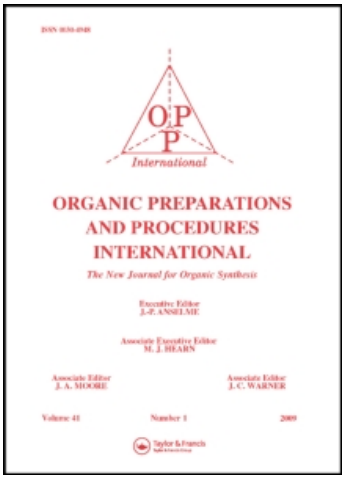


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# ASYMMETRIC EPOXIDATION OF UNFUNCTIONALIZED OLEFINS *via* FORMATION OF CRYSTALLINE CYCLODEXTRIN COMPLEXES

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# ASYMMETRIC EPOXIDATION OF UNFUNCTIONALIZED OLEFINS *via* FORMATION OF CRYSTALLINE CYCLODEXTRIN COMPLEXES

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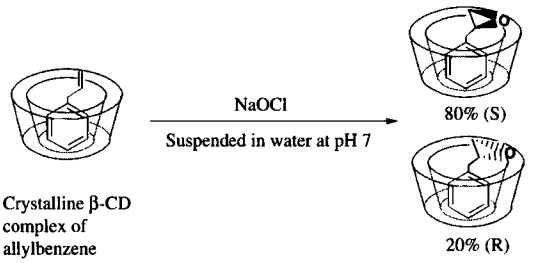
The chiral epoxide functional group is one of the most useful building blocks in synthesis of biologically active compounds.[1] In 1980 Katsuki and Sharpless discovered a highly effective reagent (the Sharpless reagent) for the asymmetric epoxidation of allylic alcohols,[2] but so far the oxidations of homoallylic alcohols[3] and unfunctionalized olefins with this reagent have not been achieved to the required highly enantioselective production of the epoxides.

As molecular reaction vessels, cyclodextrins (CDs) have been expected to induce asymmetry in molecules interacting with their chiral micromatrices in some useful reactions.[4] To date a few studies have reported very limited success in the asymmetric epoxidation of functionalized olefins such as chalcone,[5] cinnamaldehyde,[6] and vitamin $K_3$ analogues[7] in homogeneous solutions of CDs to give the corresponding epoxides with 11, 8, and 48% enantiomeric excesses (% ee), respectively. We have previously found a chiral template-effect of crystalline CD which is successful for the strong

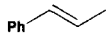
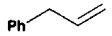
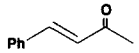



chiral inductions (> 80% ee) into the functionalized substrate as guest molecule included in it.[8,9,10] In connection with our interest in these solid-state reactions, we have investigated the asymmetric epoxidation of the unfunctionalized and functionalized olefins mediated by crystalline CD as a rigid chiral matrix controlled by the crystalline lattice.[11]

As shown in Table 1, moderate enantioselectivity has been observed for the asymmetric epoxidation of olefins having a phenyl moiety included in the crystalline β- or γ-CD complexes. These optical yields are more three times higher than the reported values (≤11% ee) observed for the epoxidations of the functionalized olefins such as chalcone[5] and cinnamaldehyde[6] in an aqueous solution of α-, β-, or γ-CD. As a guest in the solid α-CD complex having a smaller cavity than those of β- and γ-CDs, chalcone gives no reaction at all with NaOCl at 0° (no. 8). The differential enantioselectivity between heterogeneous and homogeneous asymmetric reactions were also shown in the combination of the unfunctionalized olefins and β-CD (no. 5 and 6). When the epoxidation of (*E*)-1-

phenylpropene was run in the β-CD complex, (1*S*,2*S*)-1-phenyl-1,2-epoxypropane was obtained in 80% yield and in 40% ee (no. 5). The reaction in an aqueous solution of β-CD, however, was very slow (15% yield) and showed almost no enantiosectivity (1% ee) (no. 6). The reactions of styrene in the cavity of β-CD with each of NaOCl, $CH_3CO_3H$, and $H_2O_2$ afforded (*S*)-1-phenyl-1,2-epoxyethane in 35, 29, and 10% ee and in 75, 48, and 40% yields, respectively (no. 1-3), suggesting that NaOCl is the optimum oxidizing agent. The reaction of the β-CD complex induced the same (*S*) chirality

**TABLE 1.** Asymmetric Epoxidation of Olefins in Crystalline Cyclodextrin Complexes[a]

| No. | Olefin | Cyclo-dextrin (CD) | Oxidizing agent | Time (days) | Yield[b] (%) | ee[c] (%) (Config)[d] | bp. (°C/torr) or mp.(°C) (reported) | Elemental Analyses (Calcd) C | H |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  | β-CD | NaOCl | 8 | 75 | 35 (*S*)[e] | 86-88/20 (89-90/23)[e] | 80.12 (79.97) | 6.54 (6.71) |
| 2 | " | β-CD | $CH_3CO_3H$[f] | 8 | 48 | 29 (*S*)[e] | 87-90/21 | | |
| 3 | " | β-CD | $H_2O_2$[f] | 8 | 40 | 10 (*S*)[e] | 86-89/20 | | |
| 4 |  | β-CD | NaOCl | 4 | 72 | 40 (*S*)[g] | 81-84/14 (83-84/14)[h] | 80.78 (80.56) | 7.66 (7.51) |
| 5 |  | β-CD | NaOCl | 4 | 80 | 40 (1*S*,2*S*)[i] | 80-82/10 (82-83/10)[j] | 80.41 (80.56) | 7.24 (7.51) |
| 6 | " | β-CD[k] | NaOCl | 4 | 15 | 1 (1*S*,2*S*)[i] | 81-84/10 | | |
| 7 |  | β-CD | NaOCl | 8 | 45 | 60 (*S*)[l] | 123-125 (124.5-126.5)[m] | 80.39 (80.56) | 7.34 (7.51) |
| 8 |  | α-CD | NaOCl | 8 | 0 | — | | | |
| 9 | " | β-CD | NaOCl | 8 | 87 | 30 (2*S*,3*R*)[n] | 81-82 (82-84)[n] | 80.61 (80.34) | 5.20 (5.39) |
| 10 | " | γ-CD | NaOCl | 8 | 90 | 31 (2*R*,3*S*)[n] | 81-83 | | |

a) The crystalline CD complexes of olefins (2 mmol) were dispersed in water (5 mL) and reacted with oxidizing agents (2 mmol) at 0° under argon. b) Isolated yields. c) Determined by $^1H$ NMR spectroscopy in the presence of $Eu(hfc)_3$. d) Assigned by comparison of polarimetry measurements with literature values. e) Based on the sign of optical rotation of (*R*)-(+)-1-phenyl-1,2-epoxyethane in benzene: G. Berti, F. Bottari, P. L. Ferrarini, and B. Macchia, *J. Org. Chem.*, **30**, 4091 (1965). f) In aqueous 0.1M $K_2CO_3$ solution (5 mL). g) Configuration of (-)-enantiomer is *S*: C. R. Johnson and C. W. Schroeck, *J. Am. Chem. Soc.*, **95**, 7418 (1973). h) S. Mitsui and S. Imaizumi, *Nippon Kagaku Zasshi*, **86**, 219 (1965); Chem. Abstr., **63**, 4133 (1965). i) Configuration of (+)-enantiomer is 1*R*, 2*R*: H. E. Audier, J. F. Dupin, and J. Jullien, *Bull. Soc. Chim. France*, , 2811 (1966). j) F. Montanari, I. Moretti, and G. Torre, *Gazz. Chim. Ital.*, **104**, 7 (1974). k) The solid complex of (*E*)-1-phenylpropene (1 mmol) was dissolved in water (200 mL) and oxidized with an equimolar amount of NaOCl at 0° under argon in the homogeneous system. l) Configuration of (-)-enantiomer is *S*: T. Hirano, S. Inoue, and T. Tsuruta, *Makromol. Chem*, **177**, 3245 (1976). m) Z. A. Zeller, *Helv. Chim. Acta*, **26**, 1614 (1943). n) Configuration of (-)-enantiomer is 2*R*, 3*S*: B. Marsman and H. Wynberg, *J. Org. Chem.*, **44**, 2312 (1979).

regardless of the oxidizing agents in contrast to that in aqueous solution[6] and further irrespective of the olefinic substitution patterns. However, the epoxidation of chalcone included in γ-CD reversed the chiral induction from that observed with the β-CD complex (no. 9 and 10). These results show that β- and γ-CDs form complexes with chalcone such that the oxidation with NaOCl occurs at different enantiofaces of the olefin to yield the epoxides of opposite chiralities.[11] The highest optical yield, 60% ee, was achieved in the combination of NaOCl and 3-phenyl-1-propene (allylbenzene) in the crystalline β-CD complex suspended in water at the oxidizing condition of 0° under argon, which gave predominantly (*S*)-(-)-3-phenyl-1,2-epoxypropane in moderate chemical yield (no. 7).

In the chlorination of anisole with HOCl in aqueous α-CD solution, Breslow *et al.*[12] suggested the covalent participation by the host molecule: the chloronium cation transferred first to a hydroxy group of the α-CD, then to the guest. Such a path seems to occur in solutions in the presence of NaOCl and CDs. However, in the heterogeneous epoxidation of olefins with NaOCl, no chlorine-substituted products such as *p*-chlorostyrene derivatives and chlorinated CDs were detected from the $^1$H NMR spectra of the recovered guest and CDs after reaction. Thus, the reaction pathway through the initial formation of CD-hypochlorite[12,13] is negligible in the heterogeneous oxidation of the crystalline CD complexes.



## EXPERIMENTAL SECTION

Mps are uncorrected. $^1$H NMR spectra were obtained from a JEOL GSX-270 (270 MHz) spectrometer in DMSO-$d_6$ or $CDCl_3$ by using $(CH_3)_4Si$ as an internal standard. IR spectra were recorded on a Shimazu IR-460 spectrophotometer. The X-ray powder diffraction (XRD) patterns of the solid CD complexes were taken in the region of 5 to 35° by a Rigakudenki Model 2037 X-ray diffractometer using Ni-filtered Cu-Kα radiation. Optical rotations were measured in various organic solvents on a Union Giken PM-101 spectropolarimeter equipped with a 1 dm cell at 25°. α-, β-, and γ-CDs were purchased from Mercian Co. and recrystallized from water. *tris*[3-(Heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III), (Eu(hfc)$_3$), as a chiral shift reagent in NMR analysis was obtained from Aldrich Chemical Co. and used as received. All the other reagents used were commercially available and were used without further purification.

**Epoxidation Procedure.**- The crystalline inclusion complexes were prepared by adding the olefins to a saturated aqueous solution of CD. To 100 mL of an aqueous solution containing α-CD ($8 \times 10^{-1}$ M), β-CD ($1 \times 10^{-1}$ M), or γ-CD ($8 \times 10^{-1}$ M) were added equimolar amounts of olefins at 70° and further by cooling to 0°. The CD complexes were collected and used without drying *in vacuo*; the order of their crystallinity was found to decrease on dehydration.[14] The XRD patterns of these wet precipitates showed that they were highly crystalline and not physical mixtures of CDs and olefins at the same molar ratio as that of the corresponding complexes. All olefins formed 1:1 inclusion compounds with β-CD as determined by $^1$H NMR spectroscopy in DMSO-$d_6$. (*E*)-1,3-diphenyl-2-propen-1-one (chalcone) formed a 1:2 (guest : host) crystalline complex with α-CD and a 1:1 complex with γ-CD. The crystalline inclusion compounds (2.5-3 g wet weight, 2 mmol) were suspended in a water (5 mL) containing sodium hypochlorite (3 mL of 5% NaOCl, 2 mmol), which was adjusted to pH 7 by using 0.1 M aqueous HCl solution before use, at 0° over 4-8 days under argon. Nearly all the complexes

were insoluble in water under these reaction conditions and the crystallinity of the complex was not altered very much during the reaction over 8 days, judging from the changes of the XRD patterns. After the reaction, 0.1 M aqueous $Na_2S_2O_3$ solution (10 mL, 1 mmol) was added to decompose the unreacted NaOCl, and then water was added to dissolve the complex. The aqueous solution was extracted three times with $CH_2Cl_2$ or ether. The organic layer was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The extract was recovered in 90-95% yields and was chromatographed on Wako C-300 silica gel with $CH_2Cl_2$ as the eluent. The products isolated were identified by comparison of their $^1H$ NMR and IR spectra with those of authentically racemic epoxides. Enantiomeric excesses were determined from the $^1H$ NMR spectra of the optically active epoxides in $CDCl_3$ in the presence of 0.1-0.5 equivalents of $Eu(hfc)_3$. The absolute configuration was determined from the reported sign of optical rotation given in the literature.

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