Organic Process Research & Development **1997**, *1*, 258

Highlights from the Literature

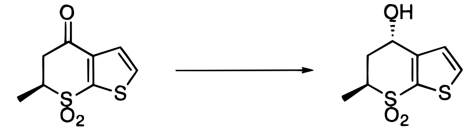
Some Items of Interest to Process R&D Chemists and Engineers, Selected by the Editor

Methods of asymmetric reduction of carbonyl compounds are always of interest. A recent report (*Tetrahedron Lett.* **1997**, *38*, 2641) by workers at Merck announced a cheap and simple method of making β-chlorodiisopinocampheylborane (Ipc)$_2$BCl, a reagent which has previously been demonstrated by H. C. Brown's group to be extremely useful in asymmetric reduction. Previously the reagent has been made using borane−sulphide complexes which are expensive and environmentally unfriendly on an industrial scale.

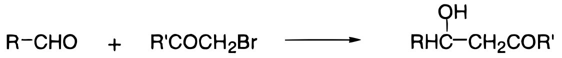
A new method was first devised in which BH_3, generated in situ from $NaBH_4$ and BF_3 etherate, was reacted with α-pinene and then treated with BCl_3. However, the Merck workers found that the enantiomeric excess of the alcohols, formed by reducing ketones with this "in situ" reagent, varied from 30 to 95% ee, depending on the amount of excess $NaBH_4$ used. Once the reason for this variation was investigated, it was discovered that BH_3 could actually be generated from $NaBH_4$ and BCl_3 and that (Ipc)$_2$BCl could be prepared in dimethoxyethane and diglyme (but interestingly not in THF or diethyl ether).

A variety of aromatic ketones are reduced at −25 °C in 80−100% yields with enantiomeric excesses in the 88−99% range—generally above 95%, but reactions take 6 h minimum and, in some cases, days to reach completion. Interestingly, asymmetric amplification is observed in this reaction, as with many asymmetric processes. Thus, although α-pinene of 85% ee was used in generating the reagent, the product still has the same enantiomeric purity as when the more expensive 97% ee pinene was used. It is suggested that, of the three diastereomeric reagents (+,+), (+,−), and (−,−) (Ipc)$_2$BCl, the (+,−) is essentially unreactive but the others gave asymmetric induction.

Alternative biological methods of asymmetric reduction are also described in the second volume of *Chirality in Industry* (Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; Wiley: Chichester, 1997). Zeneca workers describe in Chapter 12 of this excellent new book how they developed an efficient asymmetric and diastereoselective reduction of keto sulphone **1** using bacteria, yeasts, and fungi. The final process used the fungus *Neurospora crassa* which was grown in a fermenter. Addition of the keto sulphone **1** at a rate matching the rate of bioreduction allowed highly selective reduction with little racemisation of the existing chiral centre. On a plant scale, a yield of **2** of 80% was obtained with 99% chemical purity and >98% of the required diastereoisomer.

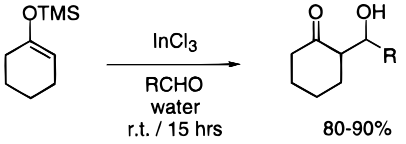

(1) (2)

Process chemists are always interested in reactions that can be performed in water, whether biochemical or chemical. It often surprises me what chemical reactions can be persuaded to occur in the presence of water; a good review appeared last year in *Chemistry and Industry* (**1996**, 123) by one of the pioneers in this area, Professor Lubineau. More recent reports (*Tetrahedron Lett.* **1997**, *38*, 2733) indicated that Reformatsky-type reactions can occur in water—or as a suspension in water—in the presence of bismuth chloride and aluminium powder. Reactions of α-bromo ketones with aldehydes give good to excellent yields of β-hydroxy carbonyl compounds; a significant disadvantage, however, is that some of the α-bromo ketone may get debrominated, particularly at elevated temperatures.


$$\text{R-CHO} + \text{R'COCH}_2\text{Br} \longrightarrow \text{RH}\overset{\text{OH}}{\text{C}}\text{-CH}_2\text{COR'}$$

The reaction does not take place with $BiCl_3$ alone, nor in the presence of Al powder.

The Mukaiyama-aldol reaction was one of the first Lewis acid catalysed reactions shown to proceed in water. More recently, indium trichloride has been found to be a water stable catalyst for a number of C−C bond forming reactions of interest to process chemists. However, purified indium and freshly distilled silyl enol ethers are required. In a recent publication (*Tetrahedron Lett.* **1997**, *38*, 3465) workers at the National University of Singapore have reexamined the reaction of benzaldehyde with [(trimethylsilyl)oxy]cyclohexene, studying effects such as order of addition of reagents and rates of addition, too. It was found that prestirring the liquid aldehyde with indium trichloride before addition of the silyl enol ether and water, together with vigorous stirring, was necessary for good yields. Following the reaction by NMR shows that a different complex between the indium and aldehyde occurs when water is absent compared to when the reagents are added to water. These observations are discussed in terms of the "hydrophobic effect". The indium chloride can be removed in the workup and reused.



Trevor Laird
Editor

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