

## Highlights from the Literature

### A Selection of Recent Papers Chosen by the Editor

The discovery of new chemical reactions is always of interest to process R & D chemists so that an automated way of searching for the key reaction that one needs to efficiently manufacture a molecule would be wonderful. In a stimulating article entitled “Discovery of New Multi-Component Reactions with Combinatorial Methods,” Lutz Weber and colleagues from Morphochem AG (*Synlett* 1999, 366) discuss concepts and methodologies. The technique has been used to optimise reactions, too, for example, the Ugi 4-component coupling reaction using eight different solvents in combination and varying additions times of the components in a series of 1 572 864 combinations. Using feedback cycles of synthesis and screening, the yield was increased from 13 to 78%.

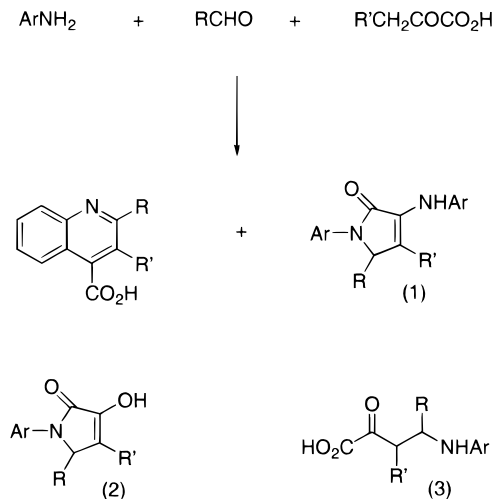
The three-component reaction of anilines, aldehydes, and pyruvic acid derivatives—the Doebner synthesis of quinolones—carried out in ethanol at room temperature is known to give not only quinolines but also arylamino-dihydro-pyrrol-2-ones (1), a four-component product. Using a combinatorial approach, however, it was shown the certain substituents give rise to two other reaction types, leading to products 2 and 3, depending on the conditions (Scheme 1).

The hydrolysis of amides under mild conditions can be a difficult process and enzyme methodologies are often the only way to achieve a selective process. Amides are stable species; it has been estimated that the half-life for peptide hydrolysis under neutral conditions at 25 °C is 7 years! In an aim to mimic nature a group from Brown University in Providence, RI, have announced that simple molecules such as cyclohexanone and particularly heterocyclic analogues (e.g., tetrahydropyranone) can increase the rate of amide hydrolysis by up to 10 000 times under aqueous conditions at 25 °C (Ghosh, M. et al. *Angew. Chem., Int. Ed.* 1999, 38, 514). The amides studied contained a thiol group, however, and it is suggested that interaction of the HS group with the carbonyl group plays a key role in the mechanism of amide hydrolysis.

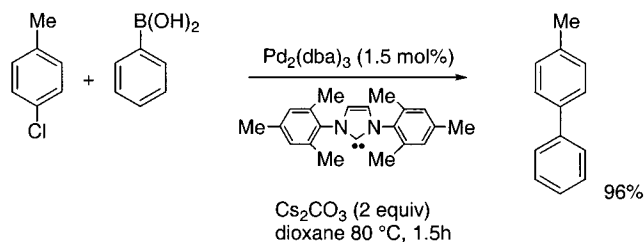
A new method of oxidation of  $\alpha$ -hydroxyketones has been discovered (Kirihara M. et al. *Chem. Commun.* 1999, 1387). Oxidation takes place in the presence of an oxygen atmosphere when vanadium catalysts are used—VOCl<sub>3</sub> seems to be the best—and  $\alpha$ -diketones are produced at room temperature using acetone or acetonitrile as solvent.

Highly active, non-phosphine catalysts for the Heck reaction have been discovered (Ohff, M. et al. *Chem. Commun.* 1999, 357). They are prepared simply by reaction of Pd(OCOCF<sub>3</sub>)<sub>2</sub> or Pd(Ac)<sub>2</sub> with imines such as Ph(CH<sub>3</sub>)C=NCHMe<sub>2</sub> or oxazolines. The complexes are very stable, are not oxygen sensitive (the reactions can be carried out without a nitrogen atmosphere), and lead to turnover numbers of 10<sup>6</sup>

Scheme 1



Scheme 2

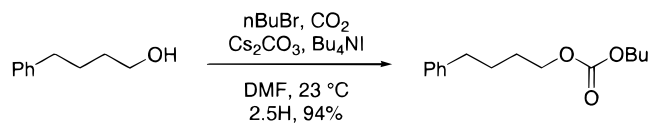


with a rate of  $8 \times 10^4$ /h in the reaction of acyliodides with methyl acrylate. Aryl bromides can also be used, but not chlorides, and a turnover number of 137 100 was found.

Following on from the reports of Buchwald and Fu on the development of catalysts which give good yields of Suzuki-coupled products using inexpensive aryl chlorides, the group of Nolan in New Orleans (Zhang, C. et al. *J. Org. Chem.* 1999, 64, 3804) have found that nucleophilic N-heterocyclic carbenes (so-called “phosphine mimics”) act as good ligands for palladium catalysis of the Suzuki reaction with aryl chlorides. The important observation is that addition of caesium carbonate as base results in a rate increase and a high yield of product compared to sodium or potassium carbonates (Scheme 2). The process was tolerant of a wide variety of functional groups in either aromatic ring.

Alkyl carbonates would probably be more widely used if there were a good versatile synthetic method. Now there is! Reaction of alcohols with carbon dioxide in the presence of caesium carbonate, followed by alkylation with an alkyl halide gives excellent yields of unsymmetrical alkyl carbonates (Kim, S-I. et al. *J. Org. Chem.* 1999, 64, 4578). Use of chiral alcohols did not lead to any racemisation (Scheme 3).

### Scheme 3



### Scheme 4

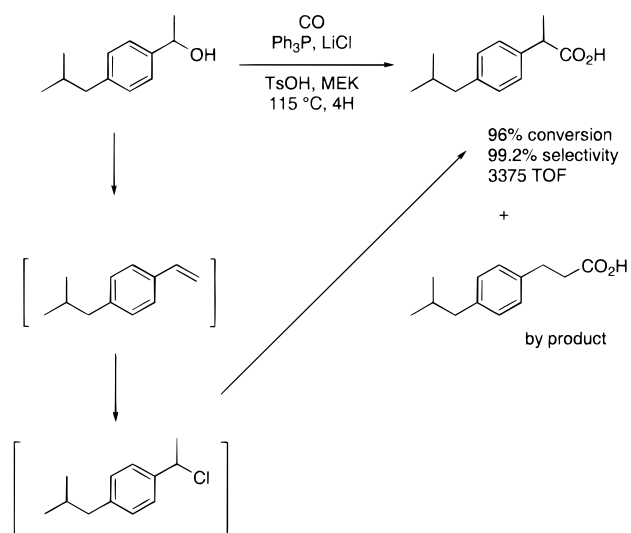


The demand for polyurethane products continues to grow prompting chemists to search for new routes to isocyanates which avoid the use of phosgene. Typically carbonylation methodologies or synthesis of carbonates followed by elimination have been used. A recent paper (Saylik, D. et al. *J. Org. Chem.* **1999**, *64*, 3940) describes reactions of primary aliphatic and hindered arylamines with carbon dioxide under Mitsunobu conditions, giving high yields of isocyanates (Scheme 4). At present the reaction is stoichiometric in phosphine and azodicarboxylate, but yields the phosphine oxide as byproduct. The question is—can it be made catalytic?

The carbonylation of 1-arylethanol has been used for the synthesis of anti-inflammatory drugs such as ibuprofen, naproxen, etc. The Hoechst Celanese manufacturing process for ibuprofen is based on an efficient palladium-catalysed carbonylation of 1-(4-isobutylphenyl)ethanol, but it appears that the high selectivity (98%) can only be achieved at high pressure. A group from the National Chemical Laboratory in Pune, India, have now found that supported palladium catalysts, in combination with  $\text{PPh}_3$ ,  $\text{LiCl}$ , and  $\text{TsOH}$  give high selectivity (99.5%) at low pressure and with better turnover (Jayasree, S. et al. *Chem. Commun.* **1999**, 1067). Although the reaction appears to occur by heterogeneous catalysis, and there is no Pd in the liquid phase at the end of the reaction, when samples of the reaction mixture (at  $115\text{ }^\circ\text{C}$ ) were taken, there was significant Pd leaching. This indicates that the reaction is probably homogeneous. The authors favour the mechanism in Scheme 5, via the chloro-intermediate, although no evidence for the presence of this intermediate was provided. The process allows for efficient recycling of the catalyst.

One would imagine that there was little to discover about the polymerisation of olefins, but scientists continue to find new catalysts which allow the fine-tuning of the polymerisation, and the resultant products may have somewhat different properties which can be exploited. After the metallocene catalysts of the 1980s came the nickel-diimine catalysts of the mid-1990s, marketed under the name Versipol by DuPont. As I mentioned in an earlier highlights issue, iron (and to a lesser extent cobalt) can also be used in catalysts, and a recent article from Vernon Gibson at Imperial College, London (Gibson, V. et al. *Chem. Br.* **1999**, July, p 20) in collaboration with BP Amoco Chemicals discusses ligand structure, mechanisms, and effect on products. This is a highly readable account of new chemistry, showing the importance of academe—industry collaboration. The final sentence is worth quoting: “...the only limitation to the discovery and application of new catalysts is the imagination

### Scheme 5



TOF = no. of moles of Ibuprofen produced per mole of metal per hour

of the co-ordination and organometallic chemist.”

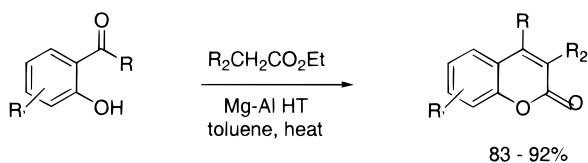
In an earlier review article, the team from Imperial College London examine in detail the “search for new-generation polymerisation catalysts” (Britovsek, G. J. P. et al. *Angew. Chem., Int. Ed.* **1999**, *38*, 428). The review highlights the recent advances in the discovery and development of non-group 4 metallocene catalysts, covering groups 3 (including lanthanides) to group 9. In the introductory section on catalyst activity the authors issue a “health warning” when comparing catalyst activities by groups of different researchers, “since experimentally determined values are **highly dependant upon the precise reaction conditions including stirring rate and reactor configuration**. Also, often little or no information is given about the kinetic profile or lifetime of the catalyst, with the consequence that a short polymerisation run with a catalyst that is active only for 30 seconds before dying may give an inflated figure of merit compared to an activity reported for a 1-hour run.” How refreshing for authors to come out with such statements!

Work by the group of Brookhart (Small, B. L. et al. *J. Am. Chem. Soc.* **1998**, *120*, 7143) had also showed how tailoring the catalyst can influence the properties—especially the MW of the resultant polyolefins. A recent review from Alison Bennett of DuPont (*CHEMTECH* **1999**, July, p.24) summarises the current state of the art in iron and cobalt catalysis of olefin polymerisation, focussing on the use of bis imine ligands.

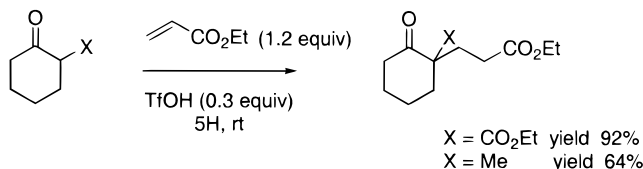
For a comprehensive review of transition metal catalysed living-radical polymerisation, used in the polymerisation of acrylates, styrenes, etc., see the June issue of *CHEMTECH* (Sawamoto, M. et al. p 30).

The dimerisation and oligomerisation of higher olefins such as I-butene in the presence of group 8 transition metals gives typically mixtures of branched chain isomers. Linear  $\text{C}_8$  dimers are highly desirable products since they could be converted to  $\text{C}_9$  plasticizers, exhibiting better thermal properties than those produced from branched  $\text{C}_8$  olefin feedstocks.

### Scheme 6



### Scheme 7



In the past the best catalyst was Ni (cod) (CF<sub>3</sub>CO)<sub>2</sub>CH<sub>2</sub> with a turnover frequency of 500 h<sup>-1</sup> at 90° but the product quality (overall dimer selectivity 85%; linear dimer selectivity 75%), high ligand costs and difficult catalyst recovery have prevented industrial development. Use of a buffered ionic liquid as solvent, however, leads to enhancement of activity of several catalysts, retention of high selectivity, and easy catalyst recovery and recycle (Ellis, B. et al. *Chem. Commun.* **1999**, 337). The best solvent is made by mixing 1-butyl-4-methyl pyridinium chloride with AlCl<sub>3</sub> and then buffering with organic bases such as *N*-methylpyrrole, pyrrole, quinoline, and pyridine derivatives.

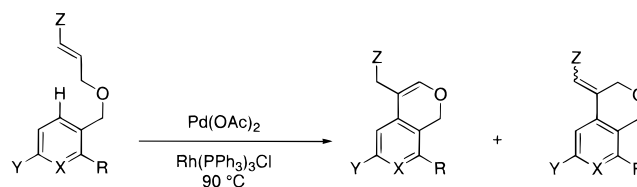
In a short review on alkyne metathesis as a synthetic tool, the possibilities for producing polymers with a regular distribution of acetylene groups is examined (Bunz, U. H. F. et al. *Angew. Chem., Int. Ed.* **1999**, 30, 478).

Hydrotalcites (HT) are a relatively new family of catalysts represented by the general formula Mg<sub>6</sub>Al<sub>2</sub>(OH)<sub>16</sub>·H<sub>2</sub>O. Upon calcination at ~700 K, highly basic mixed metal oxides are formed. These oxides are useful in base-catalysed processes such as Knoevenagel condensation to form coumarins (Scheme 6) (Ramani, A. et al. *Green Chem.* **1999**, 1, 163).

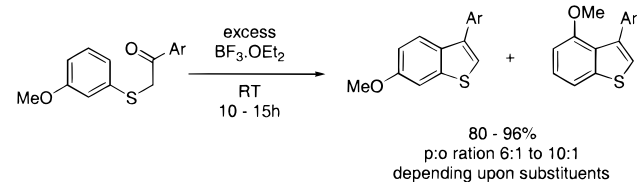
A recent review examines new approaches to rate enhancement in heterogeneous catalysis (Hutchings, G. *Chem. Commun.* **1999**, 301). Detailed discussion of two reactions is included in the review; enantioselective hydrogenations using cinchona-modified platinum and modification of zeolites with chiral molecules leading to heterogeneous epoxidation and aziridination catalysts.

The Michael addition reaction is widely used for carbon-carbon bond-forming reactions but the conditions (base-catalysis) may mean that some functional groups are incompatible. In the 1990s, several groups have reported Lewis acid catalysts for the reaction and triflates of the lanthanide elements are often the preferred catalysts. In some cases, however, reactions are slow. It has now been found that triflic acid itself is a good catalyst for the reaction (0.3 equiv are required, thus catalyst is not strictly the correct term; use of 0.2 equiv leads to a much slower reaction!) and the process can be carried out without solvent when acrylates are the Michael acceptors (Scheme 7). The fast reaction is attributed to the enhancement of the nucleophilicity of  $\beta$ -ketoesters via their enol forms and also enhancement of the electrophilicity of the acceptor (Kotsuki, H. et al. *J. Org. Chem.* **1999**, 64, 3770).

### Scheme 8



### Scheme 9



A group from the Chemical Development department at Glaxo-Wellcome U.S.A. have reported on the use of rhodium complexes to synergistically act with palladium acetate in the Heck reaction of crotyl ethers to give benzopyrans. Selectivity is improved, rates are enhanced, and reproducibility is better (Bankston, D. *J. Org. Chem.* **1999**, 64, 3461). The temperature at which the catalysts are added and the concentration both affect the yield of products (Scheme 8). The combination of two precious metal catalysts, however, will make recovery more difficult and thus increases the cost of the process considerably.

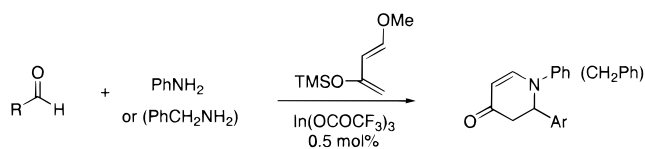
The integration of two techniques which are of interest to industry, namely, biphasic catalysis and supercritical carbon dioxide solvents for reactions such as hydrogenation has recently been published (Bhanage, B.M. *Chem. Commun.* **1999**, 1277). In the hydrogenation of cinnamaldehyde, for example in the scCO<sub>2</sub>·H<sub>2</sub>O system, the high solubility of H<sub>2</sub> in the CO<sub>2</sub> layer and of the catalyst [Ru-P(C<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>Na)<sub>3</sub>] in the aqueous phase eliminates mass transfer problems and gives better activity and selectivity.

Benzothiophenes are of industrial interest but the synthesis of 3-arylbenzothiophenes often causes problems, since acid conditions used in the synthesis often causes aryl migration leading to 2-arylbenzothiophene. It has now been found by workers at Merck, U.S.A. (Kim S. et al. *Tetrahedron Lett.* **1999**, 40, 2909) that the use of boron trifluoride etherate at room temperature is the best reagent for preparing 3-arylbenzo-thiophenes from  $\beta$ -ketosulphides (Scheme 9). Some of the ortho-cyclised product is obtained, but no aryl migration occurred.

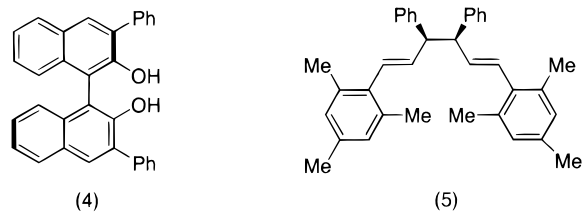
Indium is a metal which is increasingly being used as a catalyst, and transformations such as allylations, Reformatsky reactions, and cyclopropanations have all been reported as well as its use as a Lewis acid catalyst. The group of Frost at Bath, UK, (Ali, T. et al. *Tetrahedron Lett.* **1999**, 40, 5621) have found that indium triflate is an excellent catalyst for hetero Diels-Alder reactions between aldehydes (and imines) with dienes. Reactions are fast even at -20 °C. Imines can be generated "in situ" from aldehydes and amines and the reaction should be applicable to large-scale use or to parallel synthesis techniques (Scheme 10).

Whereas  $\beta$ -amino alcohols are excellent ligands for addition of Et<sub>2</sub>Zn to aldehydes, diols (with one or two

**Scheme 10**



exceptions) are poor. The group of Mikami at the Tokyo Institute of Technology (Ding, K. et al. *Angew. Chem., Int. Ed.* **1999**, 38, 4 97) has examined the effect of mixtures of a diol and a bis imine ligand, arguing that the nitrogen ligand will stabilise the complex because of strong co-ordination to the zinc. By high throughput screening methods, they examined five chiral diols and five chiral activators (di-imines) with results varying from 1 to 65% ee. In a second generation screen which involved more fine-tuning of the imine ligands, the reaction was optimised, giving 100% yield (90% ee), but the ee could be increased to 99% at  $-78^{\circ}\text{C}$ . The best combination was when diol ligand **4** and activator **5** were used.



Whilst in this example, the combinatorial approach gave a new catalyst combination for a known reaction, there is, in principle, no reason why catalysts could not be screened to discover new reactions, or to optimise a reaction of poor yield or selectivity. In the same issue, a group from Symyx Technologies, a company set up to exploit combinatorial approaches in materials science and catalyst production, have examined the optimisation of the catalyst for oxidation of CO to CO<sub>2</sub> (Cong, P. et al. *Angew. Chem., Int. Ed.* **1999**, 38, 484). High throughput parallel screening has also been used to optimise the choice of ligands in the ruthenium-catalysed asymmetric hydrosilylation of ketones (Moreau, C. et al. *Tetrahedron Lett.* **1999**, 40, 5617).

The removal of THP and THF protection groups often entails harsh acidic conditions which may damage other functionality in the molecule. The group of Markó at Louvain-la-Neuve, Belgium, recommend the use of ceric ammonium nitrate in catalytic amounts under neutral conditions in MeCN–borate buffer (Markó, I. E. et al. *Tetrahedron Lett.* **1999**, 40, 5613). Under these conditions no oxidation of aromatics, sulphides, olefins, alkynes, etc. takes place, and a wide variety of functional groups including esters, nitrites, ketones, halides is tolerated.

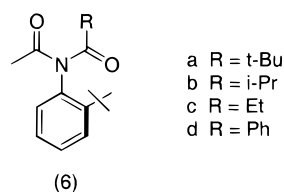
Very simple transfer reduction of ketones, using isopropanol as reducing agent, occurs under catalysis by a number of transition metals and is known to be dramatically accelerated by the presence of base (rate increase of  $10^4$ ). This process can be used in both directions, so Oppenauer oxidations are also viable. It has now been shown by the group of Backvall at Stockholm using NMR studies that reaction of the catalyst RuCl<sub>2</sub>(Ph<sub>3</sub>P)<sub>3</sub> with isopropanol in the

presence of base yields a ruthenium dihydride species and that there is an induction period until the active species is formed. Once the active species has been generated “in situ”, base is no longer required, and the reaction proceeds rapidly. The mono hydride species RuCl(H)(Ph<sub>3</sub>P)<sub>3</sub> is not active in this reaction (Aranyos, A. et al. *Chem. Commun.* **1999**, 351).

Reduction of malonate derivatives to the corresponding hydroxyester is usually difficult, unless enzymic processes are used. A new report, however, indicates that use of LiAl(O-*t*Bu)<sub>3</sub>H gives good results provided temperature and stoichiometry are optimised for each substituent (Ayers, T. *Tetrahedron Lett.* **1999**, 40, 5467). Diethyl malonate derivatives work better than the dimethyl analogues, significant over-reduction occurring in the latter case. Use of the Buchwald system (polymethylhydrosiloxane–Cp<sub>2</sub>TiH) gives slightly inferior results and requires reflux temperatures.

The production of single-enantiomers from achiral compounds continues to attract academic and industrial attention. The first report of an asymmetric reduction of cyclic enol acetates has recently been reported (although some acyclic enol acetates have previously been reduced using Duphos catalysts). The new procedure from the group at Penn State (Jiang, Q. et al. *Angew. Chem., Int. Ed.* **1999**, 38, 516) uses Rh(cod)<sub>2</sub>BF<sub>4</sub> in the presence of one of the PennPhos ligands discovered by this group. Hydrogenation of cyclic and acyclic enol acetates at RT for 24 h in the presence of the catalyst (approximately 1 mol %) gave quantitative yields of alcohols in 80–99% ee.

The compounds (**6a–d**) are chiral by virtue of restricted

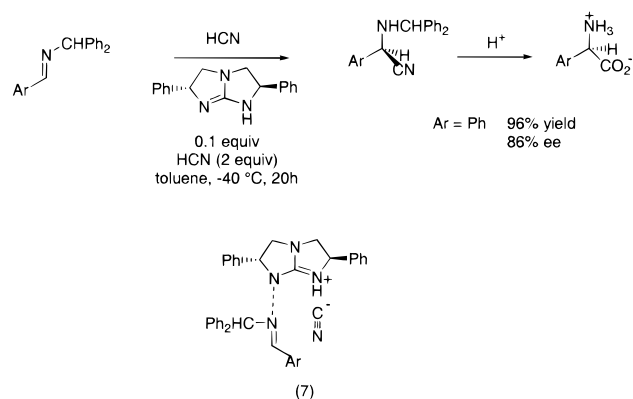


rotation about the C–N bond. Interestingly, the compound bearing the more bulky substituent *t*-Bu racemises fastest, indicating that this is more twisted around the *t*-BuCO–N bond (Kondo, K. et al. *Tetrahedron Lett.* **1999**, 40, 5577).

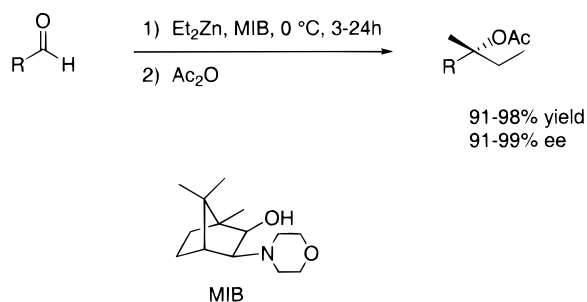
We normally imagine that chiral carboxylic acids can easily be resolved by crystallisation of salts with various single enantiomer amines, but occasionally this fails. It is suggested in a recent communication (Jourdain, F. et al. *Tetrahedron Lett.* **1999**, 40, 2509) that simply making the amide from the acid and resolving agent (e.g.,  $\alpha$ -methylbenzylamine) using, for example DCC, yields amides which can be easily separated by direct crystallisation. Acid hydrolysis then releases the free acid and allows recovery of the amine.

In my first highlight from the new journal, *Organic Letters*, launched by ACS in July, it should come as no surprise that the article comes from the group of E. J. Corey at Harvard (Corey, E. J. et al. *Org. Lett.* **1999**, 1, 157). The paper describes a novel catalytic enantioselective Strecker synthesis of  $\alpha$ -aminonitriles and aminoacids. The key feature of Corey’s process is the use of the chiral bicyclic guanidine (**7**), synthesised from (*R*)-phenylglycine, as catalyst. The

Scheme 11



Scheme 12



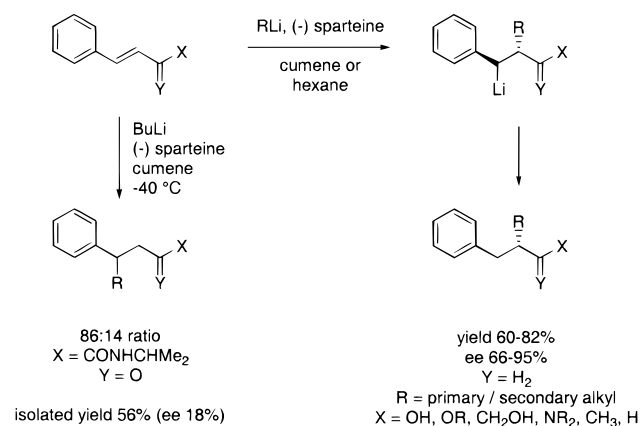
origin of the enantioselectivity is the pre-transition state assembly in which the 3-dimensional arrangement is pre-disposed to attack by CN from one face (Scheme 11).

A key aspect in the transition state is the  $\pi$ -stacking interaction between the two phenyl groups on the benzhydrylamine unit with the phenyl in the catalyst. Thus, changing to an imine with a benzyl or 9-fluorenyl group is deleterious, and changing to the bis-cyclohexyl analogue of the catalyst results in a 56% ee. The importance of Van der Waals attractive interactions involving non-polar groups in transition states is emphasised and provides a model for design of both new catalysts and new, enantioselective reactions using guanidine-type catalysts.

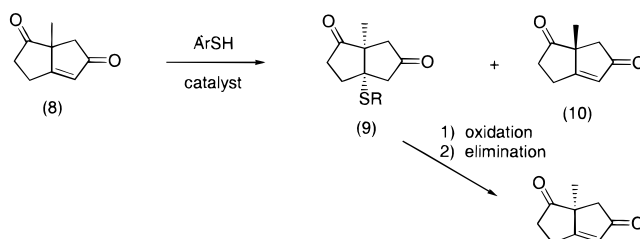
The addition of organozinc reagents to aldehydes catalyzed by enantiopure  $\beta$ -aminoalcohols can be regarded as the asymmetric counter-part of the Grignard reaction. There have been so many publications in this area but the original ligand (3-exo-dimethylaminoisoborneol) used by Noyori and co-workers is still used, despite it being somewhat air-sensitive and limited mostly to aromatic aldehydes. William Nugent from DuPont (*Chem. Commun.* **1999**, 1369) has now found that changing the NMe<sub>2</sub> group for a morpholine unit gives a crystalline derivative (MIB) which is much more air stable and has wider reactivity. Thus, not only aromatic and heteroaromatic aldehydes react with Et<sub>2</sub>Zn in the presence of MIB, but branched aliphatic aldehydes also give excellent results, too (Scheme 12).

The (-)-sparteine mediated enantioselective carbolithiation of cinnamyl substrates and of  $\beta$ -substituted styrenes is a well-documented reaction (Bremard, N. et al. *Tetrahedron Lett.* **1999**, 40, 3379 and references cited therein). However, there is an alternative—contra Michael addition mode—which is favoured with cinnamic acid derivatives when (-)-

Scheme 13



Scheme 14



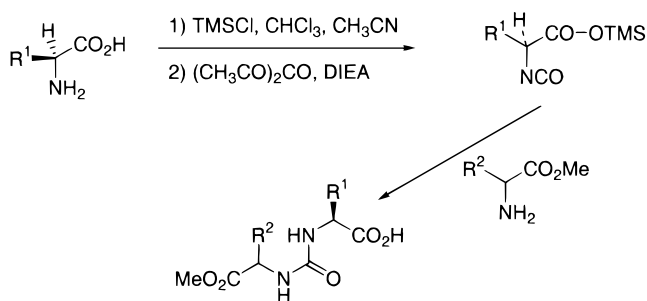
sparteine is in the reaction mixture in a non-polar solvent. However, enantioselection in this process is not as good as in the Michael addition (Scheme 13).

The efficient separation of enantiomers of a cyclic chiral  $\alpha$ - $\beta$  unsaturated ketone has been carried out using a catalytic kinetic resolution, based on asymmetric addition of thiols (Emori, E. et al. *J. Org. Chem.* **1999**, 64, 5318). The method uses the technique previously reported from the group of Shibasaki (*J. Am. Chem. Soc.* **1998**, 120, 4043). Thus, addition of thiols (e.g., *tert*-butyl-thiophenol) to the compound **8** in the presence of aluminium lithium bis(*R*)-binaphthoxide gave **9** (47% yield, 78% ee) and **10** (47% yield, 79% ee). The former compound could be reconverted to the enantiomeric  $\alpha$ - $\beta$ -unsaturated ketone (Scheme 14). Addition of phenols such as 4-methoxyphenol gave the best results—presumably by modification of the structure of the active catalyst.

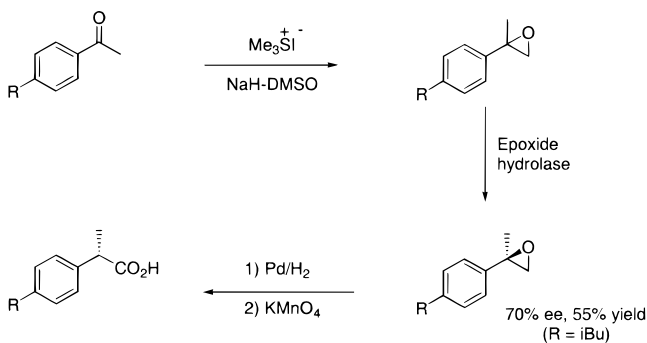
*N*-(Carbonylamino)amino acids can now be prepared in a one-pot sequence directly from  $\alpha$ -amino acids by initial in situ protection of the acid as its TMS derivative, isocyanate formation using triphosgene, and coupling with an amino acid ester (Weberth, F. J. *Tetrahedron Lett.* **1999**, 40, 2895), see Scheme 15.

A hot topic in synthesis is the preparation of optically pure epoxides, and there are a number of methods using catalytic asymmetric synthesis or kinetic resolutions which are applied commercially. Epoxide hydrolases are enzymes which have the potential to compete with chemical methods, but enantiomeric purities are still on the low side. This methodology has been used to make single enantiomer ibuprofen (Cley, M. et al. *J. Org. Chem.* **1999**, 64, 5029) as shown in Scheme 16. Whilst this will never compete with resolution methodologies, the use of an alternative asymmetric epoxidation strategy may be useful for more complex

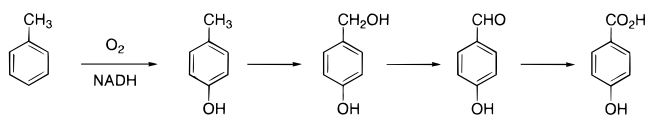
### Scheme 15



### Scheme 16



### Scheme 17



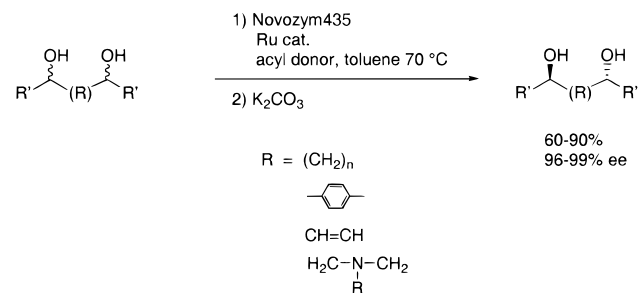
substrates where the enzyme may discriminate better than other reagents.

*p*-Hydroxybenzoic acid is made in about 7000 tonnes per annum mostly by Kolbe–Schmidt carboxylation of phenol, which is energy intensive, is not very selective, and generates lots of waste. A recent communication reports progress on a more environmentally friendly route, involving the bio-oxidation of toluene (Miller, E. S. et. al. *Green Chem.* **1999**, *1*, 143). The oxidation is rather slow, but very selective, and uses no organic solvents other than the toluene raw material. The strain of genetically engineered *Pseudomonas putida* used is capable not only of hydroxylating toluene but also of further oxidising the methyl group (Scheme 17).

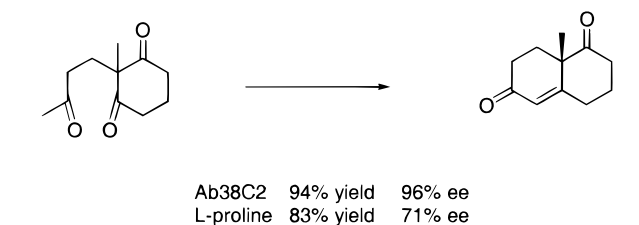
The combination of enzymic catalysis with an organo-metallic catalysed isomerisation has been reported by a number of groups to give excellent results in dynamic kinetic resolution. A recent report from the group of Backvall in Sweden (Persson, B. A. et al. *J. Org. Chem.* **1999**, *64*, 5237) provides full details for the optimal synthesis of single enantiomer 1,4-diols starting from the *DL*/*meso* mixture (Scheme 18).

Catalytic antibodies were in the news several years ago, but for organic process chemists, the potential has not been realised in terms of synthetic utility. Some of these antibodies are now commercially available so that chemists may be more willing to try them out as asymmetric catalysts. The group of Lerner (List, B. et al. *Org. Lett.* **1999**, *1*, 59) compare results on aldol cyclodehydrations using an aldolase

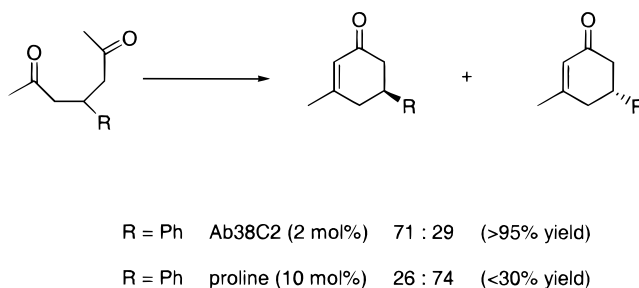
### Scheme 18



### Scheme 19



### Scheme 20



antibody 38C2 with those where proline is used as catalyst (Scheme 19).

Interestingly, in contrast to Scheme 19 with some substrates the catalytic antibody and proline give different enantiomers (Scheme 20).

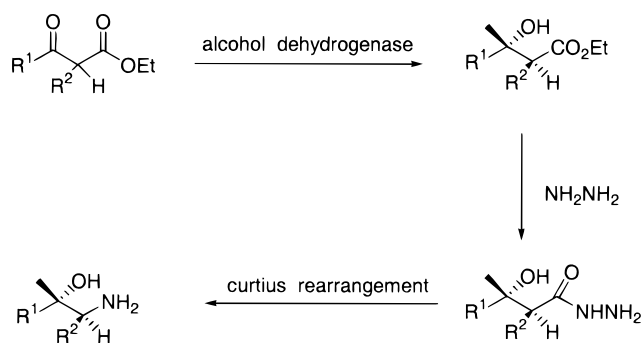
In general, product yields and purities were better than with proline, and reactions were much faster.

A provocative article entitled “Biocatalysis at commercial scale: myths and realities” by David Rozzell from Biocatalytic Inc. (*Chim. Oggi* **1999**, May/June, p 42) makes interesting reading. He discounts the myths surrounding biocatalysis, namely that enzymes are too expensive, unstable, and have low productivities, that co-factors are difficult to recycle, and that enzymes do not catalyse INTERESTING industrial reactions, by citing many examples including some from his own work. One notable example involves the stereoselective reduction of ketoesters—these products can then be converted to aminoalcohols (see Scheme 21) useful as building blocks for the synthesis of HIV protease inhibitors.

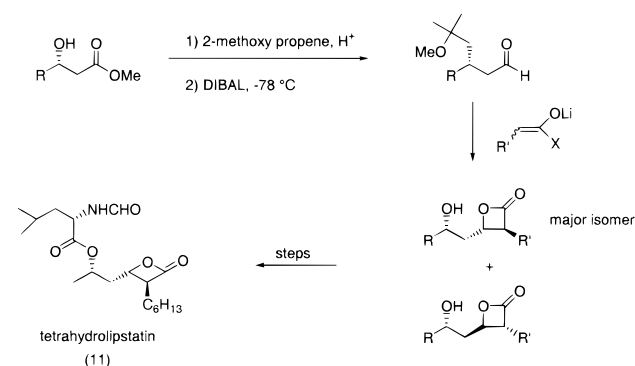
An efficient three-step protocol for the synthesis of  $\beta$ -lactones, such as the anti-obesity drug, tetrahydrolipstatin (**11**) has recently been published (Wedler, C. J. *J. Org. Chem.* **1999**, *64*, 5301). The methodology uses a tandem aldol-lactonisation strategy (Scheme 22).

A novel one-step diastereo and enantioselective formation of *trans*- $\beta$ -lactams from commercially available 3-(*S*)-hydroxy- $\delta$ -lactone has been reported from a process R & D

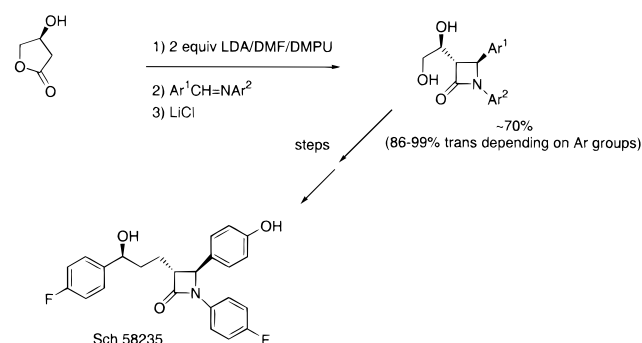
### Scheme 21



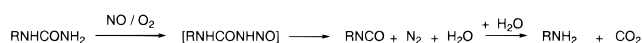
### Scheme 22



### Scheme 23



### Scheme 24

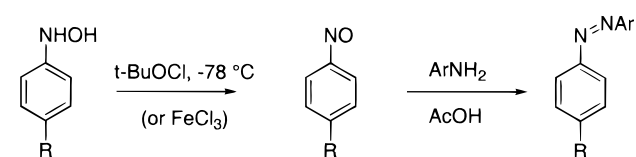


group at Schering-Plough, U.S.A. (Wu, G. et al. *J. Org. Chem.* **1999**, *64*, 3714). The methodology has been used as the key step on an efficient synthesis of the potent cholesterol absorption inhibitor Sch 58235 (Scheme 23).

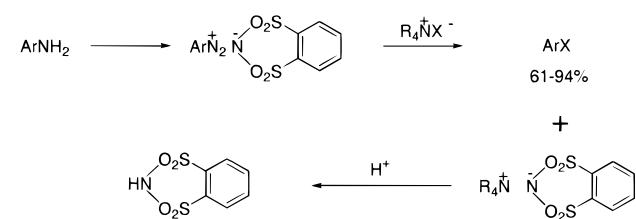
Ureas know to be quite stable compounds so have not been used as protection groups for amines because of the vigorous hydrolysis conditions required. Workers at the University of Montpellier, France, (Coll, H. et al. *Tetrahedron Lett.* **1999**, *40*, 3355) have discovered that nitrosation of mono alkyl ureas in water leads to smooth conversion to the alkylamines with nitrogen and carbon dioxide as the only byproducts. The reaction presumably proceeds via the *N*-nitrosourea and isocyanate. No racemisation occurs in the R group so that the method is applicable to peptides (Scheme 24).

Azo compounds are valuable in industry not only as dyes and photographic chemicals. They have also been extensively

### Scheme 25



### Scheme 26



used in the area of nonlinear optics (NLO) often displaying higher hyperpolarisabilities and thermal stabilities than their stilbene counterparts. Of course, they are usually made by standard diazonium coupling techniques, but other methods, such as the condensation of aryl nitroso compounds with amines, are occasionally used. However, nitroso compounds are not always easy to synthesise, and the methods used in the past have disadvantages. A new method of oxidising arylhydroxylamines to nitroso analogues uses *tert*-butylhypochlorite as oxidant (Scheme 25)—high yields of nitroso compounds are produced (Davey, M. H. *J. Org. Chem.* **1999**, *64*, 4976). In contrast, many other oxidising agents give azoxy compounds instead of nitroso.

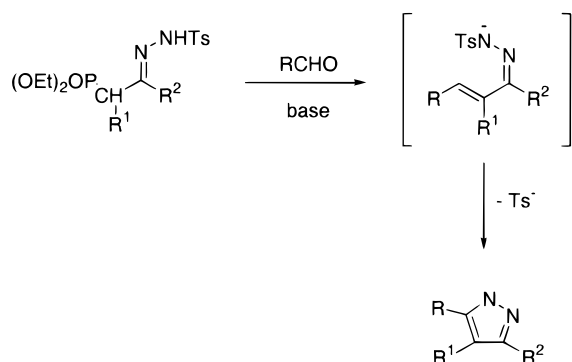
The conversion of aryl diazonium halides to aryl halides by heating in the presence of copper salts is a well-known industrial process but doesn't always give high yields and, depending on the way the process is carried out, can have safety problems owing to the instability of the diazonium salt. A recent paper from a group in Turin (Barbero, M. et al. *J. Org. Chem.* **1999**, *64*, 3448) suggests that use of the diazonium *O*-benzenedisulphonamide, which is an extremely stable diazonium salt, under a variety of conditions, gives good to excellent yields of aryl halides. The *O*-benzenedisulphonamide can be easily recycled (Scheme 26).

In previous highlights I have mentioned the use of methylrhodium trioxide (usually referred to as MTO) in a number of oxidations. It has now been found that MTO, in combination with H<sub>2</sub>O<sub>2</sub> can be used in place of other oxidants (e.g., CrO<sub>3</sub>) in the industrially important oxidation of 2-methyl naphthalene to the corresponding quinone (Hermann, W. et al. *J. Mol. Cat. A* **1999**, *138*, 115) and that selectivity for oxidation of the methyl-substituted ring is high (~89%).

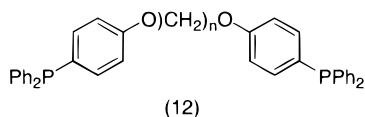
In a search for regiospecific ways to make pyrazoles—important intermediates for drugs, agrochemicals, and colour chemicals, workers at Sigma Tau (Italy) have examined [1 + 4] approaches using  $\beta$ -tosylhyrazono phosphonates in a counterpart of a Horner–Emmons condensation (Almirante, N. et al. *SynLett* **1999**, 299). The resultant one-step reaction gives polysubstituted pyrazoles in good to moderate yields (Schemes 27).

The major problem with industrial scale Wittig reactions is the generation of byproduct triphenylphosphine oxide, its

**Scheme 27**

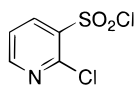


separation and recycle by reduction methodologies. A recent report suggests that a water soluble phosphine, based on the polyethylene glycol system (**12**) gives good results when



quaternised with alkyl halides and reacted under aqueous conditions with aldehydes in the Wittig reaction. The resultant water-soluble phosphine oxide is easy to remove and recycling can be achieved by reduction with alane (Experimental details of this paper are not available in the hard copy of *J. Org. Chem.* only from the Web).

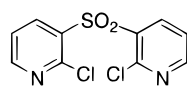
An article in *Chemical Communications* from Gary Sharman of AstraZeneca, entitled “Development of a selective TOCSY experiment and its use in analysis of a mixture of related compounds” excited my interest (Sharman, G. J. *Chem. Commun.* **1999**, 1319). This new NMR method has been used to detect and produce NMR spectra of low-level related impurities in a mixture. Thus in the production of the sulphonyl chloride (**13**), the product mixture was shown by NMR experiments (which took only 15 min) to contain three impurities **14**, **15**, and **16**, and the NMR spectra of those impurities were obtained without further sample purification. At present 0.5% is the limit of detection, but no doubt this will soon be lowered.



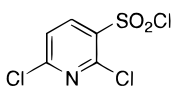
(13)



(14)



(15)



(16)

In an article entitled “Separate ways with Chiral molecules,” scientists at the University of Sunderland, UK, describe the use of capillary electrophoresis as a fast and efficient method of separation of enantiomers (Soo, E.C. *Chem. Ind.* **1999**, 15 March, p 220).

An intriguing title of a recent article in *Pharmaceutical Technology, Europe*, is “Inherent Errors in HPLC analysis” by P. Coombes et al. (*Pharm. Technol. Eur.* **1999**, June, p

40). The conclusions are that valid data from HPLC impurity profile methods are produced only when:

- The sensitivity to **all** peaks is known and the system correctly calculated the ratio of impurity peak areas to the main peak.
- All of the peaks (most importantly the main peak) are pure and **fully** resolved.
- The analysis is linear, from the smallest impurity peak to the main peak.
- All the peaks measured as impurity peaks relate only to the sample.
- **All** of the impurities present in the sample are found in the chromatograms.

The latter is usually the major assumption and requires other test methods to prove it.

An excellent review on the use of ultrasound in synthesis has appeared (Cintas, P. et al. *Green Chem.* **1999**, 1, 115). The conclusion is, however, that to reach the application stages further study of the chemical engineering aspects is needed (for example, in the homogeneous distribution of energy).

For those chemists and chemical engineers able to read German, the last issue in 1998 of the Swiss journal *Chimia* contains a number of articles related to the safety and thermal hazards of a number of industrial processes.

In a letter to *Chem. Ind.* (March 15, p 202), a fire resulting from the simple operation of transferring solid sodium chlorite from a large plastic sack to reagent bottles with a plastic scoop is described. In the past, explosions resulting from handling sodium chlorite on a large scale have been reported to the UK Health and Safety Executive. It is believed that in the recent incident the plastic scoop was the ignition source, by way of static, and the plastic bag the source of organic matter.

A recent incident at a Bayer agrochemical plant in Wuppertal, Germany, led to 100 people being injured (but fortunately no deaths) and the destruction of a five-storey plant. It is reported (*Chem. Engineer* **1999**, June 24, p 3) that the explosion and subsequent release of material was caused when potassium hydroxide was inadvertently substituted for potassium carbonate in a batch recipe. The process involved the conversion of 2-chloro-5-nitro-toluene in DMSO solvent to an intermediate in the synthesis of the antiparasitic agent toltrazuril. The explosion not only caused damage at the plant (estimated at 100 million DM) but also damaged houses nearby, caused a power cut, and disrupted trains in the region.

The incident emphasises the importance of good operating practices in manufacture. Why the substitution of KOH for  $\text{K}_2\text{CO}_3$  took place is not known—presumably the KOH then reacted with DMSO to give the well-known dimsyl anion, which has been implicated in other runaway incidents. I always worry when I see DMSO being used as a solvent, particularly if it is being recycled—there have been many incidents in the past due to DMSO’s properties (instability in strong base, in acid, and at high temperature, oxidising properties, susceptibility to trace impurities, etc.).



Tantalum is a metal that is used in chemical reactors (temperature probes, repairs to equipment, heat exchangers, etc.) and thus can come into contact with a wide variety of chemicals. It is a very corrosion-resistant metal (comparable to gold and platinum) owing to a layer of Ta<sub>2</sub>O<sub>5</sub> on the surface so that reagents which attack this film will corrode the tantalum. Thus, fuming sulphuric acid, HF, and fluoride ion at concentrations above 5 ppm will all react (remember that organics containing CF<sub>3</sub> groups under base and acid conditions may release fluoride ion in sufficient concentration to etch glass-lined reactors and presumably tantalum surfaces! One company—which shall remain nameless—recently destroyed a glass-lined reactor under these circumstances!).

Tantalum can also be embrittled by hydrogen—especially nascent hydrogen—which rapidly attacks the grain boundaries causing the metal (and niobium and zirconium, too) to crumble to powder (Rowe, D. *Chem. Engineer* **1999**, June 24, p 19).

The hierarchy of preferred options for handling waste is:

1. Avoid
2. Reduce
3. Recycle
4. Contain
5. Treat

For solvents in complex organic reactions, it is difficult to avoid using them, thus reduction and recycle are generally

the preferred options. Perhaps an extra category for solvents should be 2A. avoid mixing, since solvent recovery is often made more difficult because of the number of solvents in the waste stream. Ted Lees from Novartis (*Chem. Engineer* **1999**, July 2, p 23) describes some examples of difficult separations by solvent recovery including a THF—isopropanol—water—hexane—heptane mixture and a THF—ethyl acetate—water—methanol—methyl acetate—ethanol—acetic acid mixture. In the latter case both of the principle components THF and ethyl acetate were recycled.

And finally, although not of interest in process chemistry, but to all scientists, the examination of meteorites has shown that they contain a plethora of amino acids ( $\alpha$ ,  $\beta$ ,  $\delta$ , and  $\lambda$ ) as well as other organic compounds associated with the origins of life. Some of the amino acids are not normally seen naturally on earth, yet they display interesting enantiomeric enrichment. The implication is that extraterrestrial factors may have some bearing on the origins of life on earth! For more details see the brief review (Podlecki, J. *Angew. Chem., Int. Ed.* **1999**, 38, 477).

Dr. Trevor Laird

*Editor*

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