Synthesis and catalytic activity of new macrocyclic chiral salen complexes

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New macrocyclic chiral salen complexes were synthesized and then the efficiency of these fully symmetrical ligands as catalysts was evaluated in the asymmetric epoxidation of olefins and borohydride reduction of ketones. The symmetrical macrocyclic salen complexes exhibited a relatively high enantioselectivity in these reactions.

Keywords: 3-*tert*-butyl-2,6-diformylphenol, salen, asymmetric reduction, ketone, epoxidation, vibrational circular dichroism

1. Introduction

Considerable interest has been given to the development of chiral Schiff base ligands for enantioselective catalytic reactions. It has been reported that the Mn(III) salen catalyst is capable of epoxidizing a wide variety of unfunctionalized olefins with a high enantiomeric excess, which is one of the most widely applied reactions in asymmetric synthesis [1–3]. Generally, the structural and electronic properties of salen ligands play an important role in the catalytic activities [4,5]. In almost all the salen complexes studied to date, the two identical salicylaldehyde derivative moieties are connected to both sides of one diamine in the ligands [1–8].

Lopez et al. [9] have reported the synthesis of a new class of unsymmetrical chiral salen ligands which possess two different salicylaldehyde derivatives, each with different substituent groups. This combination allows modifying both the electronic properties and the steric effects simultaneously. Ito and Katsuki [10] reported that the new optically active Mn(III) salen complex having a carboxylate group on the ethylenediamine moiety was a very efficient catalyst for the asymmetric epoxidation of 2,2-dimethylchromene derivatives. They have achieved a high level of enantioselectivity (upto 99% ee) using that non-symmetrical salen Mn(III) complex. The pseudo-axially oriented carboxylate was postulated to coordinate to the Mn ion and the high enantioselectivity of the complex bearing a monosubstituted diamine moiety was strongly related to the asymmetric induction by non-planarity of the salen ligand in that system.

We report herein the synthesis of the fully symmetrical macrocyclic chiral salen Schiff bases through the condensation of two diamine molecules with two 2-diformylphenols. These new macrocyclic chiral salen ligands afforded an enantioselective catalytic activity in the asymmetric epoxidation of olefins and the borohydride reduction of ketones, as a Mn(III)- and Co(II)-type catalyst, respectively. The relation between the enantioselectivity and the structural feature of these new macrocyclic salen ligands was evaluated in this work.

2. Experimental

New symmetrical macrocyclic chiral salen complexes were synthesized from 2,6-diformylphenol and 3-*tert*-butyl-2,6-diformylphenol. These two diformylphenol derivatives were prepared according to the method reported in the literature. The 2,6-diformylphenol was synthesized by a three-step procedure from 2,6-dimethylphenol with high yield and good reproducibility, as reported by Zondervan et al. [11]. 3-*tert*-butyl-2,6-diformylphenol was also prepared by the procedure similar to that described by Chang et al. [12]. The outlines of syntheses are given in schemes 1 and 2. For the synthesis of a fully symmetrical macrocyclic chiral Schiff base, 1.0 equiv. of 2,6-diformylphenol (**1a**) or 3-*tert*-butyl-2,6-diformylphenol (**1b**) was added to 1.0 equiv. of the corresponding diamine derivatives, respectively.

Two kinds of conventional chiral salen ligands (**4**, **5**) were also synthesized by the synthetic sequence shown in scheme 3 and they were used as catalysts to compare the enantioselectivity with new macrocyclic salen catalysts in the same asymmetric reactions. The chiral salen **6** was also chosen as one of the salen ligand catalysts for this purpose, which was obtained from Aldrich Co. The salicylaldehydes with *tert*-butyl group were synthesized by direct formylation according to the method reported by Casiraghi [13].

In the first step to obtain the salen ligands **4** and **5**, salicylaldehyde derivatives **1a** and **1b** (2.0 equiv.) were added to the solution of (1S,2S)-(−)1,2- diphenylethylenediamine (1.0 equiv.) in EtOH, respectively. The mixture was heated

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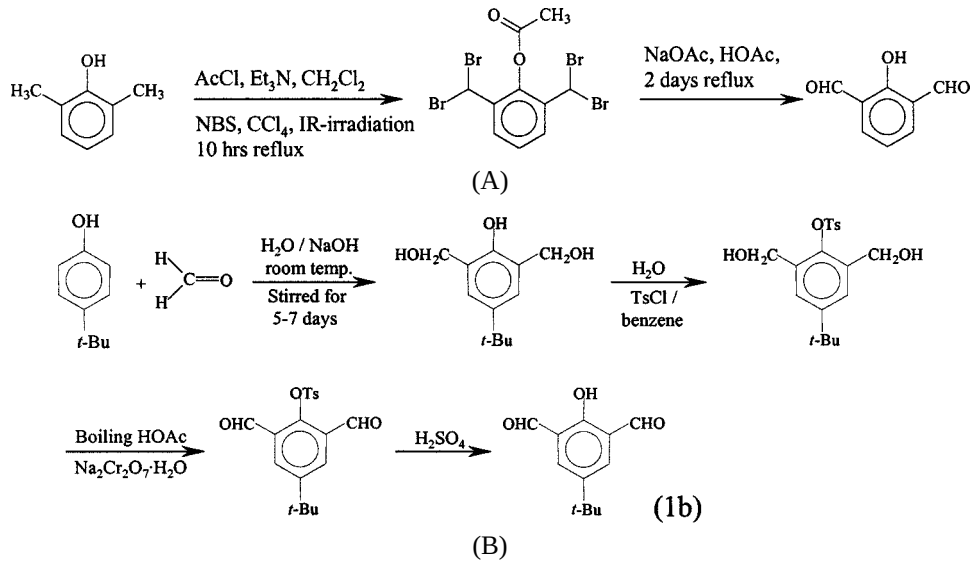
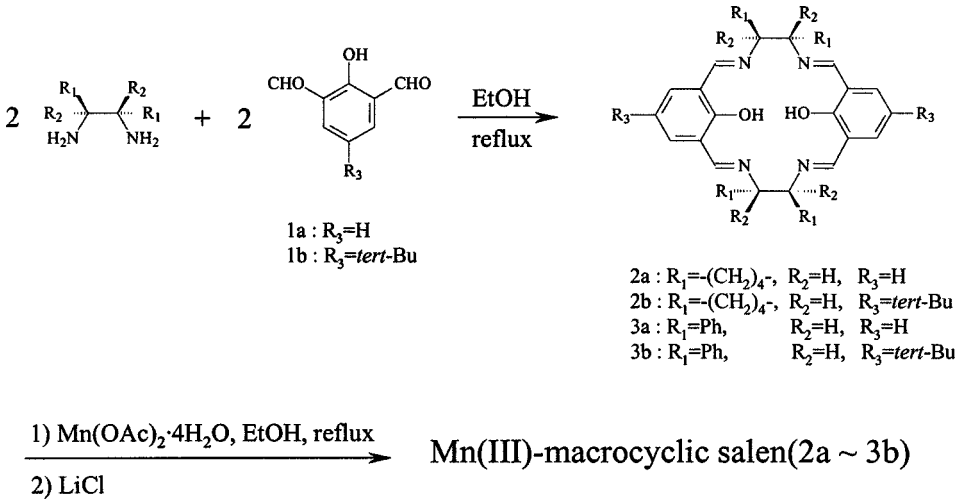


Scheme 1. (A) The synthesis of 2,6-diformylphenol. (B) The synthesis of 3-*tert*-butyl-2,6-diformylphenol.

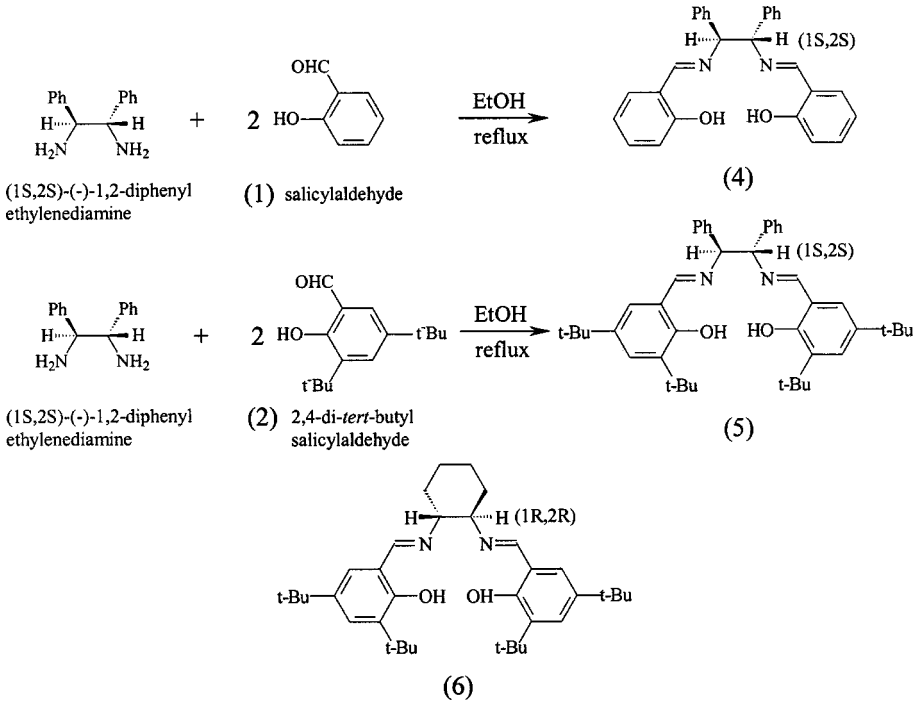


Scheme 2.

to reflux for 5 h and then H_2O was added dropwise to the cooled yellow solution. The resulting crystalline solid was collected by filtration. The compound of **2a**–**3b** and **4**–**6** in EtOH solution was heated with excess $Mn^{II}(OAc)_2{\cdot}4H_2O$ to reflux for insertion of the Mn(II) center, respectively. Then, 3.0 equiv. of LiCl was added and the mixture was heated to reflux for an additional 1.0 h to obtain the Mn(III) complexes, as shown in scheme 2. The resulting dark brown crystal of the Mn(III) complex was collected by filtration after cooling the mixture to 0 °C. In addition, chiral salen Co(II) catalysts were also obtained by the reaction of $Co^{II}(OAc){\cdot}4H_2O$ with corresponding chiral salen ligands in refluxed EtOH solution. We selected the epoxidation of olefins and the borohydride reduction of ketones as test reactions to evaluate the catalytic property of new macrocyclic salen ligands.

The epoxidation was run mainly at 0 °C according to the general procedure using *m*-chloroperoxobenzoic acid (*m*-CPBA) as a terminal oxidant in the presence of *N*-methylmorpholine *N*-oxide (NMO) additive. A solution of 0.96 mmol styrene, 4.80 mmol NMO, and 0.057 mmol Mn salen complex in 10 ml CH_2Cl_2 was cooled to 0 °C. 1.92 mmol of *m*-CPBA was added in four roughly equal portions over a 2 min period. The reaction mixture was stirred for 2 h and 10 ml of 1 N NaOH was added. The organic phase was separated after adding 20 ml CH_2Cl_2 and washed with brine and water. This organic phase was dried over Na_2SO_4 and concentrated to about 2 ml. Residual salen catalyst was removed by the filtration through a silica gel bed. The resulting filtrate was analysed after complete removal of solvent.

In addition, the asymmetric borohydride reduction of ketone was examined at −20 °C. The modification of $NaBH_4$ with tetrahydrofurfuryl alcohol (THFA)–ethanol was applied to the asymmetric reduction of acetophenones and tetralone as reported by Nagata et al. [14]. 0.75 mmol of $NaBH_4$, 5.15 mmol THFA and 0.75 mol EtOH were stirred for 3 h at 0 °C in 5 ml $CHCl_3$ solvent before



Scheme 3.

reaction. The formation of alkoxyborohydride could be monitored by the evolution of hydrogen during the reaction of $NaBH_4$ with alcohols. 0.25 mmol salen catalyst and the reaction substrate were added to the above pre-modified borohydride solution at $-20\,^{\circ}C$. After reaction for 3 h, the organic layer was washed with water, dried and concentrated under reduced pressure. The crude product was distilled under vacuum to afford the corresponding secondary alcohol. The ee% values for the respective reactions were determined by capillary GC using chiral columns (CHIRALDEX^{TM}, Gamma-cyclodextrin trifluoroacetyl, 40 m $\times$ 0.25 mm i.d. (Astec) and BETA-DEX 120^{M} 60 m $\times$ 0.25 mm i.d. (Supelco)) and vibrational circular dichroism spectroscopy (Chiral IR, Bomem).

The characterization of the samples was carried out using FT-IR and UV-vis reflectance spectroscopy. The ^{1}H-NMR and ^{13}C-NMR spectra of chiral salen ligands were also recorded with on a Bruker NMR spectrometer.

3. Results and discussion

The synthesized samples of diformylphenols and macrocyclic salen ligand were characterized by spectroscopy. The typical H-NMR spectra of 2,6-diformylphenol and 3-*tert*-butyl-2,6-diformylphenol are presented in figure 1. The H-NMR peaks at 10.3 and 11.7 ppm are assigned to hydrogen in the CH=O bond and that in phenolic OH position, respectively. This result indicates clearly that 2,6-diformylphenol and 3-*tert*-butyl-2,6-diformylphenol were synthesized successfully. 2,6-diformylphenol was obtained as a long white needle crystal and 3-*tert*-butyl-2,6-diformylphenol as a brownish yellow crystal. As also shown in figure 1, the H-NMR spectrum of macrocyclic salen compounds shows that the condensation of 2,6-diformylphenol (or 3-*tert*-butyl-2,6-diformylphenol) with diamines occurred. The peak at 10.3 ppm in the ^{1}H-NMR spectra (shown in figure 1) due to the CH=O bond was completely lost after condensation of 2,6-diformylphenol with (1S,2S)-(−)1,2-diphenylethylenediamine (or after condensation of 3-*tert*-butyl-2,6-diformylphenol with (1S,2S)-(+)1,2-cyclohexanediamine). New bands developed at 4.7, 7.2, 8.4 and 8.9 ppm in the ^{1}H-NMR spectra after synthesis of macrocyclic salen complex **3a**, which were not found on the H-NMR spectrum of 2,6-diformylphenol. The peaks at 6.5–8.8 ppm are due to the aromatic (=C–H) protons and those at 1.2–1.5 ppm assigned to the protons of terminal *tert*-butyl group. Then, the signals at 1.6–1.9 ppm are for the protons of CH_2 in cyclohexane. Tokunaga et al. [15] have assigned the bands at 3.3 and 4.4 ppm to the proton in the CHN bond. Belokun et al. [16] have reported that the H-NMR peaks of 2H due to the CH=N bond were found at 8.2–8.4 ppm in the salen compounds. For the samples of macrocyclic salen shown in figure 1, the proton peak at 8.42 ppm can be assigned as a proton in the CH=N bond.

The macrocyclic salen complexes exhibited strong signals for the aromatic carbon at 126.6–129.7 ppm on the ^{13}C-NMR spectra. The peaks due to CH_2 in cyclohexane and terminal CH_3 in the *tert*-butyl group were found at 20–40 ppm on ^{13}C-NMR spectra after synthesis of macrocyclic salen complex by the condensation of 3-*tert*-butyl-2,6-diformylphenol with (1S,2S)-(+)1,2-cyclohexane diamine.

Figure 2 shows the FT-IR spectra of chiral salen complexes and 3-*tert*-butyl-2,6-diformylphenol. In the IR spectra, diformylphenols show the characteristic C=O band near 1400 and 1700 cm^{-1} and these peaks disappeared after

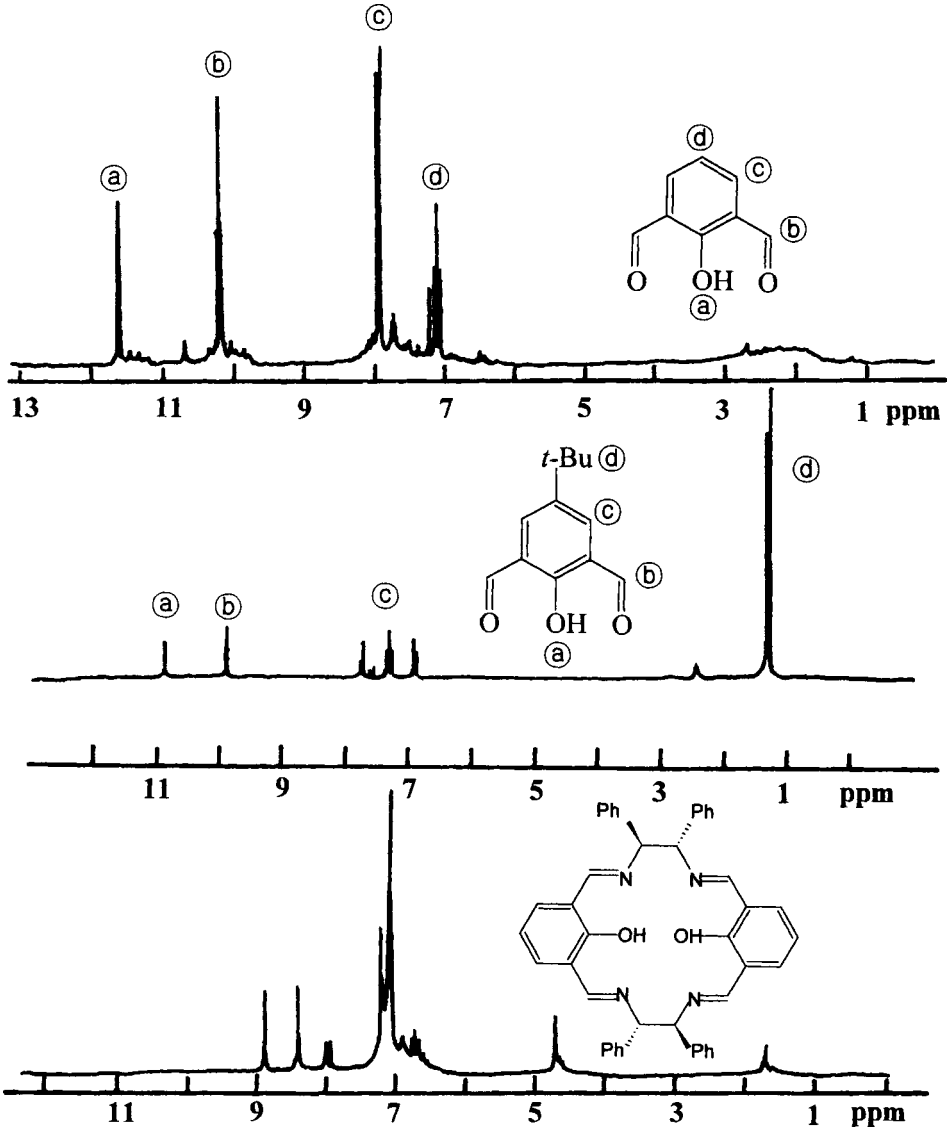


Figure 1. H-NMR spectra of 2,3-diformylphenol, 3-*tert*-butyl-2,6-diformylphenol and macrocyclic salen ligand. Spectra were recorded in $CDCl_3$ relative to TMS.

condensation with optically pure diamines. Then, all the salen complexes as well as macrocyclic chiral salen ligand exhibited the characteristic imine band at 1640 cm^{-1}. The formation of the C=N bond of salen can be characterized by the new band at 1640 cm^{-1}. This peak was not found on the IR spectrum of diformylphenols and that of (1S,2S)-(−)1,2-diphenylethylenediamine. This observation again confirms the formation of macrocyclic chiral salen complexes with the NMR data.

The UV-vis spectra shown in figure 3 are typical of macrocyclic salen Co(II) complexes. The chiral salen ligands of Co(II) form showed the bands at near 280, 375, 430 and 495 nm on the UV spectra. The broad band at 430 nm is probably due to charge-transfer transitions and the weak peak at 495 nm may be assigned to d–d transitions in the Co ions.

The trends in reactivity and enantioselectivity of chiral Mn(III) salen catalysts were examined first for the epoxidation of styrene, α-methylstyrene and *trans*-β-methylstyrene. Especially, the newly synthesized macrocyclic chiral salen catalyst of **3b** exhibited a relatively high level of enantioselectivity in the epoxidation of styrene. With styrene as a substrate, ligand **3b** yields a styrene oxide with 71% of ee at 195 K. The reaction using the Mn(III) form of **6** gave a high optical yield, as reported by Palucki et al. [6]. The epoxidation of styrene with the chiral Mn-salen containing t-butyl groups *para* to the salen oxygens showed a maximum enantionselectivity of 86% ee. Introduction of phenyl groups *para* to the salen oxygens as in **5** and **6** has also resulted in the improvement in optical yield. The result of table 1 means that the macrocyclic Mn(III) salen catalyst of **3b** has the similar steric hindrance near the active center in the approach of styrene as compared with catalyst **5**.

The enantioselective borohydride reduction of ketones was carried out at −20 °C over chiral Schiff base–Co(II) complex catalysts to evaluate the structural feature of new

macrocyclic salen ligand. The reduction of various aromatic ketones was catalyzed by the chiral salen Co(II) complex catalysts with a combined use of THFA–EtOH.

The optically active Co(II) complexes of macrocyclic salen catalyzed the reduction of aromatic ketones with sodium borohydride. As can be seen in table 2, the enantioselectivity was strongly dependent on the structure of the Schiff base ligand. Co(II) complex of conventional salen ligand **4** was an efficient asymmetric catalyst for this reaction, having no bulky groups at the position *para* to the salen oxygens. The higher optical yield was obtained over the ligands of **4**. Introduction of a *tert*-butyl group *para* to the oxygens as in **5** and **6** resulted in a lower enantioselectivity. The new macrocyclic Co(II) salen catalyst of **2b** and **3b** afforded a more improved level of enantioselectivity in the enantioselective borohydride reduction of aromatic ketones than the salen catalysts of **5** and **6**. Introduction of a *tert*-butyl group into the macrocyclic salen ligands also resulted in a slight decrease of enantioselectivity. In this case, the *tert*-butyl group connected to the *para* position of oxygen provides a more hindered steric effect than the hydrogen group. The increased selectivity on the catalyst of **2a** may be attributed to the effective approach of the substrate by the less hindered group. The presence of bulky groups to prevent substrate approach is also crucial

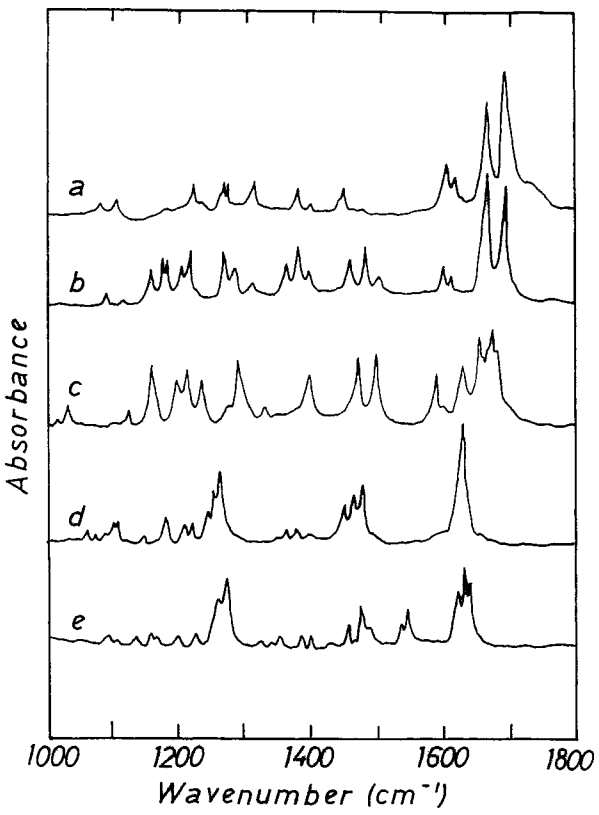


Figure 2. FT-IR spectra of (a) 2,6-diformylphenol, (b) 3-*tert*-butyl-2,6-diformylphenol, (c) salicylaldehyde, (d) macrocyclic salen ligand **2b** and (e) ligand **3b**.

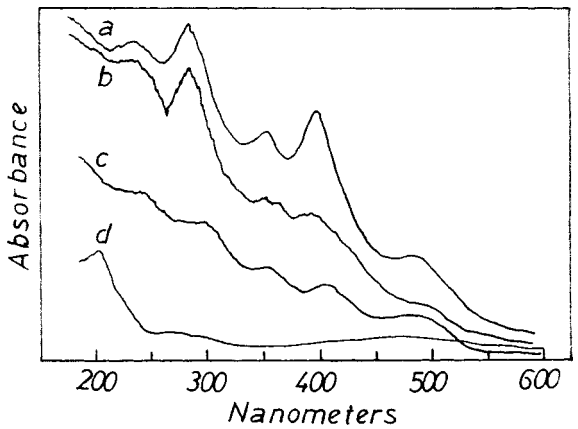


Figure 3. The UV spectra of (a) macrocyclic salen Co(II)-**2a**, (b) salen Co(II)-**6**, (c) macrocyclic salen Co(II)-**3b**, and (d) Co^{2+} ion-exchanged zeolite.

Table 1
Asymmetric epoxidation of epoxides over various chiral salen complexes.[a]

Entry	Olefin	Catalyst	Reaction temp. (K)	Conversion (%)	ee (%)
1	Styrene	**2a**	273	94	20
2	Styrene	**2b**	273	91	46
3	Styrene	**3a**	273	90	37
4	Styrene	**3b**	195	86	71
5	Styrene	**3b**	273	95	56
6	Styrene	**4**	273	93	14
7	Styrene	**5**	273	95	65
8	Styrene	**5**	195	87	78
9	Styrene	**6**	273	97	48
10	Styrene	**6**	195	91	59
11	*trans*-β-methylstyrene	**2b**	273	80	18
12	*trans*-β-methylstyrene	**3b**	273	81	29
13	α-methylstyrene	**2b**	273	95	26
14	α-methylstyrene	**3b**	273	93	38
15	α-methylstyrene	**5**	273	95	30
16	α-methylstyrene	**6**	273	98	51

[a] Catalyst, 6 mol% of olefins; m-chloroperoxobenzoic acid (m-CPBA) was used as a terminal oxidant in the presence of N-methylmorpholine N-oxide additive.

Table 2
Enantioselective borohydride reduction of ketones catalyzed by chiral salen Co(II) complexes[a]:
aromatic ketone $\xrightarrow[\text{THFA + EtOH + NaBH}_4\text{,CHCl}_3]{\text{(S,S)-Co(II) catalyst}}$ (S)-alcohol

Entry	Schiff base	Substrate	Conversion (%)	ee[b] (%)
1	**2a**	Acetophenone	96	50(S)
2	**2a**	α-tetralone	95	41(S)
3	**2a**	Isobutylophenone	63	20(S)
4	**2b**	Acetophenone	96	48(S)
5	**2b**	α-tetralone	95	35(S)
6	**2b**	Isobutylophenone	63	16(S)
7	**3a**	Acetophenone	96	43(S)
8	**3a**	α-tetralone	95	35(S)
9	**3a**	2-methylacetophenone	50	15(S)
10	**3a**	4-methylacetophenone	53	18(S)
11	**3a**	Isobutylophenone	63	28(S)
12	**3b**	Acetophenone	95	40(S)
13	**3b**	α-tetralone	96	32(S)
14	**3b**	2-methylacetophenone	50	18(S)
15	**3b**	4-methylacetophenone	53	20(S)
16	**3b**	Isobutylophenone	63	21(S)
17	**4**	Acetophenone	97	30(S)
18	**4**	α-tetralone	98	42(S)
19	**5**	Acetophenone	97	12(S)
20	**5**	α-tetralone	95	17(S)
21	**6**	Acetophenone	97	12(R)
22	**6**	α-tetralone	96	16(R)
23	**6**	2-methylacetophenone	41	12(R)
24	**6**	4-methylacetophenone	44	10(R)

[a] Reaction conditions: substrate 0.25 mmol, Co(II) catalyst 0.0375 mmol, $NaBH_4$ 0.75 mmol, EtOH 0.75 mol, THFA 5.15 mmol; $NaBH_4$, tetrahydrofurfuryl alcohol (THFA) and ethanol were stirred for 3 h at 0 °C in 5.0 ml $CHCl_3$ solvent before reaction. H_2 was released during the mixing. The catalyst and the substrate were added to this pre-modified borohydride solution at −20 °C. Reaction time = 3 h.

[b] The ee% values for the respective reactions were determined by capillary GC using chiral columns (CHIRALDEX™, Gamma-cyclodextrin trifluoroacetyl, 40 m × 0.25 mm i.d. (Astec)).

to the enantioselectivity in the borohydride reduction of ketone. The use of the ethanol–THFA combination resulted in an improvement of ee% in the reduction of α-tetralone.

Vibrational circular dichroism (VCD) spectroscopy can be used to elucidate the stereochemistries of chiral molecules, including the accurate estimation of enantiomeric excess and their absolute configurations [17]. Optically pure samples as well as a racemic sample were used as references to compare the VCD spectra. Three VCD spectra are shown in figure 4: a spectrum of 95% ee R(+)-styrene oxide obtained from Aldrich Co., one of 95% ee S(−)-styrene oxide and one of the S(−)-styrene oxide obtained on the macrocyclic Mn(III) salen complex as a catalyst. The comparison between the values of ee% determined by VCD and those measured by GC are in very good agreement to within 2% ee. Furthermore, the VCD measurements were also carried out for the product samples obtained in the borohydride reduction of acetophenone and the IR and VCD spectra of product (S)-phenylethanol are shown in figure 5. The absolute configuration and the value of ee% could be determined by VCD spectroscopy.

In conclusion, macrocyclic chiral salen complexes of new structure could be synthesized and asymmetric catalytic reactions were performed to examine the structural

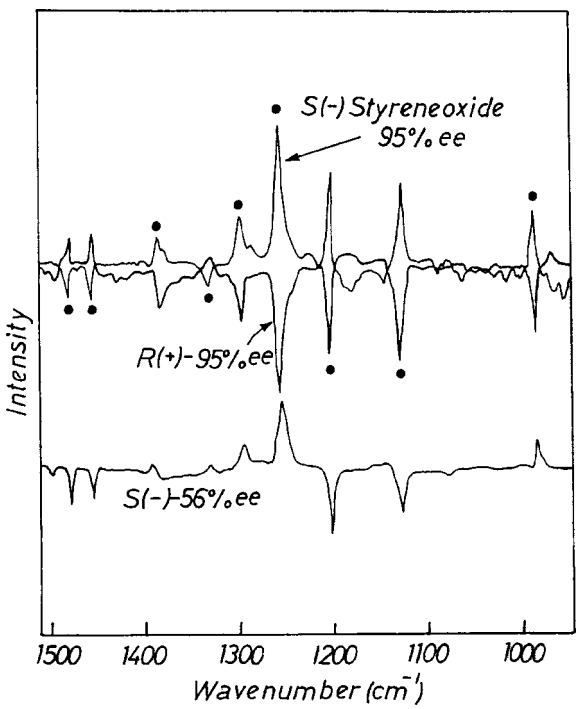


Figure 4. The VCD curves of product styrene oxide obtained in the asymmetric epoxidation of styrene.

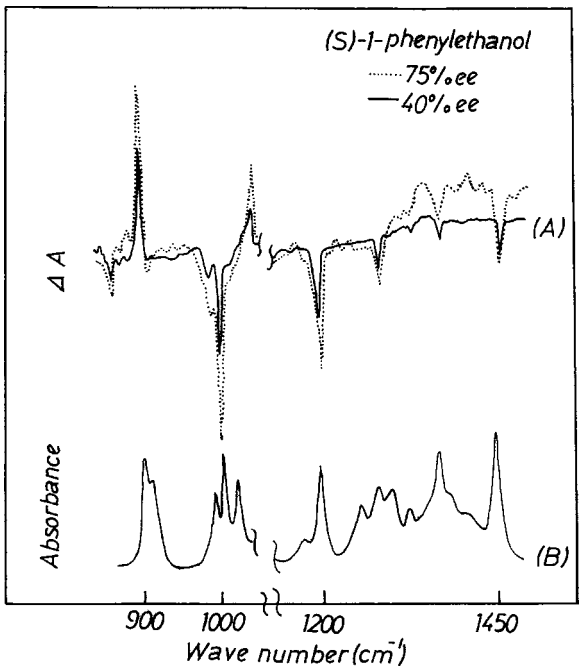


Figure 5. The VCD (A) and IR (B) spectra of (S)-1-phenylethanol obtained in the asymmetric borohydride reduction of acetophenone.

feature of these salen ligands. For the epoxidation of styrene, macrocyclic Mn(salen) complex showed comparatively high enantioselectivity as compared with conventional salen complex. In addition, a high level of enantioselectivity was attainable in the borohydride reduction of ketones using macrocyclic Co(II) salen catalyst. The present study provides a new salen complex catalyst for asymmetric reactions.

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