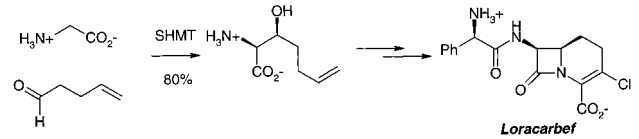
Organic Process Research & Development **2000**, *4*, 440–449

Highlights from the Literature

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

Even 70 years after the discovery of penicillin, the chemistry of β-lactams is still an area of research and development for a number of groups. A recent volume of *Tetrahedron* (**2000**, *56*(31)) devotes itself to "Recent aspects of the chemistry of β-lactams". In this issue both academic and industrial groups contribute recent developments in this area including an "Eco-friendly approach to vinyl β-lactams using microwave assisted reactions" (Manhas et al., *Tetrahedron* **2000**, *56*, 5587). An approach to the total synthesis of carbacephem antibiotic Loracarbef is described by authors from both the chemical process research and development department and the bioprocess purification development department at the Eli Lilly group (*Tetrahedron* **2000**, *56*, 5667). In their report serine hydroxymethyltransferase (SHMT) derived from recombinant *Escherichia coli* was found to be able to catalyse the condensation between glycine and 4-pentenaldehyde, affording enantiopure L-*erythro*-2-amino3-hydroxy-6-heptenoic acid. This chiral intermediate was converted in a number of synthetic transformations to Loracarbef (Scheme 1).

Scheme 1



In another collaborative effort between chemists and biologists at Bristol-Myers Squibb (*Tetrahedron* **2000**, *56*, 5687) a number of cephalosporin derivatives with potent anti-MRSA (methicillin-resistant *Staphylococcus aureus*) activity and promising physical characteristics have been identified (Figure 1). In particular a number of reactions have been performed on a multigramme scale to develop practical large-scale syntheses of these derivatives.

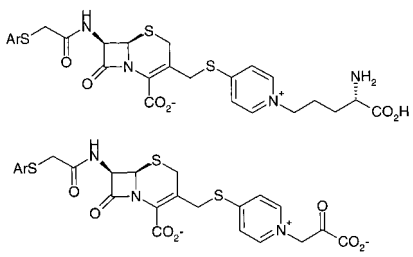
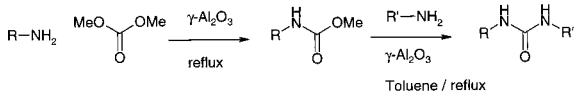


Figure 1.

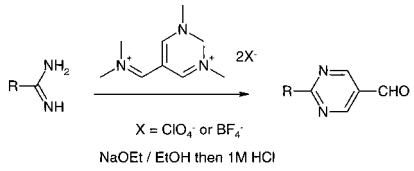
Lemaire et al. have reported "an environmentally benign access to carbamates and ureas (*Tetrahedron Letters* **2000**, *41*, 6347) in which γ-Al_2O_3 was used to catalyse the reaction between amines and dimethylcarbonate (Scheme 2). In the first step of the synthesis an amine reacts with neat dimethylcarbonate (with γ-Al_2O_3) to form the carbamate that is isolated by filtration and subsequent evaporation of the dimethylcarbonate. The second amine is introduced to form the unsymmetrical urea in refluxing toluene, again with γ-Al_2O_3 as catalyst.

Scheme 2



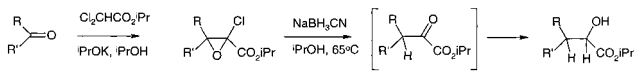
"Vinamidinium" bis-perchlorate salt (Scheme 3) has been reported by a group at Pfizer (*Synlett* **2000**, 1172) to possess remarkably high thermal energy (5020 J/g [cf. trinitrotoluene 4295 J/g]) as well as significant shock sensitivity. They have replaced it by the tetrafluoroborate salt possessing significantly lower thermal energy (260 J/g) and no shock sensitivity in their pyrimidine synthesis with equally good synthetic efficiency.

Scheme 3



A new efficient synthesis of α-hydroxyesters from carbonyl compounds via α-chloroglycidic esters has been reported by Grison et al. (*Tetrahedron Letters* **2000**, *41*, 6571). In their synthesis (Scheme 4) α-chloro glycidic esters were prepared according to Darzens-type condensations and 2 equiv of $NaBH_3CN$ used to open the epoxide and subsequently reduce the in situ α-keto ester that is generated.

Scheme 4



The piperazinone ring is a widely used structure in medicinal chemistry. Dinsmore and Zartman at Merck have recently reported (*Tetrahedron Letters* **2000**, *41*, 6309) a new strategy for the preparation of substituted piperazinones that features a tandem reductive amination and S_N2-cyclisation of a 2-chloro-*N*-(2-oxoalkyl)acetamide (Scheme 5). Asymmetry has also been achieved in the reaction when R′ is chiral as shown in the case with α-methyl benzylamine.

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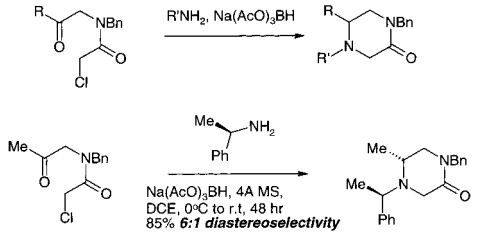
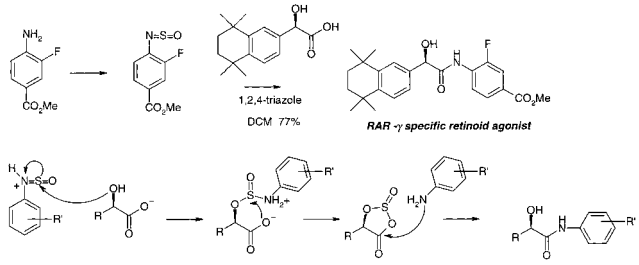
Scheme 5



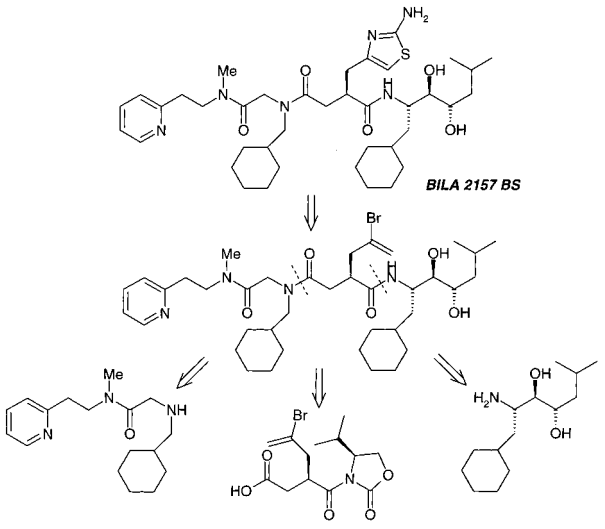
Chidambaram et al. at Bristol-Myers Squibb have developed a process for the preparation of enantiomerically pure α-hydroxy amides from chiral α-hydroxy acids. (*Tetrahedron Letters* **2000**, *41*, 6017). In their method (Scheme 6) *N*-sulfinylanilines are reacted with homochiral α-hydroxy acids in the presence of 1,2,4-triazole in dichloromethane to afford the amides in good yield without racemisation. Conventional coupling methods (carbodiimides/HOBt/DMAP, carbonyldiimidazole, benzotriazol-1-yloxy tris(dimethylamino)phosphonium hexafluorophosphate (BOP) or 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ)) proved unsuccessful.

Scheme 6



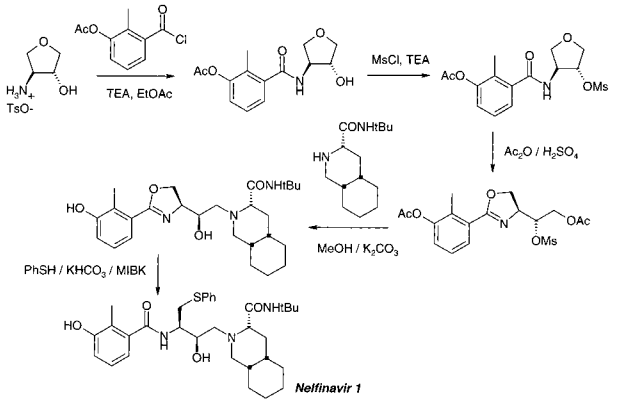
Boehringer Ingelheim have reported a stereoselective synthesis providing 0.6 kg of the renin inhibitor BILA 2157 BS (*Can. J. Chem*. **2000**, *78*, 739). Their disconnection is shown in Scheme 7 and involves the coupling of 3 fragments. The 2-amino-4-thiazolyl heterocycle was prepared from the vinyl bromide precursor in a key late-stage reaction. The paper discusses the synthesis of the coupling partners and outlines improvements made on scale.

Scheme 7



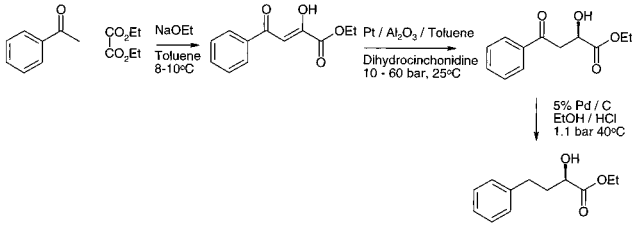
A synthesis of the HIV-protease inhibitor nelfinavir has been reported by a group at Agouron Pharmaceuticals (*Tetrahedron Letters* **2000**, *41*, 7017), Scheme 8. Treatment of the starting amino alcohol *p*-toluenesulphonate salt with triethylamine and acid chloride gave an excellent yield of amide which was converted to its mesylate and subsequently the oxazoline. Methanolic hydrolysis afforded the epoxide (with inversion at the mesylate centre) and subsequent amine opening gave the chiral alcohol, oxazoline. Ring opening of the oxazoline by thiophenol gave nelfinavir in high purity. This synthesis truly represents an atom-efficient synthesis and requires only one aqueous work up.

Scheme 8



A new synthesis of ethyl (*R*)-2-hydroxy-4-phenylbutyrate (an important intermediate for several ACE inhibitors) has been reported by Solvias (*Tetrahedron* **2000**, *56*, 6497) in >99% enantiomeric excess in an overall yield of 50−60% starting from acetophenone and diethyl oxalate (Scheme 9). Claisen condensation between acetophenone and diethyl oxalate gave the dioxoester in quantitative yield which was enantioselectively hydrogenated catalysed by a heterogeneous Pt catalyst modified with dihydrocinchonidine. Crystallisation to upgrade the enantiopurity followed by hydrogenolysis of the 4-keto group gave ethyl (*R*)-2-hydroxy-4-phenylbutyrate.

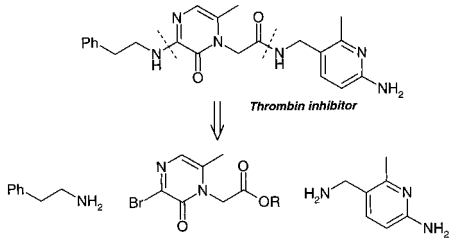
Scheme 9



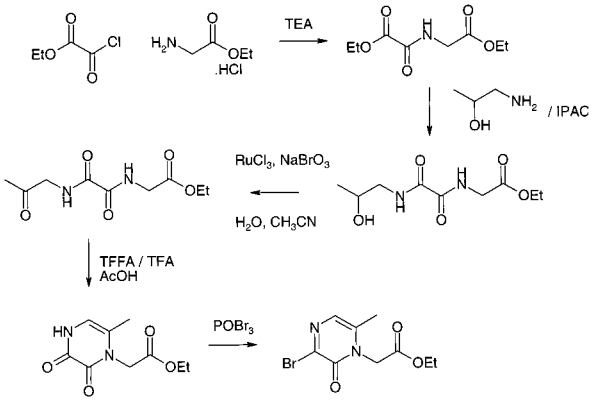
Merck have reported a kilogram-scale synthesis of the pyrazinone acetic acid core of an orally efficacious thrombin inhibitor from an unsymmetrical oxalic diamide (*Synth. Commun.* **2000**, *30*, 3171). In their approach (Scheme 10) the central core is constructed from ethyl oxalyl chloride and ethyl glycinate free base (Scheme 11).

After aqueous work up the product amide is reacted with 1-amino-2-propanol in IPAC to generate the alcohol which is oxidised to the ketone. TFFA/TFA mediated cyclisation followed by formation of the bromide using $POBr_3$ completed

Scheme 10

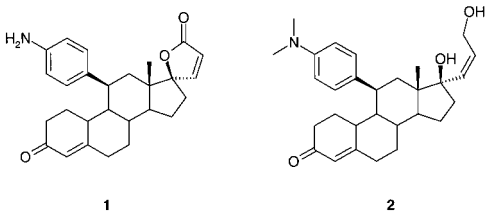


Scheme 11



the synthesis of the core fragment. The paper describes a number of process developments and optimisations, culminating in an efficient multikilogram synthesis.

A group at the process research department of Schering have reported (*Tetrahedron* **2000**, *56*, 6489) a multigram synthesis of 11β-(4-aminophenyl)spiro[estr-4-ene-17β,2′(5′H)-furan]-3,5′dione **1**, a metabolite of (*Z*)-11β-[4-(dimethylamino)phenyl]-17β-hydroxy-17α-(3-hydroxyprop-1-enyl)estr-4-en-3-one **2** (a 19-nor steroid exhibiting progesterone antagonistic activity) (Figure 2).



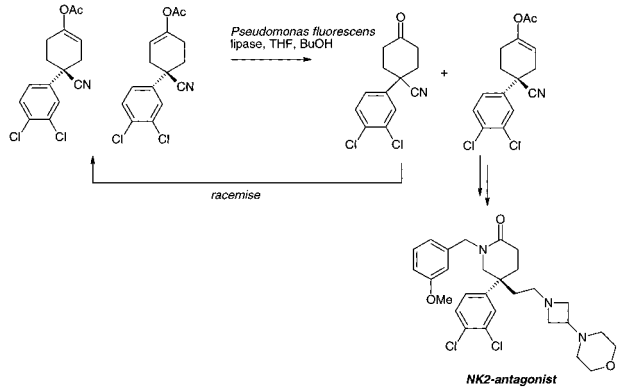
1 **2**

Figure 2.

Carnell et al. report (*Tetrahedron Letters* **2000**, *41*, 6929) the synthesis of a non-peptide tachykinin NK-2 antagonist in four steps from a chiral enol acetate which was obtained in 100% ee by resolution of the racemic enol ester with *Pseudomonas fluorescens* lipase (Scheme 12). The group have performed the chemistry on gram scale.

Asymmetric catalysis continues to attract interest in both academia and industry. A review from the group of Börner at the Institute of Organic Catalysis in Rostock, Germany, working with BASF suggests that chiral hydroxyphosphines are usually better homogeneous catalysts (in terms of both enantiomeric excess and rate of reaction) than their non-hydroxy counterparts (Börner, A. *Chim. Oggi*, **2000**, June, 48). The presence of the hydroxy group allows reactions such as hydrogenations to be carried out in water as well as in

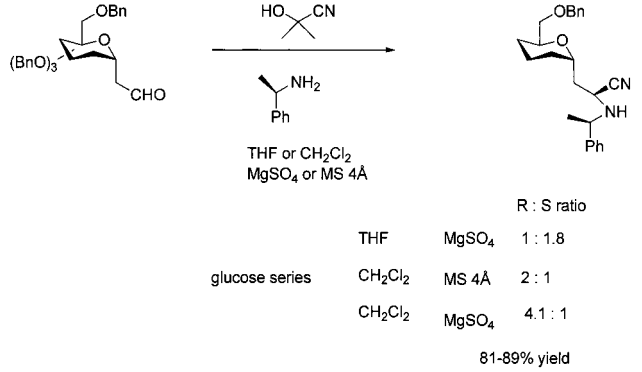
Scheme 12



organic solvents. Replacement of OH by SO_3 increases the solubility in water and gives rise to a wide range of aqueous soluble catalysts.

In the asymmetric Strecker synthesis of sugar aldehydes, solvent effects can markedly change the selectivity (Vincent, S. P. et al., *J. Org. Chem.* **2000**, *65*, 4440). Furthermore, the use of magnesium sulphate in place of molecular sieves increased the selectivity in some reactions (Scheme 13).

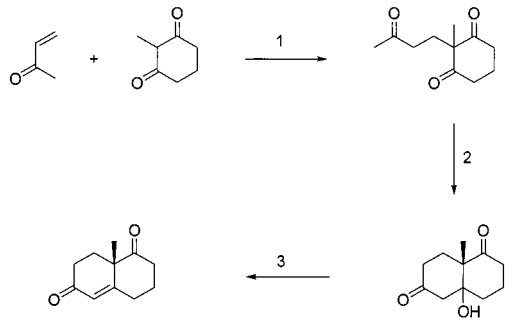
Scheme 13



The Wieland−Miescher ketone is an important intermediate in steroid synthesis and is usually prepared by addition of 2-methyl-cyclohexane-1,3-dione with methyl vinyl ketone under acid conditions followed by L-proline-catalysed cyclodehydration and crystallisation to enantiopurity. It has now been shown that L-proline and a number of other chiral amines will catalyse both the Michael addition and the cyclisation (Bui, T. et al. *Tetrahedron Letters* **2000**, *41*, 6951). Whereas, proline and some pyrrolidines catalysed all three steps, others catalysed only the first two, allowing isolation of the β-hydroxyketone (Scheme 14). The potential of chiral amine catalysts is only just being realised and was highlighted last month in the work of MacMillan (*J. Am. Chem. Soc.* **2000**, *122*, 4243).

Stable organic nitroxyl radicals belonging to the TEMPO family are excellent catalysts for the oxidation of primary alcohols to carboxylic acids. The radicals are slightly water-soluble, and in the presence of NaOH and catalytic amounts of bromide ion, they mediate the selective oxidation of only the primary alcohol, for example, in carbohydrate molecules, where it has generally been found superior to heterogeneous oxidative dehydrogenation over Pt/C. Other commercial

Scheme 14



processes for the oxidation of carbohydrate primary alcohols include enzymic or nitric acid oxidation (e.g., to make ascorbic acid).

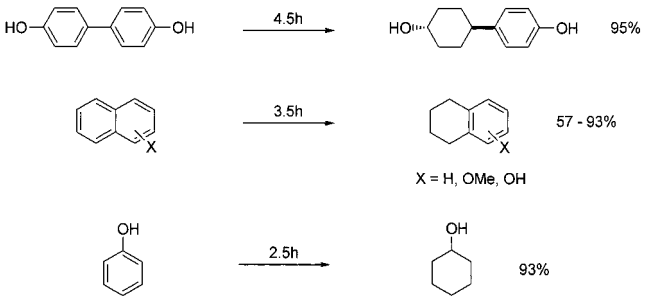
It would be preferable for large-scale oxidations if TEMPO could be immobilised within a solid support, and a number of attempts have already been made. A recent report (Cirimiana, R. et al. *Chem. Commum*. **2000**, 1441) uses the sol−gel technology for immobilisation, and the resultant catalyst (which uses a TEMPO derivative linked via an aminopropylsilyl moiety) was effective in oxidising sugars. The catalyst could be easily recycled, but although the catalyst had high activity, it was 15 times slower than a homogeneous reaction. The catalyst has been modified to improve these shortcomings (see Pagliari, M. et al., WO 99/47258, 1999).

One of the problems in the use of homogeneous catalysts in industry is separation of the product from the catalyst and subsequent catalyst recovery. If analogous catalysts could be made in polymeric heterogeneous form, some of these problems could be solved. A recent review (Santona, B. P.; Gagné, M. R. *Chem. Innovation* **2000**, August, 223) discusses progress in this area. A key element is that the polymer initially is not active until treated with an external reagent to activate it, hence the title of the article—"a wolf in sheep's clothing"! The catalysts described are used in epoxidation, hydroformylation, hydrogenation, Diels Alder reactions, and transfer hydrogenations.

Solid-supported synthesis is a powerful method of preparation of oligopeptides and oligonucleotides on a kilogram scale, but the development of methods for polymer-supported oligosaccharide synthesis has been slow. A critical step is the immobilisation of the glycosyl acceptor or donor through a cleavable linker, but most of the previously used linkers require several steps for attachment to the support or saccharide, offsetting the advantages of polymer-supported synthesis. The group of Boons at the University of Georgia in Athens, U.S.A., suggests that polystyrylboronic acid is a reusable support for oligosaccharide synthesis (Belogi, G. et al. *Tetrahedron Letters* **2000**, *41*, 6965). Loading capacities are high, and the polymer can easily be reused. Saccharides are loaded and released by acetone−water treatment.

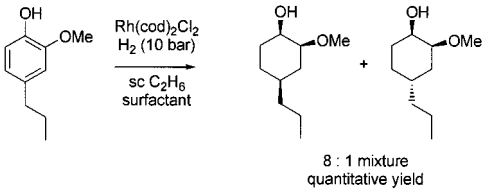
Heterogeneous catalytic hydrogenation of aromatic rings usually takes place under forcing conditions (high temperatures and pressure), and other procedures often have disadvantages for large-scale work. A new procedure from a group at Tohara University, Japan (Tsukinoki, T. et al. *Tetrahedron Letters* **2000**, *41*, 5865) uses a Raney nickel−aluminium alloy catalyst in dilute aqueous solution without any cosolvents at 90 °C and atmospheric pressure. The procedure is to add aqueous KOH solution to a mixture of the aromatic, catalyst, and water at 90 °C—the slower the KOH addition, the faster the reaction. Groups on the aromatic ring (e.g., CN) are also reduced (Scheme 15).

Scheme 15



Hydrogenation of arenes is an important chemical process in the fine chemical industry, and a wide variety of catalysts can be used including heterogeneous, homogeneous, or colloidal catalysts. It has been suggested that many "homogeneous" catalysts, prepared "in situ" in biphasic media, take place under mild reaction conditions. A recent report from the group of Jessop in California (Bonilla R. J. et al. *Chem. Commun*. **2000**, 941) indicates that colloidal rhodium catalysts in an aqueous/supercritical ethane biphasic medium give high conversion to alicyclic products, although aqueous SFC CO_2 or ionic liquid media are not effective (Scheme 16).

Scheme 16

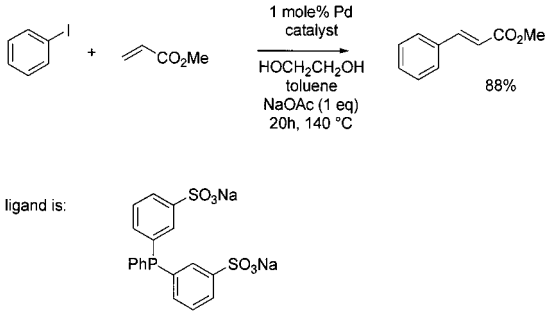


Borohydride reductions are carried out on a large scale in many companies for carbonyl-to-alcohol transformations. The main problem with sodium borohydride is that the two solvents in which it is most soluble—water and methanol—both have disadvantages. Sodium borohydride reacts vigorously with methanol at room temperature, liberating hydrogen, and it should not be used as a solvent on large scale. The problem with water is that substrates are not usually soluble; borohydride is, however, stable in alkaline aqueous solution. As a compromise ethanol, which reacts more slowly with $NaBH_4$, is the preferred solvent. However, a recent review (Yadav, V. G. et al. *Chim. Oggi* **2000**, June, 39) suggests that using phase-transfer catalysis offers the advantage of the water solubility of the borohydride with the substrate solubility of a water-immiscible solvent.

Complexes of water-soluble phosphines have attracted attention since the development of the Ruhrchemie/Rhône Poulenc process for hydroformylation, which uses a biphasic approach to catalysis. The simplest sulphonated phosphine (trisulphonated triphenylphosphine) is apparently not trivial

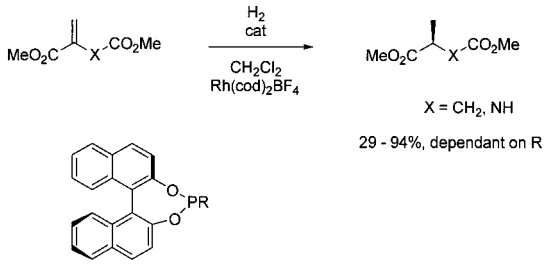
to make, whereas the disulphonated derivative is much easier to obtain. The palladium complex of the disulphonated triphenyl phosphine is just as good a catalyst in the biphasic Heck reaction as the trisulphonated version. (Thorpe, T. et al. *Tetrahedron Letters* **2000**, *41*, 4503)—see Scheme 17.

Scheme 17



We normally consider that bidendate ligands are essential for chelation in organometallic catalysis. However, it has surprisingly been found that chiral monophosphonite ligands give high selectivities in the rhodium-catalysed hydrogenation of itaconic acid derivatives and aminoacrylates. The easy synthesis of these ligands may make the process industrially relevant (Reetz, M. T. et al. *Tetrahedron Letters* **2000**, *41*, 6333)—see Scheme 18. Similar results were reported by the group of Pringle in the UK (*Chem. Comm.* **2000**, 961). The results are explained by restricted rotations, with the favoured rotamer causing effective chiral induction. These results challenge the conventional view that chelating ligands are essential for high stereocontrol and opens up new possibilities for ligand design.

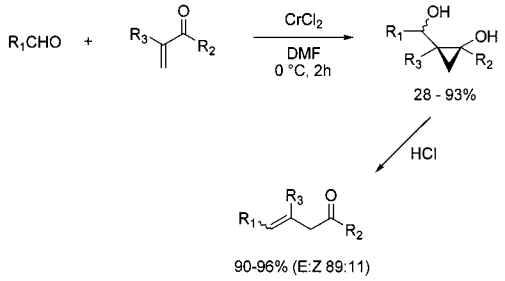
Scheme 18



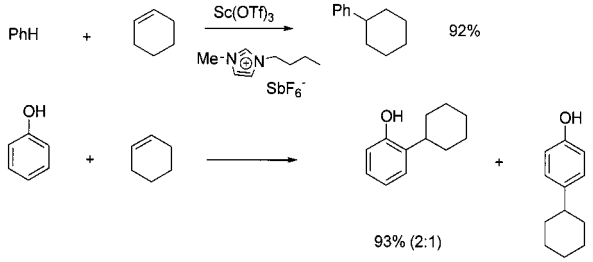
A new reaction leading to the formation of cyclopropanols is described by the group of Taki at Okayama in Japan (Toratsu, C. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 2725). Reaction of α,*β*-unsaturated ketones with chromium II species leads to an α,*β*-dianion equivalent, which reacts with aldehydes in an aldol manner to give cyclopropanols stereoselectively (Scheme 19). Substituents at the terminal portion of the olefin retard the reaction. The products are easily converted to *β*-*γ*-unsaturated ketones.

Scandium triflate catalysed Friedel—Crafts alkylation of aromatic compounds with alkenes proceeds readily in hydrophobic ionic liquid solvents based on 1,3-dialkylimidazolium salts with easy catalyst/solvent recycling, whereas the reaction did not occur in common organic solvents, water, or hydrophilic ionic liquid solvents at all (Song, C. E. et al. *Chem. Commun*. **2000**, 1695) (see Scheme 20).

Scheme 19

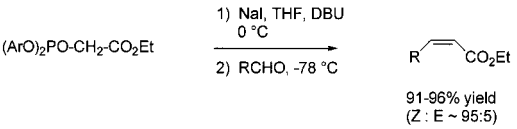


Scheme 20



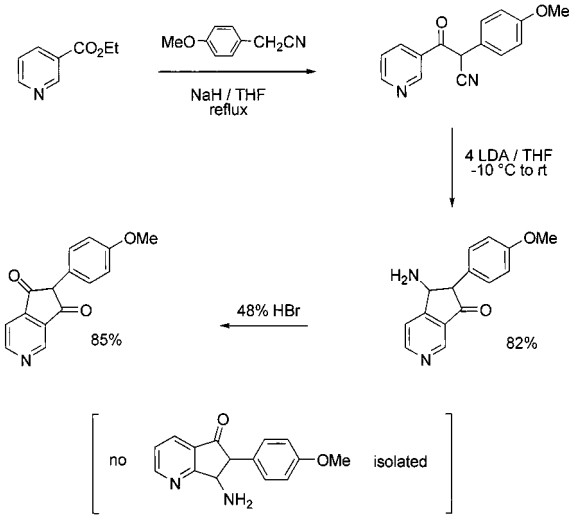
The Horner—Wadsworth—Emmons reaction is widely used for the synthesis of α,*β*-unsaturated esters using strong bases to generate the phosphate anions. Some years ago Masamune showed that the use of DBU or Hunig's base in acetonitrile, in the presence of lithium chloride gave *E*-α,*β*-unsaturated esters, and this method is now widely used in synthesis. Z,-α,*β*-unsaturated esters are more difficult to make, but a recent procedure (Ando, K. et al. *J. Org. Chem*. **1999**, *64*, 8406) reported that use of diarylphosphonoacetates with strong base was a highly selective method for production of the *Z* configuration. It has now been reported by the same group (Ando, K. et al. *J. Org. Chem*. **2000**, *65*, 4745) that milder conditions can be used (see Scheme 21). The key additive is sodium iodide—lithium chloride or sodium bromide give inferior results. The use of mild conditions allows base sensitive aldehydes to be used—under the original strong base (NaH) conditions these aldehydes give poor results. It is suggested that the salt complexes with the phosphonate reagent, enhancing the acidity of the α-proton, allowing a much weaker base to be used. Solvent effects are pronounced in these reactions—acetonitrile gave good yields of products but the *Z*:*E* selectivity was less than in THF.

Scheme 21



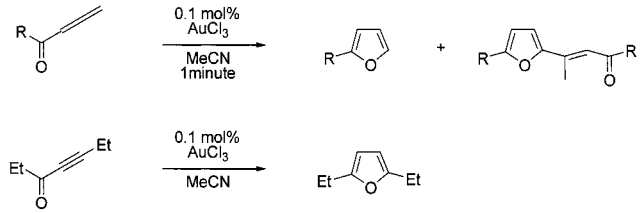
Ortho metalation is a useful strategy for industrial production of highly functionalised molecules, but despite many attempts, the ortho metalation of enolate anions has not proved useful. A recent paper suggests that the mono-anion of 2-cyanoacetophenone will, however undergo lithiation in the ortho position (Kayaleh, N. E. et al. *J. Org. Chem*. **2000**, *65*, 4515). The resultant anion attacks the cyano group leading to a useful synthesis of indanones (Scheme 22). This could *not* be extended to other systems.

Scheme 22



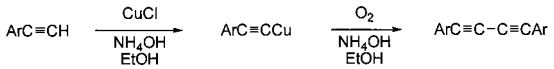
Gold is one of the few metals which organic chemists rarely use in catalysis. A recent report (Hashmi, A. S. K. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285) indicates that $AuCl_3$ in MeCN is an excellent catalyst (better than silver) for furan formation from allenic or acetylenic ketones and that sometimes unusual C−C bond formation take place (see Scheme 23).

Scheme 23



A recent review of acetylenic coupling, subtitled a powerful tool in molecular construction (Siemsen, P. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632) begins by pointing out the first reaction was discovered in 1869 by Glaser, who showed that copper acetylides are oxidised by oxygen to diacetylenes (Scheme 24). Glaser was an industrial chemist with BASF in Germany and was responsible for the technical production processes for a large number of dyes including indigo, before moving up to the board of directors, where he eventually became Chairman from 1912 to 1920. The Glaser coupling and related reactions are still widely used both in academia and in industry, and the review article indicates the latest modifications and synthetic potential.

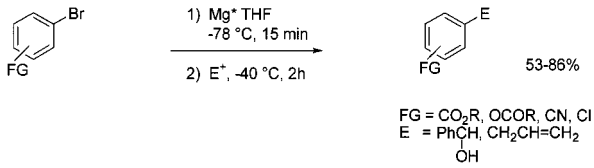
Scheme 24



Glaser coupling of acetylenes

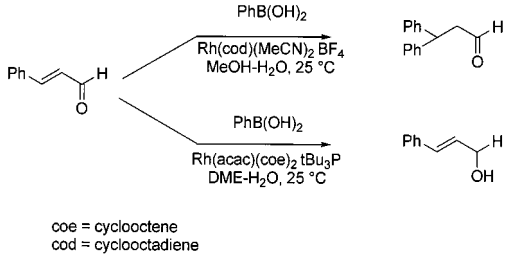
The Grignard reaction—100 years old this year—is a useful industrial process but suffers from the disadvantage of low functional group tolerance on the aryl ring or alkyl chain. By use of activated magnesium (Rieke magnesium), bromo compounds containing functional groups could react at low temperature, and coupling with carbonyl components was then achieved. (Lee, J-S. et al. *J. Org. Chem.* **2000**, *65*, 5428)—see Scheme 25.

Scheme 25



Conditions for the controlled 1,2 or 1,4 additions of arylboronic acids to α,β-unsaturated aldehydes have been worked out (Veda, M. et al. *J. Org. Chem.* **2000**, *65*, 4450). In the presence of $(t\text{-Bu})_3P$, 1,2 addition is preferred (see Scheme 26)

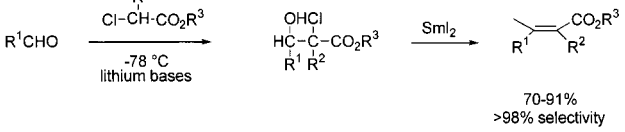
Scheme 26



coe = cyclooctene
cod = cyclooctadiene

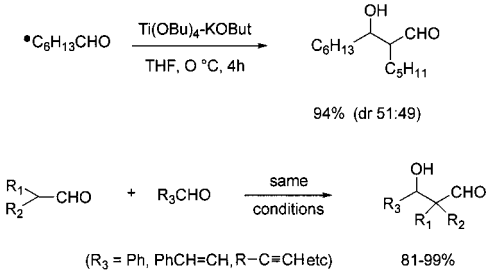
The stereoselective formation of trisubstituted double bonds in α,β-unsaturated esters and amides is reported by a group at Oviedo, Spain (Concellón, J. M. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 2773). The best reagent is samarium iodide which gives high selectivity (>98%); unfortunately the more industrially appropriate zinc gives poorer yields and selectivities (Scheme 27).

Scheme 27



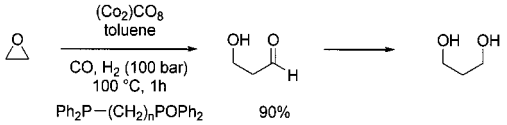
A simple procedure to produce β-hydroxy-aldehydes has been reported (Han, Z. et al. *Tetrahedron Letters* **2000**, *41*, 4415). The reagent for the effective self-condensation of aldehydes is a $Ti(OnBu_4)/t$-BuOK (see Scheme 28). It is suggested that this procedure eliminates most of the usual side reactions of aldol processes.

Scheme 28



The hydroformylation of epoxides provides an elegant and inexpensive pathway to β-hydroxyaldehydes, which can be easily reduced to 1,3-diols. The reaction is known to be catalysed by cobalt complexes of diphosphines, but a new catalyst with hemilabile P−O chelating ligands has recently been shown to be effective (Weber, R. et al. *Chem. Commum.* **2000**, 1419) see Scheme 29.

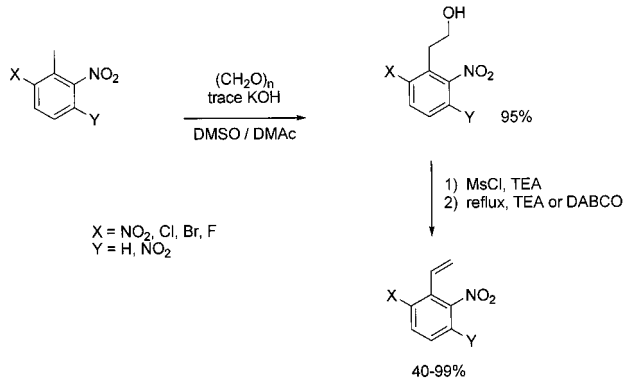
Scheme 29



Carboxylation of methane to produce acetic acid is an important industrial process, and much research effort over the past 20 years has gone into the search for new, more efficient catalysts. In a surprising paper, a Japanese group (Abdullah, M. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 2475) have found that methane and CO will react in the presence of calcium chloride to give acetic acid in high yield. Ethane can also be carboxylated to propionic acid.

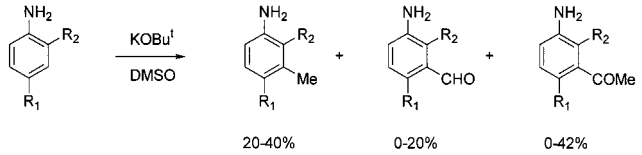
A short synthesis of styrene derivatives containing *o*-nitro groups has been reported (Mundla, S. R. *Tetrahedron Letters* **2000**, *41*, 6319). Reaction of the appropriate nitrotoluene with formaldehyde under basic conditions to give the phenylethanol followed by dehydration to the styrene derivative is an efficient process (Scheme 30). The presence of chloro and fluoro substituents sometimes inhibits the reaction.

Scheme 30



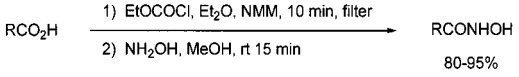
In a related reaction nitroaniline derivatives with additional electron-withdrawing groups (NO_2,CN) undergo regiospecific formylation and acylation under strong basic conditions (Kawakami, T. et al. *Tetrahedron Letters* **2000**, *41*, 7093)—see Scheme 31. Methylation also occurs.

Scheme 31



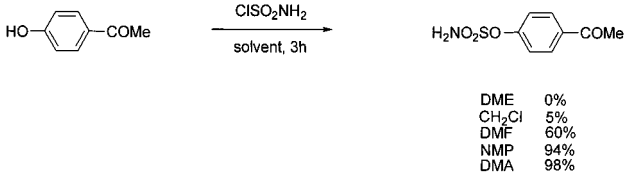
A one-step synthesis of hydroxamic acids directly from carboxylic acids has been carried out (Reddy, A. S. et al. *Tetrahedron Letters* **2000**, *41*, 6285). The process is shown in Scheme 32.

Scheme 32



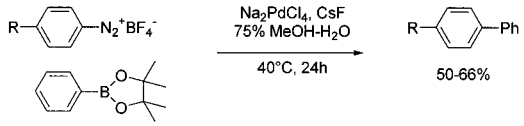
A group at Teikoku Hormone Co. in Japan have found that DMA and NMP are the best solvents for sulphamoyation of alcohols (Okada, M. et al., *Tetrahedron Letters* **2000**, *41*, 7047). For best yields, 2 mol of sulphamoyl chloride are required although 86% yield was obtained with 1 mol (Scheme 33).

Scheme 33



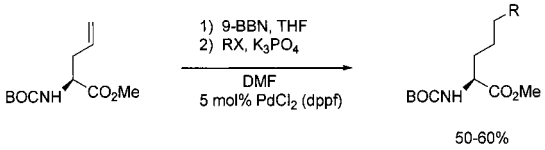
A surprising observation has been made in palladium-catalysed reactions of aryl diazonium salts with aryl boronates. In anhydrous solvents (THF, acetone, DMF, MeCN) no reaction takes place, but in aqueous mixtures, cross coupling occurs to give moderate yields of biaryls (Willis, D. M. et al. *Tetrahedron Letters* **2000**, *41*, 6271). With further optimisation, this could prove to be easy scaleable conditions (Scheme 34).

Scheme 34



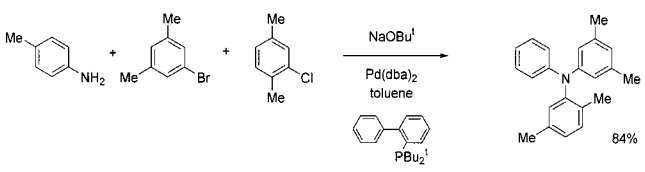
Unusual amino acids have been obtained by reaction of a protected allylglycine under hydroboration conditions followed by a direct Suzuki coupling of the intermediate organoborane (Collier, P. N. et al. *Tetrahedron Letters* **2000**, *41*, 7115) see Scheme 35.

Scheme 35



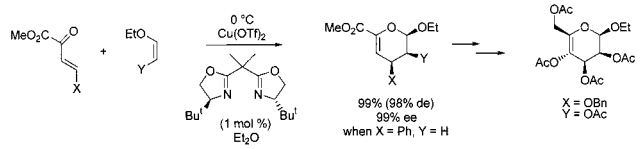
A one-pot system for triarylamine synthesis from an aniline and two different aryl halides has been described (Harris, M. C. et al. *J. Org. Chem.* **2000**, *65*, 5327). The catalytic system is Pd(dba)$_2$-*t*-Bu$_2$P-*o*-biphenyl (Scheme 36).

Scheme 36



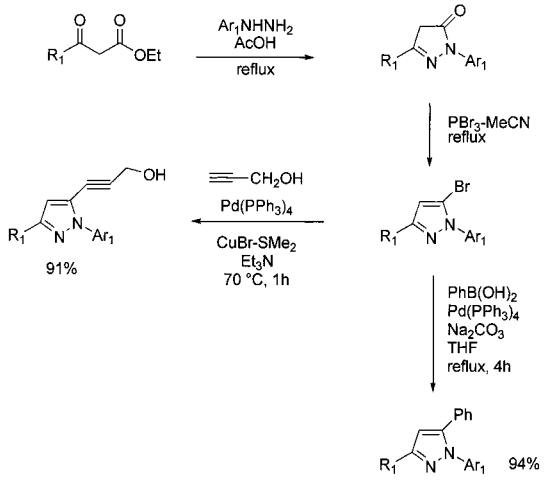
The hetero-Diels−Alder reaction is an attractive procedure for synthesising heterocyclics and has been used for the synthesis of some carbohydrates, since it allows control of several stereocentres in a single step and with a broad choice of substituents. It has only, to date, been used in an achiral environment, whereas for useful carbohydrate synthesis, an asymmetric version would be preferred. The group of Jorgensen at Aarhus, Denmark has now reported (Audrain, H. et al. *J. Org. Chem.* **2000**, *65*, 4487) that bis-oxazolines in combination with copper triflate is an enantioselective catalyst for the cycloaddition of α,β-unsaturated carbonyl compounds to electron-rich alkenes (Scheme 37). Although the reaction gives outstanding results with aryl groups on the unsaturated ketone, when the more useful alkoxy groups are presen,t the de and ee are lower.

Scheme 37



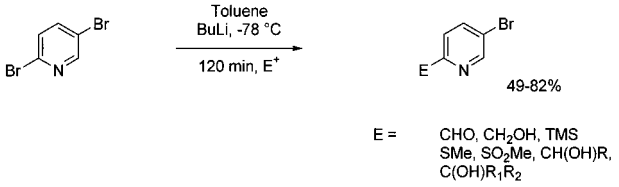
A group from Boehringer Ingleheim Pharmaceuticals in Connecticut have reported (Wang, X-J. et al. *Tetrahedron Letters* **2000**, *41*, 4713) a regioselective synthesis of 3,5-disubstituted-1-arylpyrazoles (Scheme 38). Normally this synthesis is complicated by the production of mixtures of isomers, when arylhydrazones are used as raw materials. Conversion of acetoacetates to the pyrazolone followed by bromination with PBr_3 gives the required 3,5 selectivity, and cross-coupling with a variety of reagents including acetylenes, boronic acids, etc. gives a range of products in good yield.

Scheme 38



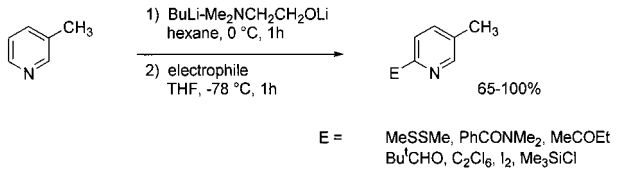
Solvent and concentration are two factors, which affect the position of lithiation of 2,5-dibromopyridine. Workers at Merck process research in Canada and U.S.A. have worked out conditions where lithiation can take place at predominantly the 2-position or the 5-position (Wang, X. et al. *Tetrahedron Letters* **2000**, *41*, 4335)). Generally, 5-bromo-2-lithiopyridine appears to be more thermodynamically stable than the 2-bromo-5-lithio isomer, whereas in coordinating solvents, the latter is kinetically favoured. In noncoordinating solvents, the 5-bromo-2-lithiopyridine is kinetically and thermodynamically favoured. This has been used to selectively produce half-kilogram quantities of substituted pyridines (Scheme 39).

Scheme 39



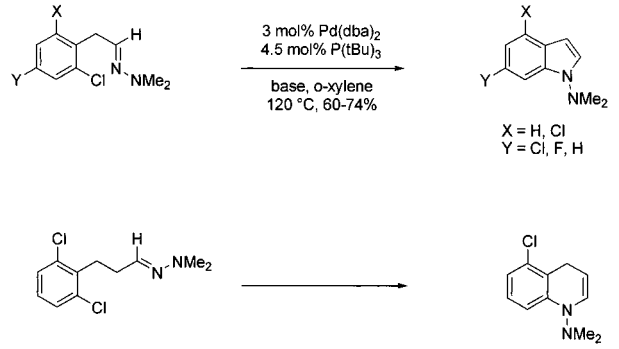
Reaction of 3-alkylpyridines with lithium reagents usually leads to lithiation of the side chain rather than the more synthetically useful 6-position, and normally derivatisation of the 6-position can only be achieved via 6-halo derivatives and halogen exchange for lithium. A group of French chemists (Mathieu, J. et al. *Chem. Commun.* **2000**, 951) have now found that use of BuLi-Me_2N-CH_2CH_2OLi as base promotes the clean functionalisation of 3-picoline, in the 6-position and that this occurs via rearrangement of the initially formed side chain lithium derivative. (Scheme 40).

Scheme 40



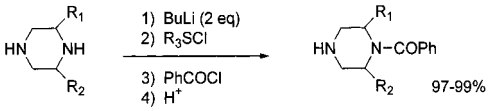
An interesting 1-aminoindole synthesis has been described by a group working at Tosoh Corporation, Japan (Watanabe, M. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 2501). The starting materials are *o*-chlorophenylacetaldehyde derivatives, which are converted to their dimethylhydrazones and then cyclised. (Scheme 41). The reaction can also be extended to make dihydroquinolines.

Scheme 41



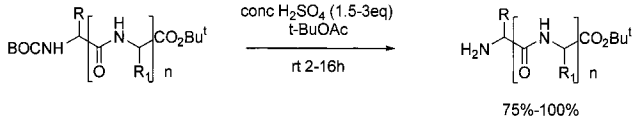
Regioselective monobenzoylation of unsymmetrcal piperazines has been accomplished in which a dianion is first formed and reacted with a silylating agent followed by benzoyl chloride. This produces the more hindered amide (Wang, T. et al. *J. Org. Chem.* **2000**, *65*, 4740)—see Scheme 42.

Scheme 42



The importance of mechanistic understanding in the design of reaction conditions is employed in a paper on the selective removal of BOC groups in the presence of *tert*-butyl esters. Normally, this can only be achieved if the required product crystallises from the reaction mixture and so is not further hydrolyzed under the acidic conditions. Workers at Merck in Medicinal Chemistry (Lin, L. S. et al. *Tetrahedron Letters* **2000**, *41*, 7013) surmised that the removal of BOC groups is an irreversible reaction, whereas deprotection of the *tert*-butyl ester is reversible. Thus use of *t*-BuOAc as solvent is suggested to prevent the *tert*-butyl ester from hydrolyzing (Scheme 43).

Scheme 43



An efficient method for the removal of protecting groups such as trityl, monomethoxytrityl, dimethoxytrityl, TBDMS, and TIPS from protected nucleosides and nucleotides under mild conditions has been reported (Hwu, J. R. et al. *J. Org. Chem.* **2000**, *65*, 5077). Silica gel-supported ceric ammonium nitrate cleaved the above groups, whereas isopropylidene groups survived.

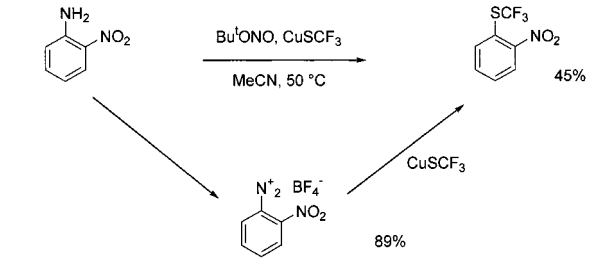
Diazomethane has often been the reagent of choice for laboratory synthesis of a range of HIV-protease inhibitors and some other drugs too. Although Glaxo and Schering Plough have both used diazomethane in production of low-volume steroid processes in the 1970s and 1980s, it is only in the 1990s that diazomethane has been used widely on tonnage scale. A recent review indicates that diazomethane is now manufactured in a batch process on 3000-L scale in California (Archibald, T. *Chim. Oggi* **2000**, June, 35). At a recent conference in Montreal, a British company also described a continuous process for diazomethane production. Diazomethane has a bp of minus 23 °C and an autoignition temperature of 150 °C. It tends to concentrate in the vapour phase, as little as 5 ppm in nitrogen gas has been reported to detonate, and an explosion with diazomethane generates as much energy as modern military explosives! Nevertheless, those who are experts in explosive manufacture have found safe and reproducible methods for diazomethane production and use, and indicate that the common mythology—ground glass joints and sharp surfaces should be avoided—cannot be true, otherwise scale up would be impossible. This is a process, however, best left to the experts.

Adipic acid is an important industrial product usually manufactured by a two-step process involving cobalt-catalysed oxidation of cyclohexene followed by nitric acid oxidation of the relevant cyclohexanol/cyclohexanone mixture. Newer processes from butadiene via carboxylation or hydrocarboxylation have also appeared. In an ideal world, cyclohexane would be oxidised catalytically by oxygen directly to adipic acid, and the catalyst would be heterogeneous for ease of product separation. Progress toward these goals has recently been published by the group of Sir John Thomas at the Royal Institution, UK (Duga,l I. M. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 2310). Using shape-selective catalysts, a carefully designed microporous Fe(III) aluminium phosphate was produced which allowed the linear oxidation products to diffuse out of the catalyst, whereas the cyclic oxidation products (cyclohexenol, cyclohexanone) are retained for further oxidation. Up to 65% selectivity is obtained at a turnover number of over 200. Whilst this may not be sufficient for an industrial process, the principle has been demonstrated. This study has built on the knowledge gained in the selective oxidation of alkanes at the terminal position (Thomas, J. M. et al. *Nature* **1999**, *398*, 227).

In the following paper (Raja, R. et al. *Angew. Chem., Int. Ed*. **2000**, *39*, 2318) the oxidation of hexane to, amongst other products, hexanoic acid and adipic acid was studied using cobalt molecular sieves as catalysts.

Incorporation of the SCF_3 group into aromatic molecules is of interest in the pharmaceutical and agrochemical industries, but normally multistep processes are required. It has now been found that treating diazonium salts with $CuSCF_3$ results in trifluoromethylsulphides in high yield. (Adams, D. J. et al. *Chem. Commun.* **2000**, 987). Best results are when electron-withdrawing groups are present on the aromatic ring. A one-pot procedure directly from the corresponding aniline derivative has also been developed, but yields are lower (Scheme 44).

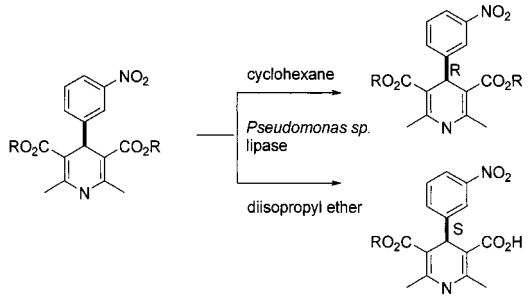
Scheme 44



Biotransformations are an effective and sometimes preferable alternative to chemical synthesis for the production of fine chemicals. The versatility of the biological approach has been widened by the use of enzymes in organic solvents, which gives enzymes important new properties (more stability, catalysis of new reactions, different selectivity). The solvent/medium can be changed easily to alter the enzyme properties and the reactions that they can catalyse. This area—sometimes called medium engineering—has been reviewed (Carrea, G. et al. *Angew. Chem., Int. Ed*. **2000**, *39*, 2227). An example quoted in the review is shown in Scheme 45.

Oils and fats are the most important renewable raw materials for the chemical industry. A review (Biermann, U. et al. *Angew. Chem., Int. Ed*. **2000**, *39*, 2207) covers recent advances in the transformation of these natural products to useful building blocks.

Scheme 45



Issue No. 4 of *Chemical Reviews* (**2000**, *100*) has a special thematic issue on "Frontiers in Metal-Catalyzed Polymerization", which highlights the latest trends in catalyst development.

For an interesting, if not particularly practical, review why not try "Chiral Autocatalysis: where stereochemistry meets the origin of Life" (Avalos, M. et al. *Chem. Commun*. **2000**, 887), which summarises recent efforts to produce optically active substances from achiral precursors. Processes include autocatalytic crystallisation or asymmetric autocatalysis.

A European Commission-funded network is to use its website to communicate the hazards of exothermic chemical reactions in batch and semibatch processes and produce recommendations, which will appear on the HarsNet website (**www.harsnet.de)**. Harsnet comprises 28 partners including fine chemical companies (BASF, Solway, Ciba, Dow, DSM, etc), pharmaceutical companies (Lundbeck, Sanofi-Synthelabo, etc) safety specialist companies (Hazard Evaluation Lab, Inburex, etc) and legislators (HSE, UK).

Finally, the *Chemical Engineer* magazine (**2000**, Sept 7, 56) has borrowed an idea from, I believe, the *Washington Post*, in compiling its alternative chemical engineering dictionary. The idea is that you take a well-known term, replace one letter (or eliminate or add one letter) and then redefine the term. Some of the alternative dictionary terms mentioned include:

Autoslave - an engineer/chemist performing routine but high-pressure tasks

Binnovation - a rubbish idea

Bitch process - one that is difficult to operate

Centrifrugal force - management pressure to reduce costs

Data baste - cooking the results

Dustillation - a separation method for powders.

Perhaps readers can think of similar terms in organic chemistry.

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