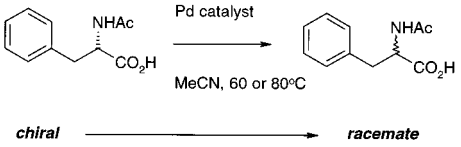
Organic Process Research & Development **2001**, *5*, 194–203

Highlights from the Literature

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

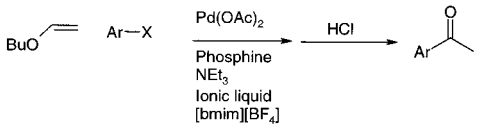
Many industrially important, enantiomerically pure compounds are still produced via the kinetic resolution of racemates, despite recent advances in asymmetric syntheses. To obtain yields of >50%, the unwanted enantiomer must be racemised, providing further feedstock into the resolution procedure. Beller et al. have reported (*Synlett* **2001**, *1*, 25) an improved procedure for the mild racemisation of *N*-acyl α-amino acids using $Pd(PPh_3)_4$ either as a preformed complex or by its in situ formation from $Pd(OAc)_2$ or $Pd_2(dba)_3$ and PPh_3 (Scheme 1). The concentration of the palladium complex catalyst required for effective racemisation is 1 mol %.

Scheme 1



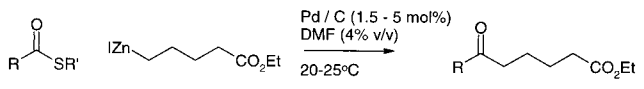
Palladium has also been used by Xiao and co-workers at the Leverhulme Centre for Innovative Catalysis at Liverpool University (*Org. Lett.* **2001**, *3*, 295) to catalyse the regioselective arylation of butyl vinyl ether and aryl halides in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) (Scheme 2). The reaction proceeds with high efficiency and remarkable regioselectivity. The authors suggest that the key to the success of this chemistry probably lies in the accelerating effect of the ionic liquid on the ionic pathway of the Heck reaction.

Scheme 2



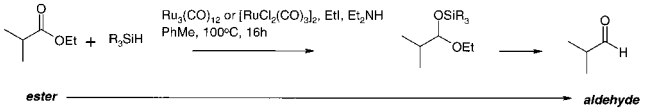
Continuing the palladium theme, Seki and Shimizu from the Tanabe Seiyaku Co. have described (*Tetrahedron Lett.* **2001**, *42*, 429) how Pd/C can be used to catalyse the "Fukuyama" coupling reaction between thiol esters with zinc reagents in the presence of DMF to provide a variety of functionalised ketones in good yields under mild reaction conditions (Scheme 3). The reaction was also applied to cyclic thiol esters (thiolactones).

Scheme 3



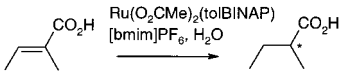
Fuchikami and co-workers from the Sagami Chemical Research centre have reported (*Tetrahedron Lett.* **2001**, *42*, 2149) the use of ruthenium catalysts in the hydrosilation of esters to the corresponding alkyl silyl acetals in moderate to good yields which are readily converted to aldehydes by hydrolysis. A variety of alkyl silanes were used in the reduction reaction as shown in Scheme 4.

Scheme 4



DeSimone and Wells have published a review titled "CO_2 Technology Platform: An Important Tool for Environmental Problem Solving" in *Angew. Chem., Int. Ed.* **2001**, *40*, 518. They describe how CO_2 is a good solvent for many substances when compressed into its liquid or supercritical fluid state. Above critical temperature and pressure (T_c = 31 °C, P_c = 73.8 bar) CO_2 has both gaslike viscosities and liquidlike densities, allowing it to be used safely within commercial and laboratory environments. Small changes in temperature and pressure cause dramatic changes in the density, viscosity, and dielectric properties of CO_2, making it a "tunable" solvent that can be tailored for a variety of applications. Jessop and co-workers (*J. Am. Chem. Soc.* **2001**, *123*, 1254) have combined the use of supercritical CO_2 ($scCO_2$) with ionic liquids for chemical separations. They describe how tiglic acid could be hydrogenated using $Ru(O_2CMe)_2$((*R*)-tolBINAP) with good enantioselectivity (>85% ee) and excellent yield (>97%) in the ionic liquid [bmim]PF_6 and subsequently extracted with $scCO_2$ (Scheme 5). Interestingly, the catalyst remained in the ionic liquid and could be used in a further four runs without loss of yield or enantioselectivity.

Scheme 5



Carreira has recently reported (*Org. Lett.* **2000**, *2*, 4233) the enantioselective addition of inexpensive 2-methyl-3-butyn-2-ol to aldehydes (Scheme 6) in the presence of $Zn(OTf)_2$, Et_3N and (*R*)- or (*S*)-*N*-methylephedrine. The isolated adducts undergo subsequent fragmentation to give propargylic alcohols in excellent yields and up to 99% ee which provide useful and versatile chiral terminal acetylene building blocks for further synthesis.

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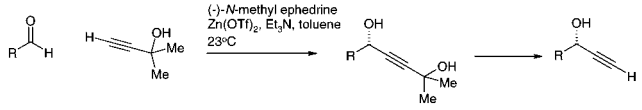
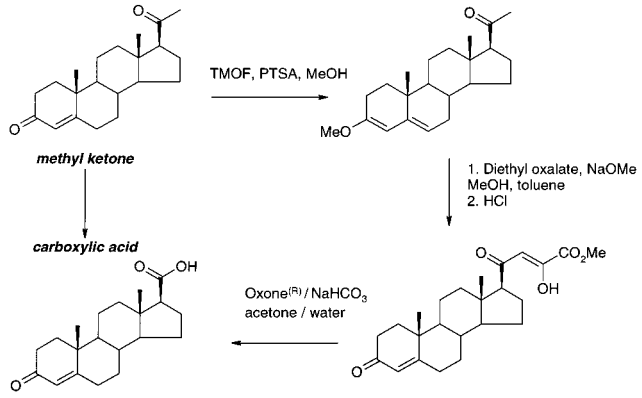
Scheme 6



Ashford and Grega from Pharmacia have described (*J. Org. Chem.* **2001**, *66*, 1523) the oxidative cleavage of 1,3-dicarbonyls to carboxylic acids with oxone. After attempting a number of synthetic alternatives for the direct conversion of a methyl ketone to a carboxylic acid, Scheme 7 describes the series of transformations to convert progesterone to androst-4-ene-17-β-carboxylic acid using their key reaction. The group report this method to be complementary to existing synthetic methods and in general to be a milder alternative to the haloform reaction.

Scheme 7



Ikemoto and co-workers have described their synthesis of TAK-779, a nonpeptide CCR5 antagonist (*Tetrahedron* **2001**, *57*, 1525) (Figure 1).

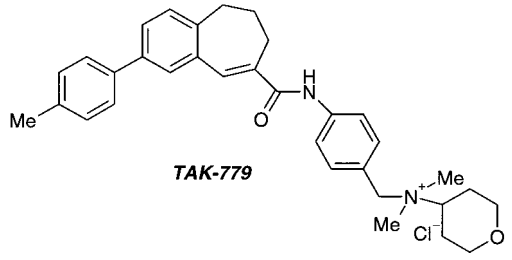
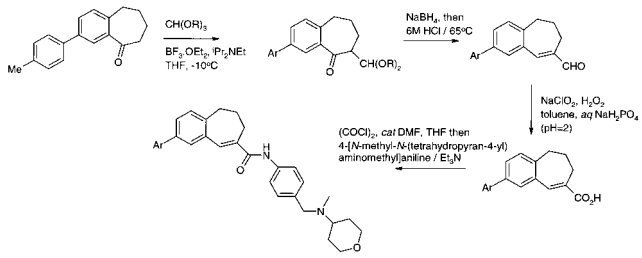


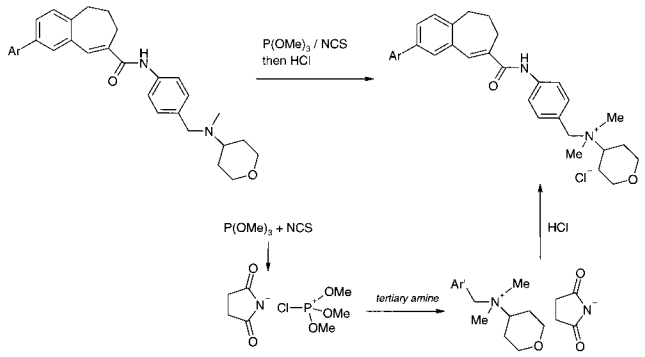
Figure 1.

Their synthesis (Scheme 8) starts with a dialkoxymethylation reaction using 6 equiv of carbenium ion prepared from methyl orthoformate. Subsequent reduction, hydrolysis, and elimination gave the ene-aldehyde which could be oxidised to the ene-acid using $NaClO_2$ in a toluene/phosphoric acid buffer with the addition of H_2O_2 to scavenge HOCl. Activation of the acid to the acyl chloride and susequent reaction with 4-[*N*-methyl-*N*-(tetrahydropyran-4-yl)aminomethyl]aniline gave the amide precursor to TAK-779. Methylation of the tertiary amine to generate TAK-779 was achieved (Scheme 9) using trimethyl phosphite and *N*-chlorosuccinimide followed by the addition of HCl in excellent yield without requiring chromatography.

Scheme 8

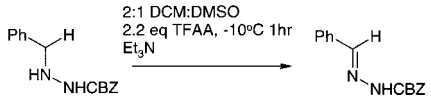


Scheme 9



Ripin and co-workers at Pfizer Research and Development have reported oxidation of carbamate-protected alkyl hydrazines to the corresponding hydrazones under Swern conditions in good yields (76−87%) (*Tetrahedron Lett.* **2001**, *42*, 1453). The reactions were performed using 2:1 DCM:DMSO as solvent and 2 equiv of TFAA at −10 °C followed by triethylamine (Scheme 10).

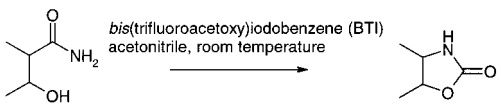
Scheme 10



87%

Retrosynthetic analysis of organic molecules can often lead to many possibilities for forward synthesis with some approaches being more attractive than others either from a cost, robustness, ease or environmental point of view. 2-Oxazolidinones are often "disconnected" back to the amino alcohols and, in the forward synthesis, prepared by reaction with a carbonyl equivalent such as carbonyl diimidazole, ethyl chloroformate, or diethyl carbonate. Hu and co-workers have reported (*Tetrahedron Lett.* **2001**, *42*, 1449) a facile synthesis of 2-oxazolidinones via Hofmann rearrangement mediated by bis(trifluoroacetoxy)iodobenzene and intramolecular cyclisation of the intermediate isocyanate in excellent yield (Scheme 11).

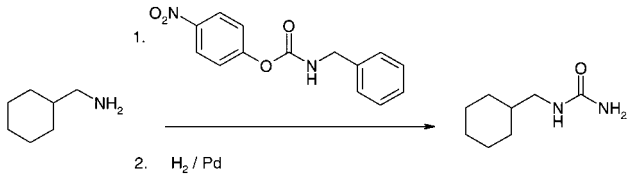
Scheme 11



A versatile and efficient synthesis of monosubstituted ureas is described by Tor and co-workers (*Tetrahedron Lett.* **2001**, *42*, 1445) by the reaction of amines with 4-nitrophenyl-*N*-benzyl carbamate followed by hydrogenolysis (Scheme

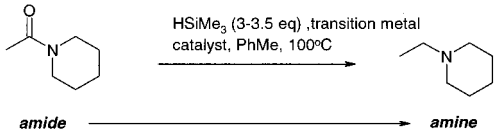
12). 4-Nitrophenyl-*N*-benzyl carbamate was prepared in high yield from benzylamine and 4-nitrophenyl-chloroformate. In particular this approach was used by the group to functionalise *water-soluble* polyamines when other reagents (such as benzylisocyanate) failed to give significant amounts of product.

Scheme 12



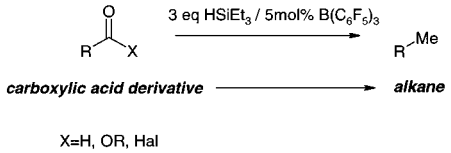
The reaction of amides with hydrosilanes can be catalysed using a variety of transition metal complexes in the presence or absence of halides as cocatalysts to afford the corresponding amines in good yields according to a recent report by Igarashi and Fuchikami (*Tetrahedron Lett.* **2001**, *42*, 1945) (Scheme 13) [*also compare to Scheme 4*]. The reaction works for a variety of amides including cyclic and acyclic tertiary amides.

Scheme 13



Continuing the theme of reduction using silanes, Et_3SiH has been used by Gevorgyan et al. (*J. Org. Chem.* **2001**, *66*, 1672) to reduce an *aliphatic* carboxylic group to a methyl group in the presence of catalytic amounts of $B(C_6F_5)_3$ (Scheme 14). Although this removal of functionality may seem wasteful, this trivial functional group manipulation may open up alternative opportunities during the planning stages in new route investigations.

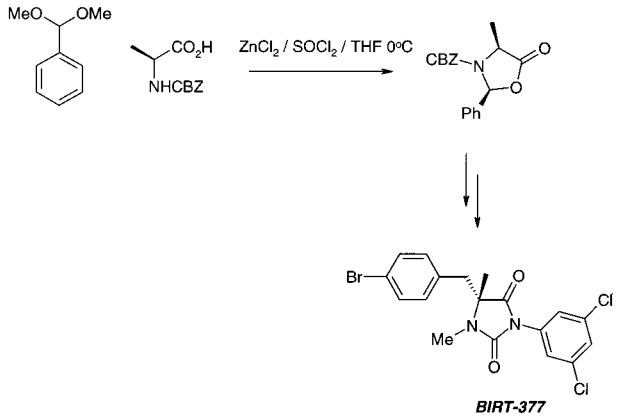
Scheme 14



An improved synthesis of chiral α-(4-bromobenzyl)-alanine ethyl ester and its application to the synthesis of LFA-1 antagonist BIRT-377 has been described by Kapadia and co-workers from Boehringer Ingelheim Pharmaceuticals (*J. Org. Chem*. **2001**, *66*, 1903). In their method (Scheme 15) Cbz-protected alanine is reacted with 1 equiv of thionyl chloride and benzaldehyde dimethyl acetal in the presence of $ZnCl_2$ to give the *cis* product in >15:1 selectivity. This protocol gave the key chiral oxazolidinone which was alkylated (with self-regeneration of stereocentres) and further manipulated to give BIRT-377.

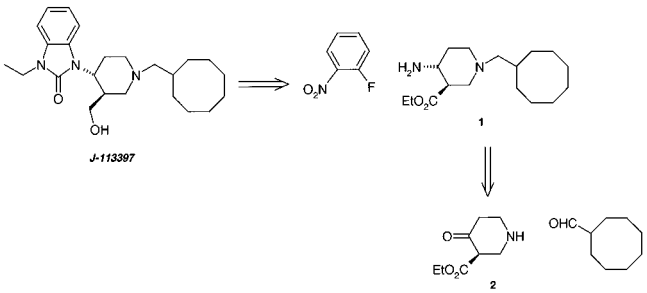
A group from the Banyu Tsukubu research institute in collaboration with Merck have recently disclosed (*Tetrahedron* **2001**, *57*, 981) their synthesis of J-113397, a potent

Scheme 15



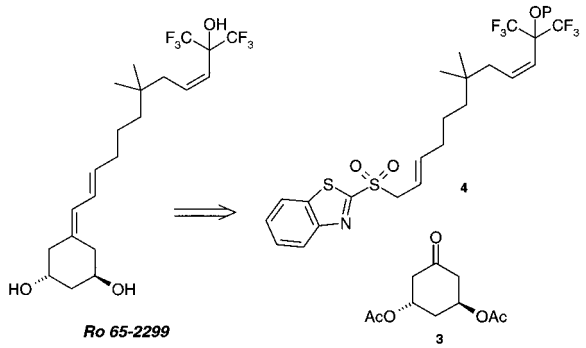
and selective ORL1 antagonist. Their retrosynthetic analysis is shown in Scheme 16 and involves a coupling between amine **1** and 2-fluoronitrobenzene. Amine **1** was prepared in a number of steps from the cyclooctane aldehyde and amine **2**.

Scheme 16



A short and efficient route to the *des*-C,D vitamin D_3 derivative (Ro 65-2299, Scheme 17), a potential antipsoriatic, has been developed by workers at Hoffmann-La Roche (*Tetrahedron* **2001**, *57*, 681). The route features an assembly strategy thus far unexplored in vitamin D chemistry, involving a modified Julia olefination of ketone **3** and 2-benzothiazolyl sulphone **4**.

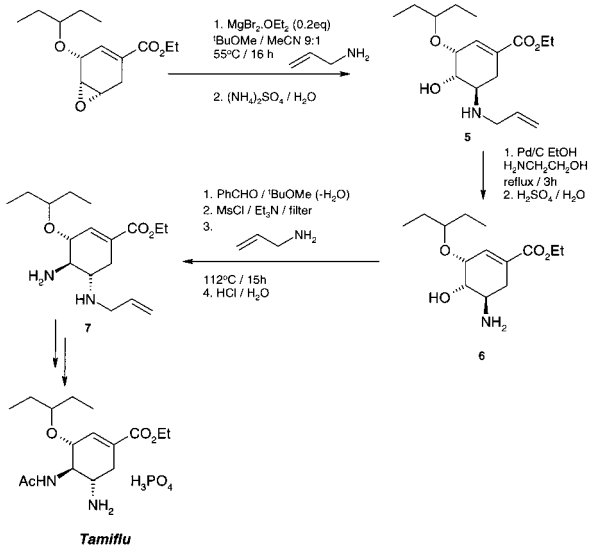
Scheme 17



Karpf and Trussardi from Hoffman-La Roche have recently disclosed (*J. Org. Chem.* **2001**, *66*, 2044) a new azide-free transformation of epoxides into 1,2-diamino compounds with application to the synthesis of the anti-influenza neuraminidase inhibitor oseltamivir phosphate (Tamiflu). In their synthesis (Scheme 18) catalytic $MgBr_2 \cdot OEt_2$ was used to effect epoxide ring-opening with allylamine to

generate **5**. Deallylation of **5** gave the amine **6** which was further converted to diamine **7** through imine protection, mesylation of the secondary alcohol, deprotection of the imine with allylamine, internal SN2 inversion of the mesylate, and allylamine opening of the aziridine. Interestingly, the overall yield of this Tamiflu synthesis exceeds the azide route and does not require any chromatographic purifications.

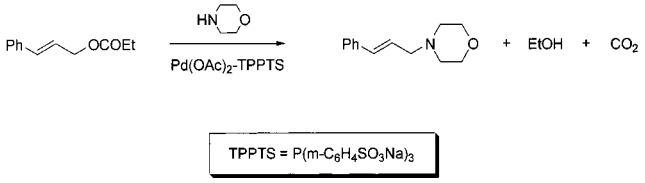
Scheme 18



Significant progress has been made in demonstrating the speed and economic advantage of a combinatorial approach to heterogeneous catalysis, where new materials have been discovered in a matter of days (sometimes even hours). A very readable review on this topic has recently appeared (Senkan, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 313). In the same issue, the use of combinatorial and evolution-based methods in the creation of enantioselective catalysts is also reviewed (Reetz, M. T. *Angew. Chem., Int. Ed.* **2001**, *40* 285). This review spends a considerable portion examining assay methods such as UV/visible methods, fluorescence-based systems, IR thermography, CD, chromatography methods, electrophoresis, MS methods, and radioactivity assays. The availability of improved screening methods should now open up this field since large libraries of catalysts can now be rapidly screened.

Most heterogeneous catalysts designed for use in fine chemical manufacture are usually supported on inorganics (SiO_2, C) or organic synthetic polymers. About 10 years ago supported aqueous phase catalysts were developed; this technique takes advantage of the hydrophilicity and high specific surface area of any inorganic support. The catalyst is usually in the water film which remains attached to the catalyst surface (usually silica). Mesoporous glass beads of controlled pore size distribution are the favourite support in this type of process. The first example of a catalyst supported in an aqueous film on an organic support, cellulose, is now reported (Quignard, F. et al. *Chem. Commun.* **2001**, 21). The water-soluble catalyst precursor ($Pd(OAc)_2$−TPPTS is immobiled on silica and used as shown in Scheme 19. No leaching of Pd from the catalyst occurs.

Scheme 19

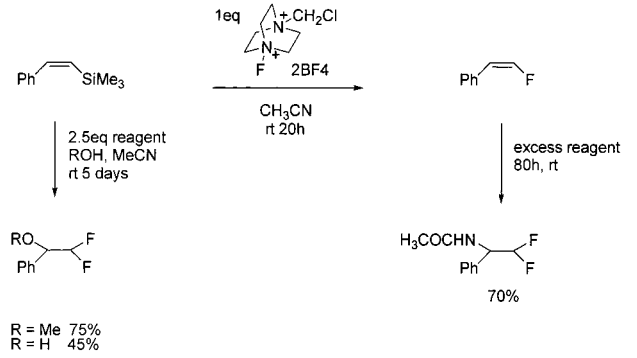


The yield of any chemical process is dependent not only on the efficiency of the chemical reaction but also on the ease of isolation of the product. A relatively new technique which is designed to improve the separation of products from reagents/catalysts is fluorous phase chemistry, which allows simple 2- or 3-phase liquid−liquid extraction techniques to be used. Alternatively, fluorous chromatography can be used. One of the pioneers in the field is Denis Curran of University of Pittsburgh, and a special feature on his work is included in the latest issue of *Green Chemistry* (February, 2001, p G3). One area which may be of interest to process chemists is the use of fluorous tin hydrides in radical cyclisation. Depending on the alkyl chain length, the degree of fluorination in the chain, and the solvent fluorine content, reactions can be designed where the tin reagent is easily removed from the product during work-up and has the potential for recycling (Curran, D. P. et al. *J. Am. Chem. Soc.* **1999**, *121*, 6607; **1996**, *118*, 2531).

A new company, Fluorous Technologies Inc., has been set up and has licensed from the University of Pittsburgh several patents on the use of fluorous organic chemistry (see http://www.fluorous.com for further information). It should come as no surprise that the Chairman of the Scientific Advisory Board for the new company is Denis Curran.

The introduction of the fluorine atom into organic molecules continues to be of interest. Whereas fluoro desilyation has been used for aryl-trimethylsilanes, it has not been used to make fluoro alkenes (although the other halides can replace silyl groups to make haloalkenes. Use of Selectfluor, however, has now been shown to give efficient replacement of $SiMe_3$ by F in a variety of alkenes (Greedy, B. et al. *Chem. Commun*. **2001**, 233)—see Scheme 20.

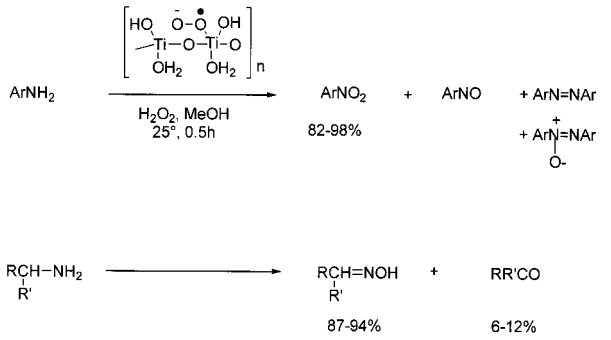
Scheme 20



Whilst the reduction of nitro compounds to amines is a widely used process, the oxidation of amines to nitro compounds is difficult to achieve. In a study aimed at looking at the reactions of superoxide ion ($O_2^{\bullet -}$), which plays an important role biologically, Indian workers have found an

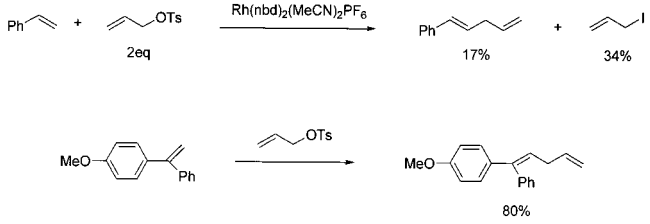
exceptionally stable titanium superoxide radical ion which is an excellent heterogeneous catalyst for NH_2 oxidation (Sudalai, A. et al. *Angew. Chem., Int. Ed*. **2001**, *40*, 405). The catalyst is prepared by action of 50% H_2O_2 on $Ti(OR)_4$ in anlydrous methanol at 25 °C. For the oxidations, the catalyst is used in methanol with H_2O_2 as oxidant (Scheme 21). Aliphatic amines are oxidised to oximes.

Scheme 21



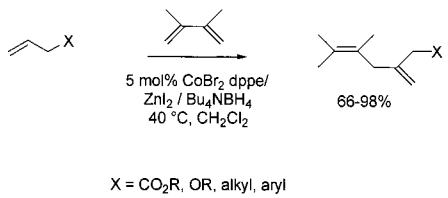
The efficient reaction of alkenes with simple allyl compounds to afford 1,4-dienes has remained a difficult process to achieve efficiently with simple substrates. It has now been found that rhodium catalysts in dioxane can catalyse the desired reaction (Scheme 22) and works best with electron-richer alkenes (Tsukuda, N. et al. *Chem. Commun*. **2001**, 237).

Scheme 22



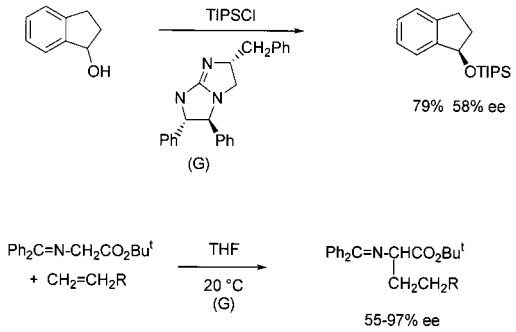
We normally think of a reaction between a diene and an olefin as leading to cycloaddition via a Diels−Alder reaction. An alternative process, and one with potential industrial utility for C−C bond formation, is hydrovinylation, and this type of reaction is used in the copolymerisation of ethylene and 1,3-butadiene on an industrial scale by Dupont, the resulting hexadiene being transformed into synthetic rubber and other unsaturated polymers. A new catalyst for 1,4-hydrovinylation has recently been reported (Hilt, G. et al. *Angew. Chem., Int. Ed*. **2001**, *40*, 387) which allows high yields of products to be obtained (see Scheme 23).

Scheme 23



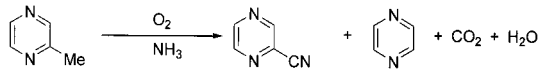
Modified guidelines have been found to effectively mediate asymmetric silylation of secondary alcohols (Scheme 24). This simple process allows recovery of the expensive chiral guanidine and separation of product (Isobe, T. et al. *Chem. Commun*. **2001**, 243). The following paper describes the asymmetric Michael addition of glycine imines to acrylates (Ishikawa, T. et al. *Chem. Commun*. **2001**, 245).

Scheme 24



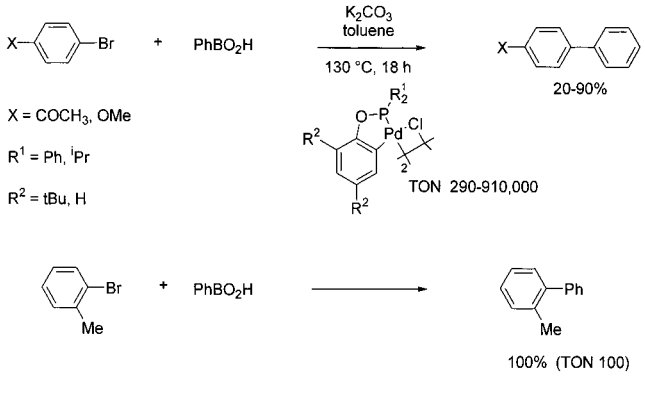
2-Amidopyrazine (pyrazinamide) is an important anti-tubercular drug. Its usual method of synthesis involves reaction of glyoxal with 1,2-propylene diamine, but this generates a lot of waste products. A more recent and environmentally attractive method involves catalytic ammoxidation of 2-methylpyrazine to 2-cyanopyrazine followed by hydrolysis. An article from workers at the Indian Institute of Technology (Rao, K. N. et al. *Green Chem.* **2001**, *3*, 20) describes the use of a new catalyst (12-molybdophosphoric acid, prepared "in situ") which is highly selective for the desired ammoxidation (see Scheme 25).

Scheme 25



Interest in the Suzuki reaction continues, and new catalysts are constantly being developed. A highly active palladacyclic phosphinite complex seems to work well even with hindered and electronically deactivated aryl halides (Bedford, R. B. et al. *Chem. Commun*. **2001**, 129)—see Scheme 26. These are the highest activities yet reported for a Suzuki reaction.

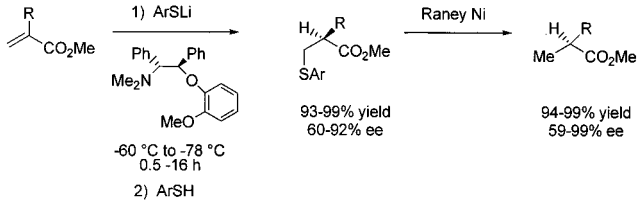
Scheme 26



Enantioselective protonation of prochiral enolates has always seemed an attractive way to generate enantiomers (for reviews, see Fehr, C. *Angew. Chem., Int. Ed*. **1996**, *35*, 2566; Yanagisawa, A. et al. *Synlett* **1997**, 411). Recently, a catalytic enantioselective protonation of lithium ester eno-

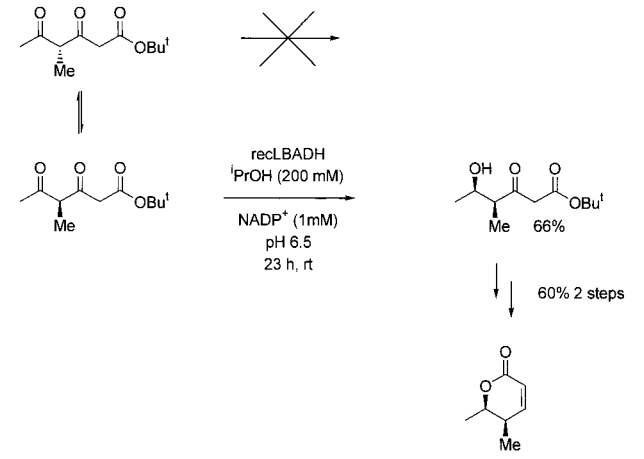
lates, generated by conjugate addition of thiols to enoates, has been achieved (Nishimura, K. et al. *Angew. Chem., Int. Ed.* **2001**, *40*, 440). The results are shown in Scheme 27, and the process has been used to make chiral drugs such as naproxen. However, this seems an expensive way to do an asymmetric reduction. The value appears in the first step, and attempts to make drugs with sulphur in (captopril, nelfinavir) might have better demonstrated the utility of the reaction.

Scheme 27



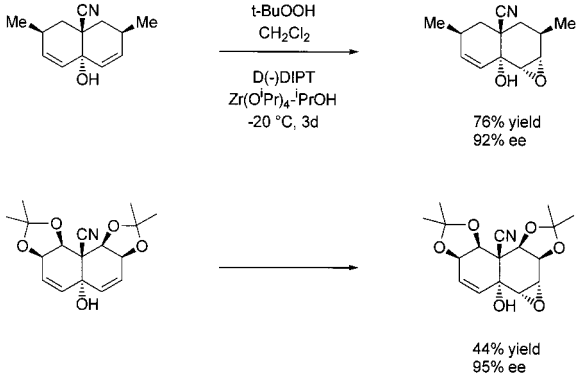
Although the dynamic kinetic resolution of α-substituted *β*-ketoesters by chemical or biocatalytic reduction is well-known, the corresponding asymmetric reduction of 1,3-diketones has proved more difficult. The method is attractive since it allows the simultaneous introduction of two stereogenic centres usually in a high yield. By using isolated enzymes, however, this difficult transformation has been achieved (Ji, A. et al. *Chem. Commun*. **2001**, 57). Recombinant alcohol dehydrogenase from *Hactobacillus brevis* is used in combination with 2-propanol as reducing agent (Scheme 28).

Scheme 28



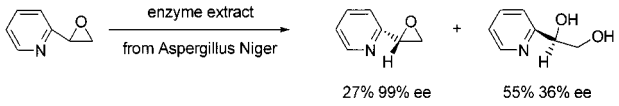
The group of Spivey at the University of Sheffield have discovered a useful modification of the Sharpless asymmetric epoxidation (AE) reaction conditions which may prove useful for tertiary alcohols and other hindered substrates (Spivey, A. C. et al. *Angew. Chem., Int. Ed.* **2001**, *40*, 769). Under standard AE conditions the allylic alcohol (see Scheme 29) gave product in up to 70% yield but only 10−20% ee. Known variations including changing the ligand or adding CaH_2/silica failed to improve the situation. It was reasoned that replacement of titanium by zirconium would lead to better complex formation (increased Zr−O bond strength). As a result, increased ee's of up to 92% resulted when stoichiometric amounts of $Zr(OiPr)_4$•^{i}PrOH were used in the presence of di-isopropyltartrate. In the latter case 3 equiv of oxidising agent were used, and some overoxidation (21%) accounts for the low yield. Enhancement of the ee of the mono epoxide, however, is expected to change with increased conversion. After 24 h, the ee was only 82%. Attempts to employ substoichiometric amounts of zirconium alkoxide have not been successful.

Scheme 29



Kinetic resolution of epoxides is efficiently carried out by aqueous hydrolysis using organometallic catalysts (e.g. the Jacobsen approach which has been commercialised by Rhodia-Chirex). An alternative approach is to use microbial epoxide hydrolase enzymes. (Genzel, Y. et al. *J. Org. Chem*. **2001**, *66*, 538). If the enzyme can be obtained at low cost, this method may be industrially attractive, although 10 g/L is still rather dilute. Comparison with chemical methods is given in the article (see Scheme 30).

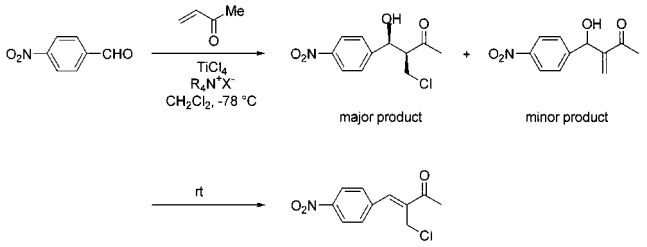
Scheme 30



The Baylis−Hillman reaction continues to attract a lot of attention to try to overcome its shortcomings (slow reaction, limited range of substrates). In the presence of titanium tetrachloride and quaternary ammonium bromides or iodides, two types of products are produced when α−*β*-unsaturated ketones are the subtrates (Shi, M. et al. *J. Org. Chem*. **2001**, *66*, 406)—see Scheme 31. If the temperature is raised to room temperature, a third product is formed. The reaction is sensitive to the relative amounts of $TiCl_4$ and R_4NX (and its structure) so that it is easy to find conditions in which the normal Baylis−Hillman product is reduced to low levels. The reaction is successful for a variety of aldehydes, although as expected, aromatics are more successful than aliphatics.

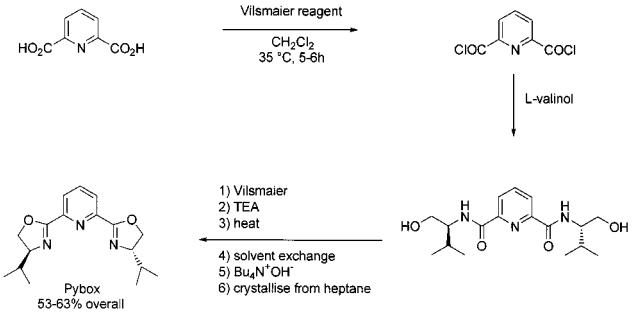
Pyridine bisoxazoline ligands (pybox) have been used in a variety of asymmetric catalytic processes, and thus it is desirable to have a safe and scaleable process for large-scale preparation. Workers from the Process R & D Department at Bristol Myers Squibb suggest that previously described processes—including one from Merck's Process Department—have disadvantages, and they have proposed an alternative

Scheme 31



method (Totleben, M. J. et al. *J. Org. Chem.* **2001**, *66*, 1057). The process is shown in Scheme 32.

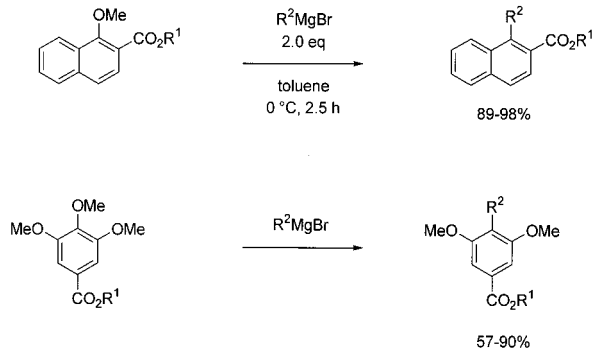
Scheme 32



Simple transformations are always of interest to the process R & D chemist. A recent note from Taiwan (Talukdar, S. et al. *Tetrahedron Lett*. **2001**, *42*, 1103) reports the conversion of aldehydes to nitriles by treatment with iodine in aqueous ammonia in THF at room temperature. The reaction works well for aliphatic, aromatic, heterocyclic, and $\alpha-\beta$-unsataurated aldehydes, usually in greater than 90% yield. The method is ideal for water-soluble substrates such as carbohydrates. It is pointed out that excess iodine should be avoided since this may lead to the explosive $NI_3 \cdot NH_3$. Thus, iodine should be added to the aldehyde in excess aqueous ammonia. The reaction is envisaged to proceed via the *N*-iodoimine followed by loss of HI.

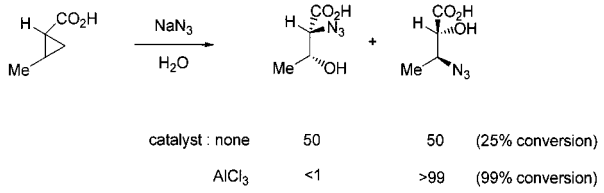
The group of Kotsuki in Japan have recently announced a novel method for nucleophilic aromatic alkylation of ortho- and para-substituted aromatic esters, using Grignard reagents (Kojima, T. et al. *Tetrahedron Lett*. **2001**, *42*, 1709). Examples are shown in Scheme 33.

Scheme 33



There is much current interest in the reactions of organic compounds in water, since a surprising number of processes can take place. Lanthanide triflates are the most common water-tolerant Lewis acids to catalyse these reactions. A recent publication (Fringuelli, F. et al. *Tetrahedron Lett.* **2001**, *42*, 1131) indicates that aluminium trichloride is also effective. For example, the sodium azide-induced ring opening of epoxides is enhanced in water by $AlCl_3$. After extraction of the product, the aqueous solution containing the hydrated aluminium species could be reused (Scheme 34).

Scheme 34



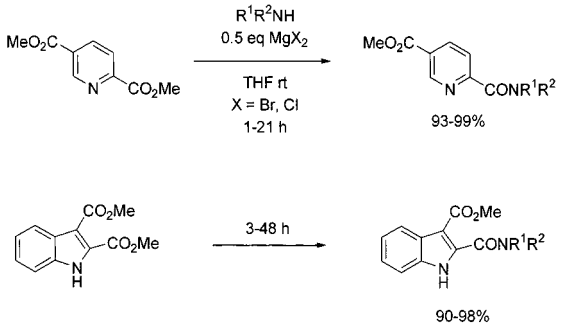
Catalytic semihydrogenation of alkynes to 2-alkenes is an important process. The most often used catalysts are Lindlar palladium and P-2-nickel in the presence of ethylenediamine, although numerous other catalysts (e.g., nickel boride) work well in some situations. A group from Sicily (Gruttadauria, et al. *Tetrahedron Lett.* **2001**, *42*, 2015) have been investigating the use of palladium on pumice with metal loadings as low as 0.5%. High selectivities and excellent steroselectivity (>99%) have been achieved, and in the presence of a catalytic amount of base, the semihydrogenation is self-terminating. The palladium-on-pumice catalysts do not need any pretreatment and are stable to oxygen. The major disadvantage for industrial users is that the catalysts have to be prepared, and a method is given in the article (from palladium diallyl). Perhaps they will soon be commercially available. I wonder if the source of pumice is a key factor—presumably the Sicilian chemists get theirs from Mount Etna!

The conversion of amides to amines can be a difficult transformation. Simple catalytic hydrogenation requires elevated temperature and pressure, and thus stoichimetric reductions with metal hydride complexes are used, but these can be problematical on scale. Recently rhodium-catalysed silane reductions have been reported using aryl dihydro and trihydrosilanes. It has now been found (Igarashi, M. et al. *Tetrahedron Lett.* **2001**, *42*, 2001) that a number of transition metals will catalyse the reduction of amides to amines with triethylsilane in toluene at 100 °C. The presence of an amine (e.g., Et_2NH) and an alkylating agent (e.g., EtI) at 5 mol % level is sometimes beneficial. Yields are usually above 90% when osmium or ruthenium carbonyl derivatives are used.

A novel method for the monoamidation of diesters has been published by a group from Bristol-Myers Squibb (Guo, Z. et al. *Tetrahedron Lett.* **2001**, *42*, 1843). This simple process uses 0.5 equiv of a magnesium halide in THF to catalyse the process (see Scheme 35). When *tert*-amines are used with $MgCl_2$ as catalyst, the reaction is very slow, but use of $MgBr_2$ speeds up the process. Changing the solvent to acetonitrile also improves the process.

The latest issue of *Chemical Innovation* contains a very readable account of the progress made at the University of Aachen, Germany, on devising a green route to caprolactam,

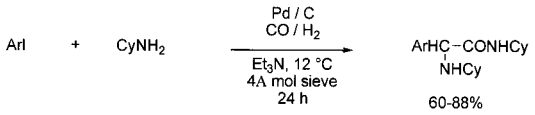
Scheme 35



precursor of Nylon-6 (Hoelderich, W. F. et al. *Chem. Innovation* February, 2001, p 29). The focus is on the last step, the Beckmann rearrangement of cyclohexanone oxime to caprolactam. In the old, fuming sulphuric acid-mediated process, 2 tonnes of ammonium sulphate is produced per tonne of caprolactam. The new process uses a zeolite catalyst, and the paper describes the fine-tuning and optimisation work, reactor design, and process development which had to be carried out before an economically viable process was achieved.

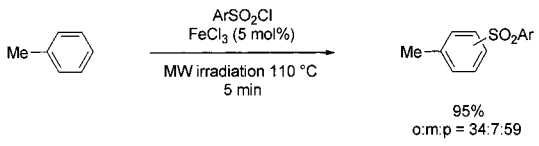
A novel approach to amino acid amides involves a one-pot double carbohydroamination reaction catalysed by palladium (Lin, Y.-S. et al. *Angew. Chem., Int. Ed.* **2001**, *40*, 779). The group of Alper at Ottawa, Canada, has already carried out extensive work on double carbonylation reactions, which have proved synthetically useful. Now they have extended the scope to a "domino" reaction, combining double carbonylation, amine condensation, and hydrogenation in one step (Scheme 36). The by-product is the simple arylamide. We await the asymmetric version of this reaction.

Scheme 36



Sulphonylation of aromatic molecules under Friedel−Crafts (F−C) conditions is problematical because the product sulphone forms a complex with traditional catalysts ($AlCl_3$ or Fe Cl_3), but Brønsted acids, which work well in acylation, poorly catalyse sulphonylation of arenes. A number of solutions to this problem have been suggested, but many require prolonged heating or large amounts of sometimes expensive catalyst. On the basis of recent successes with F−C acylation under microwave conditions in the absence of solvent, a similar procedure is suggested for sulphonylation, using $FeCl_3$ as catalyst (Marquié, J. et al. *J. Org. Chem.* **2001**, *66*, 421). Results are shown in Scheme 37. The authors, some of whom work at Rhodia Fine Chemicals, suggest the method has industrial potential.

Scheme 37



A comprehensive review on "functionalised polymers, emerging versatile tools for solution-phase chemistry and automated parallel synthesis" has appeared (Kirschning, A. et al. *Angew. Chem., Int. Ed*. **2001**, *40*, 650). The review focuses on the reactions which can be carried out—oxidations, reductions, halogenations, C−C coupling, nucleophilic substitution, as well as purification methodology. The outlook for large-scale work is far from ideal, owing to the need for improved polymer supports with higher loading capacity, but miniaturisation techniques and microreactor technology may hold out promise for the future.

High-speed experimentation techniques have been used to optimise a catalyst used in the epoxidation of l-octene by *tert*-butyl hydroperoxide. The silsesquioxanes, $(RSiO_{1.5})_a - (H_2O)_{0.5b}$ where R is organic and $a \geq 1$, $b \geq 0$, are obtained by slow hydrolysis of $RiSiX_3$ and complexed with $Ti(OiPr)_4$. The robot carried out experiments varying composition, R group and solvent, measuring the activity of each (Pescarmona, P. P. et al. *Angew. Chem., Int. Ed.* **2001**, *40*, 740). In some cases mixtures of silanes yield more active catalysts than when a single silane is used—this would have been difficult to identify without using a combinatorial approach.

A novel method for rapid chiral quantification at low ee values by a mass spectometric technique has been described by a group at Purdue University (Tao, W. A. et al. *Angew. Chem., Int. Ed*. **2001**, *40*, 757). The gas-phase method involves two parallel ion−molecule reactions followed by low-energy dissociations. High selectivity is not required to quantify enantiomers at low ee values. The experiments are carried out by mixing the compound to be analysed (A_r/A_s) with $CuCl_2$ and a chiral reference compound in aqueous methanol. In the MS, the solution is transformed into gas-phase cluster ions of $[Cu^{II}(A_r)(ref)_2-H]^+$ and $[Cu^{II}(A_s)(ref)_2-H]^+$ through electrospray ionisation. Each cluster undergoes dissociation, and the relative abundances in the MS can be measured. The method has been used in the peptide field.

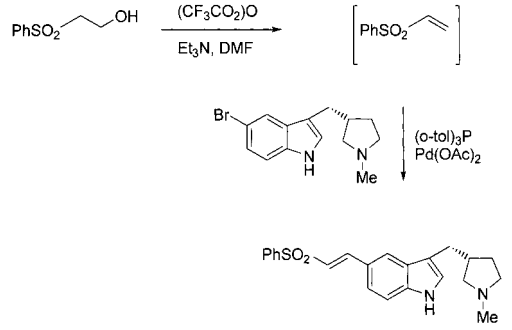
Two articles from GlaxoSmithKline on environmental issues make interesting reading. The first is entitled "So You Think Your Process Is Green; How Do You Know? Using Principles of Sustainability To Determine What Is Green − A Corporate Perspective" (Curzons, A. D. et al. *Green Chem.* **2001**, *3*, 1). This is an attempt to quantitatively and systematically evaluate organic reactions and processes on "green" principles. Close attention to effective use and reuse of solvents gives the largest gains for reducing life-cycle impact in batch chemical processes.

In the following article entitled "Green Chemistry Measures for Process R & D", a set of metrics is described which enables a simple assessment of batch/semibatch processes in terms of waste, energy usage, and chemistry efficiency (Constable, D. F. C. et al. *Green Chem.* **2001**, *3*, 7).

One way to minimise waste in a chemical synthesis is to *not* to isolate intermediates (particularly if they are highly toxic) and to telescope reactions. These principles are evaluated in an article on the synthesis of β-sulphonylvinylindoles (Orita, A. et al. *Green Chem.* **2001**, *3*, 13)—see Scheme 38. The toxic vinylsulphonylbenzene is not isolated,

just generated "in situ" and subjected immediately to a Heck reaction.

Scheme 38



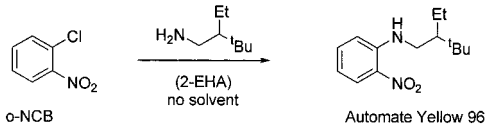
And finally, I was intrigued by a report which suggested that CDs could be used as mobile-phase additives to enhance enantioselectivity in capillary electrophoresis analysis. As I read on, I realised that CD stood for cyclodextrin not compact disc! The high efficiency of these resolutions should be attractive for industry (Valoti, E. et al. *J. Org. Chem.* **2001**, *66*, 1018).

Special Highlight on Safety

I wish to bring to the attention of all process R & D and production chemists and engineers an explosion and fire which took place at Morton Specialty Chemicals (now Rohm and Haas) in Paterson, New Jersey, U.S.A., on April 8, 1998. This incident has been the subject of an investigation by the U.S. Chemical Safety and Hazard Investigation Board, and their full report has been published on the web (http://www.chemsafety.gov/reports/2000/morton/index.htm#TOC). We can all learn from the mistakes of others, and this is why this report is discussed below on detail.

Work began on the chemistry shown in Scheme 39 in the UK in the 1980s, and a process to make the product—known as Automate Yellow 96 Dye—was developed.

Scheme 39



(The dye is used to tint petroleum fuel products). This was a semibatch process involving addition—in four equal portions—of the *o*-nitrochlorobenzene (ONCB) (a low-melting solid) to the neat 2-ethylhexylamine (bp 169 °C). The dosing was carried out to control the exothermic process. The process was then transferred to the Paterson, New Jersey, U.S.A., site with a number of recommendations regarding reaction control and safety.

The recommendations included:

- running the process in semibatch mode with cooling to control the exotherm
- in view of the highly exothermic nature of the process and the decomposition of the product above 220° (by DSC), ARC tests should be run to determine the rate of reaction under worst-case conditions, the rate of decomposition of the finished product, and pressure rise data which could be used to size emergency venting equipment.

None of these recommendations were carried out! Instead, a batch process was conducted to minimise worker exposure to *o*-NCB. Both *o*-NCB and 2-EHA were added to the reactor, heat was applied to initiate the reaction followed by cooling (if necessary) to control the exotherm.

Production started on this batch process in September, 1990, on 1000-gal (3800-L) scale with the *o*-NCB charged as a melt, then 2-EHA was added, heating to 90° to initiate with further heating to 150−153 °C. The Morton staff had indicated that they thought this process safe if the procedure was correctly followed. They did not carry out a preliminary hazard assessment as recommended by the Centre for Chemical Process Safety's publications.

Batch records for runs 3 and 5 contained operator comments stating that the reaction temperature was overrunning and that cooling was inadequate or not controlling the temperature. In runs 14, 15, and 18, the temperature was >150 °C (although the recording charts could only measure up to 150 °C!)

In 1995 a process hazard analysis was eventually carried out using the "what if" approach which analysed all of the equipment and the chemical reaction. Although the failure of the heating system was considered, the consequences of inadequate cooling were not. The answer to the question "What if runaway occurs?" was "Not applicable".

To make matters worse, the batch size was increased in 1996 by 9% and a 2000-gal (7600-L) vessel was used, despite the fact that 20% of batches at the 1000-gal scale had shown temperature excursions. The result of the scale-up was to reduce by a further 10% the available heat transfer area per unit volume. It should not be a surprise, therefore, that 50% of batches run at 2000-gal scale showed temperature excursions.

Despite the warning signs in batches 28, 30, and 31, where the temperature was off-scale for 3−45 min, batch 32 was started on April 8, 1998. Once the exotherms had been initiated, it was found difficult to control, and cooling was applied at 100 °C. Two minutes later the temperature was off-scale (>150 °C). The reactor began to vibrate, vapour appeared in the condenser, and the bursting disk ruptured at 180−190 °C. The temperature continued to rise, the reactor began to rumble and shake violently, and eventually the operators decided to run for it.

The manway blew off, and the reactor contents were ejected and blown through the next floor and roof and ignited. Nine employees were injured, two seriously, and potentially hazardous materials were released into the community.

The above catalogue of errors and omissions is hard to believe. In subsequent safety evaluation, it was found that the reaction onset was 38 °C not 75 °C as the operators believed. Product decomposition occurred at 195 °C, although the operators were not told of any decomposition reaction. The vent size should have been twice the diameter of the one fitted.

There are a number of lessons which all of us can learn from this.

Every time there is a process transfer from one part of an organisation to another, or from one company to another, there is the possibility of loss of information. Management practices should ensure that this information loss (which more often leads to quality issues rather than safety issues) should be dept to a minimum. One way to do this is to have the minimum number of process/technical transfers between research and manufacture. This has implications for outsourcing!

There is a need for adequate training in thermal hazard evaluation for all chemists and engineers involved in scale-up and for all companies to have a procedure in place (*and to follow that procedure*) for process hazard analysis.

Pressure relief requirements need to be evaluated according to the Design Institute for Emergency Relief Systems (DIERS) methodology and to be tested accordingly.

Companies need to have a programme that ensures that deviations from normal operational limits for reactive chemical processes are documented, investigated, and that action is taken, where required, to modify the process. In the pharmaceutical industry, this will be done for quality reasons as well as for safety under GMP guidelines. GMP and process validation, normally considered as quality assurance principles, have great value in "safety assurance" and some of the principles could usefully be applied by safety management in nonpharmaceutical companies. The incident in Germany at Bayer a couple of years ago, when an operator charged potassium hydroxide instead of potassium carbonate to a reactor containing a nitro compound and DMSO, would probably have been prevented if the process had been operating under GMP conditions.

I urge you to read the CSB report on Automate Yellow in full—it is a very readable account of what can go wrong. The only omission from the report is the cost to Morton/Rohm and Haas of the incident.

Trevor Laird
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