidov, *Org. Lett.* **2001**, *3*, 3025).



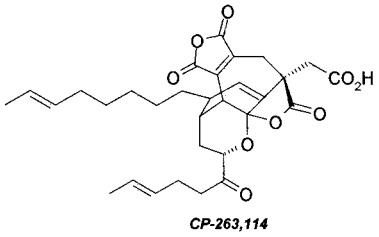
Problem 2. First efficient preparation of enantiopure 10-bromofenchone (Martinez et al. *Tetrahedron Lett.* **2001**, *42*, 6539).



Problem 3.



Evolution of a synthetic approach to CP-263,114 (Njardarson and Wood *Org. Lett.* **2001**, *3*, 2431).



Trevor Laird
Editor
Stephen A. Hermitage
GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK

OP010082R