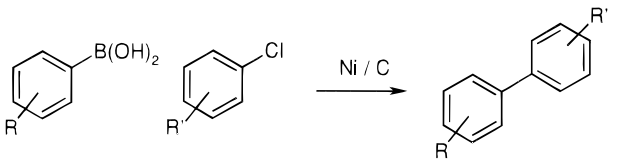
Organic Process Research & Development **2000**, *4*, 236–245

Highlights from the Literature

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

Suzuki couplings which form aryl carbon−carbon bonds have received much attention in the organic chemistry community. Bruce Lipshutz and his group at the University of California (*Tetrahedron* **2000**, *56*, 2139) have reported the biaryl coupling between aryl chlorides and boronic acids in good isolated yields using the heterogeneous catalyst nickel on charcoal (Scheme 1). The catalyst is prepared by

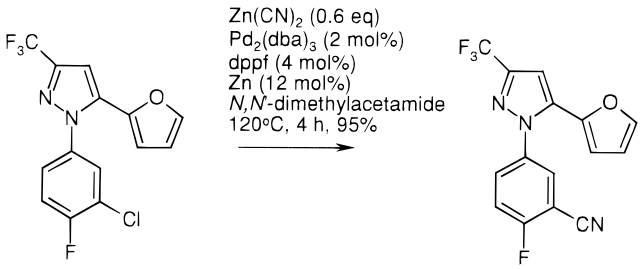
Scheme 1



impregnating $Ni(NO_3)_2$ onto charcoal followed by reduction by stirring with PPh_3 and BuLi in dioxane. The group report little nickel is released from the charcoal as established by ICP experiments.

Jin et al. at the DuPont Pharmaceuticals company have discovered (*Tetrahedron Lett.* **2000**, *41*, 3271) an efficient cyanation reaction of aryl chlorides which employs $Pd_2(dba)_3$, dppf, and zinc as the catalyst and $Zn(CN)_2$ as the cyanide source (Scheme 2). Both electron-rich and electron-deficient

Scheme 2

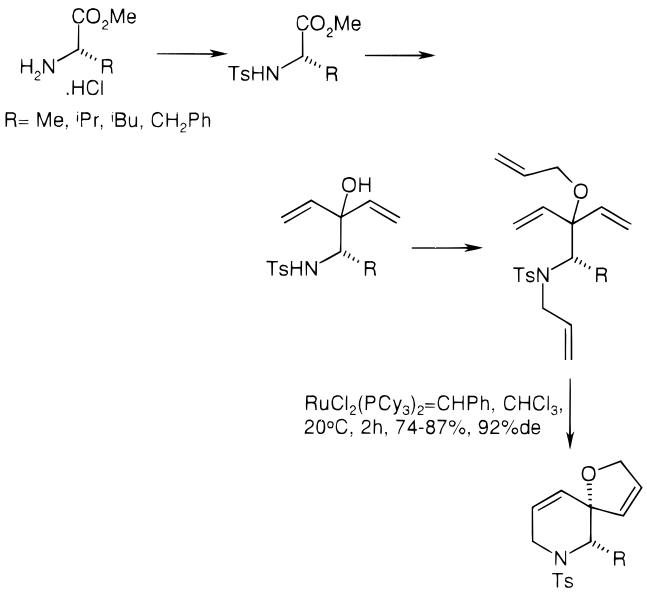


aryl chlorides are effectively cyanated under these conditions.

Ring-closing metathesis (RCM) has evolved recently to become a major tool for synthetic organic chemists. In particular this has been used by a group at Merck to effect a stereoselective double ring-closure generating spirocycles (*Tetrahedron Lett.* **2000**, *41*, 2027) for use in their NK-1 receptor antagonist programme. The metathesis precursors were prepared from commercially available amino acid esters (Scheme 3) and subjected to the key RCM reaction using 5−7 mol % Grubbs catalyst to generate the spirocycles in good yield.

An efficient large-scale deoxygenation reaction has been reported by the process development group at Abbott

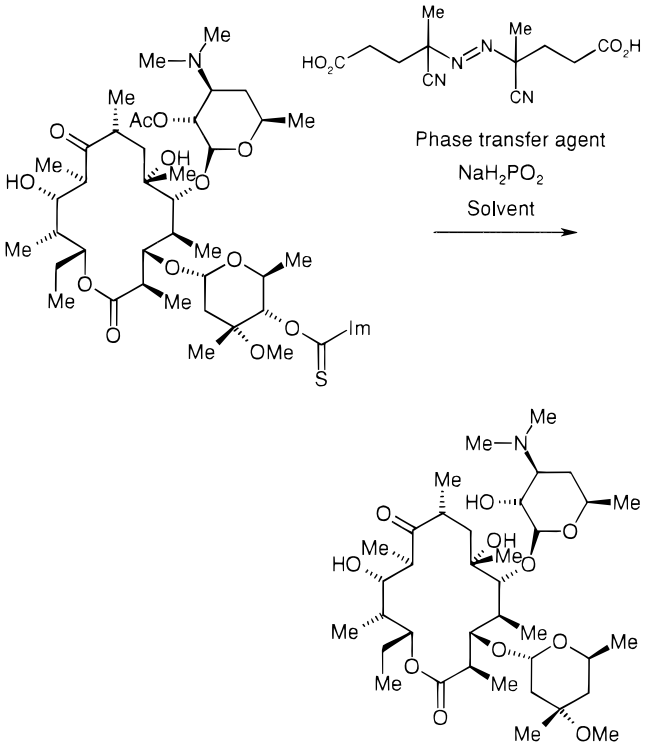
Scheme 3



R= Me, ^{i}Pr, ^{t}Bu, CH_2Ph

Laboratories (*J. Org. Chem.* **2000**, *65*, 2583). Their method (Scheme 4) to achieve radical deoxygenation on an erythromycin derivative involves treatment of an imidazole

Scheme 4



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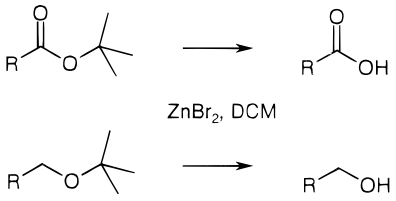
thionocarbamate with 4,4′-azobis(4-cyanovaleric acid) (ACVA) (a water-soluble free radical initiator) in a solvent (EtOH, PrOH, iPrOH, 2ME [2-methoxyethanol]) with NaH_2PO_2 and phase-transfer agent (e.g., tetrabutyl ammonium hydroxide). The method demonstrates a sensitive functional group manipulation on a complex molecule on large scale (15 kg, 17.2 mol input).

The challenges of process scale up R&D are plentiful, one of which is the discovery of mild methods for functional group manipulation. Wu et al. have reported (*Tetrahedron Lett.* **2000**, *41*, 2847) $ZnBr_2$ in DCM as a mild reagent for the deprotection of *tert*-butyl esters and ethers (Scheme 5).

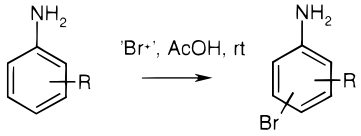
Scheme 5



Interestingly an *N*-BOC-protecting group survives intact under the reaction conditions.

A group at Novartis have disclosed a mild and regioselective oxidative bromination of anilines using potassium bromide and sodium perborate (*Tetrahedron Lett.* **2000**, *41*, 2083). The use of ammonium molybdate as catalyst accelerates the rate of reaction but was found not essential to obtain good yields and high selectivities. (Scheme 6). Strong para

Scheme 6

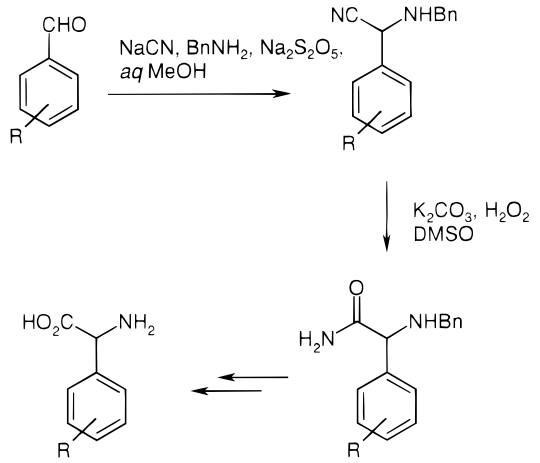


direction is observed, and in the case where the para position is blocked strong ortho direction is observed. In most cases the yields are high, and small amounts of dibromination is observed.

A convenient scalable process for the preparation of substituted phenyl glycines has been reported by a group at Merck (*Synth. Commun.* **2000**, *30*, 1095) using a modified Strecker reaction (Scheme 7). In particular the bisulphite mediated addition of benzylamine and cyanide anion to substituted benzaldehydes gave aminonitriles which were hydrolysed to the N-protected amino acids. These improvements prevented the troublesome "retro"-Strecker reaction and were performed on kg-scale.

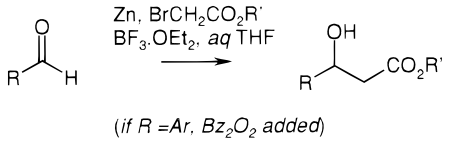
A practical method for the Reformatsky reaction has been reported by Chattopadhyay and Salaskar (*Synthesis* **2000**, 561). In their report Reformatsky reaction of *aliphatic* aldehydes was performed successfully by the addition of $BF_3{\cdot}OEt_2$ to a stirred suspension of aldehyde, bromoester, and Zn dust in aqueous THF. For aromatic aldehydes,

Scheme 7



addition of benzoyl peroxide was required to effect reaction (Scheme 8). A general, simple practical method is described

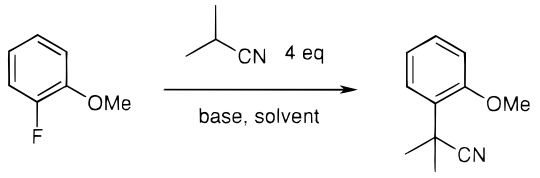
Scheme 8



on 0.03 mol scale.

Caron et al. from Pfizer report the preparation of tertiary benzylic nitriles from aryl fluorides in a recent communication (*J. Am. Chem. Soc.* **2000**, *122*, 712). The use of KHMDS as base in either toluene or THF to promote SNAr reaction of aryl fluorides with secondary nitriles is described on a variety of substrates (Scheme 9).

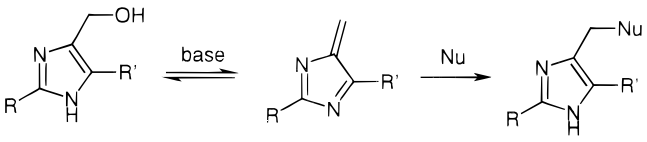
Scheme 9



Simple chemical transformations when telescoped together can be powerful tools in organic synthesis which are exemplified by the following two examples.

Macor et al. at Bristol-Myers Squibb have reported (*Tetrahedron Lett.* **2000**, *41*, 2777) the direct displacement of −OH from 4- and 5-hydroxymethylimidazoles by simply heating with the appropriate nucleophile in refluxing basic water. The postulated mechanism is shown in Scheme 10,

Scheme 10

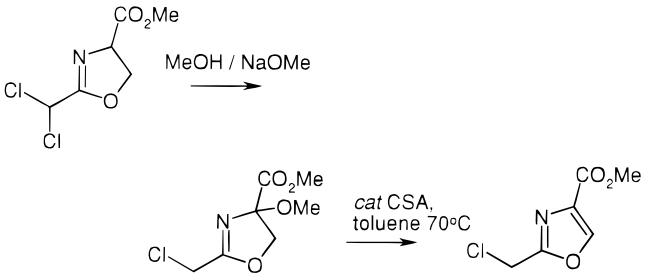


and the synthetic versatility of this substitution reaction relies on the vinylogous iminium intermediate being captured by

a nucleophile. To date the group have successfully used nitrogen nucleophiles in this reaction generally in high yield.

In a recent communication from our labs at Glaxo Wellcome we have converted oxazolines to oxazoles in a one-pot method, transferring oxidation state through a molecular framework (*Tetrahedron Lett.* **2000**, *41*, 4239). The method, outlined in Scheme 11, circumvents the need

Scheme 11

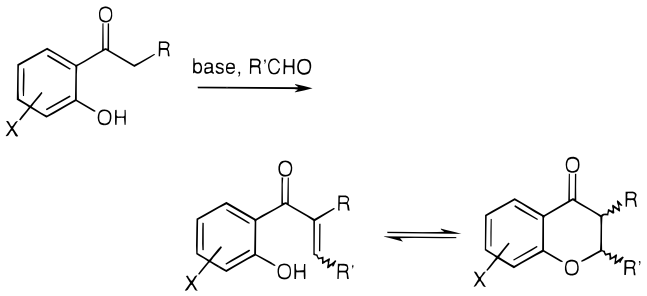


for environmentally unacceptable metals, solvents, and reagents generally employed in the oxazoline-to-oxazole conversion.

The DuPont Pharmaceutical company have reported (*Tetrahedron Lett.* **2000**, *41*, 3015) the synthesis of DPC961, a second generation HIV non-nucleoside reverse transcriptase inhibitor. Their approach starts with the reaction between the hydrate hydrochloride keto-aniline and isocyanate in aqueous acid/THF as shown in Scheme 12. Careful control of the reaction temperature and the use of 2 equiv of the isocyanate (as 1 mol equiv is hydrolysed under the reaction conditions) gave the hemiaminal. Reaction conditions to promote conversion of the hemiaminal to the 2(3H)-quinazolinone were established, and subsequent stereoselective organometallic addition furnished the dihydroquinazolinone in ~92% ee and good yield. Acid deprotection gave DPC961 in excellent yield.

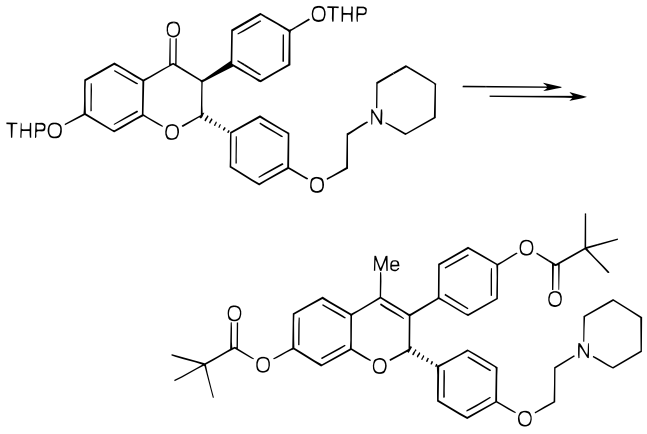
A group at Schering-Plough have described the piperidine catalysed Knoevenagel condensation of 2′-aryl/alkyl-2-hydroxyacetophenones and aryl/alkylaldehydes in refluxing isopropyl alcohol with azeotropic removal of water to give equilibrium mixtures of *E*/*Z* chalcones and *cis*/*trans*-chroman-4-ones. The *cis*/*trans* mixtures could be effectively isomerised in situ by the addition of DBU and the products isolated by simple filtration (Scheme 13). In particular the

Scheme 13



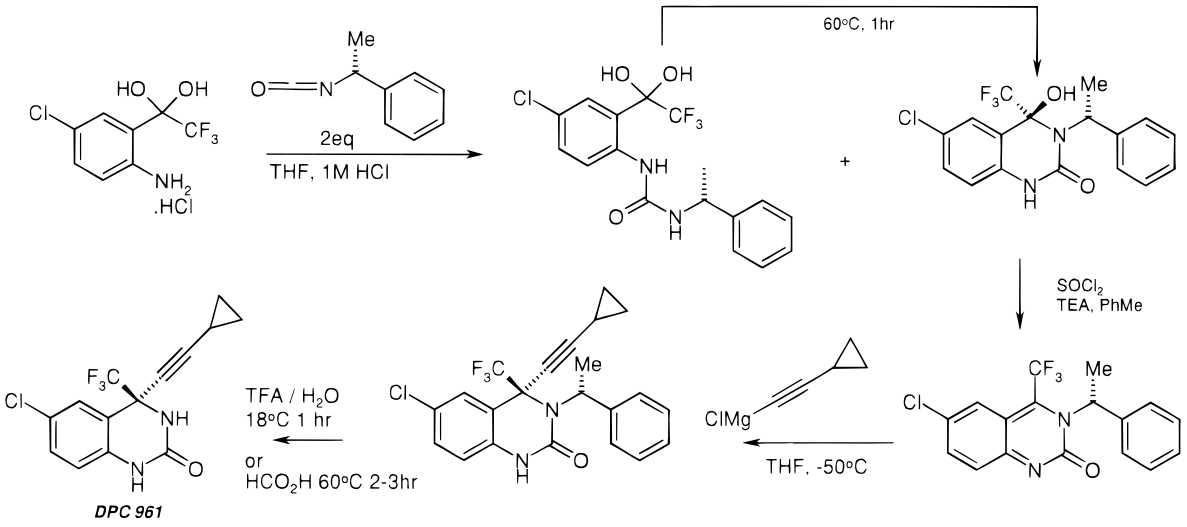
group have been interested in applying this chemistry towards the synthesis of Sch 57050, an anti-estrogenic compound (Scheme 14).

Scheme 14



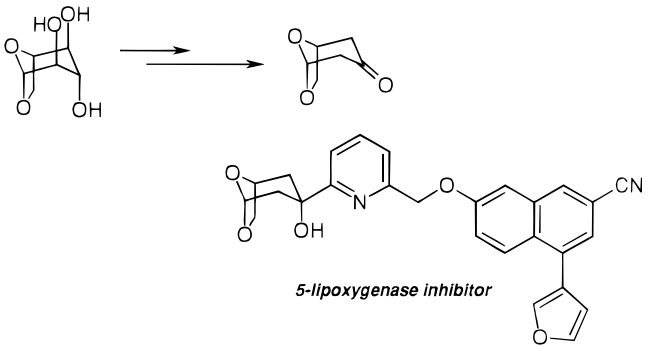
Only a few efficient methods for the large-scale preparation of 1,6-anhydro-2,4-dideoxyhexopyranoses exist, until a recent report (*J. Org. Chem.* **2000**, 65, 2588) by the process

Scheme 12



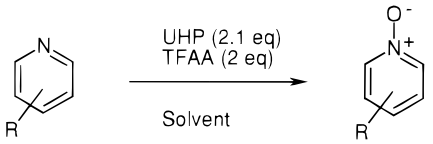
research group at Merck. They describe a "chromatographic free" process for the conversion of 1,6-anhydro-D-glucose to 1,6-anhydro-2,4-dideoxy-β-D-glycero-hexopyranos-3-ulose (Scheme 15) amenable to multi-kg scale preparation. This key fragment was required in the synthesis of the potent 5-lipoxygenase inhibitor shown in Scheme 15. A general

Scheme 15



method for the oxidation of electron-poor pyridines to their *N*-oxides (Scheme 16) using commercially available urea

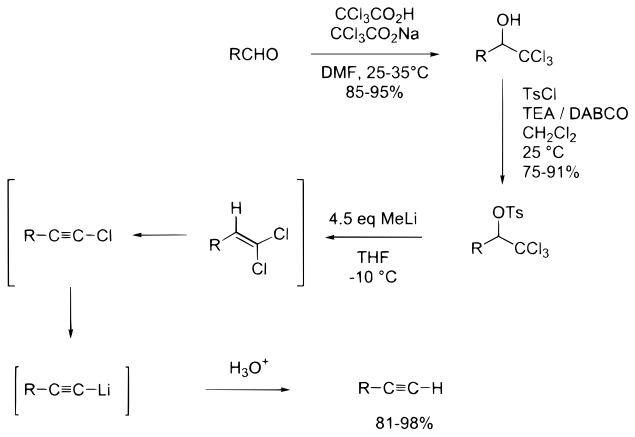
Scheme 16



hydrogen peroxide complex (UHP) and trifluoroacetic anhydride (TFAA) has been reported by Caron et al. at Pfizer (*Tetrahedron Lett.* **2000**, *41*, 2299). The method was performed in DCM or MeCN and proved successful on substrates containing a variety of functional groups.

Cyclopropylacetylene is a key raw material in the synthesis of Efavirenz (Sustiva), a marketed non-nucleoside reverse transcriptase inhibitor for the treatment of AIDS, and a number of syntheses have been reported (see Patent Highlights in OPRD). The group at DuPont Pharmaceuticals (Wang, Z. et al. *J. Org. Chem.* **2000**, *65*, 1889) suggest that standard ways of converting cyclopropyl carboxaldehyde to cyclopropylacetylene—Corey—Fuchs, Wittig/Horner-Emmons methods, etc.—are unsuitable for large-scale work because the phosphorus reagents required have toxicity, environmental, and exothermicity problems. An alternative method, involving addition of a dihalomethyl lithium followed by sulphonation and elimination, was reported last year (Wang, Z. et al. *J. Org. Chem.* **1999**, *64*, 6918). However, this method requires the handling of a thermolabile and moisture-sensitive species, dihalomethyl lithium, at −78 °C, for good yields. They now report that trichloromethyl anion—generated from trichloroacetic acid—will react with aldehydes and the resultant alcohols can be converted to acetylenes according to Scheme 17. The process works well on 300-400 g scale, in approximately 80% overall yield. My concerns for the future scale up of the process would be the potential hazards of the chloroacetylene intermediates (which

Scheme 17

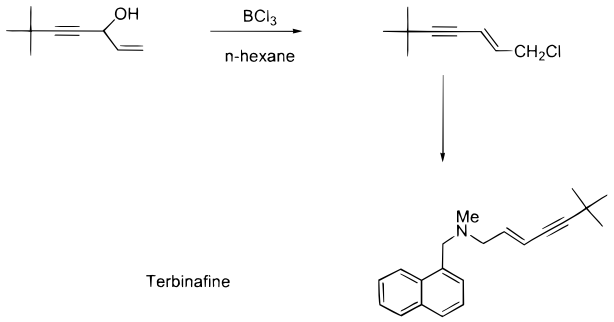


often have low autoignition temperatures), low atom efficiency of the process, and the reagent excesses (e.g., 4.5 equiv of methyl lithium). However, the process has general applicability and may be better than any of the alternatives.

A synthetic method for specific para-hydroxylation of nitroarenes has been developed by a group at Boehringer Ingelheim, U.S.A. (Zhu, L. et al. *Tetrahedron Lett.* **2000**, *41*, 3519). Treatment of naphthalenes with cumene hydroperoxide in aqueous alkaline DMSO leads to regiospecific introduction of the hydroxy group into the para position. The product ratio is sensitive to the DMSO—water ratio, a 75:25 mixture giving the best selectivity. The reaction was carried out on a molar scale to give >80% yield of nitronaphthols.

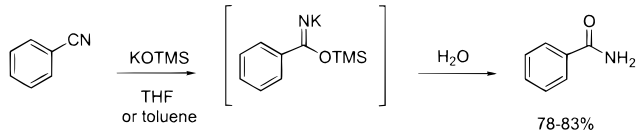
The selective formation of *Z*-enynes from acetylenic vinyl alcohols has been shown to proceed cleanly in the presence of BCl_3 at room temperature (Chou, S.-Y. et al. *Tetrahedron Lett.* **2000**, *41*, 3895). The products are useful in the synthesis of antifungal agents such as terbinafine (Scheme 18).

Scheme 18



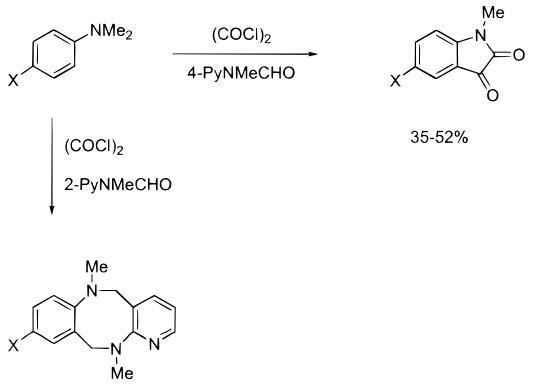
Transformation of nitriles to carboxamides can be a tricky reaction to control selectivity. A new protocol involves treating the nitrile with lithium, sodium, or potassium trimethylsilanolate in THF or toluene. The intermediate salt precipitates and is filtered off and hydrolysed to the amide (Merchant, K. J. *Tetrahedron Lett.* **2000**, *41*, 3747). The process is reminiscent of the conversion of benzonitriles to amides using lithium bis(trimethylsilyl) amide. The reaction works best with aromatic and heteroaromatic nitriles and is less successful with aliphatic nitriles, although cinnamonitrile and phenylacetonitrile gave 68−69% yields (Scheme 19).

Scheme 19



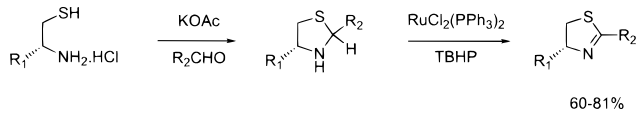
An interesting cyclisation is the one shown in Scheme 20 for the conversion of aryl dimethylamines to *N*-methylisatins, reported by a collaborative effort from China and UK (Cheng, Y. *Tetrahedron Lett.* **2000**, *41*, 3475). The mechanism of this unique reaction is open to speculation. The corresponding 2-pyridyl *N*-methyl formamides reacted under similar conditions to give diazocines.

Scheme 20



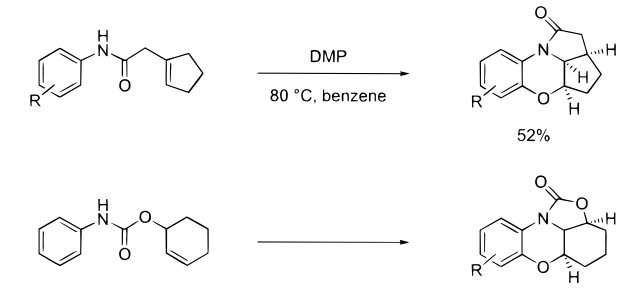
A new synthesis of thiazolines has been reported (Fernandez, X. et al. *Tetrahedron Lett.* **2000**, *41*, 3819). The key step is the ruthenium-catalysed oxidation, using TBHP, of the easy-to-prepare thiazolidines (Scheme 21).

Scheme 21



The rapid and efficient construction of bonds should be the aim of any industrial synthesis, and a new method from the group of Nicolau (*Angew. Chem., Int. Ed.* **2000**, *39*, 622) opens up lots of possibilities for the synthesis of ring compounds. The method was discovered by chance—but chance favours the prepared mind! The original discovery was that simple anilides react with Dess–Martin periodinane reagent (DMP) to give polycyclic compounds (Scheme 22),

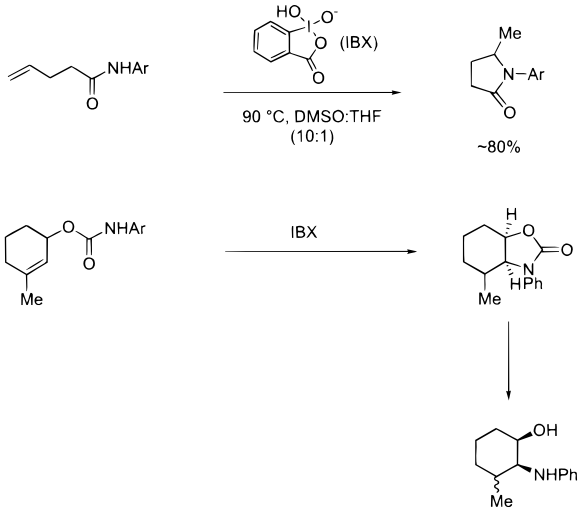
Scheme 22



but this was later extended to include cyclisation of a variety of compounds, easily made from the reaction of phenylisocyanates and isothiocyanates with allylic alcohols and amines.

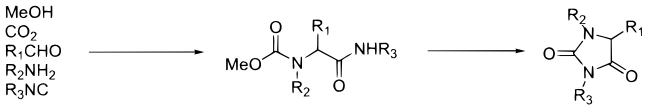
In the following paper (p 6250), the reactions of similar substrates with the closely related reagent 1BX were studied, but a completely different cyclisation occurred. The reactions are envisaged to proceed via radical processes, but are robust processes proceeding in the presence of air or water (Scheme 23).

Scheme 23



The Ugi reaction and variants of the 3-, 4-, and 5-component coupling reactions look like potentially interesting convergent approaches to a variety of molecules. Scheme 24 here shows a summary of what can be achieved in the

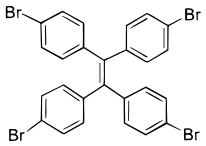
Scheme 24



synthesis, in remarkably good yield, of heterocyclic compounds using a five-component reaction of simple materials (Hulme, C. et al. *Tetrahedron Lett.* **2000**, *41*, 1889).

All process development chemists would like to be able to obtain single enantiomers from racemic mixtures without using expensive resolving agents. A recent report (Tamaka, K. *Chem. Commun.* **2000**, 413) indicates that recrystallising the chiral olefin in Scheme 25 from certain solvents gives

Scheme 25



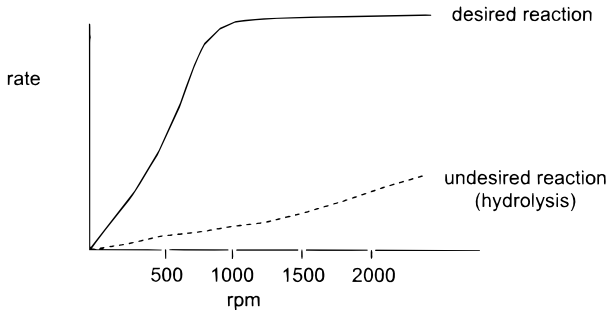
1:1 inclusion crystals which are "conglomerates" with *p*-xylene, acetone, dioxan, and benzene but are true racemates with cyclohexanone, THF (a 1:2 crystal was found here), B-picoline and toluene. When exposed to *p*-xylene vapour at room temperature for 24 hours, however, the racemic form

was converted to the chiral crystalline complex. Interestingly, gas−solid interaction of the racemate with solvents which, in the liquid phase, gave racemic crystals also gave the conglomerate form (THF, B-picoline), whereas acetone, which gave chiral crystals in the liquid phase, did not give an inclusion complex in the gas phase.

When the complexes were heated under reduced pressure the solvent was removed but the desolvated crystals still retained the chiral space group.

My (T.L.) experience in the scale up of two-phase reacting processes such as phase-transfer catalysed (PTC) reactions, is that they can be sensitive to the position of the agitator in relation to the interface, and to the agitation speed. Normally, one could expect that fast agitation would be best. A word of warning, however, comes from Mark Halpern in his latest PTC communications (Vol. 13, p 2, see http://www.phasetransfer.com) in which he describes PTC examples where one of the components in the reaction is sensitive to hydrolysis (e.g., an acid chloride or anhydride). At low agitation, the non-PTC-catalysed hydrolysis is negligible but at higher agitation rates it may be significant, and substantial amounts of by-product may ensue. The recommendation is that every PTC-catalysed process should be examined, prior to scale up, to look at the effect of agitator speed on the rate and selectivity of product and by-product formation. Often the curves shown in Scheme 26 are obtained.

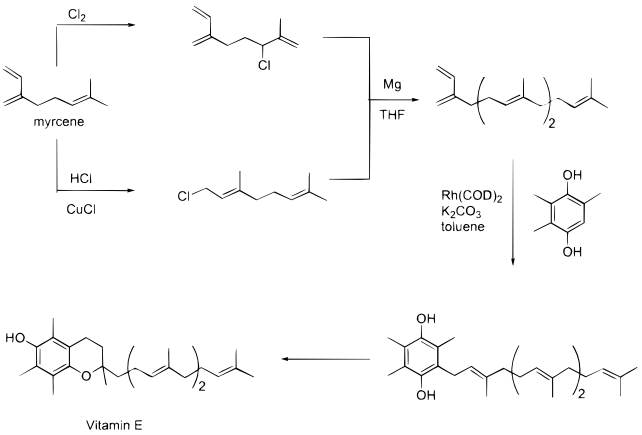
Scheme 26



The importance of organometallic chemistry in modern production of organic compounds is highlighted in Rhone Poulenc's new synthesis of vitamin E (DL-α-tocopherol), which has a world-wide annual production of over 10 000 tonnes—it is used as a food additive. The usual synthetic process relies on Friedel−Crafts alkylation of trimethylhydroquinone (TMHQ) with isophytol followed by ring closure. However, isophytol may take 6−9 synthetic steps to make. A more convergent and atom economical synthesis has now been discovered by the R-P/Rhodia workers (Bienaymé, H. et al. *Tetrahedron Lett.* **2000**, *41*, 41, 3339). Myrcene—a cheap raw material derived from *β*-pinene—is reacted with chlorine and in a separate process with HCl/CuCl. The two products are then combined and reacted with TMHQ as shown in Scheme 27.

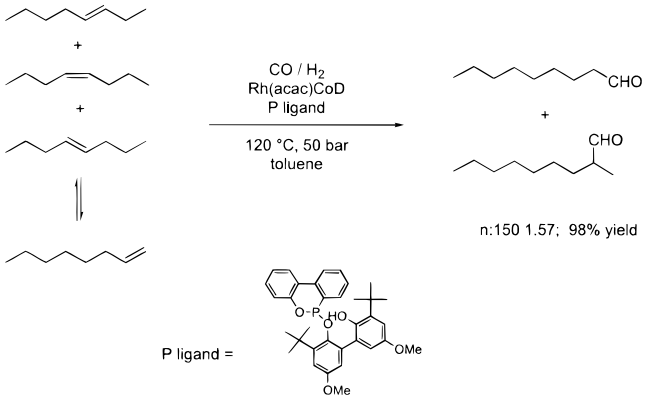
Hydroformylation (oxo synthesis) is one of the most useful industrial processes carried out using homogeneous catalysis with over 6 million tonnes per annum of products being produced, mostly for the plasticiser industry. Hydroformylation of octene isomers, for which control of regio-

Scheme 27



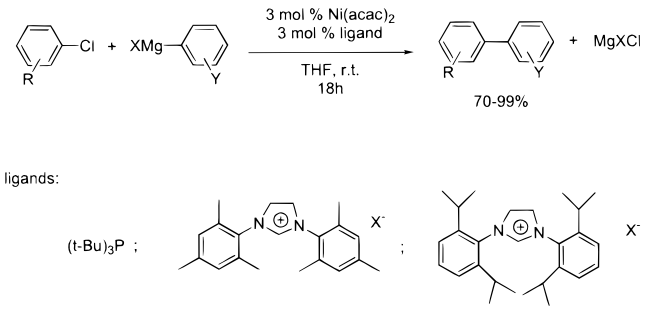
selectivity to give terminal aldehyde products is crucial and complete conversion of all isomers present is also important, can only be carried out with cobalt catalysis under severe reaction conditions. Rhodium catalysts have been shown to be useful for conversion of terminal olefins but not for internal olefins. A recent report (Solent, D. et al., *Angew. Chem., Int. Ed.* **2000**, *39*, 1639) indicates that variation of the ligand on rhodium can give good results even with mixed olefins under relatively mild conditions (Scheme 28).

Scheme 28



The group of Herrmann at Munich continues to produce organometallic catalysts which are often of potential industrial importance. Their latest publication (Bohm, V. P. W, et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 1602) demonstrates that nickel catalysed cross coupling between aryl chlorides and aryl Grignard reagents can occur at room temperature in the presence of nickel catalysts (see Scheme 29). In

Scheme 29

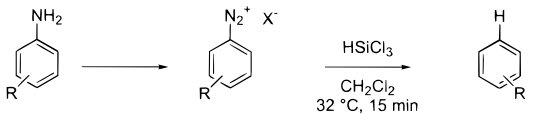


general, the catalysts are less sensitive to steric bulk on the Grignard than on the aryl chloride. Minor amounts (<1%) of by products such as terphenyls occur, suggesting radical side reactions as in other nickel-catalysed cross-coupling reactions.

Aqueous biphasic hydroformylation is an important industrial process (see *Aqueous Phase Organometallic Catalysis*; Cornils, B. and Herrmann, W. A. VCH: Weinheim, 1999). Most of the catalysts used to date have been rhodium complexes of sulphonated phosphines, sugars, or water-soluble polymers. It has now been shown that biopolymers, formed from $Rh(CO)_2$ (acac) and human serum albumin are effective in the hydroformylation of a variety if olefins under mild conditions (Marchetti, M. et al. *Tetrahedron Lett*. **2000**, *41*, 3717). Yields are high with styrene, isobutene, 1-octene, etc., but the catalyst does not work with bulky olefins such as 1,1-diphenylethene.

The reduction of aromatic diazonium compounds to the corresponding unsubstituted arene is a useful process, but many of the currently used reagents are not general and give moderate yields for electron-rich olefins. It is now suggested that trichlorosilane is a versatile reagent for this transformation and is compatible with a wide variety of functional groups (Lormann, M. et al. *Tetrahedron Lett*. **2000**, *41*, 3813) see Scheme 30.

Scheme 30



Although asymmetric catalysis is used widely for the synthesis of optically active compounds on small scale, large-scale industrial applications are still rare. One of the reasons is the high catalyst (both metal and ligand) cost and the difficulty of recycling homogeneous catalysts effectively A number of attempts to heterogenise catalysts by attaching ligands to polymers have been carried out. A new approach is to incorporate the ligand in the polymer, thus giving a molecule with backbone chirality (ter Haller et al. *Tetrahedron Lett*. **2000**, *41*, 6431). Polymers of BINAP, named POLYNAP when complexed with ruthenium, are effective hydrogenation catalysts at loadings as low as 0.1 mol %. The catalyst could be reused, but activity falls off.

Interest in supported homogenenous catalysts is high, owing to the need to recycle complex ligands and precious metals and to ease product separation from catalyst and product contamination by the catalyst. Two groups in Ottawa, Canada, in collaboration with DuPont have investigated the scope of dendritic multivalent ligands, anchored onto beads for heterogeneous catalysts (Arya, P. et al. *J. Org. Chem*. **2000**, 65, 1881). These catalysts, when complexed with rhodium, can give >99% conversion of styrene phenylpropionaldehyde with high selectivity. The conversion remains high when the catalysts are recycled four times but drops to 78% on the fifth and 47% on the sixth recycle. However, the catalysts are very active for polymer systems and, whilst not immediately practical, may show promise for the future.

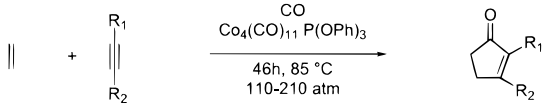
One often learns more from failures than from successes. In this respect, it was refreshing to see an article entitled "Dead Ends and Detours En Route to Total Synthesis of the 1990s" (Sierra, M. A. et al. *Angew Chem, Int. Ed.* **2000**, *39*, 1539). Such headings include:

- Working models that do not work
- Troublesome protecting groups
- The unexpected influence of remote substituents
- The trivial functional group transformation
- Reluctant ring closures

Development chemists will have met most of these.

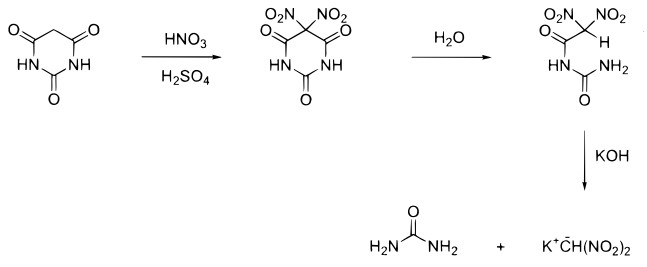
Supercritical fluids (SCF) are being studied as alternative reaction solvents for conventional organic reactions, and a couple of good reviews of the topic appeared last year (*Chemical Synthesis using Supercritical Fluids*; Jessop, P. I., Leitner, W., Eds.; Wiley-VCH: Weinheim, 1999, and Jessop, P. G. et al. *Chem. Rev*. **1999**, *99*, 475). The advantages of SCF include the high solubility of gaseous reactants, rapid diffusion of solutes, easy separation of products, and recycling of the solvent. Disadvantages, of course, are the use of pressure and therefore specialised equipment, which has hindered the general use on-scale, although specialist companies such as Thomas Swan in the UK have invested heavily in this area. Although CO_2 is often the preferred solvent, others can be used. A recent report (Jeong, N. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 636) indicates that the Pauson−Khand reaction occurs in supercritical ethylene (as reactant) to give cyclopentanones in high yield, Scheme 31.

Scheme 31



An efficient and safe method of making salts of dinitromethane, useful in the explosives industry has been reported (Langlet, A. et al. *Tetrahedron Lett*. **2000**, *41*, 2011). Barbituric acid can be dinitrated in nitric−sulphuric acid, and ring cleavage with water leads to dinitroacetylurea. Further, more vigorous hydrolysis in base leads to salts of dinitromethane (Scheme 32).

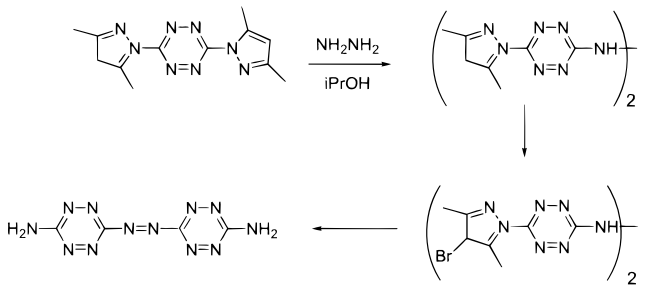
Scheme 32



Many of these dinitro compounds are, surprisingly, thermally stable. The paper, however, points out, that all nitro compounds are potential explosives and must be handled with appropriate precautions.

High-nitrogen compounds form a unique class of energetic materials, deriving most of their energy from their very high positive heats of formation rather than from oxidation of the carbon skeleton, as with traditional energetic materials. These high nitrogen compounds are used in propellants, explosives, and pyrotechnic applications. 3,3-Azobis (6-amino-1,2,4,5-tetrazine has been synthesised for the first time (see Scheme 33) and has shown to be thermally stable (to 252 °C) despite a very high heat of formation of 862 kJ mol. It is also surprisingly stable to impact and to ignition by sparks or friction (Chavez, D. E. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 1791). In the presence of oxidising agents, however, the energy may be released—do not try this at home!

Scheme 33



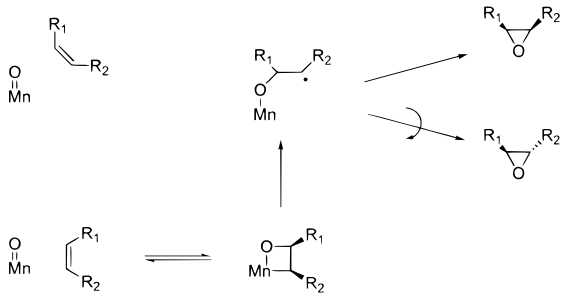
A footnote in an article (Jeong, V. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 636) warns that highly purified catalysts $Co(CO)_8$ and $Co_4(CO)_{12}$ can spontaneously ignite on contact with air and that the authors preferred to use the more stable $Co_4(CO)_{11}$−$P(OPh)_3$ to avoid any potential danger.

Racemisation is an important industrial process, necessary for the recycling of unwanted materials produced in resolution or kinetic resolution processes. Usually this is carried out by heating in the presence of bases or occasionally acids. The group of Beller at Rostock in Germany have recently demonstrated what they claim is the first transition metal-catalysed racemisation of *N*-acyl α-amino acids (Hateley, M. J. et al. *Tetrahedron Lett.* **2000**, *41*, 3821). The best catalyst appears to be $[Rh(cod)C1]_2$ in the presence of tricyclohexylphosphine. As yet, the racemisations are slow taking over 48 h at 60 °C, but, no doubt, more active catalysts will be discovered in the future. The results are significant not only for kinetic resolutions but also for asymmetric hydrogenation where similar catalysts may cause racemisations, particularly under low-pressure conditions, at the end of the reaction where product concentrations are highest.

An efficient method for the synthesis of peptide bonds is what many companies are searching for. Chemical methods often require expensive activating agents and enymatic methods would offer useful alternatives, since processes effect peptide bond formation under mild conditions with minimum side-chain protection and with no racemisation. However, the disadvantage is the unfavourable thermodynamics in water, and use of organic solvents or aqueous organic media leads to low enzyme activity. A number of methods have been investigated to try to overcome these difficulties, but a recent publication (Basso, A. et al. *Chem. Commun.* **2000**, 467) indicates that a very simple procedure can give good results, and scale up of the method looks simple. The method exploits the ability of Celite R-640 rods to absorb large amounts of water (>90% of its weight). The concentrated aqueous solution of the enzyme is added to a toluene suspension of Celite R-640 leading to a uniform coating of the enzyme around the Celite. The suspension of the enzyme/support in toluene is then used in the reaction of α-protected amino acid ester and the amino group of an amino acid ester giving conversion of 95−EnDash98% in 24−144 h at 30 °C. Equimolar amounts of each reagent are used. The method is suitable for the immobilisation of thermolysin, α-chymotrypsin, and penicillin G amidase. The disadvantage of the method is the long reaction time mainly caused by the very slow kinetics at the end of the reaction, when the concentration of reactants are low. Using of a two fold excess of the amino component shortens the reaction time, but the purification of the product is much more difficult. When 1 mol of each reagent is used, the high conversion means that product isolation is very simple (extraction into MeCN, filtration, evaporation), and products of >98% are obtained directly.

There has been much debate over the mechanism of the Jacobsen−Katsuki epoxidation reaction, which is potentially a useful reaction in large-scale chemistry. Recent calculations from the group of a different Jacobsen (Cavello, L. and Jacobsen, H. *Angew. Chem., Int. Ed*. **2000**, *39*, 589) confirm that the epoxidation occurs by direct attack of the olefin on the oxo ligand of the manganese catalyst and that radical intermediates are most likely involved (Scheme 34). A

Scheme 34



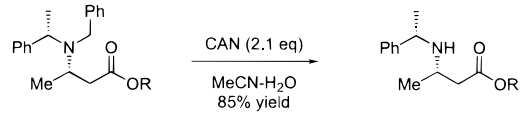
pathway via an oxametallacycle was excluded for energy reasons.

Asymmetric reduction of nitrones, using an iridium complex generated from $IrCl(cod)_2$, (*S*)-BINAP and $Bu_4N^+ BH_4^-$ gives the corresponding hydroxylamines, generating a new chiral centre; ee's of up to 86% are obtained. (Muraheshi, S.-T. *Chem. Commun*. **2000**, 409)

The treatment of tertiary amines, containing one or more *N*-benzyl-protecting groups with aqueous ceric ammonium nitrate results in clean debenzylation to give the correspond-

ing secondary amine (Bull, S. D. et al. *Chem. Commun.* **2000**, 237). As example is shown in Scheme 35.

Scheme 35

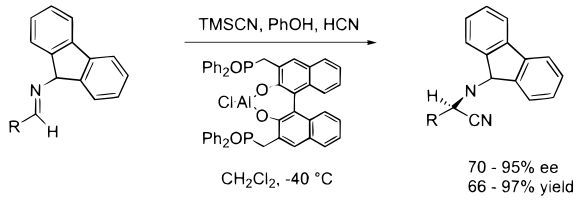


An intriguing essay entitled "How long have non-linear effects been known in the field of catalysis" has appeared from Heller's group at Rostock (*Angew. Chem., Int. Ed.* **2000**, *39*, 495). The work of Langenbeck (also from Rostock) in 1936 was the first example of non-linear effects and it is clear that Langenbeck—in some farsighted research—understood the process quite well. The Heller essay analyses Langenbeck's work and more recent examples. It follows on from Kagan's review (*Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2923) which gives more comprehensive coverage of the literature and was highlighted on these pages.

In the same issue the non-linearity of effects of temperature on diastereo- or enantioselectivity has been examined (Cainelli, G. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 523). In the reaction of alkyl lithiums with (silyloxy aldehydes in hexane or THF, the inversion temperature (where the non-linearity occurs) correlates with a change in solvation—as shown by NMR spectroscopy—as the temperature changes. The inversion temperature is, of course, different in different solvents, and this emphasises the need to study more closely solvent effects and concentration effects (which affect aggregation) in the scale up of diastereoselective processes. The addition of alkyl lithiums to substituted aldehydes is a common process in the manufacture of diols and amino alcohols.

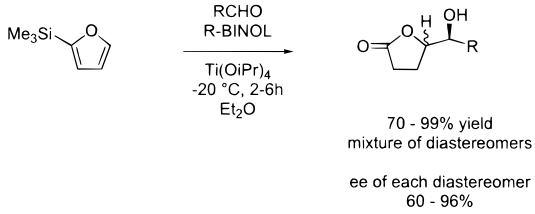
The group of Shibasaki at the University of Tokyo have reported (*Angew. Chem., Int. Ed.* **2000**, *39*, 1650) an improved asymmetric Strecker reaction which works for aliphatic as well as aromatic imines (Scheme 36). The presence of phenol accelerates the reaction possibly via formation of TMSOPh, but the reaction is mechanistically quite complex and sensitive to changes in reaction conditions.

Scheme 36



The first catalytic asymmetric autoinductive aldol reaction has been reported by a group from Paris (Szlosek, M. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 1799). The enantiomeric excess and yield of the aldol reaction of silyloxy-furans with a variety of aromatic and aliphatic aldehydes is dependent on the mode of addition. A stepwise addition of a mixture of the reagents to the catalyst (e-BINOL—titanium isopropoxide) results in a modification of the asymmetric catalyst by incorporation of the product itself in the catalyst. The resultant new catalyst results in amplification of the enantiomeric excess of the product. Use of a more bulky silane improves the diastereomeric ratio. Perhaps we should all be more conscious of the importance of the rate of addition of reagents which may affect the enantiomeric purity of products, particularly in catalytic processes (Scheme 37).

Scheme 37

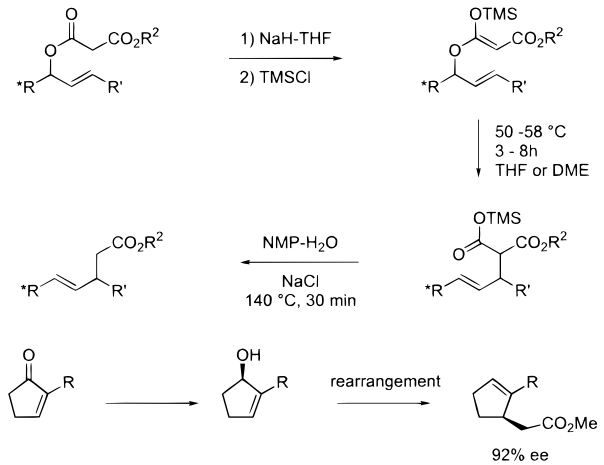


The group of Fehr at the Swiss fragrance company Firmenich have produced some novel methodologies in the area of asymmetric protonation in the past 10−15 years. A recent publication from the group demonstrates a useful variation of the Ireland−Claisen rearrangement of ortho esters which gets around the industrial disadvantages:

- Excess ortho ester
- Unsuitability for methyl esters since trimethyl ortho-acetate boils at 105−110°
- The need for later transesterification if a methyl ester is required.

The new version uses TMS−ketene acetals in the reaction allowing a lower temperature rearrangement, and this enables excellent chirality transfer to occur (Fehr, C. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 569), Scheme 38. The process is used to make jasmone derivatives.

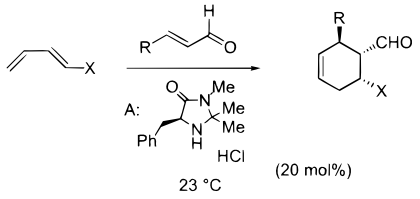
Scheme 38



And finally, one us (T.L.) recently heard an outstanding lecture from David MacMillan (of University of California at Berkeley) at a Chiral Conference, in which he showed how organic catalysts could be used for a variety of enantioselective processes. Some of this work has already been published (Ahreddt, K. A. et al. *J. Am. Chem. Soc*. **2000**, *122*, 4243). In the published paper, the organic catalyst (A) was shown to catalyse the addition of acrolein or crotonaldehyde to dienes with high selectivity under mild conditions. The reactions clearly proceed via transient

iminium ion species. This area promises to revolutionise organic chemistry and is of great interest to industrial chemists, both for combinatorial studies and for scale up (Scheme 39). Reactions can be carried out in the presence of air and water—in fact water sometimes enhances the selectivity end rate.

Scheme 39



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