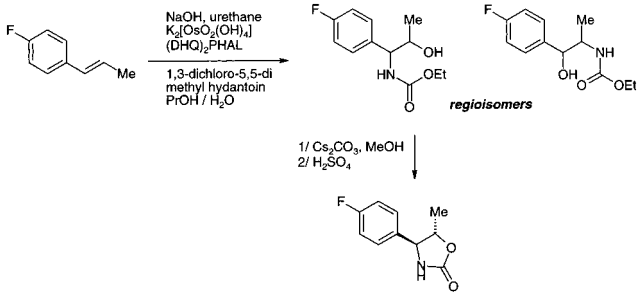
Organic Process Research & Development **2001**, *5*, 2–8

Highlights from the Literature

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

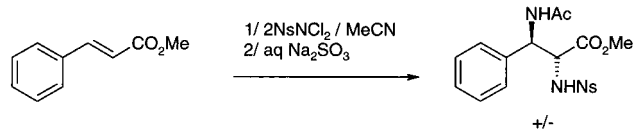
The process research group at Merck have recently published (Barta et al. *Org. Lett.* **2000**, 2821) some modifications and applications of the Sharpless asymmetric aminohydroxylation reaction (Scheme 1). In this paper they report examples of a practical one-pot conversion of styrene derivatives to chiral oxazolidin-2-ones. The requirement for 3 equiv of freshly prepared *tert*-butyl hypochlorite was untenable for large-scale work, and the group successfully replaced this reagent with the easily handled, commercially available substitute—1,3-dichloro-5,5-dimethyl hydantoin. The regioselectivity of aminohydroxylation remains moderate in their protocol; however, the group were able to separate regioisomers since, in the presence of base, the benzylic amine derivative cyclised much more rapidly than the benzylic alcohol derivative. Treatment of the mixture with sulphuric acid transformed the uncyclised benzylic alcohol isomer to the corresponding amino alcohol, leaving the oxazolidinone untouched.

Scheme 1



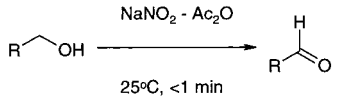
Li et al. have reported (*Tetrahedron Lett.* **2000**, *41*, 8699) α,*β*-differentiated tandem diamination of cinnamic esters using *N*,*N*-dichloro-2-nitrobenzenesulfonamide (2-NsNCl$_2$) and acetonitrile as the nitrogen sources (Scheme 2). The products of the reaction have *anti* stereochemistry and are differentially "protected" (*N* α-(2-Ns), *N* *β*-Ac). In addition to ene-esters, unsubtituted alkenes also undergo this reaction; for example, cyclohexene gives diaminated products in 92% yield.

Scheme 2



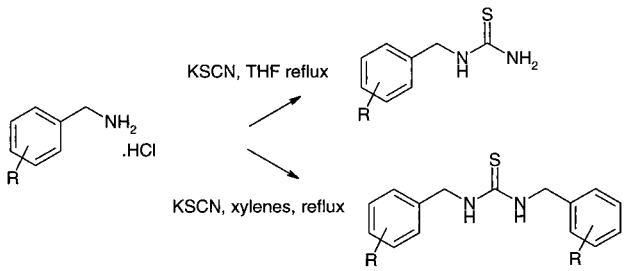
Bandgar et al. have reported (*J. Chem. Soc., Perkin Trans. 1* **2000**, 3559) selective and rapid oxidation of primary, allylic, and benzylic alcohols to the corresponding carbonyl compounds using $NaNO_2$—acetic anhydride under mild and solvent-free conditions (Scheme 3). The method offers an alternative to the more commonly accepted methods for this transformation and is simple, inexpensive, and rapid.

Scheme 3



A method for the preparation of primary and symmetrical *N*,*N*′-disubstituted thioureas has been reported by Meckler et al. from Albany Molecular Research Inc. (*Synthesis* **2000**, 1569). Their process, outlined in Scheme 4, is based on the condensation of amine hydrohalides and potassium thiocyanate. The approach tolerates sterically bulky primary amine substrates, and the products are isolated by simple filtration. The method is an attractive alternative for the synthesis of thioureas when the corresponding isothiocyanate is unavailable or difficult to prepare.

Scheme 4



Scott et al. from the process research department at Pfizer have described (*Tetrahedron Lett.* **2000**, *41*, 8207) *β*-selective nucleoside analogue synthesis from chlorofuranoses (Scheme 5). In their method exceptional *β* selectivity is observed using DMSO as the solvent and NaO^{t}Bu as base. An important aspect of the reaction is that the starting ratio of α and *β* chlorides does not affect the *β*-selectivity of the product. The stereoselectivity of the product is thus controlled solely by the stereochemistry of the 2,3-*O*-isopropylidene group.

An easy synthesis of the versatile synthetic class of building block "enaminones" in water as solvent has been described by Stefani et al. (*Synthesis* **2000**, 1526), Scheme 6. The reaction is particularly efficient for water soluble amines; but for partially soluble amines, an excess of amine was required.

List, from the Scripps Research Institute, has reported (*J. Am. Chem. Soc.* **2000**, *122*, 9336) the "direct catalytic asymmetric three component Mannich reaction". In this

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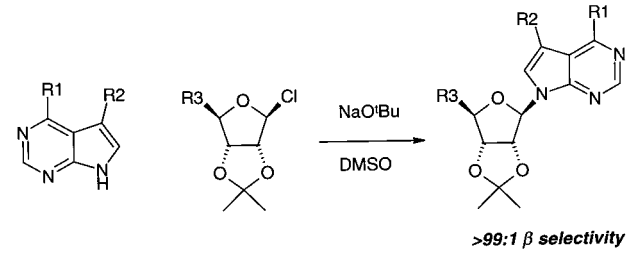
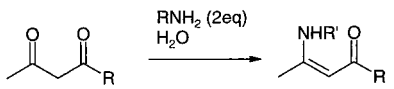
Scheme 5

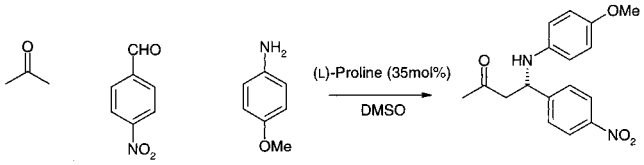


Scheme 6



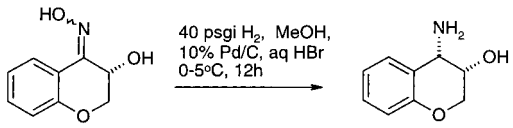
publication (L)-proline (35 mol %) has been used as the chiral component to induce enantioselectivity in the reaction between *p*-nitrobenzaldehyde (1 equiv) and *p*-anisidine (1.1 equiv) in acetone/DMSO (1:4) for 12 h to give the corresponding Mannich product in 50% yield and 94% ee (Scheme 7). Since both enantiomers of proline are available, there is enormous scope for this reaction in the preparation of useful building blocks.

Scheme 7



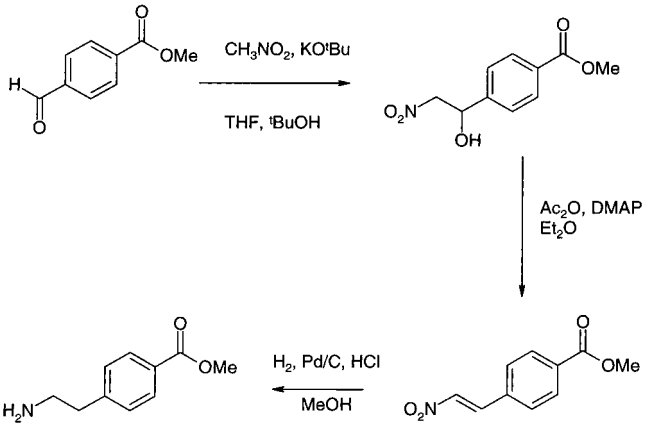
One of the most "atom-economical" ways of preparing an amine is the hydrogenation of the corresponding oxime where the only by-product is water. Davies and co-workers at Merck have recently published (*Tetrahedron Lett.* **2000**, *41*, 8021) the stereoselective hydrogen bromide-promoted hydrogenation of an α-hydroxyoxime to give the corresponding amino alcohol. In their example (Scheme 8) *cis* selectivity was observed (25:1 *cis*:*trans*) in the reduction of 4-chromanone α-hydroxyoxime to give *cis*-aminochromanol. A variety of acids in MeOH solution were screened, with HBr being the best and bromide ion being implicated in the selectivity. The group do not have a clear explanation of the role of HBr, but it is speculated that it serves to "reorganise the catalyst surface to provide an optimal site for selective hydrogenation".

Scheme 8



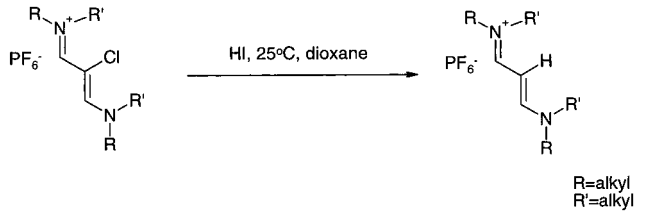
Wright from Pfizer has published a convenient practical preparation of methyl 4-(2-aminoethyl)benzoate which is an important intermediate in the preparation of a variety of pharmaceuticals including the antidiabetics Meglintide and S15261, the leukotriene D_4 antagonist LM-1376, and the antiarteriosclerotic BM-15766 (*OPPI Briefs* **2000**, *32*, 376). The synthesis is shown in Scheme 9.

Scheme 9



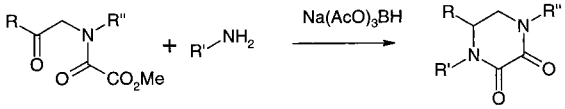
In a continuation of the story that we have been highlighting surrounding vinamidinium salts, Merck have published (*Org. Lett.* **2000**, *2*, 3385) the hydrogen iodide-promoted reduction of β-chlorovinamidinium salts to the vinamidinium salts in essentially quantitative assay yield and 55−85% isolated yields following recrystallisation. The reaction (depicted in Scheme 10) proceeds via protonation of the β-carbon atom of the vinamidinium and dechlorination via the formation of ICl.

Scheme 10

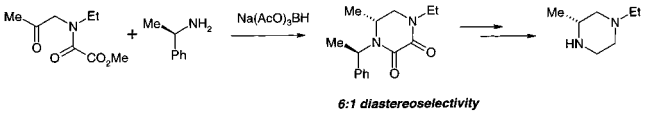


Beshore and Dinsmore have continued another Merck story reporting (*Tetrahedron Lett.* **2000**, *41*, 8735) an efficient synthesis of 1,4-disubstituted-2,3-diketopiperazines and 1,4,5-trisubstituted-2,3-diketopiperazines, which feature a tandem reductive amination and acylation. The reaction is depicted in Scheme 11 in which aliphatic and aromatic primary amines serve as viable nucleophiles under mild reaction conditions. Using (*R*)-α-methyl benzylamine as a chiral auxiliary, asymmetry was incorporated in the product diketopiperazine which could be further transformed (Scheme 12) to the piperazine analogue.

Scheme 11



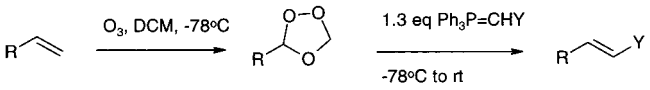
Scheme 12



Hon and co-workers have described how ozonides derived from terminal alkenes react with 1.3 mol equiv of stable

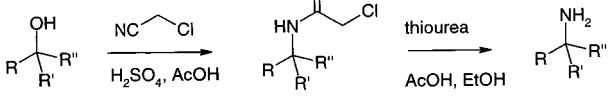
phosphonium ylids to give (*E*)-α,*β*-unsaturated carbonyl compounds in good to excellent yields (Scheme 13). No reducing agent was used in the reactions. The group have found that alkoxyalkyl-substituted ozonides afford a mixture of (*Z*)- and (*E*)-α,*β*-unsaturated carbonyl compounds. This reaction clearly offers advantages in terms of speed and simplicity, and in general the one-pot process offers higher yields than the more traditional multistep approach.

Scheme 13



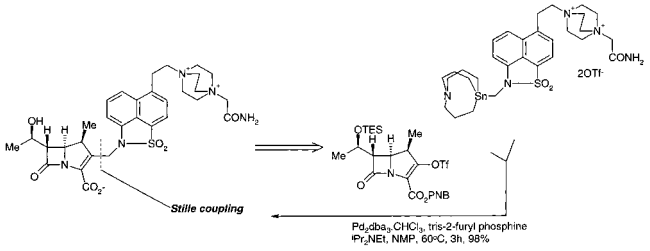
Jirgensons and co-workers have reported (*Synthesis* **2000**, 1709) the Ritter reaction between tertiary alcohols and chloroacetonitrile. The product of the reaction, a chloroacetamide, is removed using thiourea, and the process offers a facile and high-yielding conversion of tertiary alcohols to the corresponding tertiary amines (Scheme 14).

Scheme 14



Jensen and co-workers at Merck have described a short synthesis of an anti-methicillin-resistant *Staphylococcus aureus* (MRSA) carbapenam (*Org. Lett.* **2000**, *2*, 1081). The key step (Scheme 15) involves the cross-coupling of an enol triflate with an amino-substituted sp^3 carbon. This cross coupling, which allows the introduction of the complete side chain in one step, utilises a stannane as the heteroalkyl transfer reagent.

Scheme 15

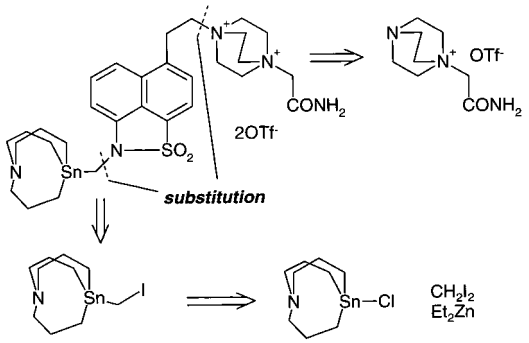


The stannane (depicted in Scheme 15) can be assembled from 1-aza-5-chloro-5-stannabicyclo[3.3.3]undecane as shown in the retrosynthetic analysis in Scheme 16.

In a separate communication the group report (*Tetrahedron Lett.* **2000**, *41*, 8677) a simple and scalable method for the preparation of the 1-aza-5-chloro-5-stannabicyclo[3.3.3]-undecane by disproportionation of $N(CH_2CH_2CH_2SnBu_3)_3$ and $SnCl_4$ at 70−100 °C. The reaction requires the addition of water to proceed efficiently, and the product was isolated in ∼50% after a simple acid/base extraction sequence.

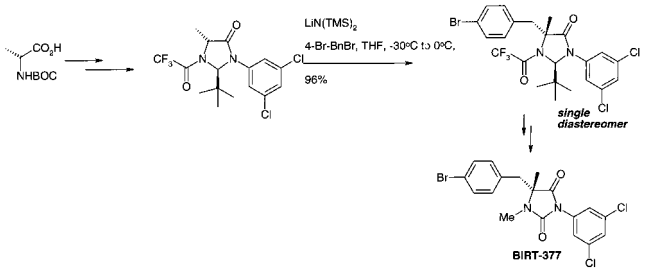
Yee from Boehringer Ingelheim has reported an enantiospecific synthesis of the LFA-1 antagonist BIRT-377 in eight steps (*Org. Lett.* **2000**, *2*, 2781). The key transformation

Scheme 16



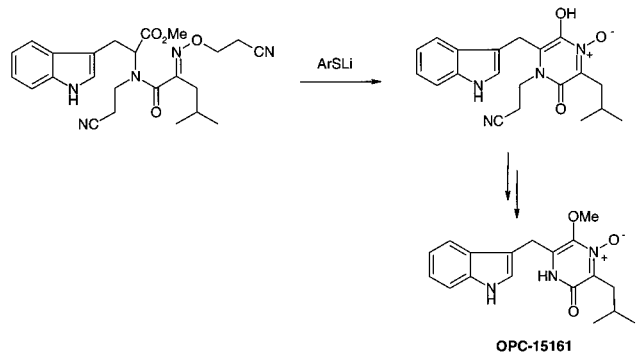
(Scheme 17) involves the stereospecific formation of the *trans*-imidazolidinone and subsequent alkylation with "self-regeneration of stereocentres". The process is reported to be practical, robust, and cost-effective and has been successfully implemented in pilot plant to produce multikilogram quantities of the drug substance.

Scheme 17



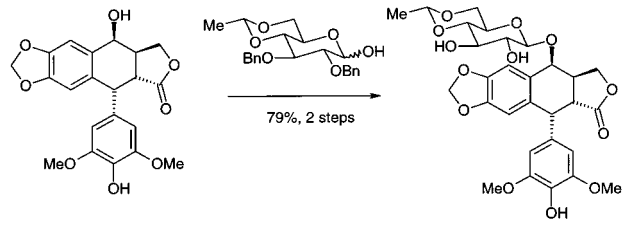
Minamikawa et al. have reported (*Tetrahedron* **2000**, *56*, 7427) a novel thiolate-mediated cyclisation to OPC-15161. In their synthesis the *N*,*O*-diprotected ester (Scheme 18) was cyclised using a lithium arylthiolate. The pyrazine product could be elaborated in two steps to OPC-15161 via *O*-methylation and deprotection.

Scheme 18



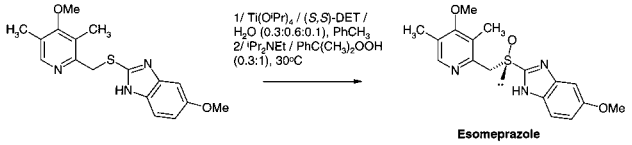
A group from Bristol-Myers Squibb have reported (Silverberg, L. J. et al. *Org. Lett.* **2000**, *2*, 3281) a crystallisation-induced stereoselective glycosidation reaction. In their report the anticancer drug etoposide (Scheme 19) is prepared in 79% overall yield from readily available 4′-demethyl-4-epipodophyllotoxin and 4,6-*O*-ethylidene-2,3-*O*-dibenzyl-D-glucose, via a crystallisation-induced stereoselective glycosidation reaction followed by catalytic hydrogenation.

Scheme 19



The key chiral oxidation in the kilo-scale synthesis of esomeprazole has been described by the process chemistry and medicinal chemistry groups at AstraZeneca (*Tetrahedron Asymmetry* **2000**, *11*, 3819), Scheme 20. The asymmetric sulphide oxidation was achieved by titanium-mediated oxidation with cumene hydroperoxide (CHP) in the presence of (*S*,*S*)-diethyl tartrate [(*S*,*S*)-DET]. The enantioselectivity was provided by preparing the titanium complex in the presence of the substrate at an elevated temperature and during a prolonged preparation time and by performing the oxidation in the presence of an amine. Good enantioselectivity (>94% ee) was obtained.

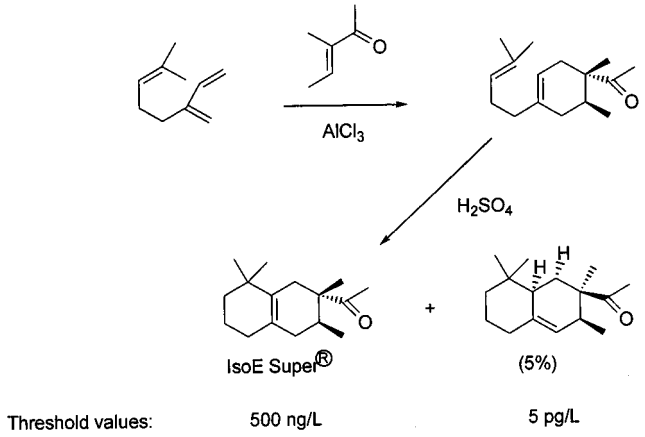
Scheme 20



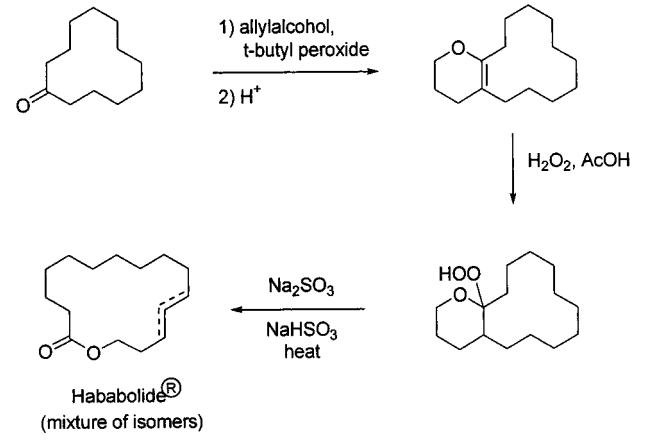
A fascinating review on "Recent Developments" in the chemistry of Odourants (Kraft, P. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 2980) not only contains some interesting chemistry, but the odour of some of the products is also available—microencapsulated fragrances are on some of the pages so that a quick "rub and smell" releases the perfume. The article focuses on the discovery of new fragrance molecules and their properties, but for the process chemist, the industrial synthesis of some of the fragrances is given. For the manufacture of Iso E Super, an aluminium chloride-catalysed Diels–Alder reaction of myrcene with (3E)-3-methylpent-3-en-2-one gives an adduct which is cyclised by acid (Scheme 21). The major product, Iso E Super is contaminated by 5% of the isomer—it is the latter, however, which imparts the woody odour to the product. The odour threshold of this powerful impurity is about 100,000 times lower than that of the main product.

Habanolide is one of the least expensive macrocyclic musks available to the perfumer—the industrial synthesis from cyclododecanone is shown in Scheme 22. Not all musks, however, are macrocyclic and a BASF product, Cyclomusk, is manufactured by one of the methods shown in Scheme 23. A reaction which is useful in the synthesis of macrocyclic compounds, for the fragrance industry, is olefin metathesis. It is appropriate, therefore, that the following review (Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012) is on this subject. The review probes recent advances including catalyst design, preparative aspects, applications in synthesis, etc. A potential problem in scale up of metathesis reactions is in the work up—how to remove traces

Scheme 21

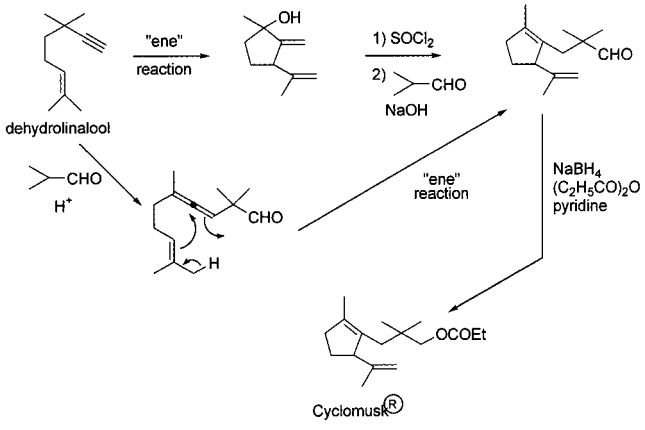


Scheme 22



of metal salts and phosphine impurities. The method of Grubbs involving addition of tris-hydroxymethylphosphine to complex ruthenium works well (Maynard, et al. *Tetrahedron Lett.* **1999**, *40*, 4137), whereas the method of Paquette (*Org. Lett.* **2000**, *2*, 1259) involving $Pb(OAc)_4$ may not be appropriate for large-scale work ups.

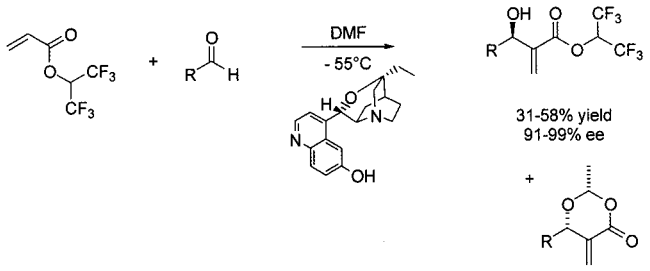
Scheme 23



A brief review of recent progress in the development of asymmetric versions of the Baylis–Hillman reaction has appeared (Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049). Some of these methodologies have already been highlighted in earlier editions of OPR&D, but one method that escaped

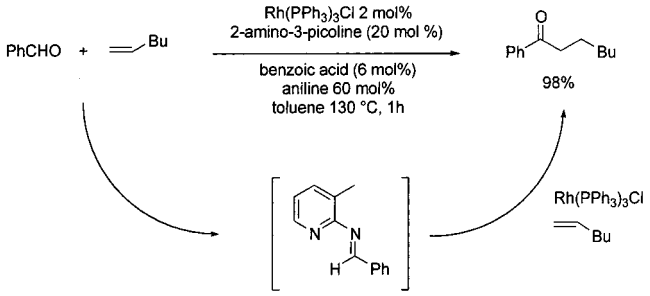
our attention is shown in Scheme 24 (Iwasushi, Y. et al. *J. Am. Chem. Soc.* **1999**, *121*, 10219). The disadvantage is the large amount of by-product dioxanone, which forms.

Scheme 24



The addition of aldehydes to olefins to give ketones (hydroacylation) is rarely successful except intermolecularly, and thus it was interesting to read of Korean workers' success with an intermolecular version (Jun, C.−H. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 3070). The reactivity of aldehydes improves if they are contaminated by the corresponding acid, which probably assists in initial imine formation with the catalyst (Scheme 25).

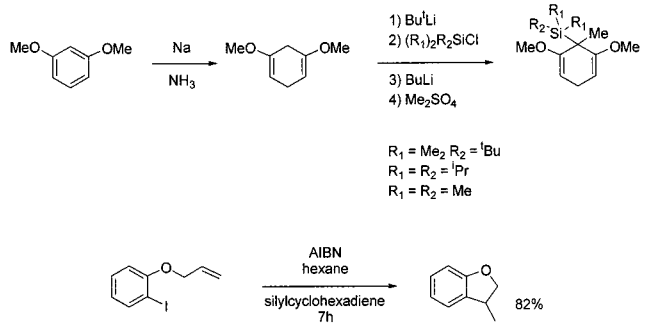
Scheme 25



Whilst radical chemistry using tributyltin hydride is useful in the laboratory, the problems associated with the removal of tin residues from products and effluent disposal mean that there are few industrial processes using tin chemistry.

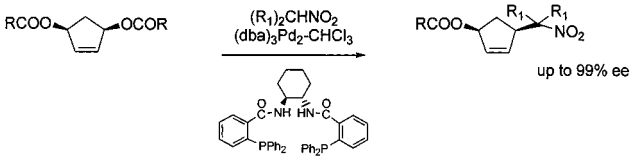
Alternatives to Bu_3SnH, such as $(TMS)_3SiH$, have been suggested, but they are expensive and easily oxidised in air. New silylated cyclohexadiene reagents have now been shown to be useful in radical reductions and radical cyclisations—they are easily made according to the process shown in Scheme 26 (Studer, A. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 3080).

Scheme 26



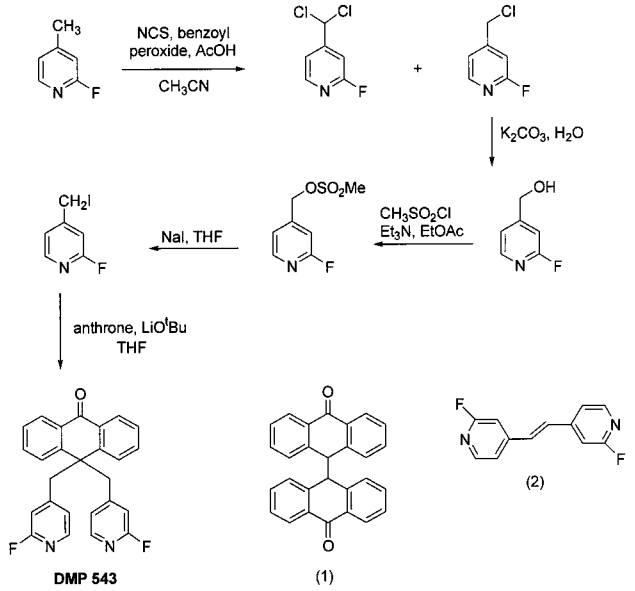
Alkylation of nitronate anions does not normally yield good results, but Pd catalysed-allylic alkylations have had some success. The group of Trost at Stanford have now reported (Trost, B. M. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 3122) that asymmetric allylic alkylation can proceed in higher yields and enantioselectivities when cyclic allyl esters are used (Scheme 27). The reaction conditions to give good results depend on the R group, on the base solvent combination, and on the R group on the nitronate.

Scheme 27



Jaan Pesti of DuPont Pharmaceuticals has outlined some of the trials and tribulations of chemical development in an article entitled "A better drug for Alzheimer's" (*Chemical Innovation* **2000**, *30*(10), 29). Process concerns of the original discovery method included stability of intermediates, toxic solvents ($CC1_4$), by-product formation, lengthy purification procedures, and polymorphism of the final drug substance DMP 543. The optimised synthetic route is shown in Scheme 28. Pesti describes a classic example of a disappearing polymorph of DMP 543, when the original needle-/rod-shaped crystals could no longer be produced, but were replaced by a higher-melting form (rounded crystals). The new form was first produced at laboratories in Canada, but within a few days, the DuPont laboratories in Wilmington, Delaware, were producing the new form! The new form arose after an improved synthesis had been discovered—this resulted in a much cleaner product. The removal of certain impurities can often be the trigger for appearance of a new polymorph, that is, the problem is most likely to arise in late development or even after the launch of a new product, when process R&D chemists have improved the process AND the product quality. See last month's OPR&D for further examples.

Scheme 28



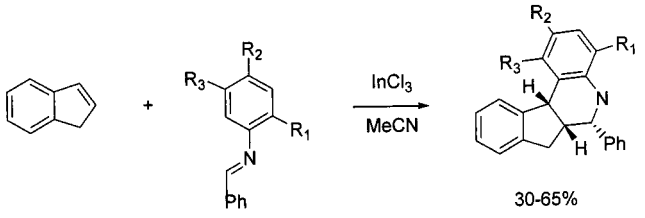
The article also emphasises the importance of understanding reactions in process optimisation. The DuPont chemists replaced carbon tetrachloride as a solvent for NCS chlorination, with acetonitrile, but some reactions were complete in 2 h, others in 8 h. It was found that traces of water caused the problem, reacting with NCS to produce HC1 which catalysed in the process. This could then be used to advantage by adding 0.03 equiv of acetic acid at the start to get reproducible and fast chlorination in the absence of light. Further details are given in another paper (*J. Org. Chem*. **2000**, *65*, 7718).

The impurities **1** and **2** were identified in the final step of the process. The bianthrone (**1**) could arise by radical coupling (or other mechanisms) but probably results from exposure of the anthrone to NaI. The olefin (**2**) was shown to arise from the alkylating agent on contact with strong base and NaI. This suggested that the ideal process to make DMP 543 would involve mixing the anthrone and strong base and adding this to NaI and the acylating agent. In practice, a 87−92% yield of DMP 543 was obtained with substantial reduction in impurity formation.

Optimising the efficiency of reactor agitation is an important parameter in scale up of batch and semibatch processes, particularly for gas−liquid reactions. A recent article (Lametasis, C. *Chem. Engineer* **2000**, Oct 5, p 19) examines recent developments including some novel thin-blade impellers, from the French company, Robin Industries. These triple-blade agitators produce high turbulence with very thorough mixing of the phases. The equipment has been tried in range of oxygenation, hydrogenation, and nitration processes at volumes from 0.8 to 12 m^3, with pressures up to 200 bar and temperatures to 280 °C.

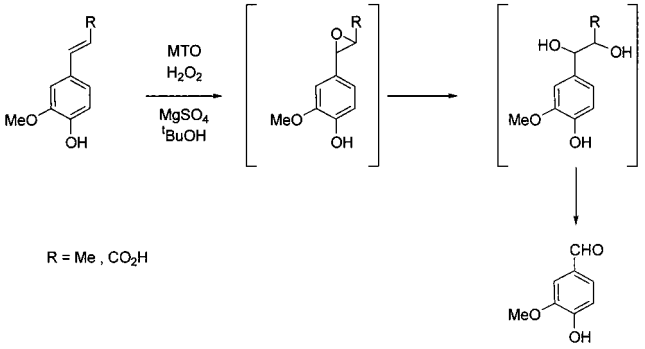
A recent review entitled "Synthetic Applications of Indium trichloride Catalysed Reactions" (Babu, G. et al. *Aldrichimica Acta* **2000**, *1*, 16) shows the value of this water-compatible catalyst in Friedel−Crafts, Diels−Alder, aldol, and other reactions. The reaction of simple olefins with Schiff bases is shown in Scheme 29. The article suggests that mixing $InCI_3$ with silver perchlorate enhances the activity in Friedel−Crafts reactions, producing $InCI_2(C10_4)$ or $InC1(C10_4)_2$. The warning given in previous highlights of the explosion dangers associated with even small quantities of dry perchlorates may also apply here.

Scheme 29



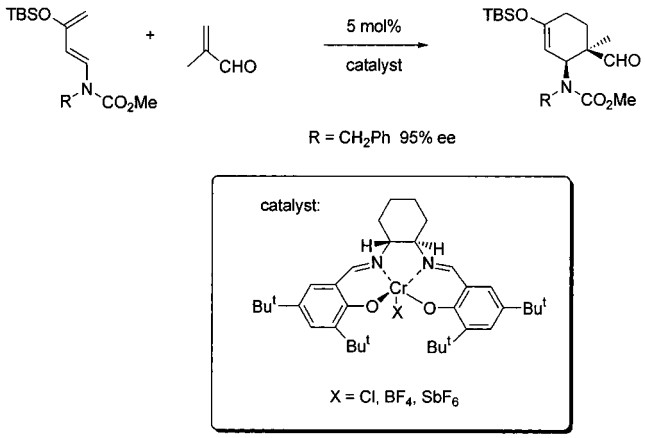
An oxidation system containing methyltrioxorhenium and hydrogen peroxide catalyses the cleavage of double bonds, and by changing reaction conditions either aldehyde or carboxylic acid products can be obtained (Herrmann, W. A. et al. *J. Mol. Cat. A* **2000**, *153*, 49). The process is demonstrated by the conversion of isoeugenol or *trans*-ferulic acid to vanillin with excellent catalyst turnover (Scheme 30).

Scheme 30



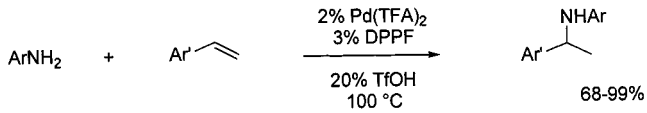
Enantioselective Diels−Alder reactions can be catalysed by chromium (III) salen complexes (Huang, et al. *J. Am. Chem. Soc*. **2000**, *122*, 7843) to yield highly functionalised products stereoselectively (Scheme 31). The reaction is solvent-dependent, being faster in CH_2Cl_2 than MTBE or toluene, and the counterion of the catalyst impacts on enantioselectivity. The alkyl group on nitrogen is also important, with best results achieved when a benzyl group is attached.

Scheme 31



The catalytic intermolecular addition of amines to olefins is a highly desired process, but success has been limited, whereas intramolecular hydraminations have been more successful. A recent report from the group of Hartwig at Yale (Kawatsura, M. et al. *J. Am. Chem. Soc*. **2000**, *122*, 9546) shows that the reaction can occur efficiently, once the conditions are closely defined, and a range of arylanines have been added across olefins in an anti-Markovnikov manner (Scheme 32). Addition of aniline to trifluoromethylstyrene proceeded enantioselectively in the presence of R-BINAP-$PD(OTf)_2$ to give a product of 81% ee.

Scheme 32



The group of Reetz at the Max Planck Institute in Mulheim, Germany, has previously shown that lipases can be immobilised efficiently using cheap methods and that such

immobilised enzymes can be recovered and reused without loss of activity. In some cases lipases entrapped in sol−gel materials display long-term stability as well as enhanced activity, for example, in esterifications in organic solvents. In the latest paper (Reetz, M. T. et al. *Synthesis* **2000**, 781) the enzymes are entrapped in hydiophobic sol−gel materials [derived from $RSi(OMe)_3$ and $Si(OMe)_4$] and show remarkable activity even in aqueous media. The catalysts can be isolated and reused several times—it was shown that leaching is, at most, at low levels. In contrast, enzyme absorbed on glass beads soon loses its activity; if the sol−gel process is performed in the presence of glass beads, however, then activity is maintained or even enhanced.

A review entitled "Solvent Free Organic Synthesis" has recently appeared (Tandka, K. et al. *Chem. Rev.* **2000**, *100*, 1025). The number of reactions which can be carried out without solvent is impressive (Grignard, Reformatsky, Wittig, pinacol, aldol, Beckmann, Dieckmann, etc.) and the authors conclude that solid-state reactions should endear themselves to industry. No mention of the heat of reactions is made, however, nor of the need for good mixing. It would have been useful to see some of the industrial process examples from patents included in the review, with an analysis of why they had succeeded where many have failed.

In the letters pages of *Chemical and Engineering News*, *Chemistry in Britain*, *Chemistry and Industry*, etc. there are repeated warnings on the use of organic perchlorates, which often give rise to explosions. A recent letter from John Long of GFS Chemicals in Columbus, Ohio, who specialises in handling these reagents, emphasises that it is essential to evaluate by DSC and other techniques the thermal hazards and shock sensitivity before any organic perchlorate is used beyond the milligram scale (*Chem. Eng. News* **2000**, *78*(25), 8). The rule of thumb is that hazards are increased with increasing temperature, dryness, and concentration and if attention is paid to these factors, explosions can be avoided. For further information, contact GFS at gfschem@gfschemicals.com

In the same issue, (p 15) a report on an explosion at Nisshin Chemicals, Japan, in which four people were killed and 28 injured, emphasises the dangers of working with anhydrous hydroxylamine, which has an explosive power similar to that of TNT. The material is used in the manufacture of semiconductors. In February, 1999, a hydroxylamine plant run by Concept Sciences in Allentown, Pennsylvania, also blew up. A previous explosion had also occurred in Japan in November, 1998. The blasts at Nisshin and Concept Services have made BASF the only remaining supplier of purified hydroxylamine.

An article by Michael McCoy in *Chem. Eng. News* **2000**, *78*(25), 17, summarises the current state of play in simulated moving bed technology (SMB) on large scale. Whilst SMB has been used for decades in the separation of xylene isomers in the Parex process pioneered by UOP, it is only recently that pharmaceutical companies and contract chemical companies have used the technique for separation of enantiomers of chiral drugs and late-stage intermediates, particularly when the unwanted isomer can be recycled. Facilities on the tonne scale already exist at many companies including UCB Pharma in Belgium and Lundbeck in Denmark (where the antidepressant drug *S*-citalopram is produced after SMB separation of a key intermediate), whereas Aerojet Fine Chemicals in Sacramento, CA, Universal Pharma Technologies (UPT) in Lexington, MA, and Honeywell Speciality Chemicals in Arklow, Ireland, hope to have facilities on stream in the next few months. Bayer will also introduce SMB on 5 tonnes per annum capacity at Leverkusen, Germany. Most of the facilities use the technology developed by Novasep in France. The reason for the current activity is that equipment is now very reliable, modelling software is available to speed scale up and make the separations more efficient, and costs for separation often are cheaper than the conventional resolution methods. FDA inspection of SMB facilities has not yet occurred but is unlikely to be a problem since other chromatographic methods have been accepted by FDA in the past. What the article does not point out is the high capital cost of the stationary phase in chiral separations on tonne scale, so that the lifetime of the columns is a key issue. In practice, little deterioration is seen over a 2-year period for dedicated use.

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