Organic Process Research & Development **1999**, *3,* 2–4

Highlights from the Literature

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

Whilst the manufacture of polyolefins dates back over 60 years, the production of polyketones, derived from olefins and carbon monoxide, only began in 1996. These relatively new plastics show a strong rigidity and impact strength and good chemical resistance to acids, bases, and solvents (superior to polyolefins, polyamides, polyacetals, etc.), which may make them useful in the chemical industry. The early synthesis by Reppe was never commercially viable, and the breakthrough was achieved by using palladium−phosphane complexes which catalyse the formation of a perfectly alternating copolymer from ethene or propene and carbon monoxide under mild reaction conditions (Drent, E.; et al. *Chem. Rev.* **1996**, *96*, 663). Of course, the expensive palladium catalyst is not recovered. It has now been shown that an aryl nickel(II) complex containing *o*-tolyl, triphenylphosphine, and tris-3-phenyl-pyrazolyl borate ligands is effective at catalysing the polymerisation of ethene and carbon monoxide at 60 °C and up to 50 bar pressure and that the resultant polymer is strictly alternating (Klaui, W.; et al. *Angew. Chem. Int. Ed.* **1998**, *37* (21), 3050). It is suggested that the flexibility of the pyrazolylborane ligand permits a facile alternation between bidentate and tridentate coordination and prevents reduction of Ni(II) to Ni(0) complexes, which would result in termination of catalysis.

In recent editions of *Organic Process Research & Development*, books on organic reactions in water have been reviewed. There is much current interest in reducing waste by using solvent-free organic syntheses (and workups, of course!). In many ways, the ideal reaction is one which has no solvent, and there are numerous industrial examples, mostly involving gaseous or liquid reactants. A recent short review article (Metzger, J. O. *Angew. Chem. Int. Ed.* **1998**, *37* (21), 2975) discusses solvent-free organic synthesis, including polymerisations, referring to the new Hoechst solvent-free polypropylene process and the Asahi environmentally friendly process for polycarbonate manufacture, which requires neither phosgene nor solvent. The rest of the article discusses radical additions of iodo compounds to unsaturated esters, enzyme-catalysed processes, and catalytic oxidations, all proceeding in the absence of organic solvent. Unfortunately, the subject of exothermicity and heat transfer, relevant to scale-up of solvent-free organic processes, is not mentioned. This is unfortunate, since the last section of this interesting, informative, and well-referenced article discusses ionic reactions such as the Finkelstein alkylation of amines. This can be an extremely exothermic process, and my experience of scale-up of these reactions in the absence of solvent is that the exotherms were difficult to control, resulting in release of volatile alkylating agent−not very environmentally friendly. Solvents can be vital for the control of exotherms on scale and for improving heat and mass transfer. As always in scale-up, we must compromise!

Although carbon dioxide's properties make it an excellent candidate for polymer synthesis, there are few reactions which exploit this potential. A recent report (Coates, G. W.; et al. *J. Am. Chem. Soc.* **1998**, *120*, 11018) announces the first example of an efficient reaction between epoxides and CO_2 to produce polycarbonates. The reaction takes place under mild conditions using a catalyst prepared by treating a diisopropylaniline derivative with butyllithium followed by zinc acetate.

The first hydration of terminal alkynes in an anti-Markovnikov sense has recently been announced (Tokunaga, M.; et al. *Angew. Chem. Int. Ed.* **1998**, *37* (20), 2867). Using a catalyst such as $RuCl_2(C_6H_6)PPh_2C_6F_5$, hydration of octyne gave an 80% yield of carbonyl products with an aldehyde: ketone ratio of 17:1.

Whilst the Wacker oxidation of olefins to ketones works well with low-molecular-weight olefins, for higher olefins the rate of reaction is reduced owing to low solubility in water, and raising the temperature results in Pd black formation. There is a need for a superior Wacker oxidation system, preferably avoiding copper, chloride ions, and polar organic solvents. The rationale for this is discussed in a paper from the group of Sheldon at Delft (*Chem. Commun.* **1998**, 2359), where water-soluble palladium(II) complexes of bidentate diamine ligands, such as bathophenanthroline disulphonate (**1**), are shown to be stable, recyclable catalysts for the Wacker oxidation of olefins in a biphasic system. A paper describing an improved procedure for Wacker oxidations using substoichiometric amounts of copper(II) acetate has also appeared (*Tetrahedron Lett.* **1998**, *39* (48) 8765).

The selective oxidation of aromatic alcohols to aldehydes or to acids is never as easy as it appears, particularly on a large scale. A new methodology from the group of Noyori (*Tetrahedron Lett.* **1998**, *39* (41), 7549) provides a practical, low-cost, and environmentally friendly approach. Aldehydes are produced by treatment of the benzylic alcohol with Na_2WO_4 and 30% H_2O_2 in the presence of a phase-transfer catalyst at 90 °C. Yields are in the range of 80−90%, with *p*-nitrobenzyl alcohol being the worst example (59%). The reactions are preferably carried out without solvent, for liquid alcohols, or in a toluene−water biphasic system (e.g., for 4-methoxybenzyl alcohol). Oxidation to acids in 80−90% yield occurs when 2.5−5 mol of H_2O_2 in used. In the

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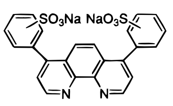
experimental detail, it is indicated that 1000 rpm stirring is used.

In a fascinating review article, Professor Henri Kagan and Christian Giraud (*Angew. Chem. Int. Ed.* **1998**, *37* (21), 2923) discuss nonlinear effects in asymmetric synthesis and stereoselective reactions, where a catalyst or auxiliary with a rather low enantiomeric excess can be used to prepare products in high enantiomeric purity. Of course, many of these effects, which could be of value in optimisation of enantioselective processes, are due to aggregation and self-assembly and, therefore, will depend on experimental conditions such as concentration and temperature. Attention to detail is a characteristic of most of the processes discussed in this very readable review.

Although it is generally accepted that recrystallisation of a true racemic compound (i.e., not a conglomerate) will not lead to resolution, there are occasions when the crystal contains a very slight enantiomeric enrichment (<1%). Repeated crystallisation of the racemate and each crop of deposited crystals can result in a remarkable alternating enrichment of the two enantiomers up to 100% ee in the mother liquors. A further amazing characteristic is that recrystallisation of nonracemic crystals with low ee values leads to the deposition of crystals *of the opposite chirality* but having a higher ee! This has been termed “preferential enrichment”; for more details and full explanation, see the paper by Tanura et al. (*Angew. Chem. Int. Ed.* **1998**, *37* (20), 2876).

Enantioselective hydrogenation is attractive from a manufacturing viewpoint, provided good selectivity, catalyst turnover, or recycle and simple product isolation can be achieved. The range of substrates is still, however, rather limited, normally requiring the presence of polar groups that coordinate to the catalyst. Enantioselective hydrogenation of unfunctionalised olefins is particularly difficult, the best results coming from Buchwald’s work with chiral titanocenes. A recent report from the group of Pfalz in Germany (*Angew. Chem. Int. Ed.* **1998**, *37* (20), 2897) indicates that iridium phosphanodihydrooxazole catalysts (e.g., **2**) are the most effective to date with trisubstituted olefins. The results are shown in Chart 1. Replacement of the PF$_6^-$ anion by tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate (BARF) usually increased the conversion and allowed a reduction in the catalyst loading to below 1 mol %. The best ligands were those where Ar is *o*-tolyl and X is *tert*-butyl.



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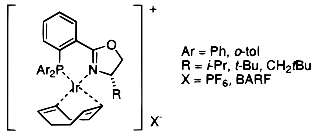

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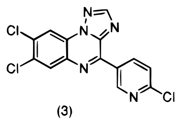

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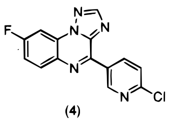

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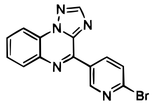

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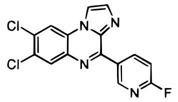

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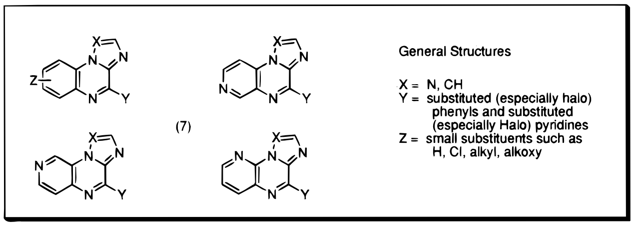
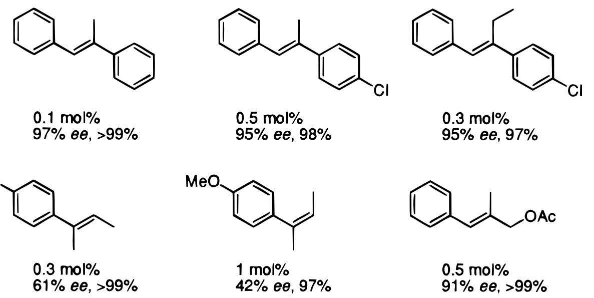


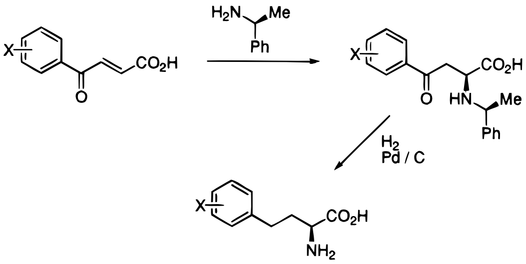
General Structures

X = N, CH
Y = substituted (especially halo) phenyls and substituted (especially Halo) pyridines
Z = small substituents such as H, Cl, alkyl, alkoxy

Chart 1



Scheme 1

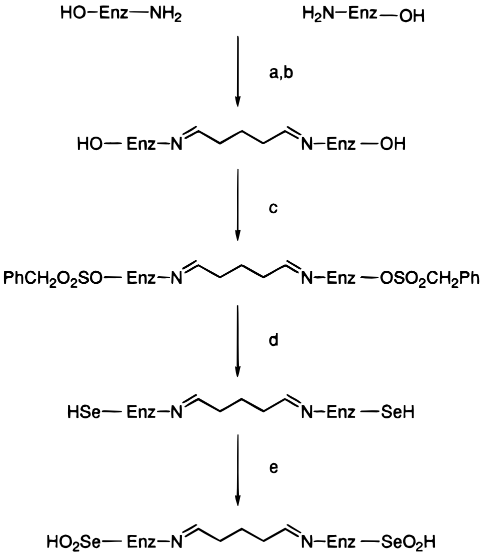


A diastereoselective Michael addition of a chiral amine to an unsaturated ketone forms the basis of a new process for making homophenylalanines from the Japanese company Kaneka (*Tetrahedron Lett.* **1998**, *39* (49), 9019). Although the Michael addition is initially not so selective, the required product crystallises from the reaction mixture, even at reflux. At higher temperatures, the unwanted isomer reverts back to amine and unsaturated ketone, so under the correct conditions, the process can be driven by the crystallisation, with the best selectivity occurring at high temperature (90–99% de). Hydrogenation/hydrogenolysis of the keto-acid provided the homophenylalanines in high yield (Scheme 1).

Although enzymes are widely accepted as valuable catalysts in synthetic chemistry, their “natural” properties, such as activity, selectivity, or stability, are often insufficient. Several methodologies have been developed to overcome these problems. Genetic engineering techniques can improve the overall stability, whereas new catalytically active sites are hard to achieve. Monoclonal catalytic antibodies opened up many opportunities in this field, but it is difficult to obtain useful catalysts for asymmetric synthesis. Efforts have been made to design synthetic enzyme mimics, but the breakthrough in terms of catalytic efficiency and enantioselectivity still lies ahead.

The oldest techniques for enzyme tailoring are “chemical” engineering methods, and specific chemical modification of

Scheme 2. **Conversion of subtilisin into cross-linked microcrystals of seleno-subtilisin**[a]



[a] Crystallization; (b) glutardialdehyde; (c) phenylmethanesulfonyl fluoride; (d) NaSeH; (e) H_2O_2.

the catalytically active site has yielded semisynthetic enzymes with completely changed catalytic properties. A report on a new type of chemically engineered semisynthetic enzyme for organic synthesis which combines altered catalytic activity, reasonable substrate selectivity, and exceptional stability in one biocatalyst has now appeared. (Häring, D.; et al. *Angew. Chem. Int. Ed.* **1998**, *37* (18), 2471). The serine proteinase, subtilisin, which is manufactured on a tonnage scale, was isolated as cross-linked crystals and modified as shown in Scheme 2. The resultant seleno-modified enzyme shows very high activity and selectivity for kinetic resolutions, with the advantage of easy recycle of the enzyme, which is insoluble in both organic solvents and water. In comparison with other methods of enzyme development, this method is attractive for the organic chemist and chemical engineer, requiring only basic chemical equipment. The methodology should be widely applicable in the future.

Ionic liquids offer potential benefits as solvents in chemical processes if the products can be easily separated from the solvent (Seddon, K. *Ionic Liquids Review,* at http://www.ch.qub.ac.uk/kre/kre/html). A characteristic of these salts is that they are liquids at room temperature. A recent paper (Anderson, J.-A.; et al. *Chem. Commun.* **1998**, 2341) suggests that higher melting quaternary salts such as phosphonium tosylates are excellent solvents for hydroformylation processes, with simple product recovery. Interestingly, changing the nature of the salt altered the selectivity of the process.

A safety warning has appeared in the letters columns of a few magazines and journals (for example, *Chem. Br.* **1998**, December, 18), and it is worth repeating here to disseminate the information widely. Chemists at Pfizer UK have found that compounds **3**−**6** caused chloracne in workers exposed to the substances and suggest that compounds of general structure **7** should be considered as potential chloracnegens in humans. The problems at Pfizer were caused by handling these compounds on milligram to gram scale in well-managed laboratories, so the implication is that very small quantities can cause severe problems. The good news is that the chloacnegens can, over a period of time, be expelled from the body, and that the affected individuals are recovering from the exposure. A further issue for process chemists may be the possible generation of trace quantities of these materials as byproducts in synthesis of new molecules, particularly where chlorination procedures are used on heterocyclic molecules. Our thanks must go to Pfizer for alerting the chemical community to this issue.

In another letter to the same issue of *Chemistry in Britain* (December 1998, p 19), it is reported that an explosion occurred at the University of Leicester (UK) when a student was handling tetramethylammonium periodate (transferring 14 g of solid to a reaction flask). Severe injuries and hospitalisation resulted. It is well known that ammonium periodate explodes under similar circumstances, and there have been previous reports of problems with the tetraethylammonium compound, which were originally attributed to the presence of excess periodic acid. This explanation now seems doubtful. It is suggested that all periodates, especially ammonium salts, be treated with caution, especially when dry or in mixtures with organics. Of course, the same is true for all compounds in higher oxidation states in combination with organics, especially salts.

Trevor Laird
Editor

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