Strong Asymmetric Induction without Covalent Bond Connection

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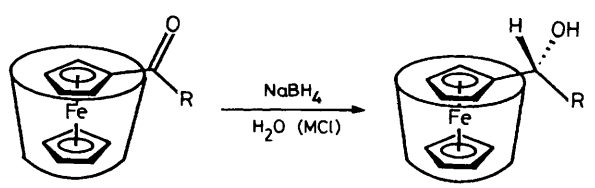
The reduction of ferrocenyl ketones using the aqueous suspension of β-cyclodextrin inclusion complex with sodium borohydride gave optically active alcohols.

Considerable attention has been given to cyclodextrins (CDs) as enzyme models which provide both a chiral receptor and reactive sites.[1] Despite such attractive properties, however, CDs were seldom used as a tool for asymmetric synthesis. In general, asymmetric reaction in a chiral solvent affords only low enantioselectivity. Similarly, it is thought that the asymmetric ability of β-CD is low. The asymmetric reduction of β-CD aryl trifluoromethyl ketone inclusion complexes has been investigated,[2] but the resulting alcohols showed very low optical yields in the range of 0 to 10.0% enantiomeric excess (e.e.). The results suggested that the low enantioselectivity might be attributed to the low chiral environment of the binding site. Recently, however, Sakuraba *et al.*[3] achieved improvement of enantioselectivity by the use of an aqueous suspension of α- or β-CD-arylhalomethyl ketone inclusion complexes in the presence of some sodium or potassium salts. From these results, it is known that the heterogenous



(1) R = Me
(2) R = Ph

MCl = LiCl, NaCl, KCl

Scheme 1

Table 1. Asymmetric reduction of ferrocenyl ketones in β-CD inclusion complexes.

R	MCl	Time/h	Chemical yield/%	$[\alpha]_D^{25}$[a] (Solvent)	Optical yield/% e.e.
Me	None	24	54	−10.46 (Benzene)	34.3[b]
Ph	None	48	52	−12.70 (Ethanol)	49.2[c]
Me	LiCl	24	56	−9.82 (Benzene)	32.2[b]
Ph	LiCl	48	52	−11.10 (Ethanol)	43.0[c]
Me	NaCl	24	40	−15.78 (Benzene)	51.7[b]
Ph	NaCl	48	38	−21.16 (Ethanol)	82.0[c]
Me	KCl	24	59	−12.41 (Benzene)	40.7[b]
Ph	KCl	48	55	−21.66 (Ethanol)	84.0[c]

[a] Measured by JASCO DIP-140 Digital Polarimeter using 1 dm cell (*c* 1.0). [b] Calculated from the reported $[\alpha]_D^{25}$ value in ref. 8. [c] Determined by the separation of enantiomers with h.p.l.c. using DAICEL CHIRALPAC OP (+) (eluent: n-hexane : propan-2-ol = 20 : 1).

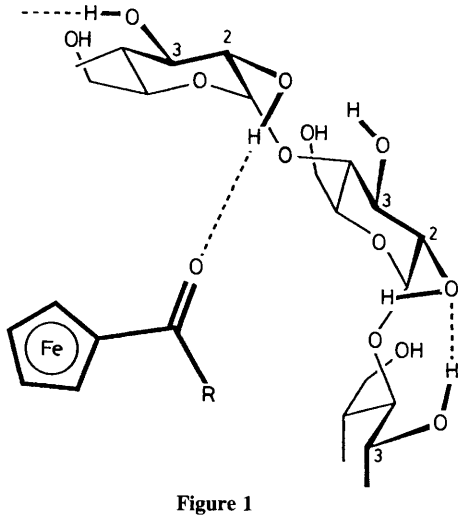


Figure 1

condition is critical in order to achieve asymmetric induction in the reaction of β-CD inclusion complex.

Meanwhile, the ferrocene itself and its derivatives are strongly bound into the cavity of β-CD and form a 1:1 inclusion complex.[4,5] Breslow *et al.*[6] reported a great rate acceleration and high enantioselectivity in the acylation of β-CD by ferrocene derivatives. Sokolov *et al.*[7] have also attempted the asymmetric reduction of ferrocene derivatives, but the reaction was homogeneous, therefore the optical yield was estimated at 30%. Here, we wish to report the strong asymmetric induction from β-CD as a chirality source. The reduction of acetylferrocene (**1**) and benzoylferrocene (**2**) gave optically active alcohols (Scheme 1). Owing to salting-out effects, the values of the maximum optical yield showed more than 80% e.e.

An ethereal solution of ferrocenylketones (2.5 mmol) was added to a suspension of β-CD (5.68 g, 5.0 mmol) in 100 ml of water. The mixture was stirred in a round-bottomed flask, uncovered, at room temperature until the ether was completely evaporated. The suspension of inclusion compounds thus obtained was cooled to 0 °C, and to this was added sodium borohydride (946 mg, 25 mmol). The reaction mixture was then stirred for one or two days at 0 °C. The mixture obtained was partitioned between the water and ether, and the ether layer was washed with saturated brine and dried over anhydrous sodium sulphate. After removal of the ether on a rotary evaporator, the residual crude alcohol was purified by column chromatography on silica gel. Reduction by salting-out was carried out as follows. The aqueous suspension of inclusion compounds prepared by the above method was saturated with lithium chloride, sodium chloride, and potassium chloride, respectively. The suspension of inclusion compounds obtained was reduced by sodium borohydride.

As shown in Table 1, fairly high enantioselectivity has been observed in the region of asymmetric induction from non-covalently bonded media. This strong asymmetric induction may be attributed to the steric requirement in the inclusion complex formation. The ferrocene framework can be tightly and entirely included in the β-CD cavity, by axial inclusion mode;[5] hence, the rotation of acyl groups might be inhibited with the edge of β-CD. Furthermore, molecular model construction predicted the arrangement of inclusion complexes shown in Figure 1, suggesting the presence of hydrogen bonds between the secondary hydroxy group (C-2) of β-CD and the carbonyl group. In this complex, sodium borohydride may attack from the opposite direction of the host molecule. This assumption is supported by the fact that the absolute configuration of (−)-1-ferrocenylethanol is *R*.[8] It is clear that the addition of sodium chloride and potassium chloride contributes to the increased optical yield. This augmentation can probably be ascribed to the salting-out effect. Addition of lithium chloride did not produce the same effect, instead it served as a homogenizer.[3] From this experiment, it can be seen that CDs have great potential for exploitation as a useful tool for asymmetric induction.

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