Organic Process Research & Development **1998**, *2,* 340–343

Highlights from the Literature

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

One of the most practically useful papers to appear this year is a technique for resolution of racemates by using the "family" approach (Vries, J.; et al. *Angew. Chem. Int. Ed.* **1998**, *37* (17), 2349). This was first reported at the Chiral '98 meeting in San Francisco in May 1998. The technique involves, instead of using a single resolving agent, using a mixture of resolving agents of similar type (from the same family), and much better results are obtained than those using single resolving agents in the examples studied (over 200 to date). Interestingly, the products contain more than one component in the crystal, and this nonstoichiometry is retained after several crystallisations (sometimes after 20 recrystallisations). The method allows rapid resolution of a previously unresolved racemate in high yield and enantiomeric purity, and with a high success rate. This circumvents the usual "trial and error" method of finding a good resolving agent. The families of resolving agents used were a series of oxaphosphorinanes (previously reported by the Dutch group), dibenzoyl tartaric acids, phenylethylamines, mandelic acids etc. A further article from the same group also has appeared (Broxterman, Q. B. *Chim. Oggi* **1998** (Sept), 34). Readers are reminded that this work has been patented (Eur. Patent EP-A-838448, 24 Sept 1998; Dutch Pat. Appl. NC 1004346, October 1996).

Amines and nitrogen-containing compounds are well-known poisons for palladium catalysts used for hydrogenation, but rarely is this used for synthetic advantage. Scientists at Gifu, Japan (Sajiki, H.; et al. *Tetrahedron Lett.* **1998**, *39* (39), 7127) have discovered that 2,2-bipyridyl poisons Pd−C catalysts but only suppresses hydrogenolysis of phenolic O-benzyl groups, allowing reduction of olefins and nitro groups, as well as hydrogenolysis of benzyl esters and NHCbz, to take place in the presence of $ArOCH_2Ph$ groups.

Sodium 2-ethylhexanoate is a useful reagent, being soluble in hydrocarbon solvents, thus allowing the easy preparation of sodium salts as carboxylic acids when other methods have failed. Now workers at Novartis, in East Hanover, NJ (Fitt, J. *Tetrahedron Lett.* **1998**, *39* (39), 6991), have used the base as a scavenger for HCl in N-acylation reactions, where classical Schotten−Baumann conditions are impractical (e.g., for water-soluble products such as amino acid esters). The mechanism does *not* involve mixed anhydride intermediates, as was shown by crossover experiments.

Whilst the Mitsunobu reaction is an excellent laboratory methodology, on scale-up the disadvantages of poor atom economy, triphenylphosphine oxide as a byproduct, and use of potentially explosive azo dicarboxylates may be problematical. The group of Barrett at Imperial College, London (*J. Org. Chem.* **1998**, *63* (18), 6273), suggest that Vilsmaier type reagents, prepared from DMF and oxalyl chloride, can achieve the same result; the intermediate imidate esters are attacked by carboxylates and imides with clean inversion of stereochemistry (as in the Mitsunobu), but the byproducts (KCl, DMF) are easily removed.

The removal of byproduct triphenyl phosphine oxide from reaction mixtures continues to be a problem whether on laboratory or plant scale, and modified phosphorus reagents are often being suggested. For the Staudinger (aza-Wittig) and Mitsunobu reactions, it is suggested by workers at the University of Liverpool (O'Neil, I. A. *Tetrahedron Lett.* **1998**, *39* (42), 7787) that 1,2-bis(diphenylphosphinoethane) can replace triphenylphosphine without loss of yield, and with the advantage of a simple purification procedure. However, in some cases 1 equiv rather than the expected 0.5 equiv was required for good yields. All that is required is a simple way to recycle the phosphine oxide!

Another British group (Lawrence, N. J. *Synlett* **1998**, 497) report an alternative phosphonium salt to triphenylalkylphosphoniums for the Wittig reaction when trans selectivity is required. References to earlier work in this area are also summarised. When the phosphorus atom is contained in a six-membered ring, the phosphonium salt reacts with aldehydes to give >97% trans olefin if KHMDS is used as base. The resultant phosphine oxide (which is an intermediate in the synthesis of the phosphonium salt) is easily reduced to a phosphine, so recycling is a possibility.

The group of Reetz has previously reported on the use of a new catalyst, $PdX_2 6Ph_3PCl$, in the Heck reaction of aryl chlorides (*Angew. Chem. Int. Ed.* **1998**, *37*, 481) and that addition of 10−12 mol % of the inexpensive additive *N*,*N*-dimethylglycine (DMG) facilitates the reaction. The same group now report that the *phosphine-free* system $Pd(OAc)_2$−DMG or $PdCl_2(PhCN)_2$−DMG is an excellent Heck catalyst for aryl bromides, possibly one of the best to date. Catalyst levels are typically 1.5% to give >99% conversion in 10 h; reduction of catalyst levels to 0.0009% increased the reaction time to 96 h at 130 °C in NMP, but conversion and selectivity were good. The mechanism is unknown, but the experimental observation is that, in the presence of DMG, reaction mixtures do not turn black until all aromatic bromide has been consumed, in contrast to reactions without DMG, where a black colour is obtained immediately. Does this, I wonder, offer a solution to the process chemist/engineer's problem of colloidal palladium production in these reactions (and

10.1021/op980085c CCC: $15.00

Suzuki couplings), the residues being particularly difficult to remove from both product and reactor? We await future developments.

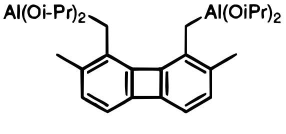
In previous Highlights, I have commented on the use of methyltrioxorhenium (MTO) as a catalyst for oxidations using hydrogen peroxide. The group of Jacobs in Belgium (*Tetrahedron Lett.* **1998**, *39* (46), 8521) now report on the selective epoxidation of industrially important terpenes with MTO and suggest that this is the reagent of choice in many instances, being far superior to peracid oxidations. For each terpene compound, the choice of reaction conditions may be different depending on reactivity, but usually pyridine is required in order to get good yields. Competing pyridine oxidation is not a problem, except with relatively unreactive alkenes, in which case 3-cyanopyridine is substituted. Pyridine suppresses the Lewis acidity of MTO and prevents epoxide rearrangement, which can be a problem with peracids. The use of a two-phase reaction system also helps to prevent hydrolysis. For a theoretical study of the mechanism of MTO oxidation of olefins, see Gisdakis P. *Angew. Chem. Int. Ed.* **1998**, *37* (16), 2211.

Whilst the ring opening of epoxides by amines always looks on paper to be a good synthetic route to amino alcohols, in practice this can turn out to be a far from trivial reaction. David Gani from the University of St. Andrews, Scotland, now reports (*Tetrahedron Lett.* **1998**, *39* (46), 8549) that the reaction can be catalysed by ytterbium(III) triflate. The reagent has been reported before, but whereas the previous workers (Crotti, P.; et al. *Tetrahedron Lett.* **1994**, *35*, 433) had suggested that the reaction is inhibited by water, the St. Andrews group find that quantitative yields can be obtained using aqueous solutions of simple amines.

Oxidative cleavage of olefins to carboxylic acids is a useful transformation commonly carried out by ozonolysis with oxidative work up. Alternative reagents, for those who prefer to avoid ozone, are permanganate or preferably ruthenium tetraoxide, the latter often being used in catalytic quantities in the presence of a co-oxidant (NaOCl, $NaIO_4$, CH_3CO_3H). Workers at Enichem (Italy) have now published a full paper (Antonelli, E.; et al. *J. Org. Chem.*, **1998**, *63*, 7190) on the use of 40% H_2O_2 in conjunction with methyltrioctylammonium tetrakis(oxodiperoxotungsto)phosphate in a two-phase system. For liquid alkenes the reaction can be carried out without solvent. The mechanism proceeds via epoxide and β-hydroperoxyalcohol intermediates.

The use of lanthanide salts and also ligands (e.g., tartrates, triethanolamine) to accelerate the Baylis−Hillman reaction is reported by workers at Sheffield University (Aggarwal, V. K.; et al. *J. Org. Chem.* **1998**, *63*, 7183). Rate increases of up to 40-fold are observed with $La(OTf)_3$ and triethanolamine in combination.

A Japanese group have discovered an improved catalyst (**1**) for the Meerwein−Ponndorf−Verley (MPV) reduction of ketones to alcohols (Ooi, T.; et al. *Angew. Chem. Int. Ed.* **1998**, *37* (17), 2347). If a relatively inexpensive chiral alcohol such as (*R*)- or (*S*)-1-phenylethanol is used as reducing agent, then asymmetric hydrogen transfer occurs (70−82% ee), but this reaction is successful only for aromatic ketones. The catalyst also works well for the Oppenauer oxidation, the reverse of MPV.



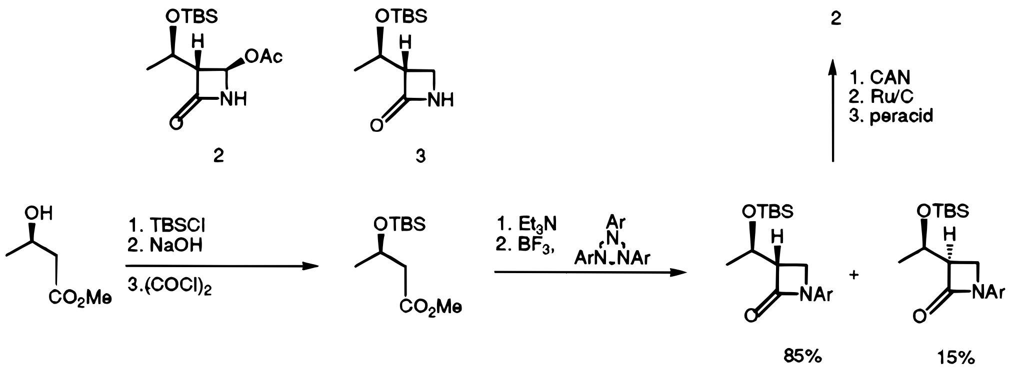
1

Whilst the Reformatsky reaction of α-haloketones and esters with aldehydes is a useful reaction, scale-up problems often occur with zinc reagents (Repic, O. *Process Research and Chemical Development in the Pharmaceutical Industry*; Wiley Interscience: New York, 1997). The same is true for zinc-catalysed Simmons Smith reactions (Nickisch, K. *Proceedings of the Third International Conference on Scale Up of Chemical Processes*; Scientific Update: Mayfield, UK, 1998, p 431). A recent note (Kagoshima, H. *Tetrahedron Lett.* **1998**, *39* (46), 8465) suggests that triphenylphosphine and scandium triflate can replace zinc for Reformatsky reactions; good yields and diastereoselectivities were obtained, particularly with α-bromo amides, which often worked well, when the corresponding esters did not. Titanium tetrachloride and ytterbium triflate also worked well but the diastereoselectivity was not as good as that with scandium, which often gave a 96% de.

A full paper on the Mn−Cu-mediated allylation of aromatic aldehydes in water has now appeared, giving experimental details of this interesting reaction (Li, D.-J.; et al. *J. Org. Chem.* **1998**, *63* (21), 7498). The presence of halogen, CH_2OH, or CN does not affect the reaction. Mn also mediates the pinacol coupling of aromatic aldehydes in good yield in water containing a trace of acetic acid, or in aqueous ammonium chloride. The fate of the manganese in these processes was not discussed—presumably, it ends up as manganese chloride/acetate.

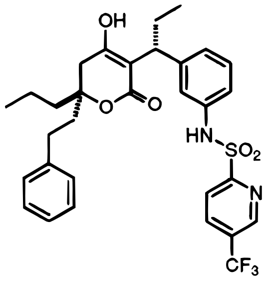
The intramolecular Pauson−Khand reaction—the cobalt-catalysed cyclisation of compounds containing both an alkene and an alkyne in the presence of carbon monoxide to give cyclopentenones—is a useful synthetic procedure, particularly for forming fused ring systems. The reaction can occur thermally, in the presence of light, and in supercritical media. Workers at Montana State University (Belanger, D. B.; et al. *Tetrahedron Lett.* **1998**, *39* (42), 7637) now report that the reaction is particularly sensitive to temperature, and only a narrow window (60−70 °C) exists for attainment of efficient catalysis. In this range, particularly if high-purity $Co_2(CO)_8$ catalyst was used, yields of 77−86% were obtained with a range of substrates, whereas at 50 or 80 °C yields dropped to 40% or below. In the following paper in that issue of *Tetrahedron Letters* (p 7641), superior catalysts for the reaction are described, and yields of up to 95% can be obtained.

A key intermediate in the synthesis of β-lactam antibiotics is compound **2**, usually obtained by direct oxidation of the precursor **3**. A new stereocontrolled synthesis of **2** from methyl (*R*)-3-hydroxybutyrate and hexahydrotriazenes is now reported (Cainelli, G. *Tetrahedron Lett.* **1998**, *39* (42), 7779). The reaction proceeds via the usual 2+2 cycloaddition of in situ-generated ketene and imine, but the stereochemical

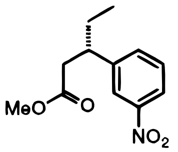


behaviour—leading directly to the diastereoisomer required for biological activity without the necessity of a Mitsunobu inversion—is unique.

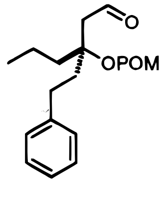
A new inhibitor, PNU-140690 (**4**), of the HIV protease enzyme was reported by Upjohn chemists last year (Thaisrivongs, S.; et al. *J. Am. Chem. Soc.* **1997**, *119*, 3627). This is the first non-peptide-like molecule to possess antiviral potency comparable to that of the peptidomimetics already on the market, but it retains activity against strains resistant to ritonavir and cross-resistant to other protease inhibitors. A new scaleable synthesis of PNU-140690 has now been published by the process department at Upjohn (Fors, K. S.; et al. *J. Org. Chem.* **1998**, *63* (21), 7348). The key step is the aldol addition of the nitroaromatic ester **5** to aldehyde **6**. The stereogenic centres were introduced in the early stages by classical resolution and enzyme-mediated kinetic resolution. A key strategy was to ensure the crystallinity of intermediates, allowing maximum opportunity for upgrading quality.



4 (PNU 140690)

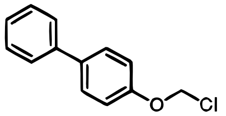


5



6

POMCl =



Lipophilic antioxidants are attracting great interest in medicinal chemistry, since active oxygen species are implicated in many diseases, and for industrial use, too. Many antioxidants (e.g., ascorbic acid) contain the aci-reductone (α-oxo-ene-diol) group, which is not so easy to synthesise, often requiring several steps. A simple oxidation of α,β-unsaturated ketones to the α,β dihydroxy enones is now reported (Beifurs, U. *Tetrahedron Lett.* **1998**, *39* (42), 7691) using aqueous peracetic acid and ruthenium trichloride in a mixture of aqueous acetonitrile and dichloromethane. Although yields are only moderate (45−60%), the procedure is simple and amenable to scale up.

The use of automated techniques to speed up the discovery and development of new catalysts is an increasingly important area for industry. A review from the group of Hoveyda and Snapper in Boston (Shimiza, K. D.; et al. *Chem. Eur. J.* **1998**, *4* (10), 1875) has now appeared. For heterogeneous catalyst libraries, an efficient method for the reliable detection of catalytic activity is required, and workers at the Max Planck Institute in Mulheim (Holzwarth, A.; et al. *Angew. Chem. Int. Ed.* **1998**, *37* (19), 2644) have developed the use of IR thermography to detect the activity of catalysts (<200 μg) in a model library. In the following paper in that issue (Reetz, M. T.; et al. *Angew Chem. Int. Ed.* **1998**, *37* (19), 247), the extension of this technique to screening for enantioselectivity in enzyme and transition metal homogeneous−catalytic processes is demonstrated. In the enzyme-catalysed processes using only 5 mg of immobilised enzyme, the exotherm could be detected by IR visualisation to approximately 0.1 °C accuracy, so that reactions on this scale which increased in temperature by 1 °C were easily followed with time. In the cobalt-catalysed ring opening of epoxides by the Jacobsen method, temperature increases of up to 10 °C were seen (in the 29−38 °C range) in the modified microtitre plates.

A more controversial article (appearing under the heading Correspondence) discusses whether combinatorial chemistry in heterogeneous catalysis is really a new scientific approach or "the emperor's new clothes". Professor Schlögl from the Fritz Haber Institute in Berlin (*Angew. Chem. Int. Ed.* **1998**, *39* (17), 2333) is sceptical that the combinatorial approach is really a breakthrough and feels it is just another tool to be used alongside traditional methods for discovery of heterogeneous catalysts. No doubt there will be future correspondence on this topic!

Benzyl azide is reported (Schildknegt, K. *Tetrahedron Lett.* **1998**, *39* (42), 7687) to be rearranged to an iminium salt under strong azide conditions, and the resultant solution can be used to effect Mannich reactions with ketones and malonates. The restriction is, of course, that only the CH_2-NHAr group can be introduced at present. Since Mannich reagents have previously been shown to undergo cycloaddition reactions with dienes, this could be an entry into useful heterocyclic compounds containing N-aryl groups, though, obviously, the hazards of using azides may make this unattractive for many companies.

A recent article in *The Chemical Engineer*, the magazine of the UK Institute of Chemical Engineers (Cox, J. *Chem. Eng. (Rugby, Engl.)* **1998**, (8 Oct), 25) reminds us that all processes, however simple, can be hazardous on scale. The mixing issues related to the exothermic dissolution of pearl caustic soda in water are discussed, and recent accidents in the chemical industry which have arisen from this phenomenon are analysed in depth, from the viewpoint of an “expert witness”. This is an excellent analysis of a mixing problem, spoiled only by the use of BTU/lb as units in the graphs.

The perennial discussions between chemists and engineers is whether processes should be batch/semibatch or continuous. Chemists traditionally prefer batch processes, but perhaps that will change in the future. An article on this topic (Higgins, S. *Chim. Oggi* **1998** (Sept), 38) discusses the issues in relation to the production and further reactions of epoxybutene at Eastman USA.

Finally, since I am interested in innovation—as all process chemists and engineers should be—I read the ACS innovator’s magazine, *CHEMTECH*. In the September issue, not only is there an article on “Building the shortest synthesis route” [Hendricks, J. B. *CHEMTECH* **1998** (Sept), 35], a description of a computerised approach to synthesis, but there are two other articles of interest. One is the editorial (innovator’s notebook) written by Abe Gelbein, entitled “Thinking out of the box”; the other, on the inside back cover, “Why thinking gives you a headache” by David Birkett. The latter is a humorous account of how the spread of ideas is suspected to be caused by a “psychovirus”. It certainly makes you think.

Trevor Laird
Editor

OP980085C