Organic Process Research & Development **1999**, *3*, 150–154

Highlights from the Literature

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

The appearance of a new polymorph of a drug is often problematical, particularly when it comes at a late stage in development. A recent article in this journal (Beckman, W.; et al. *Org. Process Res. Dev.* **1998**, *2*, 298) described such an incident and detailed the outstanding work carried out at Schering to overcome the problem. Workers at Abbott have also had problems with their anti-HIV drug Ritonavir, when an unexpected appearance (post-launch!) of a new crystal form had different dissolution and absorption characteristics. The drug has since been temporarily withdrawn from the market. In a recent article, Nicholas Blagden and Roger Davey (Polymorphs take shape. *Chem. Br.* **1999**, March, 44) describe the effects of adding small amounts (sometimes as low as 0.01%) of impurities on the crystallisation of substances. In many cases, these small quantities of impurities, which could easily be generated as part of the synthesis, inhibit the crystallisation of the more stable polymorph and lead—reproducibly—to a less stable form. This may explain why many new (more stable) polymorphs appear in late development, when the efforts of the chemical development team to improve the process and product purity may have eliminated the key impurities which control the crystal form. It also offers hope that, by rational design of additives, a desirable polymorph (not necessarily the most stable) may be reproducibly obtained.

In a letter to the Innovators magazine, *CHEMTECH* (**1999**, March, 2) Harold Huckins from Princeton Advanced Technology comments on a previous editorial on "musings on hydrogen peroxide", in which Abe Gelbein, who has now retired as editor of *CHEMTECH*, speculated that there is room for improvement in the technology to make hydrogen peroxide. Huckins suggests that H_2O_2 would be much more widely used as an oxidant if the price were lower, and the relatively high price is associated with the product isolation steps in the current anthraquinone (AQ) process. After the reaction steps, the H_2O_2 needs to be extracted into water, phase separated, distilled, and purified in a complex and hence expensive plant. A direct process from H_2 and O_2 would be more attractive if the inherent safety problems could be overcome; a patent (U.S. Patent 5641467, 24 June 1997) has appeared in which a highly turbulent environment is produced in a reactor, leading to excellent mass and heat transfer and high volume productivity, and in a nonhazardous manner. It is suggested that the new direct process could be attractive in a number of areas, not only in producing oxidised chemicals, but also for waste treatment.

Another method of H_2O_2 generation, from carbon monoxide and water, has been investigated (CO_2 being the byproduct). This reaction is thermodynamically favourable ($\Delta G^\circ = 134$ kJ mol^{-1}), but the early catalysts were inefficient. Now a group from Enichem, Italy (Bianchi, D.; et al. *Angew. Chem., Int. Ed.* **1999**, *38*, 606), report that a bidentate nitrogen ligand (usually a substituted phenanthroline) complexed with palladium under biphasic reaction conditions gives yields comparable to those of the commercial process. The biphasic system, in which the product is in the aqueous phase and the catalyst is in the organic phase, prevents oxidative decomposition of the catalyst. The best medium was a mixture of 2-methyl-2-butanol, 1,2,4-trichlorobenzene (to improve phase separation), and water. The catalyst is easily recovered and reused in batch processes, but a continuous process is presently being examined.

One of the reasons (excuses?) that chemists give for developing stoichiometric rather than catalytic processes is that it takes a long time to find the correct catalyst for a particular reaction, so with fast-tracking of projects in the fine chemicals industry, many stoichiometric processes are never converted to catalytic methodologies. A combinatorial approach may help to cut down the development time, and a novel method applied to the discovery and optimisation of heterogeneous catalysts has recently been announced (Senkan, S. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 791). Whilst the reaction chosen for study—the dehydrogenation of cyclohexane to benzene—may not appear too exciting, the methodology is certainly novel. An array of catalyst pellets, based on a ternary mixture of Pt/Pd/In absorbed on alumina, was prepared combinatorially without human intervention. The library of 66 catalysts was tested in an array microreaction system, with product analysis being via in situ resonance-enhanced multiphoton ionisation spectroscopy (REMPI). The REMPI method is said to combine the speed of optical methods with the selectivity of mass spectrometry and allows the high-speed screening of large solid-state catalyst libraries for activity and selectivity without the need to remove the samples.

The present study found that, whereas it was previously known that both Pt and Pd individually catalyse the dehydrogenation of cyclohexene to benzene and In does not, a combination of 0.8% Pt, 0.1% Pd, and 0.1% In gives the best results of all combinations studied.

One of the most interesting aspects of the paper is the final paragraph, in which the authors tabulate the approximate times associated with execution of each step in the preparation, processing, and screening of the catalyst library. A total of 2.5 days work was required (the equipment working 24 h per day, of course), compared to months by traditional

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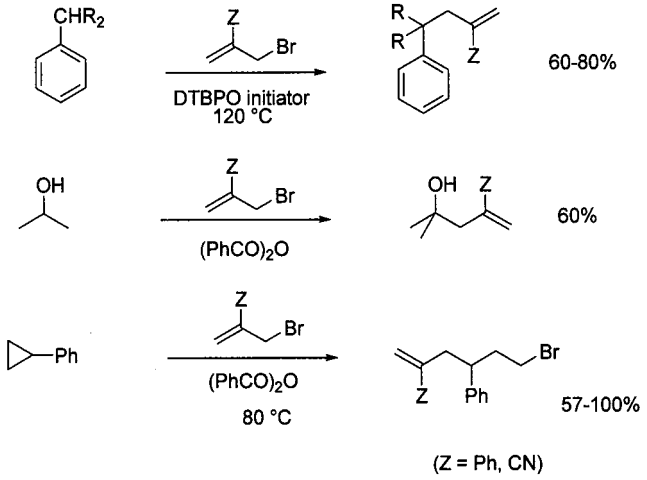
Scheme 1



methods. The 2.5 days could also be reduced considerably by having several array microreactors in parallel rather than the same equipment, which could only examine 17 catalysts at a time, being used sequentially.

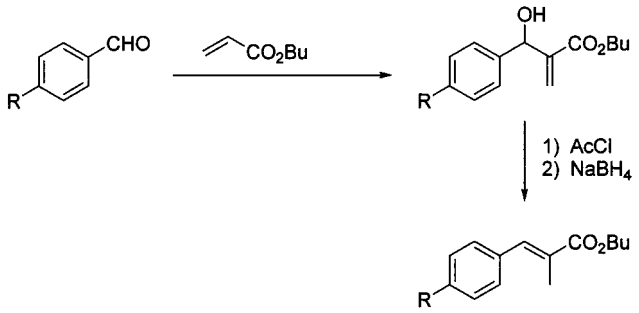
There are a number of ways to solve the problem of reacting a hydrophilic substrate with a salt (usually inorganic) which is only soluble in water. One can use aqueous−organic solvents, but, particularly on a large scale, hydrolysis may be a serious side reaction compared to substitution. Phase-transfer catalysis is often the method of choice, but another approach is to use a microemulsion. Two recent papers from the group of Johnston (*J. Org. Chem.* **1999**, *64*, 1201 and 1207) describe the use of water−carbon dioxide microemulsions for organic synthesis. Only 1.5% surfactant is needed to form the microemulsion, and the emulsion is easily broken up (for workup) by decreasing the pressure. It is suggested that this technique may be valuable for very fast (diffusion-controlled) reactions, where good mixing is required.

A further review on the use of fluorous phase separation techniques in catalysis has appeared (de Wolf, E. *Chem. Soc. Rev.* **1999**, *28*, 37−41). This complements the earlier review of Curran, which appeared last year (*Angew. Chem., Int. Ed.* **1998**, *37*, 1174). The latest work discusses the theoretical aspects as well as synthetic, including phase behaviour, miscellar critical temperature, and micelle formation. The authors in their conclusion, however, suggest that much more work on phase distribution of fluorous compounds, catalyst leaching due to nonzero solubility of the fluorous catalyst in the hydrocarbon phase, and factors which affect the solubility of fluorous compounds in the fluorous phase (particularly structure) will be required before the technique is exploited in industry.

A new radical process which gives moderate to good yields in C−C bond formation has been described (Tanko, J. M.; et al. *Angew. Chem., Int. Ed.* **1999**, *38*, 159). The reaction takes place with simple molecules such as aromatic hydrocarbons via a free radical chain process involving a bromine atom. The methodology is extended to reactions of alcohols and cyclopropanes (Scheme 1).

Organo copper reagents are important for synthesis of C−C bonds and have been used in a number of industrial processes. The structure of the cuprates, particularly those made by the Lipschutz method involving CN, has been the subject of some debate, and the term "lower order" cyano cuprate has been used to designate the species RCu(CN)Li, whereas "higher order" cuprates were compounds with the postulated structure $[R_2Cu(CN)]^{2-}2Li$. A recent article (Krause, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 79) discusses recent structural evidence based on solid-state data and comes to the conclusion that it is still not possible to completely answer the controversy, despite evidence against "higher order" species. Further kinetic and spectroscopic data may be required to finally solve this one.

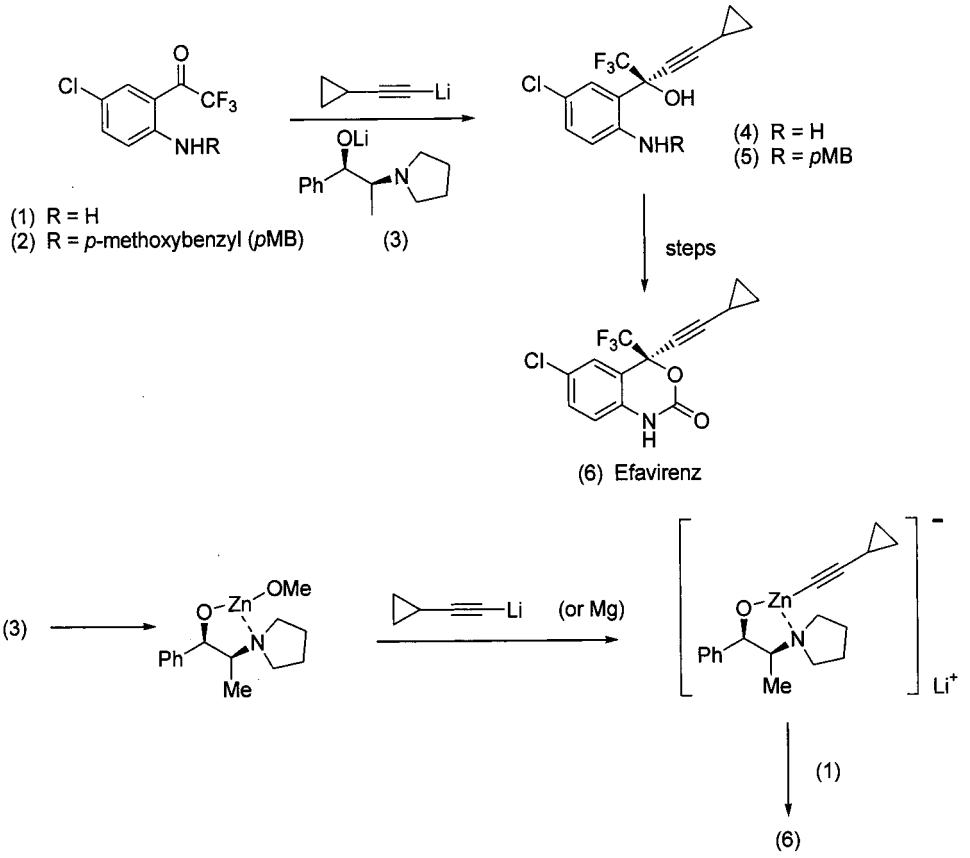
Scheme 2



In previous Highlights, I have commented on the utility of the Baylis−Hillman reaction. The products from these reactions are versatile synthetic intermediates. A recent report (Basavaiah, D.; et al. *J. Org. Chem.* **1999**, *64*, 1197) describes their conversion into *E*-α-methyl cinnamic acids (Scheme 2).

Efavirenz (**6**) is a potent non-nucleoside HIV reverse transcriptase inhibitor which has recently been approved for the treatment of AIDS. The key step in the synthesis of the drug is an enantioselective addition of cyclopropylacetylide to a protected ketoaniline (Scheme 3), but whilst early results showed very high enantioselectivity, the process required 2.2 equiv of lithium cyclopropylacetylide with 2.2 equiv of (1*R*,2*S*)-*N*-pyrrolidinylephedrine alkoxide as chiral controller and a very low temperature (−60 °C). As far as manufacture of Efavirenz is concerned, the need to protect the aniline and then deprotect at a later stage is also inefficient. It was suggested that the free aniline group is deprotonated by the

Scheme 3

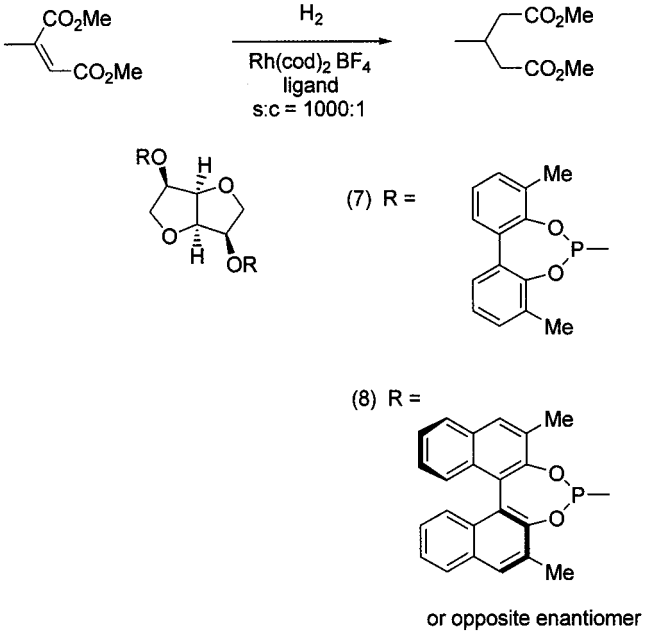


lithium cyclopropylacetylide, and this causes poor yields unless the group is protected. Workers at Merck Process Research Labs in Rahway, NJ (Tan, L.; et al. *Angew. Chem., Int. Ed.* **1999**, *38*, 711), have recently found that complexation of the lithium cyclopropylacetylide with zinc alkoxide lowers the basicity and allows reaction with the unprotected aniline (**1**) to occur in toluene−THF at room temperature (83% yield, 83% ee). The reaction was further optimised by varying the chiral auxiliary, counterion, and an achiral additive such as neopentyl alcohol, which appears to exert a steric effect on the selectivity. The reaction has been carried out on a kilogram scale and is the basis of the most efficient synthesis of Efavirenz to date.

In a novel approach to designing homogeneous catalysts for asymmetric reduction, the group of Reetz at the Max Plank Institute in Mulheim, Germany, has discovered that, in a series of closely related diphosphinite-rhodium catalysts, best results are achieved with a ligand (**7**) which has conformational flexibility when compared to those with fixed chirality (binaphthol derivitives, **8**). In the hydrogenation of dimethyl itaconate (Scheme 4), the highest ee was obtained with catalyst **7**, which is free to rotate around the biaryl unit. It is suggested that "in situ" selection between conformationally diastereomeric catalysts can take place, and this opens up an opportunity to design new catalysts based on similar principles. The chiral selectivity-determining ligand need not (and cannot) be separated into antipodes.

Asymmetric oxidation of sulphides to sulphoxides occurs with hydroperoxides in the presence of titanium complexes of trialkanolamines (Nugent, W.; et al. *Pure Appl. Chem.*

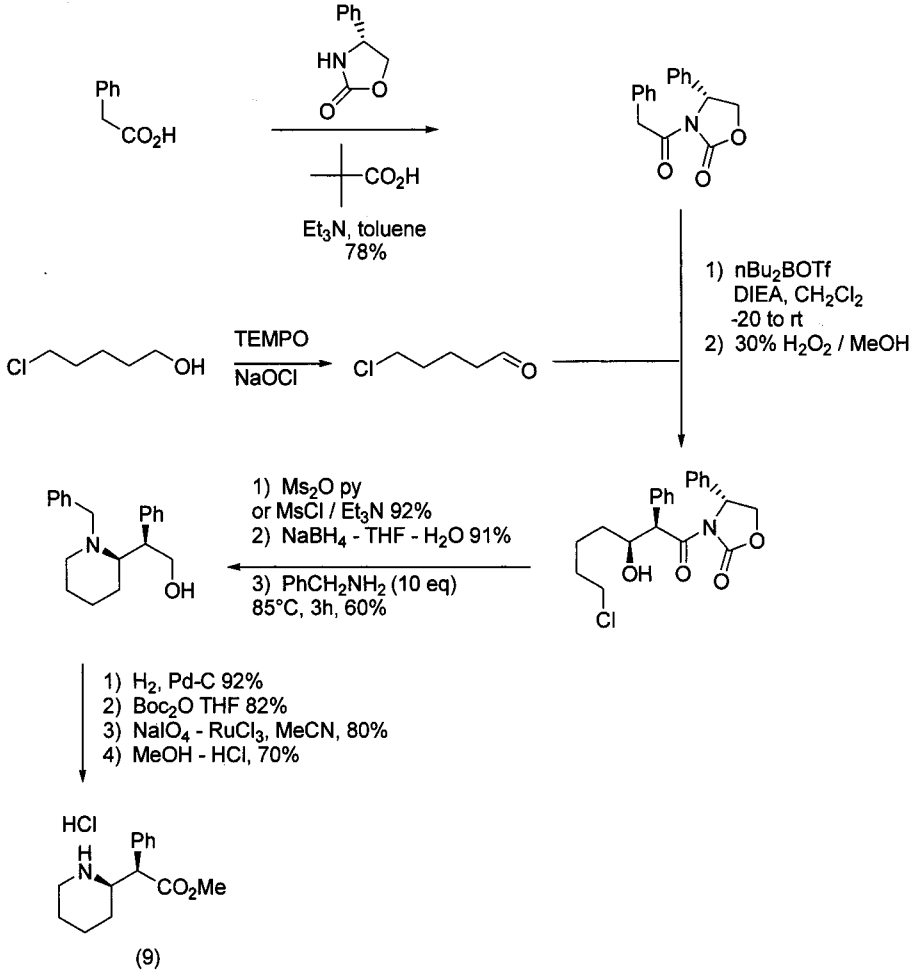
Scheme 4



1998, *70*, 1041). A new paper from the same group (Bonchio, M.; et al. *J. Org. Chem.* **1999**, *64*, 1326) reports that analogous zirconium complexes give good ee's (80−90%) but the opposite selectivity compared to the titanium complexes.

The drug Ritalin hydrochloride (**9**) is a mild nervous system stimulant marketed for the treatment of children with attention deficit hyperactive disorder as a single threo

Scheme 5



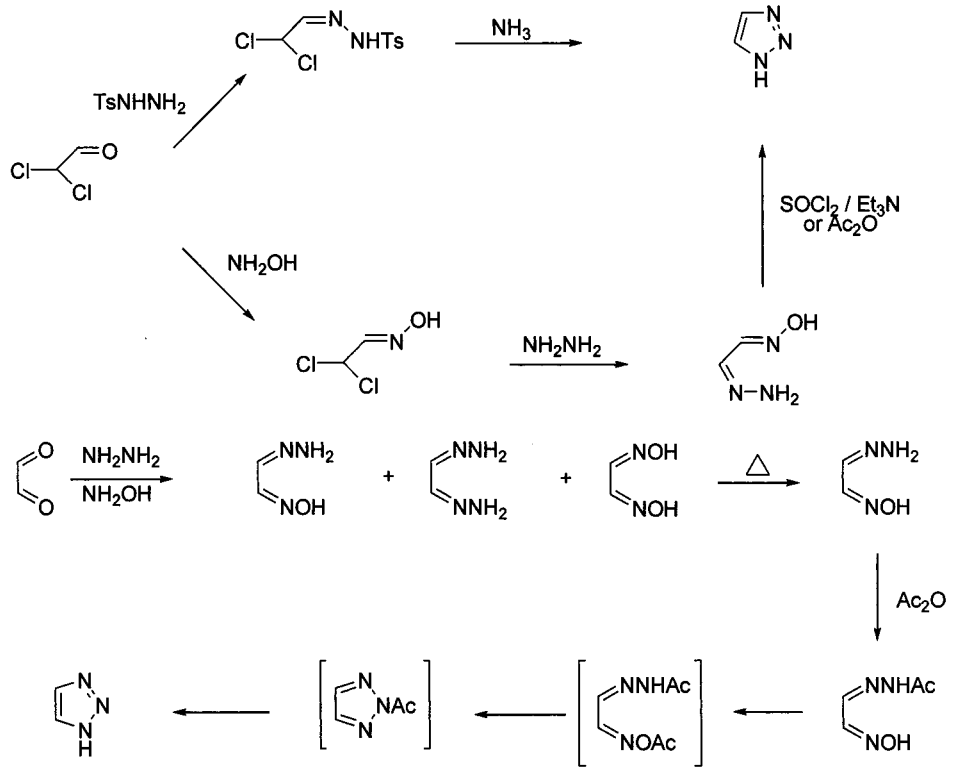
(9)

diastereoisomer but in a racemic form. Since the *RR* isomer is reported to be much more active than the *SS* isomer, a "racemic switch" has been suggested, and a number of resolution methods were published or patented in 1998. A synthesis from resolved D-pipecolic acid has also been published. Now workers at Novartis (Prashad, M.; et al. *J. Org. Chem.* **1999**, *64*, 1750) have developed an enantioselective synthesis of **9** which may be suitable for the manufacture of the drug on a commercial scale. The route is shown in Scheme 5. It uses the relatively inexpensive chiral auxiliary *R*-4-phenyl-2-oxazolidinone to introduce the chiral centres in the correct relationship. The synthesis, however, takes nine steps from phenylacetic acid, and the overall yield of 13%, together with the use of some expensive reagents, is unlikely, in my view, to be economically competitive with resolution methods. This may depend, however, on the ability to recycle the unwanted enantiomers, always a difficulty with two adjacent stereogenic centres to racemise.

During recent correspondence with an author of a possible future article, I was reminded of some papers on resolution I had missed in 1998. Whilst I discussed in these Highlights the important—some would say revolutionary—paper from de Vries (*Angew. Chem., Int. Ed.* **1998**, *37*, 2349), there was a follow-up discussion in a subsequent issue from Professor Collet (Lyon), in which he discusses the reasons why using a mixture of resolving agents should give such good results (*Angew. Chem., Int. Ed.* **1998**, *37*, 3239). The two papers I had missed related to controlled design of resolutions (Ebbers, E.; et al. *Tetrahedron: Asymmetry* **1998**, *9*, 2745) and calculation of the efficiency of purification by crystallisation of ideal multicomponent stereoisomeric mixtures (Smith, A. *Tetrahedron: Asymmetry* **1998**, 9, 2925).

A further paper I meant to highlight in 1998 is now discussed, since it contains some important hazard information (Haratha, K.; et al. *SynLett* **1998**, 431). The paper refers to an interesting new process for the manufacture of 1,2,3-triazole, discovered at the research laboratories of Ube Industries, Japan. In the early 1990s, workers at Ube patented a method of making 1,2,3-triazole from dichloroacetaldehyde tosylhydrazone in a one-pot reaction with ammonia (Scheme 6). This reaction was convenient and safe for scale-up and was used for manufacture. It is, however, not so atom efficient, and methods from glyoxal would most likely be more cost-effective. Initial efforts were aimed at the synthesis of the unknown glyoxal monohydrazone monooxime; eventually this was also prepared from dichloroacetaldehyde. Conditions were found where the simple reaction of glyoxal and an equimolar mixture of hydroxylamine and hydrazine gave a 1:1:1 mixture of bisoxime bishydrazone and monooxime monohydrazone; surprisingly, both the bisoxime and the bishydrazones disproportionate on heating to give the desired monooxime monohydrazone. Reaction of this with

Scheme 6



either thionyl chloride or acetic anhydride gives the desired 1,2,3-triazole.

The intermediates in these reactions (Scheme 6) are—as expected from their high oxygen and nitrogen content and low molecular weight—relatively hazardous. DSC detected onsets of exotherm just above 100 °C, with heat evolutions of 616−952 cal/g.

The recent explosion in the United States at the Concept Sciences Chemical Plant in Hanover, PA, which killed five people, highlights the dangers of working with reactive substances. It is believed that the explosion occurred during the distillation of hydroxylamine in the presence of KOH (*The Chemical Engineer* **1999**, 25 Feb, 3).

There is much talk these days of using microwave heating for organic processes (in the laboratory, at least). A footnote in a recent paper (Bremberg, U.; et al. *J. Org. Chem.* **1999**, *64*, 1082) reminds us that flash-heating organic reactions in a confined space, such as under microwave irradiations, can be dangerous unless equipment is fitted with a pressure-relief device.

Finally, as I mentioned in an Editorial last year, the Royal Society of Chemistry has launched a new journal, *Green Chemistry*, and the first issue of that journal has now appeared. Each of the articles is put into a "green context" by the inclusion of a short summary from the editors. Articles are relatively short, but there is much of interest to the process chemist, including solvent-free organic synthesis, Diels−Alder reactions in ionic liquids, and a short review, "Green chemistry: challenges and opportunities", by the editor, James Clark. I quote his penultimate sentence in this article: "Synthetic chemists must be more prepared to work with catalyst chemists who must, in turn, work more closely with chemical and process engineers." I wholeheartedly agree!

Dr. Trevor Laird

Editor

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