Organic Process Research & Development **2000**, *4*, 62–67

Highlights from the Literature

Some items of Interest to Process R&D Chemists and Engineers as Selected by Trevor Laird and Stephen A. Hermitage

It has been over 100 years after the discovery that led Emil Fischer to report the famous indole synthesis. A report from the Buchwald group (*J. Am. Chem. Soc.* **1999**, *121*, 10251) stamps a recent mark on this important synthetic transformation (Scheme 1). They have found that *N*-arylhydrazones are efficiently prepared from benzophenone hydrazone and a variety of aryl bromides using either a Pd/BINAP or a $Pd(OAc)_2$/Xantphos based catalyst system. These *N*-aryl benzophenone hydrazones serve as protected arylhydrazines, which are deprotected and subjected to Fischer cyclisation in a one-pot procedure to provide indole products. The hydrazone intermediates may be elaborated using further Pd chemistry to *N*,*N*-diarylhydrazones to give more highly substituted *N*-aryl indole products upon deprotection and Fischer cyclisation. Alternatively, the hydrazones may be alkylated then elaborated to produce *N*-alkyl indole products.

Many pharmaceutical compounds contain substructures that require the use of small chiral building blocks for their preparation. The development of synthetic routes to these molecules poses a challenge in organic synthesis. Hollingsworth and Wang at the Michigan State University (*J. Org. Chem.* **1999**, *64*, 1036) have reported the elaboration of (*S*)-3-hydroxy-γ-butyrolactone to useful building blocks depicted in Scheme 2. Their syntheses operate with high chemical yield and enantiopurity. Their approach circumvents the oxidative cleavage reactions of protected sugars commonly used to gain access to these structures.

The presence of an extra methyl group on the binaphthylamine system shown in Scheme 3 enhances the effectiveness of this auxiliary to induce asymmetry in the imidate Claisen rearrangement with diastereoselectivities >98%. This auxiliary, reported by Metz and Hungerhoff (*Tetrahedron* **1999**, *55*, 14941), is another addition to the pool of auxiliaries available for asymmetric synthesis. The methyl compound is prepared from the carboxylic acid in Scheme 3 by an ortho lithiation reaction followed by alkylation with methyl iodide. Elaboration and Curtius degradation gave the methyl binaphthylamine system.

Methyl *N*-unprotected α-amino acid esters are important intermediates in organic synthesis. Chen et al at the Bristol-Myers Squibb Pharmaceutical Research Institute (*J. Org. Chem.* **1999**, *64*, 9294) have reported a facile method for the transformation of *N*-BOC α-amino acids to methyl *N*-unprotected α-amino acid esters. Their method involves treatment of the *N*-BOC substrates with MeOH/TMSCl at room temperature for 18−45 h to afford clean high yields of product with no racemisation (Scheme 4). The use of TMSCl for the in situ generation of HCl is advantageous over HCl since TMSCl is easily measured and dosed into solution. A second advantage of the TMSCl is that it acts as a water scavenger later in the reaction making esterification faster and cleaner.

Merck have reported (*J. Org. Chem.* **1999**, *64*, 7751) a highly convergent multikilogram synthesis of a fibrinogen receptor antagonist (Figure 1). Highlights of the nine-step process include a high-yielding alkylation/cyclisation reaction with bromopropylamine, Michael addition of a lactam to 4-vinylpyridine and a controlled Hofmann reaction of *N*-tosylasparagine.

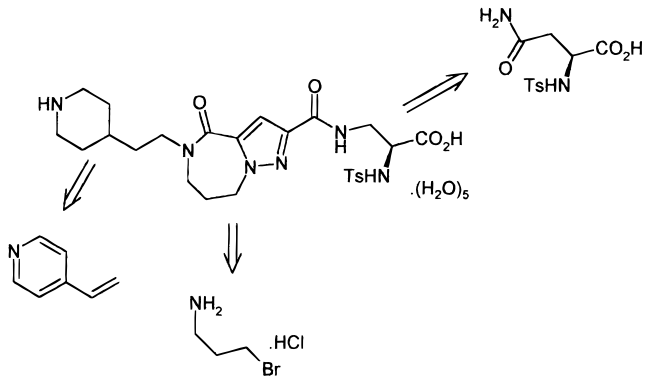

Figure 1.

Rychnovsky at the University of California has reported an improved procedure for the reductive acetylation of acyclic esters (*J. Org. Chem.* **2000**, *65*, 191). The experimental conditions are outlined in Scheme 5 and give typical yields around 80% of product. The group have extended the methodology in a further one step transformation of α-acetoxy ethers into the corresponding ethers by treatment with boron trifluoride etherate and triethylsilane in DCM at −78 °C for <30 min. The reaction is thought to progress via the oxacarbenium ion intermediate shown in Scheme 6

A mixture of boron trichloride and tetra-*n*-butylammonium iodide has been reported (*J. Org Chem.* **1999**, *64*, 9719)

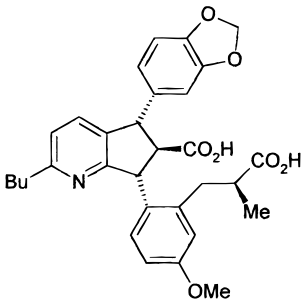

Figure 2.

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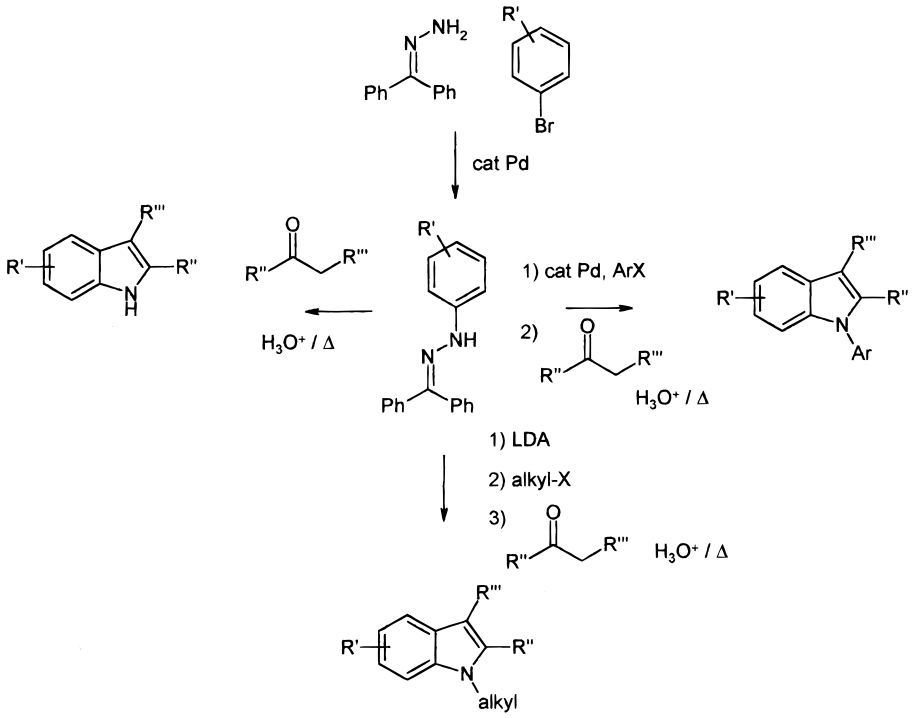
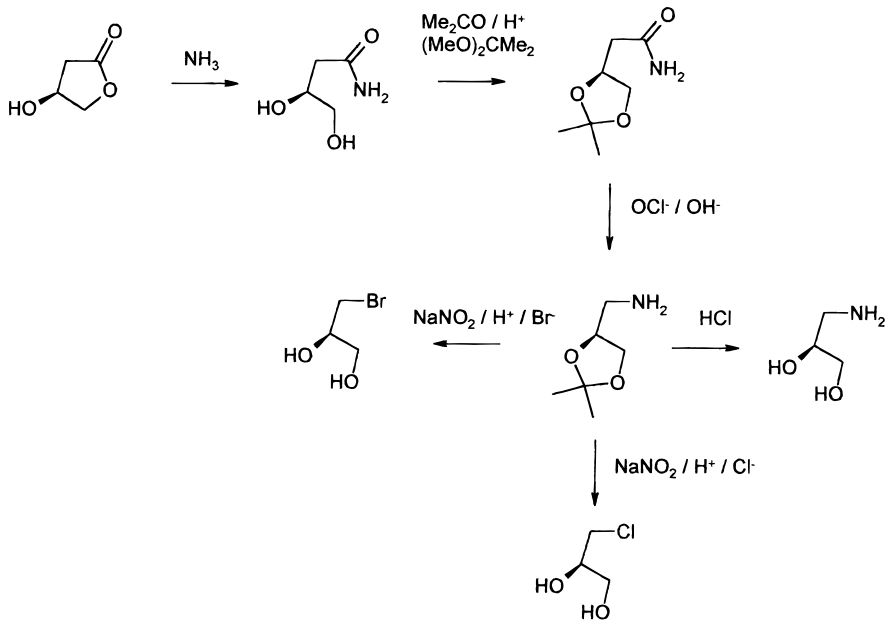
Scheme 1



Scheme 2

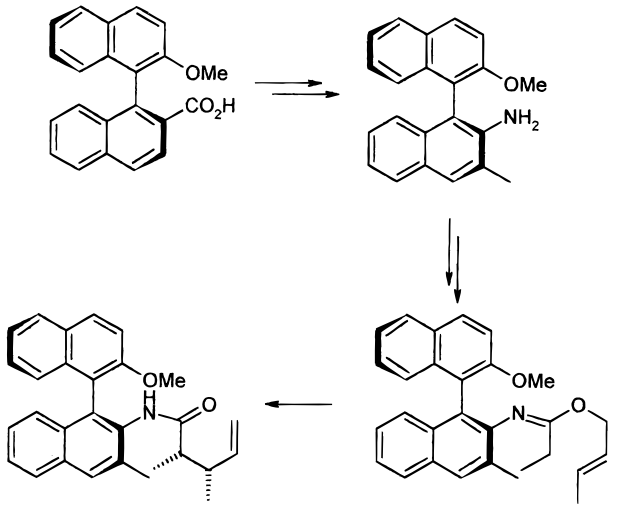


by a group at Pfizer Central Research as a powerful reagent combination for the facile cleavage of primary alkyl aryl ethers at low to ambient temperature within short reaction times (~2 h) (Scheme 7). The method provides high yields of the deprotected product, and the group postulate the reagent reactivity to be between that of BBr_3 and BI_3 (Figure 2).

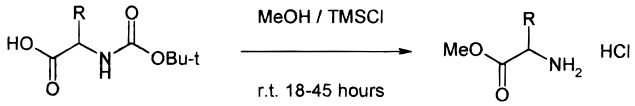
In the first issue of *Angewandte Chemie* for 2000 (*Angew. Chem., Int. Ed.* **2000**, *39*, 44) Nicolaou et al have written an article entitled "The Art and Science of Total Synthesis at the Dawn of the Twenty First Century". This look at total synthesis demonstrates how far organic chemistry has come yet also shows that the art of total synthesis is still in its infancy. This review provides a wealth of information and is a source of inspiration.

The Baylis−Hillman reaction is an atom-economical process which sometimes suffers from the disadvantage of being slow at room temperature, a situation which may not be improved by heating. Often the choice of base is crucial. (For a good review see Ciganek, E. *Org. React.* **1997**, *51*, 201). A recent report (Aggarwal, V. K. et al. *Chem. Commun.* **1999**, 2311) has surprisingly found that DBU is a superior catalyst for the B−H reaction despite the fact that it is considered a non-nucleophilic base and the accepted mechanism for the reaction is initial nucleophilic attack by the base. It is suggested the intermediate β-ammonium enolate

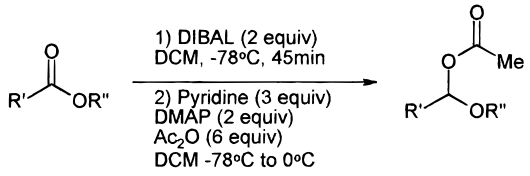
Scheme 3



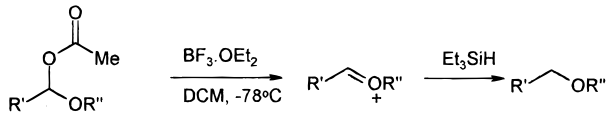
Scheme 4



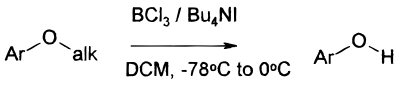
Scheme 5



Scheme 6



Scheme 7

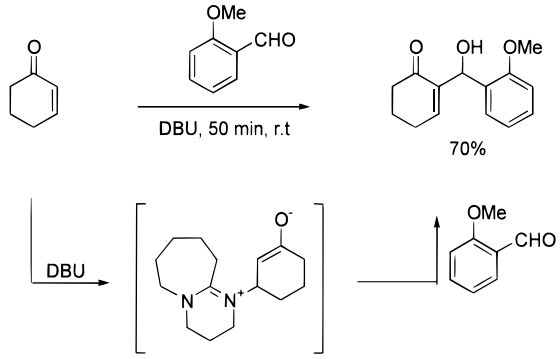


is stabilised by conjugation which increases its equilibrium concentration, resulting in significantly enhanced rates (Scheme 8). This allows aldehydes which have previously been problematical to be used (e.g., 2-anisaldehyde, pival-aldehyde).

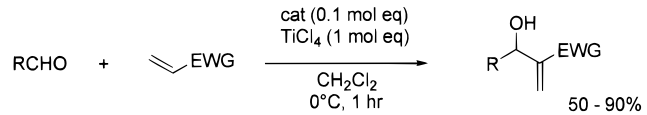
In another paper on the same topic, a new series of catalysts has now been reported which accelerate the reaction (in the presence of Lewis acids) so that reactions are complete at 0 °C after 1 h (Iwama, T. et al. *Tetrahedron Lett*. **1999**, *40* 3741). A typical reaction is shown in Scheme 9.

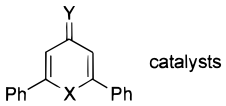
Asymmetric hydroboration has been around for about 10 years, but a recent report indicates that the products of hydroboration can be used to form interesting C−C bonds (Scheme 10). The group of Cudden at New Brunswick, Canada report that both hydrocarboxylation and hydrohydroxymethyl-action proceed efficiently (*J. Org Chem*. **1999**, *64*, 9704)

Scheme 8



Scheme 9

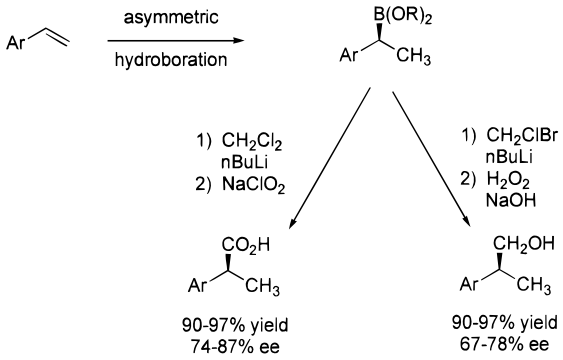




catalysts

X = S, Se
Y = O, S

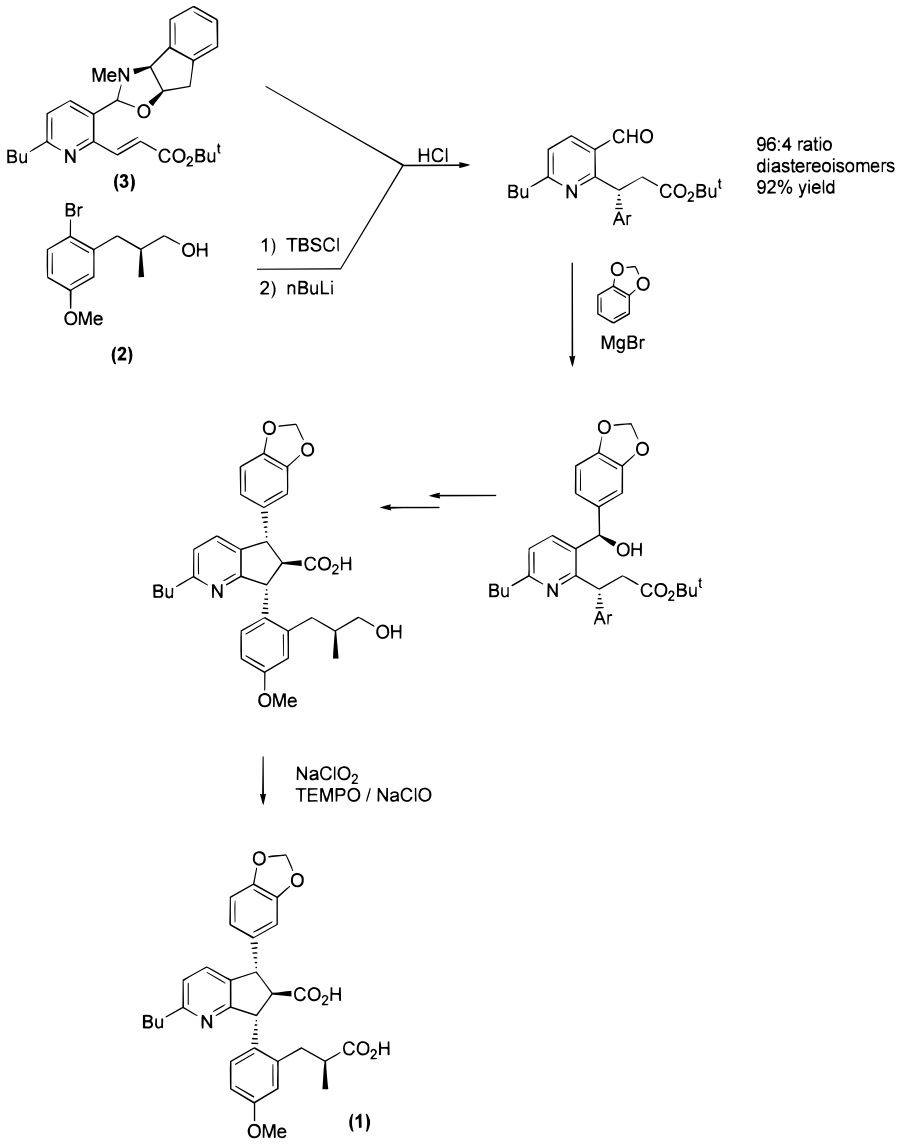
Scheme 10



A practical synthesis of the endothelin receptor antagonist (**1**) on a kg scale is described by process R&D groups from Merck and Banyu Pharmaceutical companies (Song, Z. J. et al. *J. Org. Chem.* **1999**, *64*, 9658). The key step in the synthesis was a chiral Michael addition of the aryllithium [derived from bromide (**2**)] to the unsaturated ester (**3**) containing a chiral auxiliary such as *N*-methyl *cis*-aminoindanol. The resultant aldehyde was treated with a Grignard reagent and then cyclised, deprotected, and oxidised to the final product. (Scheme 11).

The final oxidation is noteworthy in that many other methods (e.g., $RuCl_3/H_5IO_6$ or peroxygen reagents) gave low yields or caused epimerisation. TEMPO/bleach caused ring chlorination, and CrO_3 gave good yields but was environmentally unattractive for large-scale work. The use of stoichiometric sodium chlorite and catalytic TEMPO/bleach is effective but only under very strict conditions, namely pH at 6.7 and simultaneous additions of $NaClO_2$ and bleach (3 mol %) to the buffered acetonitrile solution of the substrate containing TEMPO (5 mol %). Under these conditions minimal ring chlorination takes place, and the reaction is

Scheme 11



safe to scale-up. The reaction is faster at lower pH, but chlorination is increased (up to 0.5% of difficult-to-remove byproducts). It should be noted that mixing of $NaClO_2$ and bleach (NaClO) prior to the addition is not advisable since toxic and potentially explosive chlorine dioxide may be generated.

A new class of phase-transfer catalyst (PTC) has been discovered by the group of Knochel (Tzalis, D. and Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 3685). The best PTC (**4**) synthesised as shown in Scheme 12, was soluble in non-polar solvents and catalysed the fast alkylation of enolates and Michael additions under mild conditions.

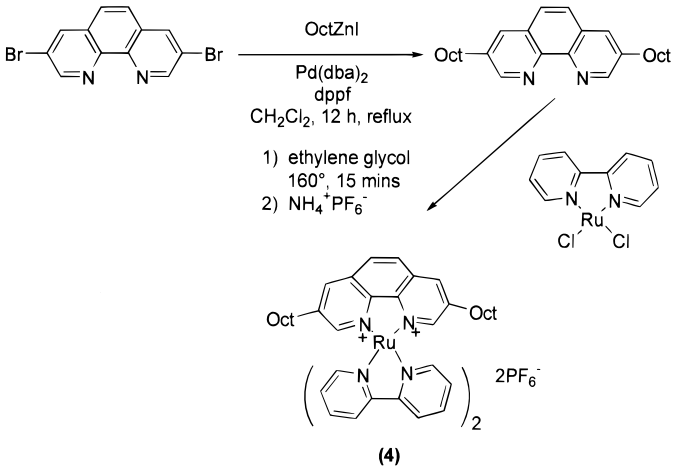
β-amino acids are of immense interest as intermediates in organic chemistry, but most methods of synthesis are tedious and not amenable to large-scale manufacture. Since racemic β-amino acids are readily available in one step from aldehydes, malonic acid, and ammonia, resolution is still an attractive and cost-effective option for larger scale work. A recent report from the Process R&D group of Novartis, East Hanover, NJ, U.S.A. (Roche, D. et al. *Tetrahedron Lett.* **1999**, *40*, 3665) describes the kinetic resolution via enantio-selective acylation with penicillin G acylase in cross-linked enzyme (CLEC) form in toluene or ethyl acetate. Moderate to good yield and good to excellent enantioselectivities are achieved.

Carbohydrates have been produced in a novel, one-pot four-step enzymatic process from glycerol and an aldehyde (Schoevaart, R. et al. *Chem. Commun.* **1999**, 2465). The reaction is envisaged to proceed via the pathway shown in Scheme 13.

Process chemists usually regard tantalum as an inert metal, useful in reactors but rarely in reactions. A recent report, however, indicates that silica-supported tantalum alkoxides are useful in a heterogeneous version of the Sharpless epoxidation (Meunier, D. et al. *Angew. Chem., Int. Ed.* **1999**, *38,* 3540).

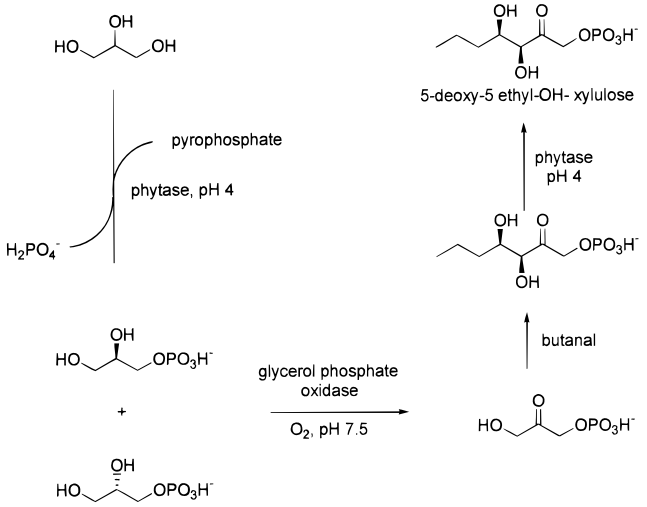
The latest report from Sharpless's group on asymmetric aminohydroxylation has now extended the scope of this useful reaction to amino-substituted heterocycles (Goossen, L. J. et al. *Angew. Chem., Int. Ed.* **1999**, *38*, 1080). Previously, reactions of heterocyclic amines in the AA reaction gave poor turnover, side reactions, or low ee.

Scheme 12

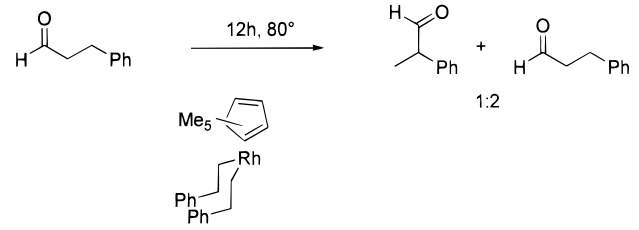


(4)

Scheme 13



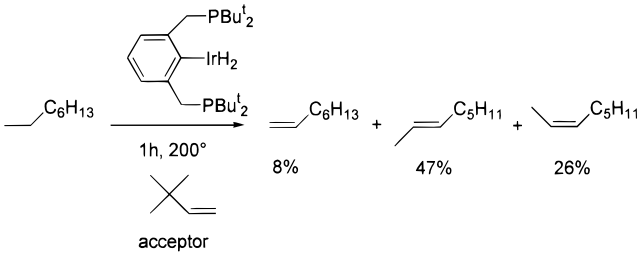
Scheme 14



When olefins are treated with H_2/CO under hydroformylation conditions, a mixture of linear and branched aldehydes is formed, the ratio depending on the catalyst and reaction conditions. Until recently, it was assumed that there was no interconversion between the linear and branched forms, but new work (Lenges, C. P. et al. *Angew. Chem., Int. Ed.* **1999**, *38*, 3533) indicates that under certain conditions linear aldehydes can isomerise to branched isomers, and mechanistic interpretations were supported by deuteration studies and crossing experiments (Scheme 14).

The October 4, 1999, issue of *Chemistry in Industry* has four articles in the general area of catalysis. These cover "Catalysing Business", "Enzyme Evolution", "A Supercritical Success Story" and "Doing the Solubility Splits". The latter is a short concise summary of the recent progress in

Scheme 15



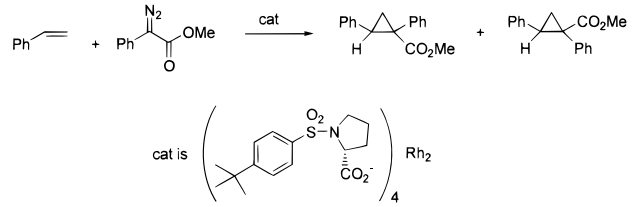
homogeneous catalysis where the emphasis has been not only on product yield and catalyst turnover but also on separation and reuse of the catalyst (Hope, E. G. et al. *Chem. Ind*. **1999**, 755).

The importance of heterogenisation of metallocene catalysts for alkene polymerisation is discussed by Hendrikus Abbenhuis from Eindhoven, The Netherlands (*Angew. Chem., Int. Ed.* **1999** *38*, 1058). Without heterogenisation, many new polyolefins could not be produced on an industrial scale, since the heterogeneous catalyst controls the morphology of the polymer. The article briefly reviews current literature in this field.

The selective functionalisation of aliphatic groups is one of the great unsolved problems of organic chemistry. A commercial dream would be to produce α-olefins via regioselective alephatic dehydrogenation reactions. The first reactions were reported nearly 20 years ago by Crabtree, but these were stoichiometric. Since then many groups have made progress in catalytic reactions and this area has recently been reviewed by Jenson (*Chem. Commun.* **1999**, 2443) focusing on iridium complexes. A typical example is shown in Scheme 15.

The use of supercritical fluids in asymmetric catalysis is increasing as chemists realise the tunability of the systems. Whereas enantioselective cyclopropanation using diazo compounds (Scheme 16) show little pressure sensitivity in sc CO_2. In sc CHF_3 the ee varies from 40% at 100 bar to 77% at 52 bar. This effect is attributed to the change of dielectric constant of sc CHF_3 with pressure—at low pressures the solvent is as nonpolar as pentane, at high pressures it is as polar as ethyl acetate or THF. Supercritical fluids are thus unique tools for probing the effect of solvents on reactions

Scheme 16



(Wynne, D. C. et al. *Angew. Chem., Int. Ed.* **1999**, *38*, 1143).

Chemists are often baffled by polymorphism or the manifestations of it. Many problems arise because two different crystalline forms are present in the crystallising medium or vessel when the crystals are filtered off. The fact that polymorphs of a substance can crystallise concomitantly has previously been recognised but rarely studied. Now a review of the topic by experts in the field has appeared (Bernstein, J. et al. *Angew. Chem., Int. Ed.* **1999**, *38*, 3440). The review outlines the factors that are responsible for concomitant crystallisation, surveys the types of molecules which undergo the phenomenon, and examines crystallisation procedures to facilitate the control of production of the desired polymorph. In one of the footnotes the authors describe an example which illustrates that two polymorphs may be stable in the presence of each other from many years—a sample of cholesteryl iodide prepared in 1937/1938 was shown at the time to be a mixture of two forms; re-examination in 1998 showed that both forms were still present in the sample!

The use of CO_2 in synthesis is to be encouraged and it may not be long before new commercial applications are viable. The group of Baiker at the Swiss Federal Institute of Technology, Zurich have reported (*Chem. Commun.* **1999**, 2303) that a mesoporous ruthenium silica hybrid aerogel has outstanding properties in the synthesis of amides by reaction of CO_2, H_2, and R_2NH. The reaction was 100% selective, and turnover frequencies of up to 18 400/h were obtained. The optimum conditions were found by using a fractional factorial design, and the key parameters were, rather predictably, temperature, total pressure, and amount of catalyst.

A short article on solving large-scale drying problems has appeared recently (*Chem. Engineer* November 11, 1999, p 19). Ian Kemp of AEA Technology, UK discusses a number of problems including one in which a slightly hygroscopic solid was being dried in a fluid bed drier, and the drying time per batch varied from 1 to 3 h with some taking as long as 7 h. It was realised eventually that the longest drying time occurred in the summer when the relative humidity was high and that the product would only dry effectively if the relative humidity was below 17%.

Finally, a warning on the use of sodium borohydride powder with trifluoroacetic acid, which caused a fire in the laboratories of SmithKline Beecham (Liddle, J. *Chem. Br.* **2000,** 19). For procedures which require the use of TFA or for large-scale work it is recommended that pelleted borohydride be used.

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