Organic Process Research & Development **1999**, *3*, 78–82

Highlights from the Literature

Some Items of Interest to Process R&D Chemists and Engineers, Selected by the Editor

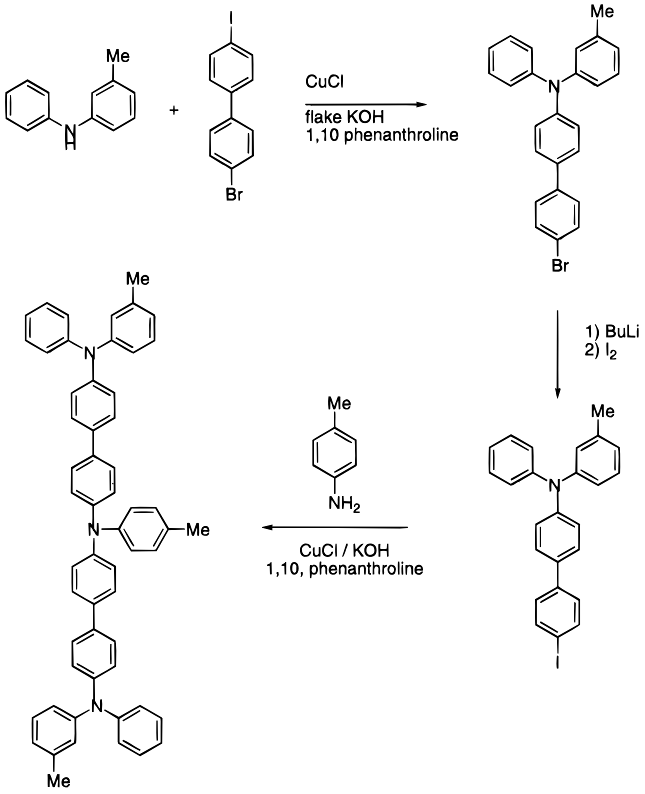
There is much interest in the formation of Ar−N bonds at the moment, particularly since the groups of Hartwig and Buchwald described palladium catalysis of the reaction of amines with aryl halides. For large scale work, conditions may need to be modified (Wullner, G.; et al. *Chem. Commun.* **1998**, 1509). It is premature, however, to judge whether this new chemistry will supplant the old Ullmann condensation for the manufacture of commodity chemicals, where economics may not permit a precious metal catalyst. Workers at Xerox, Canada, have now found that the copper-catalysed Ullmann reaction is accelerated by the addition of 1,10-phenanthroline so that reactions occur at 125 °C for 3 h (Scheme 1).

Yields are in the range 60−85% for a very wide range of substrates, and the low temperatures allow the selective substitution of iodide in the presence of bromide. Reactions on large scale can be conducted with copper(II) acetate instead of the more corrosive copper(I) chloride, so that stainless steel equipment can be used (Goodbrand, H. B.; et al. *J. Org. Chem.* **1999,** *64*, 671). This work, which has been patented, is applied to the synthesis of novel triarylamine derivatives, used in electroluminescent devices and as constituents of nonlinear optical chromophores in integrated electrooptical switches and modulators. For these applications, electronic grade purity levels are required, and a clean synthetic method, suitable for kilogram scale operation, is essential.

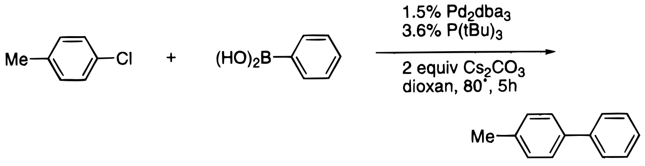
The effect of the 1,10-phenanthroline has been ascribed to ligand-accelerated catalysis. The effect is obviously very subtle, since closely related ligands had no effect. Perhaps a wide examination of ligands, possibly using combinatorial approaches, would yield further improvements.

In previous Highlights, I have mentioned modifications to the Suzuki cross-coupling reaction to make it more appropriate for large scale, particularly the use of aryl chlorides rather than bromides, iodides, and triflates. A recent publication from a group at MIT (Littke, A. F.; et al. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387) describes conditions under which a variety of electronically and sterically different aryl chlorides can be coupled with arylboronic acids in excellent yields. Cesium carbonate is the base of choice, with $Pd_2(dba)_3$ and $P(tBu)_3$ catalyst in dioxane (Scheme 2). An analogous versatile method for Suzuki cross-coupling has also been reported from the group of Buchwald (*J. Am. Chem. Soc.* **1998**, *120*, 9722).

Scheme 1



Scheme 2



Industry is always interested in atom-economical reactions using relatively inexpensive raw materials. One such reaction is the hydroamination of olefins, particularly styrenes, since the products are used in a wide variety of drugs and other products, but the reaction has been limited by low yields or drastic reaction conditions (for a review, see: Muller, T.; Beller, M. *Chem. Rev.* **1998**, *98*, 675). A more recent communication (Beller, M.; et al. *Angew. Chem., Int. Ed.* **1998**, *37*, 3389) describes the use of BuLi−K_2CO_3 or KOt-Bu as base for this transformation (BuLi or K_2CO_3 does not work alone). Best results were obtained with KOt-Bu catalyst at 10 mol % at 120 °C with an excess of amine in THF in a pressure tube. The reaction also occurs in refluxing toluene. Use of *o*-chlorostyrenes leads to formation of dihydroindoles in a "domino" reaction (Scheme 3). It is suggested that cyclisation occurs via an intramolecular aryne reaction, and proof was obtained in that 3-chlorostyrene and 2-chlorostyrene give the same 2,3-dihydroindole.

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Scheme 3

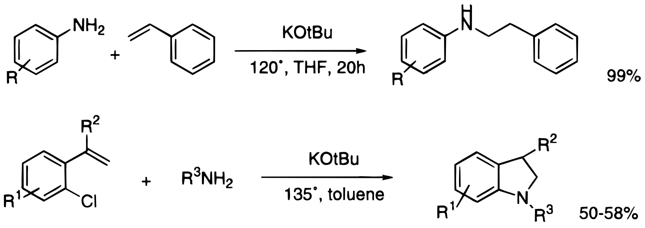
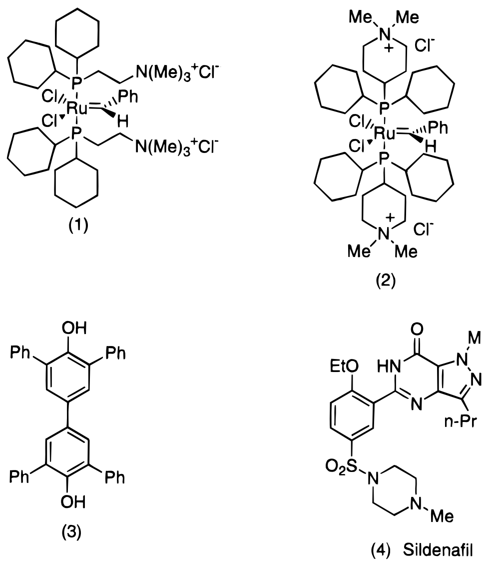
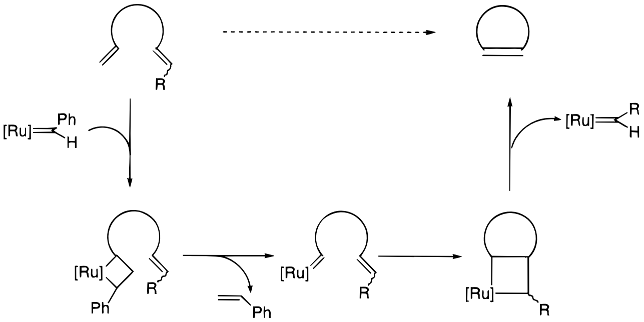


Chart 1



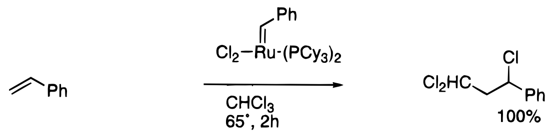
Scheme 4



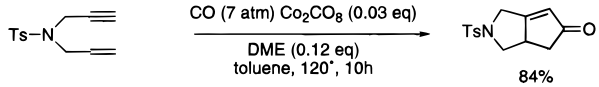
Ring-closing metathesis (RCM) is a useful method for the synthesis of both carbocycles and heterocycles but is limited by the intolerance of the usual reagents to protic functional groups, impurities, and solvents. The ruthenium catalysts $PhCHRuCl_2(PR_3)_2$ are active in the presence of protic solvents but are insoluble in solvents such as methanol and water. The group of Grubbs (*J. Org. Chem.* **1998**, *63*, 9905) have now prepared the water-soluble catalysts **1** and **2** (Chart 1), and these are effective for the RCM reaction in water. Best results are obtained when phenyl-substituted olefins are used, since this generates a more stable, active catalyst upon each catalyst turnover (Scheme 4).

In contrast, new, but rather unstable, carbyne−hydrido complexes of ruthenium, e.g., $[CH_3C{\equiv}RuHCl(PR_3)_2OEt_2]^+BF_4^-$, are effective in the ring-opening metathesis (ROM) of cyclopentene with methyl acrylate to yield multiply unsaturated polymeric esters (Stüer, W. *Angew. Chem., Int. Ed.* **1998**, *37*, 3421).

Scheme 5



Scheme 6



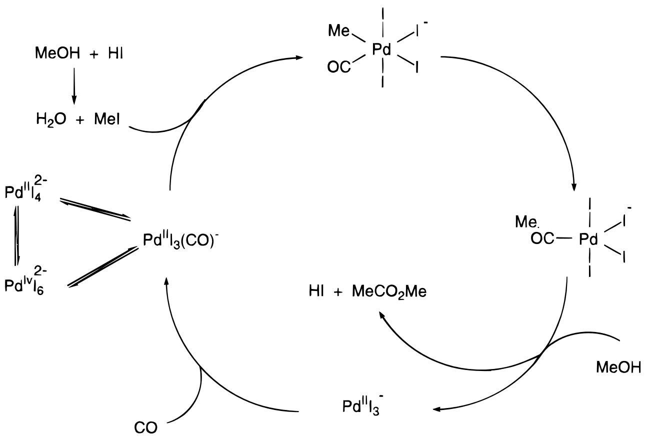
The typical Grubbs metathesis catalyst has been shown to effectively catalyse the addition of chloroform to olefins (Kharasch reaction, Scheme 5) under mild conditions (Tallarico, J. A.; et al. *J. Org. Chem.* **1999**, *64*, 344). The reaction is postulated to occur via a radical mechanism and is inhibited by radical trapping agents. The Kharasch reaction, used industrially in the manufacture of pyrethroid intermediates, is a useful carbon−carbon bond-forming strategy, is atom efficient, and leads to highly functionalised molecules. Chlorinated solvents, however, are therefore not recommended for metathesis reactions.

The Pauson Khand coupling of an alkene and an alkyne to give cyclopentanones is a useful synthetic method, but for large scale use, the stoichiometric quantity of Co_2CO_8 is inhibiting. Catalytic versions have recently appeared using $(P(OPh)_3$ or ultraviolet light, but a recent communication (Sugihara, T. *SynLett* **1998**, 1384) reports that the best promoter is 1,2-dimethoxyethane. Even a small amount of water can improve the process (Scheme 6).

Tributyl tin hydride is a useful laboratory reagent but is unlikely to be used on large scale since it is relatively expensive, unstable, toxic and causes an environmental disposal problem. Recent work has shown that Bu_3SnCl can be converted back to the hydride using polymethylhydrosiloxane (PHMS) in the presence of fluoride (Terstiege, I. *J. Org. Chem.* **1999**, *64*, 342). This opens up the possibility of doing reductions and C−C bond-forming reactions with the combination PHMS/KF and a catalytic amount of Bu_3SnCl. At present, levels of the tin catalyst are in the 6−10 mol % range, still too high for industrial use, but maybe with further optimisation this level can be reduced further.

Organofluorine compounds are extremely important in industry, and efforts to develop simple, safe, and efficient synthetic methods have escalated in recent years. The conversion of C−O to C−F bonds using nucleophilic fluorinating reagents (such as diethylamine sulphur trifluoride, DAST) is routinely used in the laboratory, but the thermal instability of DAST (DSC shows an exotherm of 1700 J/g with onset around 140 °C) inhibits its use on a larger scale. In fact, DAST and related compounds have been reported to undergo an explosion or detonation with gas evolution on heating above 90 °C (Messina, P. A.; et al. *J. Fluorine Chem.* **1989**, *42*, 137). Workers at Air Products (Lal, G. S.; et al. *Chem. Commun.* **1999**, 215) have found that bis(2-methoxyethyl)amino sulphur trifluoride (DeoxoFluor), prepared by reacting the TMS derivative of bis(2-methoxyethyl)amine with SF_4 at −30 °C, is a less thermally sensitive replacement for DAST, suitable for larger scale use. The new

Scheme 7



reagent is useful for conversion of primary, secondary, and tertiary alcohols (including the anomeric OH of sugars) to fluorides at −78 °C and for fluorinating carboxylic acids to aryl fluorides; at higher temperature, acids are converted to CF_3 groups, a reaction rarely carried out with DAST.

Graphite intercalation compounds have been widely studied and shown to have a high affinity for hydrogen. Their synthetic utility is restricted, since they are pyrophoric and have low surface area. Cesium, however, can be trapped in a high surface area nanoporous carbon, and the resultant nonpyrophoric solid may be synthetically useful. It is an excellent catalyst for double bond migration and for the conversion of benzenes to biphenyls (Stevens, M. G.; et al. *Chem. Commun.* **1998**, 2679).

The BP−Monsanto process for making acetic acid, methyl acetate, and/or acetic anhydride from methanol relies on the carbonylation of methyl iodide in the presence of rhodium and iodide, whereas the Cativa process, recently developed by BP, uses a related but more effective iridium/iodide catalyst. Because of the economic importance of the process, the search for new catalysts continues. Processes involving palladium complexes have been described, but ligands such as amines or phosphines are usually required; otherwise, inactive palladium metal is formed. A group at the University of Sheffield (Yang, J.; et al. *Chem. Commun*. **1999**, 179) have now discovered that palladium or platinum complexes can catalyse the carbonylation of methyl iodide in the presence of iodide ion and that the conditions are relatively mild (5 atm of CO, 140 °C). A catalytic cycle (Scheme 7) has been proposed involving Pd^{II}/Pd^{IV} or Pt^{II}/Pt^{IV} oxidation states—iodide presumably stabilised the Pd^{IV} oxidation state.

The selective conversion of methane into liquid chemicals, particularly methanol and its derivatives, liquid alkanes, or alkenes, is a target of many companies, but until this year no efficient or selective process existed. This has been attributed to the high energy (435 kJ/mol) of the C−H bond in methane, which requires high-temperature processes, and the resultant products are then unstable in the oxidising conditions and lead to further products (particularly CO_2!). A new process where methane is converted to methyl bisulphate in 81% selectivity at 90% conversion was recently announced (Periana, R. A.; et al. *Science* **1998**, *280*, 560). The reaction takes place in the presence of Pt complexes in fuming sulphuric acid at 220 °C. This and other similar processes are briefly reviewed and analysed (Wolf, D. *Angew. Chem., Int. Ed.* **1998**, *37*, 3351). It is suggested that, although a space time yield of 0.1 t m^{-3} h^{-1} can be achieved, the limiting factor is the stability of the catalyst, which is estimated to be completely deactivated in 14 h. This shows that further improvements may be necessary for commercialisation. Also, the subsequent work up steps—hydrolysis of the bisulphate ester, methanol recovery, recycle of SO_2 by oxidation to SO_3—will need further development and optimisation. Nevertheless, this is a significant advance on what has gone before.

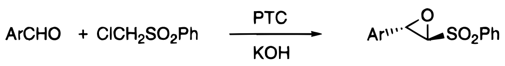
There has been much academic and industrial activity in the area of epoxidation, particularly using heterogeneous titanium catalysts, since the discovery of the properties of TS-1 (titanosilicalite) and its use in manufacture of products by Enichem in Italy. The hydrophobicity of the interior pores of TS-1 and aluminium-free titanium-β renders them active in oxidations, but aluminium containing Ti-β is less active, since the Al induces hydrophilicity. Because of their mesoporous nature (25−100-Å pores), Ti−MCM type catalysts should be more useful for larger, higher added value molecules. However, it has been observed that Ti−MCM catalysts, probably because of their hydrophilic nature, were less effective oxidation catalysts. Now workers at DuPont (D'Amore, M. B.; et al. *Chem. Commun.* **1999**, 121) report that TS-1, mesoporous Ti−MCM-41, and TiO_2/SiO_2 aerogels can be rendered hydrophobic by trimethyl-silylation, and that these catalysts are all very active for the hydrogen peroxide-induced epoxidation of olefins; even the activity of TS-1 is increased. Use of the silylated aerogel allows olefins such as cyclooctene, too large to fit in the pores of TS-1 or its silylated version, to be epoxidised.

In the same issue of that journal, the group of Baiker at ETH (*Chem. Commun.* **1999**, 197) report the preparation of a catalyst from TiO_2/SiO_2 by the sol−gel technique, followed by doping with amines. These catalysts are effective in the tBuOOH-induced epoxidation of allylic alcohols, particularly those prone to acid-catalysed rearrangements. The latter route is the major pathway with the catalyst if the amine is absent. This is presumably due to the amine neutralising the Brønsted acid surface silanol groups on the catalyst.

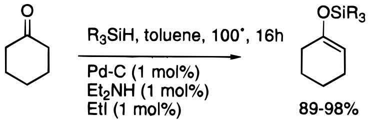
Oxidations often present a problem on a large scale. Oxone ($2KHSO_5$ $KHSO_4$ K_2SO_4) is an inexpensive, commercially available oxidant but suffers from the disadvantage of high molecular weight, poor solubility in organic solvents, and the production of salts in waste streams. A recent publication (Pietikäinen, P. *Tetrahedron Lett.* **1999**, *40*, 1001) suggests that tetrabutylammonium persulphate, which is soluble in organic solvents, gives much better results, for example, in the asymmetric Mn(III)−Salen-catalysed epoxidation of functionalised alkenes.

The Darzens reaction is a useful synthetic method for epoxy esters and sulphones and works well under phase-transfer catalysis. The asymmetric Darzens reaction has remained a challenge for chemists, particularly in developing a catalytic cycle. The group of Shioiri in Nagoya have previously reported (*Tetrahedron Lett.* **1998**, *39*, 2145) on

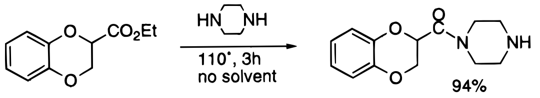
Scheme 8



Scheme 9



Scheme 10



progress in this area and now disclose (*Tetrahedron Lett.* **1998**, *39,* 8299) work on the catalytic version for sulphones (Scheme 8). In the presence of a chiral PTC, derived by alkylating quinine with 4-fluorobenzyl bromide and KOH, good yields (70−80%) and enantioselectivities (60−80% ee, increased to >95% after one recrystallisation) could be obtained. The reaction was very solvent dependent, toluene giving the best results.

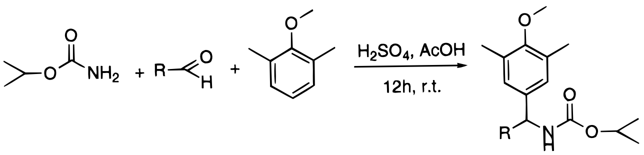
The standard method for preparation of silyl enol ethers is to treat an enolate anion with a chlorosilane. On a large scale, this method can lead to problems with separation of the product from the large amount of salt and with hydrolysis of the product. Workers at the Sagamo Chemical Research Centre in Japan (Igarashi, M.; et al. *Tetrahedron Lett.* **1999**, *40,* 711) have used dehydrogenative silylation as an alternative, the catalyst being Pd/C in the presence of diethylamine and ethyl iodide in toluene. Pt/C and manganese or iridium carbonyls also act as catalyst (Scheme 9). I find it hard to believe that Et_2NH and EtI do not react under these conditions and that the resultant quaternary salt assists the process, but the authors do not comment on this aspect.

The selective transformation of closely related molecules is always a challenge for organic chemists. Workers at Pharmacia and Upjohn needed to reduce a secondary amide in the presence of a tertiary amide and realised that all the literature methods reduce the tertiary amides *faster* than the secondary ones. They now find (Lee, B. H.; et al. *Tetrahedron Lett.* **1999**, *40,* 643) that activation of the secondary amide with a Cbz or Boc group allows fast reduction to the hemiaminal with borohydride, and deprotection and reduction gives the amine. The tertiary amide is unchanged under these conditions.

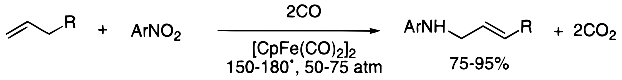
A one-pot preparation of mono-amides from esters and bifunctional amines is reported to work better in the absence of solvent (Chow, W.-C.; et al. *J. Org. Chem.* **1998**, *63,* 10015). Surprisingly, in the reaction of piperazine and similar bis-amines, little bis-amide is produced. The resultant amides are intermediates in a variety of anti-hypertensive drugs (e.g., Doxazosin, see Scheme 10).

A simple one-pot synthesis of protected benzylic amines by direct carbamoalkylation of aromatic compounds is described in a recent communication (Bensel, N.; et al. *Tetrahedron Lett.* **1999**, *40*, 879). The reaction proceeds at room temperature in a mixture of sulphuric and acetic acids.

Scheme 11



Scheme 12



Reaction of the aldehyde and carbamate generates an iminium ion which alkylates the aromatic (Scheme 11).

A new reagent is suggested for the rapid conversion of amines to isocyanates. Di-*tert*-butyltricarbonate, prepared from potassium *tert*-butoxide and carbon dioxide, followed by reaction with phosgene, reacts with amines at room temperature for 5 min to give isocyanates and is particularly useful for preparing compounds with more than one NCO group, since cyclisation to ureas is minimised (Peerlings, H. W. I. *Tetrahedron Lett.* **1999**, *40*, 1021). The reagent was used to make NCO dendrimers.

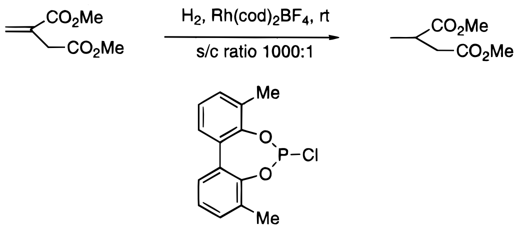
Selective reduction of multifunctional molecules is a challenge for the process chemist. Indian workers (Narasimhan, S.; et al. *SynLett* **1998**, 1321) have now found that tetrabutylammonium borohydride can reduce carboxylic acids and amides in the presence of ester groups and reduced $\alpha-\beta$-unsaturated esters to the saturated compounds. Reactions are carried out in chlorinated solvents, but it is pointed out that reduction of the solvent also occurs (in the order $CH_2Cl_2 < CHCl_3 < CCl_4 < ClCH_2CH_2Cl$).

Reduction of nitroaromatics to amines followed by alkylation is a common industrial process. A recent report, however, suggests that these processes can be carried out together (Scheme 12), though only with allylic alkylation, using iron catalysis (Srivastava, R. S.; et al. *Chem. Commun.* **1998**, 2705).

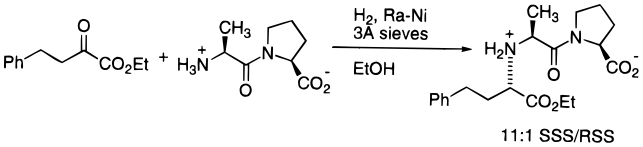
New diphosphite ligands for catalytic asymmetric hydrogenation are reported by the group of Reetz at Mulheim (*Angew. Chem., Int. Ed.* **1999**, *38*, 179). The unusual aspect of these ligands is that the most effective are derived from atropoisomeric biphenol units, where three diastereomeric metal complexes are possible (*R*/*R*, *S*/*S*, and *R*/*S*). These complexes, having a low energy barrier, rapidly interconvert, so the high enantioselectivity in the reduction of itaconic acid esters (using rhodium complexes of such ligands) is explained by the rationale that only one of the three complexes is active and exerts a kinetic preference (Scheme 13). Similar effects were noted in the reduction of acetamidoacrylates with 99% ee. The ligands proved superior to those with fixed chirality (e.g., bisnaphthol derivatives).

A new heterogeneous Lewis acid catalyst, which is effective in the catalysis of Diels−Alder reactions, is described (Saito, S. *SynLett* **1999**, 57). The catalyst, an aluminium trisphenoxide polymer, is made by treating bisphenol (**3**, Chart 1) with trimethylaluminium followed by ultrasonic irradiation. The resultant solid is active when used as a catalyst (1−2 mol %) in the cycloaddition of acrylates

Scheme 13



Scheme 14



to dienes. After the reaction, the catalyst could be filtered off and reused seven times.

Baker's yeast is used in several industrial processes, to make chiral building blocks or in carbonyl reduction steps, but there are practical difficulties which inhibit its widespread use (multiple enzymes with overlapping substrate specificities but different distereo- or enantioselectivities, poor volume efficiencies). New genetically engineered yeasts may solve these problems by increasing the amount of a specific enzyme produced by the yeast (Kayser, M.; et al. *SynLett* **1999**, 153). The new yeasts are effective in Bayer–Villager oxidation of ketones to lactones and in asymmetric *oxidation* of sulphides, dithiolanes, and dithianes.

The importance of using a multivariate approach to optimisation is emphasised in a superb paper from Merck (Huffmann, M. A.; et al. *Tetrahedron Lett.* **1999**, *40*, 831). The last step of the large scale synthesis of the ACE inhibitor enalapril involves a diastereoselective reductive amination (Scheme 14) catalysed by Raney nickel. Initially this gave a 6.7:1 ratio of diastereoisomers, but over the years this process has been in production, the ratio has been improved to 11:1 by optimisation of the grade of nickel. (Palladium on carbon only gives a 1.5:1 ratio.) Using a "combinatorial" approach, a broad screening programme of catalysts and additives was carried out; several hundred reactions were run with four catalysts and a variety of additives (chiral, nonchiral, amino acids, carbohydrates, salts, organic acids, and Lewis acids). Some dramatic effects were noted, such as a remarkable increase in yield and selectivity of a Pt/Al_2O_3 catalyst on adding NaBr and AcOH. Best results were still obtained with Raney nickel, however, and the addition of 1.25 equiv of acetic acid and 1.05 equiv of potassium fluoride increased the diastereomeric ratio to 17:1, i.e., a significant yield improvement in the production of a high-volume, high-value drug by adding inexpensive additives.

The authors point out that this discovery is unusual in that neither AcOH nor KF has any effect on its own (KF inhibits the reaction), and sodium fluoride in combination with acetic acid does not change the selectivity from 11:1. Thus, only experiments in which *more than one variable is changed simultaneously* would discover these optimised conditions. This study emphasises the value of automation in the screening of catalysts and additives in order to fine-tune reaction conditions for processes which have already been "optimised" by standard methods.

Production of sildenafil citrate (Viagra, **4**, Chart 1) is reported to be carried out at the rate of 1400 kg/week at Pfizer's factory in Ringaskiddy, near Cork, Ireland. The original synthesis of the drug is reported in a recent article (Palmer, E. *Chem. Br.* **1999** (January), 24), but the commercial process has yet to be disclosed, except in the patent literature—hopefully full details will appear in this journal!

Finally, I came across some new terminology during my reading this month. The determination of the crystal structure of large molecules is now apparently carried out by an X-ray diffraction technique known as "shake and bake" (Luger, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 3353). Inspired by this methodology, a new programme designed for the solution of structures in the 200–2000 atom range has been devised, and this has been termed "half-baked". The article suggests that, since this method has been extremely successful, then "fully baked" would be a more appropriate description.

T. Laird
Editor

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