Organic Process Research & Development **1998**, *2,* 210–213

Highlights from the Literature

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

Most of us these days find it hard to keep up with the literature, and I hope that these highlights help in this respect. They are not meant to be comprehensive, just some items of interest which I have picked out in my "leisure" reading. I always enjoy the highlights sections from other journals (e.g., *Chemistry & Industry*, *Chemtech's Heart Cut*, and in particular the relatively new section in *Angewante Chemie, International Edition in English*) and find that they remind me of articles I may have missed (or maybe from the title, I didn't gather the significance!).

One of the differences between academic chemistry and process chemistry is the functionalisation of aromatics, where in the university world iodide is used as the leaving group. Aromatic iodides are not that readily available on a large scale, so chlorides or, if necessary, bromides (or even triflates) would be preferred substrates. The Manfred Reetz group at the Max Planck Institute in Mulheim have now published a methodology for the Heck reaction, which works efficiently on aromatic chlorides. They admit the discovery of the new and simple catalyst system (a mixture of $PdCl_2$ or $Pd(OAc)_2$ and tetraphenylphosphonium salt) was serendipitous (Reetz, M. T.; et al., *Angew. Chem., Int. Ed. Engl.* **1998**, *37* (4), 481) and suggest that the two components react to give a complex which is also an active catalyst. Thus chlorobenzene reacts with styrene to give *cis*- and *trans*-stilbenes and 1,1-diphenylethene, usually with high selectivity for the *trans*-stilbene. Best results are obtained with sodium acetate as base and DMF or NMP as solvent at approximately 150 °C. Another surprising discovery was that addition of *N,N*-dimethylglycine not only increases the selectivity but also allows reduction in the level of Pd; turnover numbers in the range of 100−10000 are obtained, depending on substrates, the best results being with bromobenzene and acrylates. These results are highly significant for industrial chemists, and the relatively simple reaction conditions should lead to easier scale up of the Heck reactions. We await news of whether the new catalyst is effective in other systems (e.g., Suzuki coupling, carbonylation, amination, etc.).

Another aromatic chemical process of interest in process R&D is the displacement of aromatic halides by other functional groups (e.g., amines). In particular, the Buchwald and Hartwig groups (for leading references see, Sadighi, J. P.; et al. *Tetrahedron Lett.* **1998**, *39*, 5327) have published widely on this area in the last 2 years. The Sadighi paper announces a new catalyst system (bis(diphenyl phosphine)-phenyl ether or DPE phos with $Pd(OAc)_2$) which is easy to make from the cheap and readily available diphenyl ether by bis-ortholithiation and quenching with Ph_2PCl.

In the same issue (*Tetrahedron Lett*. **1998**, *39*, 5359), the Fort group in Nancy, France, report on the nickel-catalysed amination of aryl chlorides (also previously reported by Buchwald's group). The French team used stable liganded nickel complexes to induce bond formation, but high yields were only obtained in the presence of a hydrogen acceptor such as styrene, which prevents reduction of the aromatic halide to hydrocarbon by the hydrogen, which may be generated from the complex base (NaH−*tert*-AmONa) used in the process.

Radical chemical processes often provide synthetic methods to molecules which cannot be prepared in other ways (e.g., highly hindered carbon centres), but methods of generating radicals usually involve tin compounds, which are unlikely to be used—except in catalytic quantities—on a large scale not only because of effluent problems but also because it is quite difficult to remove the traces of tin residues from products. Whilst radicals can be generated by photolysis, by using triethyl boron in the presence of oxygen or by using silicon-based initiations, these methods all have their limitations. Carl Schiesser at the University of Melbourne, Australia, recommends the use of 9-borobicyclo[3.3.1]nonane (9-BBN) for radical reductions (*Tetrahedron Lett.* **1998**, *39*, 5437) but the method presumably is not applicable to C−C bond forming processes. Andreas Gansauer from Gottingen, Germany, suggests that rather than looking for radical chain processes in synthesis, where the substrate may affect the stereochemical outcome of the reaction, we would be better, from a synthetic viewpoint, to focus on reagent controlled, catalytic transformations of radicals, where the influence of the substrate on the chemo- and regioselectivity may be overruled. Although the ring opening of epoxides to give radical species by single electron transfer processes has been reported previously, both the electron-transfer reagent precursor (titanocene dichloride) and the reducing agent (zinc powder) were used in stoichiometric amounts. Gansauer now reports (*Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 101) that addition of various pyridinium hydrochlorides with cyclohexadiene as the reducing agent allows the titanocene to be used in catalytic amounts (5 mol %). In subsequent experiments, $MnCl_2$ was used as the reducing agent in conjunction with cyclohexadiene. Although most of the examples in the paper are simple epoxide ring openings, there are some interesting C−C bond forming reactions (Scheme 1).

Development chemists are always interested in carbon−carbon bond forming reactions, particularly if they are atom efficient as in the Stetter and Bayliss-Hillman reactions, the

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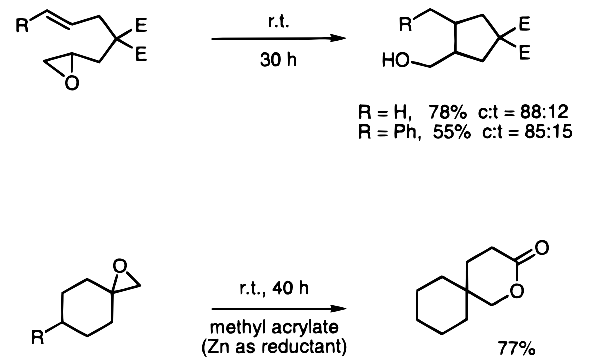
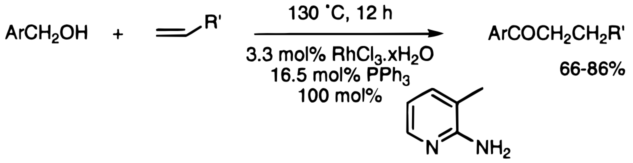
Scheme 1



Scheme 2



limitation of these processes being that the olefin must have electron-withdrawing groups attached. Addition of aldehydes to unactivated olefins to give ketones (hydroacylation) is a potentially attractive industrial process, particularly if it can be made intermolecular as well as intramolecular, and there was a report last year on how that could be achieved (Jun, C.-H. *J. Org. Chem.* **1997**, *62*, 1200).

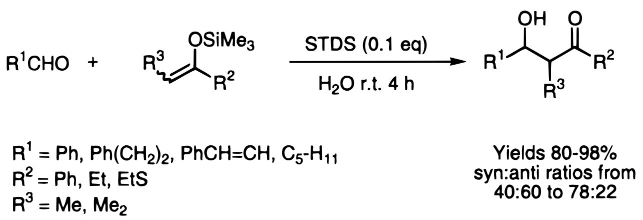
The same group now reports (*Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 145) that benzyl alcohol will react with 1-pentene to give the corresponding aromatic ketone (Scheme 2) in the presence of 2-amino-3-picoline and a rhodium catalyst. Aliphatic ketones give lower yields as do reactions of benzylic alcohols with ethylene.

The use of lanthanide salts in organic synthesis continues to attract attention. The Barrett group at Imperial College, London, has expanded on their earlier results on the use of lanthanide triflates as recyclable catalysts for atom economic nitration of arenes (*Chem. Commun.* **1997**, 613). A more recent paper (*Tetrahedron Lett.* **1998**, *39*, 1641) reports on the use of $Hf(OTf)_4$ and $Zr(OTf)_4$ for selective nitration of electron-deficient aromatics. Thus *o*-nitrotoluene is nitrated with 1 mol of concentrated (69%) HNO_3 giving a mixture of dinitrotoluenes in over 90% yield. The only byproduct is water, and the catalyst can be recycled.

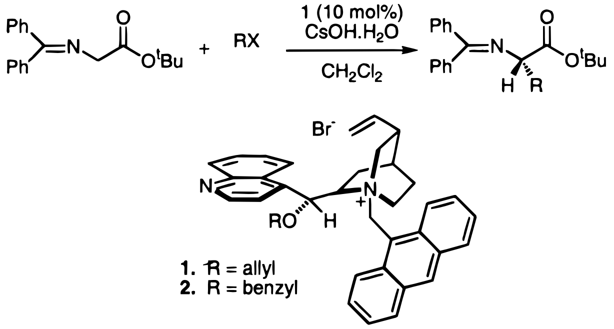
Organic reactions in water seem to be all the rage these days—there have been two books on the subject in the last year and a large number of papers. The reason is, of course, the supposed environmental benefits of doing reactions in water. This is attractive to industry only if organic solvents are not used in the work up of these reactions, and it must be remembered that disposal of an aqueous layer contaminated with toxic organic byproducts may not be as easy as an organic solvent contaminated with the same impurities, which may be more easily recycled/incinerated. To my mind, for the small volume products, a reaction in an organic solvent, where no aqueous work up is used and most of the solvent is recycled, may be just as environmentally attractive!

The academic work on reactions in water, however, has produced some outstanding results which not only challenge the way we think about chemistry but also have tremendous potential for industrial application. The group of Kobayashi in Tokyo is foremost, and his work on scandium and lanthanide triflates, which can act as Lewis acids even in water, has lead to a number of carbon−carbon bond forming processes which tolerate water in the organic solvent or can be run in water alone if a surfactant is present (Kobayashi, S.; et al. *Tetrahedron Lett.* **1997**, *38*, 4559; *Chem. Lett.* **1997**, 831). The Tokyo group have now synthesised scandium trisdodecylsulphate (STDS) and found that aldol reactions proceed smoothly in water in the presence of the catalytic quantities of STDS (Scheme 3). Catalytic activity in water is much higher than in organic solvents. Products are isolated from the dispersion in water by salting out and solvent extraction, though presumably with liquid products the latter unit operation would be unnecessary on a larger scale.

Scheme 3



Scheme 4



The aqueous reactions that process R&D chemists and engineers usually come across are phase-transfer reactions. Again, a new book has been published (see Book Reviews in this issue) to complement existing works, but a new area too late for inclusion in the book is enantioselective synthesis using new phase-transfer (P-T) catalysts. Whilst many chemists will be familiar with the outstanding work carried out in the Merck's Process Research Department at Rahway, NJ, in the 1980s on asymmetric alkylation and Michael addition on indanone derivatives and of the contribution of O'Donnell on enantioselective synthesis of α-amino acid esters, two groups published in 1997 work on new, versatile asymmetric P-T catalysts. The Harvard group have recently published new results (Corey, E. J.; et al. *Tetrahedron Lett.* **1998**, *39*, 5347) on the use of the P-T catalyst (**1**) in the synthesis of cyclic and acyclic α-amino acids with enantioselectivities as high as 200:1 in alkylations and Michael additions (Scheme 4). The key feature of the Corey process is the use of solid $CsOH{\cdot}H_2O$ as base in a solid−liquid P-T system with dichloromethane as solvent at approximately −50 °C. The catalyst can easily be recycled (if necessary) after aqueous work up and extraction, the P-T catalyst being extracted from water by dichloromethane (as the chloride salt).

The rival group from Salford, UK, have also published more recent results using similar (sometimes identical) catalysts to the Harvard group. The catalyst (**2**) works well in the two-phase (aqueous NaOCl−toluene) epoxidation of α,β-unsaturated ketones giving moderate to good enantioselectivity (69−89% ee) and excellent diastereoselectivity at room temperature, but the reactions take 48 h. (Lygo, B.; et al. *Tetrahedron Lett.* **1998**, *39*, 1599 and references cited to earlier work of both groups).

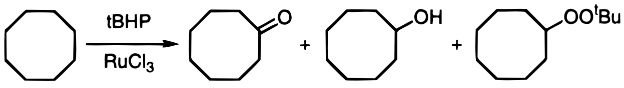
Environmentally friendly oxidation seems to be in fashion at the moment, as reported in a previous Highlights section. Heterogeneous catalysts, based on layered materials such as hydrotalcite, are reported (Kaneda, K.; et al. *J. Org. Chem.* **1998**, *63*, 1750) to catalyse the oxidation (using molecular oxygen) of allylic and benzylic alcohols to aldehydes and ketones in high conversion and good selectivity. The catalysts $Mg_6Al_2Ru_{0.5}(OH)_{16}X^-$ (best when X is CO_3) are prepared by mixing the chlorides of magnesium aluminium and ruthenium in the correct proportions in water, and precipitating with NaOH and NaX, filtering, washing, and drying. The catalysts are used as a suspension in toluene under an oxygen atmosphere, though there is no reason, I would imagine, why for a liquid aldehyde they could not be run neat. Interestingly, primary alcohols react faster than secondary alcohols. In the above examples, the catalyst/substrate ratio is high, but the catalyst can be reused without “appreciable” loss of activity. Cobalt(II) oxidation of allylic alcohols with oxygen in the presence of silanes, however, gives 1,2,4-trioxepanes (Oh, C. H. *Tetrahedron Lett.* **1998**, *39*, 2771).

The oxidation of 1,3-dicarbonyl compounds to 2-hydroxy-1,3-dicarbonyls using oxygen and a cerium(IV) catalyst has also recently been described (Nair, V.; et al. *Tetrahedron Lett.* **1998**, *39*, 2801).

The oxidation of alcohols to carboxylic acids is never an easy process (depending on what other functionality is present in the molecule). A recent report from Merck process chemists (Zhao, M.; et al. *Tetrahedron Lett*. **1998**, *39*, 5323) suggests that a catalytic quantity of CrO_3 in the presence of H_5IO_6 is the preferred reagent, but the quantity of water was found to affect the yield. Initially, they conducted experiments in MeCN−H_2O (50:50) but failed to push the reaction to completion. When acid was present and water was absent, the reactions proceeded very quickly, but when a small amount of water was added (0.75%), the oxidation strength of the system improved and the reactions were even cleaner. Yields of carboxylic acids were in the 73−100% range.

Oxidation of alkanes by oxygen is usually difficult owing to the low reactivity of hydrocarbons, so drastic reaction conditions are often employed. Consequently, chemists are always searching for new catalysts which operate under mild conditions, so that high conversion AND selectivity can both be achieved. Henri Patin and co-workers from France (*Tetrahedron Lett.* **1998**, *39*, 1353) report on oxidation of hydrocarbons to ketones in a biphasic system (the hydrocarbon being the organic phase) using $RuCl_3{\cdot}3H_2O$ and *tert*-butylhydroperoxide as the oxygen source. In situ formation of a colloidal ruthenium species is suggested to account for the relatively high selectivity (Scheme 5) for ketone versus alcohol formation (3:4) and catalyst turnover numbers up to 200. A radical mechanism is proposed. The more easily oxidised benzylic hydrocarbons can be converted to carbonyl compounds using NaOCl or PhIO and racemic manganese salen complexes (Lee, N. H. *Tetrahedron Lett.* **1998**, *39*, 1385).

Scheme 5



3 **4** **5**

In my last Highlights, I mentioned the use of fluorous biphasic catalysis as a new phase separation/immobilisation technique which promised to revolutionalise the way we carry out chemistry. A useful 3 page summary of the technique and leading references appeared in *Angew. Chem., Int. Ed. Engl.* **1997**, *36* (19), 2057. One attraction of the perfluorinated organic solvents for organic chemists is the tendency for gases to be very soluble (as in supercritical CO_2!), and these solvents are ideal for gas/liquid reactions, particularly if conditions are chosen where the organic cosolvent is miscible with the fluorocarbon at high temperature and separates as an upper layer at room temperature. The unusual solvating properties of fluorocarbons could also make them attractive for enantioselective processes. A recent communication, however, from the Pozzi group (*Chem. Commun.* **1998**, 877) indicates that the use of perfluorinated Jacobsen-Katsuki-type catalysts gives low enantioselectivity in the direct oxidation of olefins but the yields of epoxides were good. I anticipate many more papers in this area in the future, and the simple work up of these processes may make industrial applications economic if the fluorous phase (including the catalyst) can easily be reused.

Asymmetric reduction on pilot scale is now feasible using the Corey−Itsuno oxazaborolidine reagents and examples from Merck (USA) and Sipsy (France) have been presented at symposia and published. Callery (USA) is a company with expertise in boron chemistry, and one of their chemists (Burkhardt, E. *Chimica Oggi* **1998**, Jan/Feb, 6; *Tetrahedron Lett*. **1997**, *38*, 1523) recommends the use of diethylaniline−borane as the associated borane source, rather than dimethyl sulphide−borane or tetrahydrofuran−borane. From a process point of view, it has the advantages of higher boron content (5.6 M), no stench, and easy removal of the amine using an acidic work up.

The application of enzymes in organic synthesis is well established and has led to the increased demand for enzymes which exhibit high activity and selectivity in organic solvents. Commercial freeze-dried powders often exhibit low activity, but are used since they are readily available. A new report from the University of Strathclyde (Partridge, J.; et al. *Chem. Commun*. **1998**, 841) describes a simple way to immobilise enzymes on standard chromatographic silica, yet retaining high activity. The key is to keep the silica−enzyme preparation wetted at all times during the washing process. These propanol-rinsed enzyme preparations (PREP) exhibit high activities, often 1000 times more than freeze-dried materials, in MeCN and THF, comparable to the cross-linked enzymes (CLECS) which are also commercially available. This work shows that different methods of water removal from enzymes dramatically affects activity, possibly by altering the enzyme conformation.

The transition metal catalysed polymerisation of olefins, discovered by Ziegler and Natta in the 1950s, is one of the most important industrial processes. However, polyolefins are now so widely used that environmental issues, particularly reuse and recycling, will be important in the next century. Polyolefins, being essentially inert paraffinic materials, are difficult to transform into valuable products. One possible way would be to reverse the polymerisation process, and this has now been demonstrated for the first time (Dufaud, V., et al. *Angew. Chem., Int. Ed. Engl*. **1998**, *37* (6), 806). Silica-/alumina-supported zirconium monohydride catalysts, which are extremely electophilic, not only catalyse polymerisation of ethylene and propylene but also catalyse the cleavage of C−C bonds under hydrogenolysis conditions (1 atm, 150−190 °C). Products can be lower alkanes (C_1−C_9) or diesel hydrocarbons (C_{10}−C_{17}) depending on the time. The potential of these catalysts in recycling polymer waste is emphasised, but they may have other synthetic uses, too. Some catalysts cleave the C−C bond of butanes and propanes but not ethanes, a consequence of the mechanism of action (almost a reverse of polymerisation).

Research on polymerisation catalysts is directed towards providing polyolefinic materials with new or improved performance characteristics, and metallocene catalysts have been at the forefront of this technology-driven work over the past few years. Chemists are looking at other transition metals, too, and a recent report from Imperial College, London, and BP describes a new family of catalysts based on iron- and cobalt-bearing 2,6-bis(imino)pyridyl ligands (Britovsek, G. J. P.; et al. *Chem. Commun.* **1998**, 848). These are said to be the first iron-based catalysts to show significant activity for the polymerisation of ethylene. This work has presumably been patented. The catalyst activity is in some cases higher than with metallocenes.

Epoxides are versatile intermediates in synthesis and can be converted to a variety of functionalities, aldehydes being an exception, since it is often found that a mixture of aldehydes and ketones results. A recent report (Picione, J.; et al. *Tetrahedron Lett.* **1998**, *39*, 2681) advocates the use of cyclopentadienyl iron dicarbonyl complexes as catalysts for the rearrangement of 1,2-diaryl epoxides to 1,1-diaryl acetaldehydes in high yield at room temperature.

Nitro olefins are useful intermediates in synthesis, but some companies are deterred from preparing them owing to the need to use the potentially hazardous nitromethane in the Henry reaction, even though methods avoiding the use of base are now available. A new synthesis of nitro olefins by nitration of olefins with NO using heterogeneous zeolite catalysts (Sreekumar, R. *Tetrahedron Lett.* **1998**, *39*, 2695) opens up wider synthetic options.

For the process chemist and engineer, the ideal reaction from a synthetic efficiency viewpoint is one where a large number of bonds are made at the same time. The original 3- or 4-component coupling reaction dates back to 1968 (the work of Gross and Ugi) but is now seeing a resurgence of interest for the synthesis of heterocycles. Thus reaction of a δ keto acid, an isonitrile, and an amino acid ester gave lactams and bicyclic lactams in good yield (Ugi, I.; et al. *Tetrahedron Lett.* **1998**, *39*, 2725).

Maleates are often used as the salt form in the pharmaceutical industry particularly for diamine molecules. I was interested, therefore, in the curious observation (Chatterjee, S. *Tetrahedron Lett*. **1998**, *39*, 2843) that the maleate salt of 2,2′-bipyridine crystallised as expected from acetone, chloroform, ethyl acetate, and methanol, but crystallisation from DMF and DMSO gave an adduct where the maleate had been isomerised to fumarate. It is suggested that in these dipolar aprotic solvents the isomerisation occurs by a Michael addition of the bypyridine followed by elimination.

Finally, two SAFETY ISSUES. In a paper on the conversion of perfluoroalkanes to perfluoroalkyl Grignard reagents, (Beck, C. M.; et al. *Chem. Commun.* **1998**, 693), the authors remind us that fluorinated Grignards can spontaneously explode (this includes Grignards with CF_3 groups on the aromatic, see *Brethericks Handbook of Reactive Chemical Hazards*, 5th ed.; Butterworth-Heinemann: Oxford, UK, 1995).

In a letter to *Chemistry and Industry* (**1998**, 6 April, 242), Mike Jasiewicz of Lancaster Synthesis (UK) reports on the acute adverse reactions suffered by workers using pyridine-3-carboxaldehyde. This was not just the contact urticaria previously reported nor the typical facial flushing associated with analogues of nicotinic acid, but a more increased sensitivity at low concentrations. My thanks to Lancaster for publishing this. I encourage chemists/companies to report *all* such occurences in the open literature so that we build up knowledge, rather than having to “reinvent the wheel”, thus exposing staff to needless hazards.

Trevor Laird
Editor

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