Organic Process Research & Development **1999**, *3,* 238–240

Highlights from the Literature

Highlights from the Literature as Selected by the Editor

The Mannich reaction is a useful carbon−carbon bond forming reaction, often used in industry, despite its limitations, for the synthesis of β-aminoketones and esters. The group of Kobayashi et al. at the University of Tokyo now reports (*Synlett* **1999**, 543) that a three-component Mannich reaction, involving an aldehyde, an amine, and a silyl enol ether react under miscellar aqueous conditions in the presence of scandium triflate to give good to excellent yields of β-amino carbonyl compounds (Scheme 1).

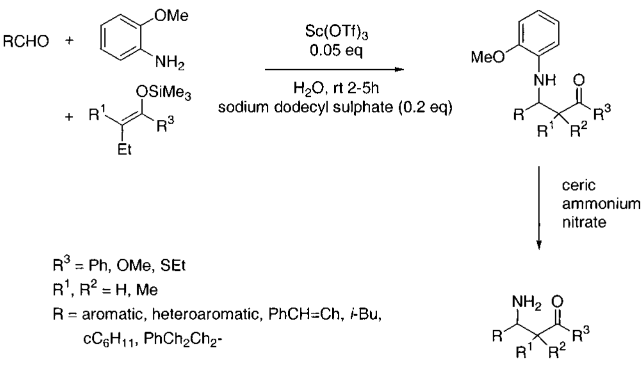
The direct oxidation of methyl ketones to carboxylic acids is an often used process in the fine chemicals industry. The reagents used, such as sodium hypohalites or chromium or manganese reagents are not always selective and produce byproducts which are toxic or environmentally unfriendly. A recent report (Gurunath, S. et al. *Synlett* **1999**, 559) indicates that rhenium heptoxide will catalyse the oxidation using *tert*-butylhydroperoxide in aqueous acetic acid (Scheme 2). Yields at present are only moderate 40−70% and need further optimisation.

The development of catalytic oxidation systems using molecular oxygen as reagent is a major challenge for both academia and industry. A recent publication (Matsunata, K. et al. *Tetrahedron Lett.* **1998**, *40*, 2165) shows that a mixture of *N*-hydroxyphthalimide and a quaternary ammonium salt catalyses the oxidation—in the absence of metal salts—of hydrocarbons and ethers. Examples are shown in Scheme 3.

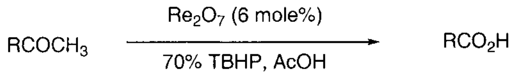
The synthesis of chiral amines is a topic of interest in industry, and new methods are constantly being developed which compete with resolution and enzyme methodologies. A recent report (Zhang, Z. et al. *J. Org. Chem.* **1999**, *64*, 1774) describes the catalytic asymmetric hydrogenation of simple enamides to amides, and this provides a potential route to amines. The catalyst (**1**) (Scheme 4) complexed to $Rh(cod)_2PF_6$ can be used in as little as 1:2000 ratio, and the hydrogenation is complete in 20h at room temperature (40 psi H_2).

The fine chemical industry uses a variety of amino acids as building blocks in synthesis, and although many can be isolated from natural products, synthetic methods are still required. Methods using racemic imidazoline-2,4-diones (hydantoins) have been used by many companies (Ajinimoto, Kanegafuchi, etc.), via a dynamic kinetic resolution, to give optically active products. There is still a need however, for alternative strategies to make hydantoins, and a new route involving palladium-catalysed amidocarbonylation of aldehydes has recently been reported (Beller, M. et al. *Angew. Chem. Int. Ed.* **1999**, *38,* 1454)—see Scheme 5.

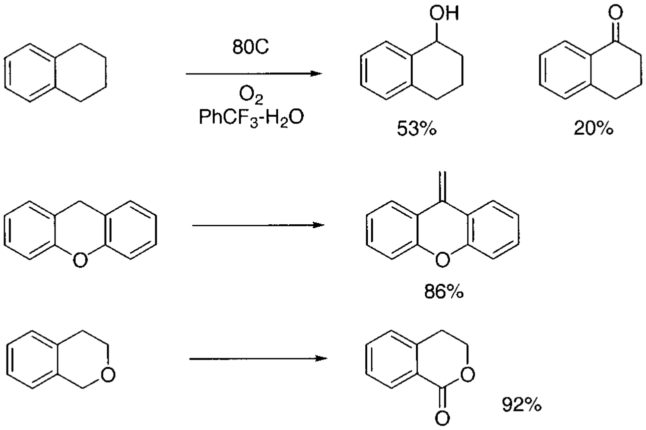
Scheme 1



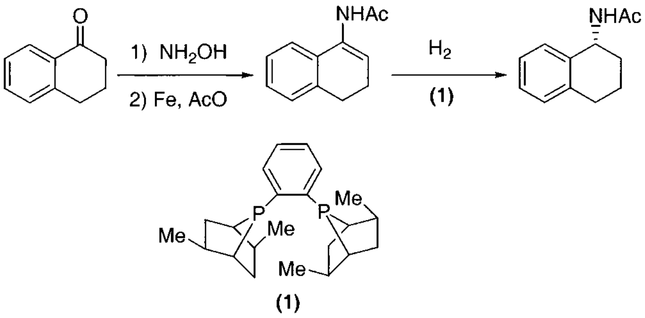
Scheme 2



Scheme 3



Scheme 4



The synthesis of propynyl alcohols by the reaction of acetylenes with aldehydes or ketones under basic conditions is a common industrial process operated on a large scale, but often requires a stoichiometric amount of base, such as Na/NH_3, alkyllithium, or organomagnesium salt. It has now been reported that cesium hydroxide will catalyse the reaction at room temperature in THF, THF−DMSO, or THF−NMP as solvent (Knochel, P. et al. *Angew. Chem. Int. Ed.* **1999**, *38,* 1463). In contrast, the reaction of acetylenes with

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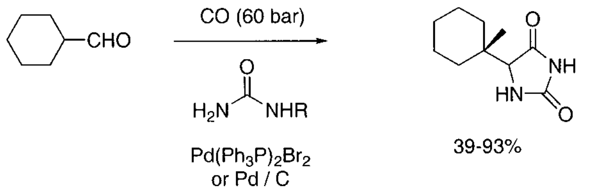
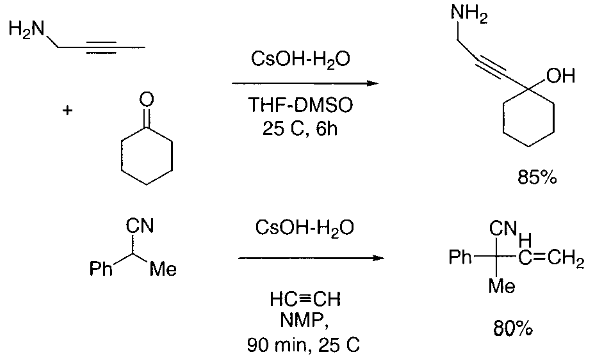
Scheme 5



Scheme 6



benzylic nitriles results in addition to the acetylene, similar to the reaction under phase-transfer conditions (Scheme 6).

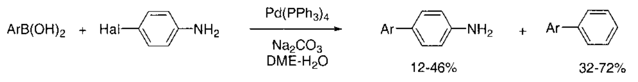
In the same issue of the journal, workers at BASF (Brever, K. et al. *Angew. Chem. Int. Ed.* **1999**, *38*, 1401) describe a new catalyst for the addition of alcohols and amines to acetylenes. Use of zinc acetate on silica gel catalysed the reaction of methanol with propyne (or alkene) to give 2-methoxypropene, an important industrial chemical. It is suggested that zinc silicate is the active catalytic species. The reduction of carboxylic acids to alcohols is often a problematic reaction and usually requires hydride reagents in anhydrous solvents, where the workups can be tricky. A new method (Falorni, M. et al. *Tetrahedron Lett.* **1999**, *40*, 4395) describes the reaction of the carboxylic acid with the cheap and readily available cyanuric chloride, followed by reduction of the intermediate with aqueous sodium borohydride. The reaction is particularly suited for protected amino acids, since Boc, Cbz, and Fmoc groups are all stable under the reaction conditions.

The subject of cross-coupling continues to attract industrial interest, and Suzuki coupling of arylboronic acids to vinyl triflates has been widely used. The high cost of triflic anhydride and the instability of some vinyl triflates, however, present disadvantages for large scale synthesis. Workers at Merck Process Research in Rahway, NJ, U.S.A. (Huffmann, M. A. et al. *Synlett* **1999**, 471) have investigated the use of alternatives, such as vinyl phosphates, mesylates, and tosylates and have identified conditions under which they can be used, despite their lower reactivity. Use in the synthesis of carbopenem antibiotics has been demonstrated.

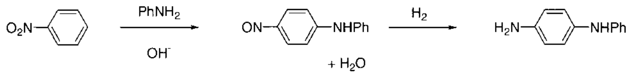
In the same issue workers at the University of Hull (Hird, M. et al. *Synlett* **1999**, 438) report that cross-coupling of arylboronic acids with haloanilines can lead to substituted amounts of deaminated products in addition to the expected biaryl (Scheme 7).

In a feature article in the latest issue of *Green Chem.* (April, 1999, G41) entitled “Taking Green Chemistry from Laboratory to Chemical Plant”, workers at Monsanto look back on their work to produce a novel route to 4-aminodiphenylamine (Scheme 8). This process is now being commercialised by Flexys. Listed as some of the success factors were:

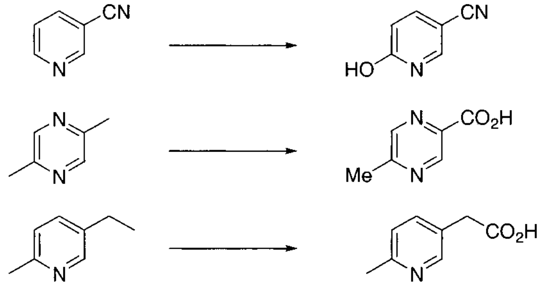
Scheme 7



Scheme 8



Scheme 9



- It was essential to know the appropriate literature but not pay it too much homage. Success was achieved by defining the ideal result and working backwards, i.e., inventing a way to couple nitrobenzene and aniline, even though the literature was not too promising!
- It was important to demonstrate that the concept worked, even if the reagents (NaH−DMSO) were not industrially viable, and then refine it in the light of production feasibility. Good communication between research and production was essential.

A useful review on the use of biocatalysis in the preparation and functionalisation of *N*-heterocycles has appeared (Petersen, M.; Kiener, A. *Green Chem.* **1999**, *1*, 99). The article describes interesting oxidative transformations such as those in Scheme 9.

An interesting observation from a Japanese group (Veji, S. et al. *Chem. Commun.* **1999**, 939) is that lipase-catalysed reactions in organic solvents are greatly improved by the addition of aqueous metal salts. For example, lipase-catalysed esterifications with butanol of a variety of acids went from 10 to 30% ee in dry solvent to 90−98% ee when 0.5% aqueous LiCl was added. The importance of fine-tuning enantioselective processes is again emphasised.

The nature of catalysis of pericyclic processes such as the Diels−Alder reaction and the Claisen cycloaddition is a topic of current interest in relation to enzymes and their effect on transition-state binding. It has been shown that the Claisen rearrangement of allyl phenyl ether to 2-allylphenol, contrary to current accepted kinetic theory, goes faster as the solvent viscosity increases and that the presence of small amounts of low-molecular weight polyethylene increases the rate significantly (Swiss, K. A.; Firestone, R. A. *J. Org. Chem.* **1999**, *64*, 2158). It is suggested that one reason for enzymes’ rate-enhancing properties is the presence of tiny “pockets” of high viscosity embedded in a low-viscosity medium (as

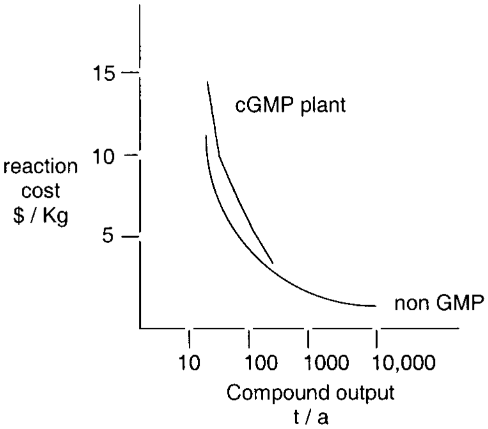


Figure 1.

with the polyethylene in a solvent) in addition to the role played by transition-state binding.

The use of combinatorial chemistry in the discovery and optimisation of catalysts was highlighted in the last issue. A new review (Crabtree, R. H. *CHEMTECH* April, 1999, p 21) entitled “Speeding Catalyst Discovery and Optimisation” discusses the important issues and limitations and emphasises that all companies—whether in fine or bulk chemical manufacture—need to be aware of recent developments even though there are barriers to entry into this field.

In the correspondence section of *Angew. Chem. Int. Ed.* (**1999**, *38*, 1216), Professor Maier, from the Max Planck Institute at Mulheim, discusses the challenge and chance for the development of new catalysts/materials using combinatorial approaches. His plea is that these methods present a unique chance for the discovery of new catalysts and that this approach should be preferred to optimisation of existing methodologies.

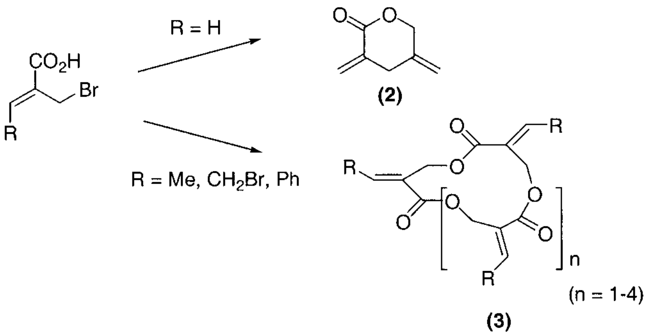
In the patent watch section of *CHEMTECH* (May, 1999, p 39) a Dupont patent for low-pressure olefin polymerisation technology, developed at the University of North Carolina, is mentioned. It is claimed to be the largest patent ever, with 501 pages, 537 examples, and 562 claims (WO 96/23010). Obviously, this is an important industrial technology for the future manufacture of polymers.

In a recent article in *CHEMTECH* (May, 1999, p 58) Albert Hahn from Ecoplan International describes a data package that can allow a quick determination of production costs (excluding raw materials) for a wide variety of multistep organic synthesis. The data are presented for 130 reactions commonly used in the fine chemical industry in the form of graphs such as that in Figure 1 for the catalytic reduction of nitroaromatics.

It is suggested that the methodology has been accurate at explaining market prices for products made by multistep synthesis and could be used for simulating the economics of alternative synthetic pathways.

The Institute of Chemical Engineers in the U.K. have launched an update of their Accident Database, collecting information from various sources. The database contains records of 10 500 accidents and incidents, many from in-company records, which have never been previously published (*The Chemical Engineer* 1999, April 15, p 40). The database can be searched under five headings (activity, causes, equipment, consequences, and substances) and is available by subscription from IchemE (e-mail: she@icheme.org.uk for more information).

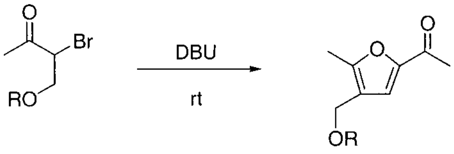
Scheme 10



(2)

(3)

Scheme 11



(4)

The advantages of using cryogenic systems to remove volatile organic compounds (VOCs) is described in an article in *The Chemical Engineer* (*TCE*, 1999, May 13, p 26). In one company VOC emissions were reduced from 34 610 kg to 21 kg. The liquid nitrogen is used twice, once in cooling the effluent stream and the second time for inerting. The system is particularly suited to applications with relative low flow rates and high concentrations of VOC (500−1000 ppm).

Synlett has this year featured a spotlight page in which a postgraduate chemist focuses on a particular reagent. In the May issue, Heike Gielen from Cambridge University (*Synlett* **1999**, 656) has chosen polyamino acids to review and highlights recent reviews and other articles which extend the scope of the Julia−Colonna epoxidation, using hydrogen peroxide and polyamino acid, to prepare epoxyketones in high enantiomeric excess.

If you wish to set your colleagues (or candidates coming for interview!) an interesting organic chemistry problem then how about the following, taken from the work of Schneider, M. F. et al. (*Synlett*, **1999**, 638). When α-bromomethylacrylic acid is treated with DBU it gives the “dimer” (**2**), whereas compounds with a β substituent give no dimer but the macrocyclic lactones (**3**) instead (Scheme 10).

In contrast the reaction in Scheme 11 gives the furan (**4**) by an extremely complex succession of reactions (Rodriguez, J. *Synlett*, **1999**, 505).

Finally, it is not often that I get to mention William Shakespeare in these highlights; however, there was a recent communication from a chemist of that name (*Tetrahedron Lett.* **1999**, *40*, 2035), who described an efficient coupling of lactams and halobenzenes under Hartwig/Buchwald conditions, to yield N-arylated products. Four-, five-, six-, and seven-membered rings are more reactive.

Dr. Trevor Laird
Editor

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