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The First Asymmetric Epoxidation Using a Combination of Achiral (Salen)manganese(III) Complex and Chiral Amine

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Abstract: A new catalyst system for asymmetric epoxidation was developed by using an achiral (salen)manganese(III) complex with chiral amine. Commercially available (-)-sparteine showed the highest asymmetric induction over the other chiral amines examined and addition of water to the reaction medium improved the induction up to 73% ee in the epoxidation of chromene derivative. Application of the system to the asymmetric oxidation of methyl phenyl sulfide to its sulfoxide was also examined (at most 25% ee). These results support our proposal that a non-planar and chiral structure of the salen ligand plays an important role in the enantioface selection of olefins by (salen)manganese(III) complex. © 1997 Elsevier Science Ltd.

Introduction

Catalytic asymmetric epoxidation is one of the most effective methods for the synthesis of various optically active compounds. Recently optically active (salen)manganese(III) complexes (hereafter abbreviated as Mn-salen complexes) having asymmetric centers at the ethylenediamine part (asterisked carbons in Figure 1) and/or the salicylaldehyde moiety (R) were developed as the best catalysts for the asymmetric epoxidation of some conjugated olefins.[2] The excellent enantiomeric excesses of more than 99% have been achieved.[3] Although further improvement of the *chiral* Mn-salen complexes for epoxidation and their application to other asymmetric reactions are still under investigation in our laboratory, an alternative approach to the asymmetric epoxidation by using a combination of simple *achiral* Mn-salen complexes and *chiral* amines will be described here.[1]

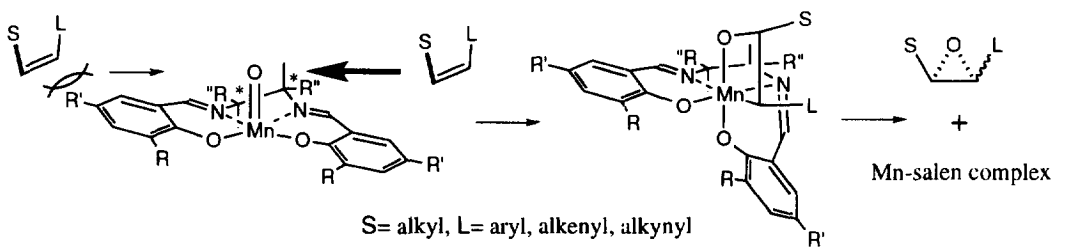
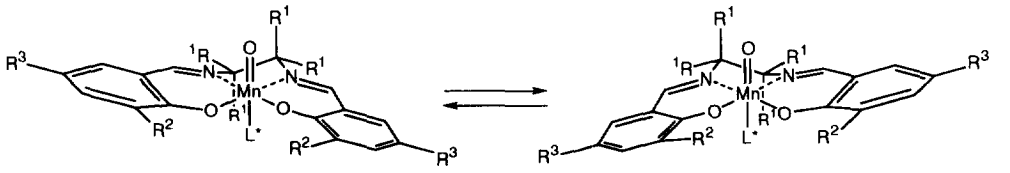


Figure 1

As for the mechanism of the epoxidation catalyzed by Mn-salen complexes, it has been proposed that these Mn-salen complexes are first oxidized to the corresponding oxo Mn-salen complexes,[4] then transfer one oxygen atom to olefins by way of metallaoxetanes, giving epoxides.[5,6a] Although the structure of these oxo species and metallaoxetane has not been determined sufficiently, the high enantioselectivity could be accounted by following two steps: enantioface selective metallaoxetane formation and subsequent diastereoselective decomposition of the metallaoxetane to optically active epoxide and Mn-salen complex (Figure 1).[5,6a] For the

former process, the non-planar structure of the ligand of oxo Mn-salen complex might play a crucial role in determining the direction of olefin' s approach.[6] The salen ligand folds in a manner that the substituents (R") at the ethylenediamine part take sterically favorable pseudo-equatorial orientation. Thus, the chiral centers on the ethylenediamine part of oxo Mn-salen complex dictate the sense of the folding of the salen ligand and induce the chirality in the salen ligand as described in Figure 1. This multiplies the asymmetry-inducing ability of Mn-salen catalyst.[6a]

If the ethylenediamine moiety does not have chiral element, Mn-salen complex is considered to exist as an equilibrium mixture of enantiomeric conformational isomers (**A** and **B** in Figure 2) in a solution. Of course, both of the isomers equally catalyze epoxidation to give a racemic epoxide. However, enantioselective epoxidation becomes possible if this equilibrium can be shifted to one side somehow, even though Mn-salen complex is achiral.



A **B**

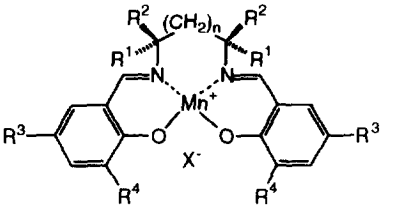
Figure 2

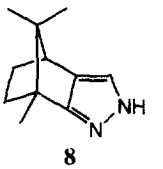
Kochi *et al.* have established the structure of oxo Cr-salen pyridine *N*-oxide adduct in which pyridine *N*-oxide coordinates chromium ion at axial position.[7] Its X-ray crystal analysis showed that this adduct took octahedral coordination and non-planar salen framework.[8] Furthermore, the effect of the axial ligands on enantioselectivity in the asymmetric epoxidation using chiral Mn-salen complexes has been revealed first by us.[9] By considering these findings, too, we expected that oxo Mn-salen complexes would accept donor ligand at axial position and the equilibration in Figure 2 might shift toward one conformer when the axial ligand (**L***) was replaced with an optically active one. Since the approaching pathway of the incoming olefin was considered to be determined by the conformation of the salen ligand (*vide supra*, Figure 1) and the orientation of the olefin by steric and electronic repulsions between the olefinic substituent and the substituent of the salen ligand,[6] it was further expected that the Mn-salen complex bearing only non-chiral substituent(s) could be a catalyst for asymmetric epoxidation, when the conformation of its ligand could be controlled by an optically active axial ligand. To explore this possibility, the epoxidation catalyzed by achiral Mn-salen complexes in the presence of optically active donor ligands was examined.

Results and Discussions

First, various combinations of achiral Mn-salen complexes **1**-**6** or Mn-salpene complex **7** (0.02 equiv.) with optically active pyrazole **8**[10] (0.4 equiv.) were examined in the presence of stoichiometric amount of iodosylbenzene as a terminal oxidant at 0 °C in dichloromethane (Scheme 1). Chromene derivative, 6-acetamide-7-nitro-2,2-dimethylchromene (**9**), was employed as a test substrate because it has been revealed to show high enantiomeric excesses in the chiral Mn-salen catalyzed epoxidation.[3] Most of Mn-salen catalysts except for **6** showed asymmetric induction obviously as expected though it was very low level of ≤7% ee (**1**:

3% ee, **2**: 6% ee, **3**: 5% ee, **4**: -4% ee, **5**: -7% ee, **6**: 0% ee **7**: 2% ee). On the other hand, it should be noted that a $Mn(OAc)_2$ or $Mn(OAc)_3$ (0.02 equiv.), excess **11** (0.4 equiv.), and PhIO system did not carry out the epoxidation at all, suggesting that the presence of Mn-salen complex is indispensable for the present reaction.





8

1: n=0, R^1=R^2=R^3=R^4= H, X= PF_6

2: n=0, R^1=R^2= H, R^3=R^4= *t*-Bu, X= OAc

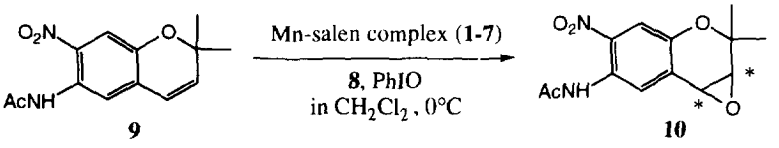
3: n=0, R^1=H, R^2= $(CH_2)_4$, R^3=R^4= *t*-Bu, X= OAc

4: n=0, R^1=R^2= Me, R^3=R^4= *t*-Bu, X= PF_6

5: n=0, R^1=R^2= Me, R^3=R^4= *t*-Bu, X= OAc

6: n=0, R^1=R^2= Me, R^3= $OSi(Pr\text{-}i)_3$, R^4= *t*-Bu, X= PF_6

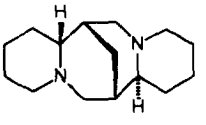
7: n=1, R^1=R^2=H, R^3=R^4= *t*-Bu, X= PF_6

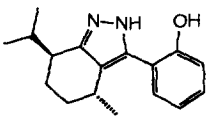


9 **10**

Scheme 1

Encouraged by these results, the effect of other chiral axial ligands was examined next by using complex **2** or **5** and various types of optically active amines, alcohols, and diamines (0.4 equiv.) such as dihydroquinidine, ephedrine, binaphthol, and cyclohexanediamine derivatives. Although most of the ligands were not effective at the point of asymmetric induction (less than 10% ee), (-)-sparteine (**11**) (18% ee with **2** and 34% ee with **5**) and pyrazole derivative **12**[11] (0% ee with **2** but 31% ee with **5**) were found to show higher level. It was also found that use of cationic Mn-salen complexes (**4** and **6**) further enhanced enantioselectivity to 60 and 52% ee's respectively when **11** was used as the axial ligand. However, chemical yields of the epoxides were unsatisfactory (11 and 28%, respectively). The absolute configuration of the epoxide was determined to be 3*R*,4*R* (see experimentals). These results and our working hypothesis on asymmetric induction by Mn-salen





11 **12**

catalyst indicate that the salen ligand of the oxo Mn-salen catalyst possesses the conformation **B** (Figure 2) preferentially in the presence of **11**.

The reaction temperature and the amount of **11** were next optimized by using **6** as a catalyst. As shown in Table 1, enantioselectivity generally diminished and the chemical yield improved as the amount of **11** decreased except for the reaction at rt. However, it is noteworthy that enantioselectivity showed maximum at 0 °C and diminished either at rt and -20 °C. Thus the highest enantioselectivity was attained when the reaction was carried out at 0 °C using 0.4 equiv. of **11**. The same tendency was observed in the reaction with **4** and 60% ee was achieved as described above.

Table 1. Epoxidation of **9** catalyzed by **6** in the presence of **11**[a)]

Entry	Equivalent of **11**	Temperature	Time	Yield (%)	Ee (%)
1	0.1	rt	5 h	27	18
2	0.1	0 °C	5 h	65	30
3	0.1	-20 °C	over night	10	12
4	0.2	rt	5 h	16	14
5	0.2	0 °C	5 h	58	31
6	0.2	-20 °C	over night	11	17
7	0.4	rt	5 h	36	34
8	0.4	0 °C	5 h	28	52
9	0.4	-20 °C	over night	5	37

a) All the reactions were carried out in dichloromethane using 0.02 equiv. of **6** and 1 equiv. of iodosylbenzene as a terminal oxidant.

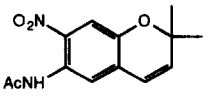
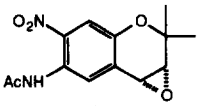
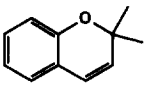
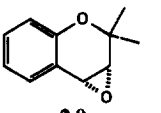
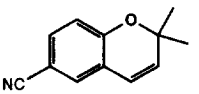
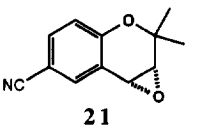
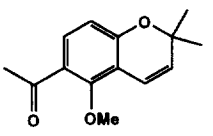
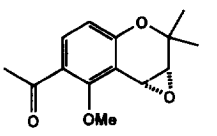
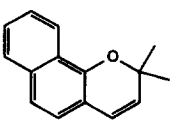
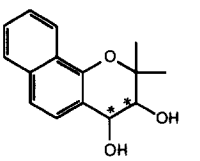
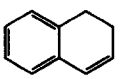
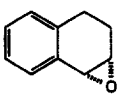
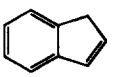
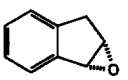
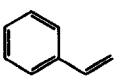
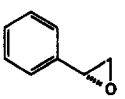
Solvent effect on the epoxidation was also examined. Some of the results were summarized in Table 2. Although clear relationship between enatioselectivity and solvent polarity has not been observed, polar solvents

Table 2. Solvent effect on the epoxidation catalyzed by **6** in the presence of **11**[a)]

Entry	Solvent	Yield (%)	Ee (%)
1	AcOEt	12	26
2	$EtCO_2Et$	9	42
3	C_6H_5Cl	7	43
4	C_6H_5F	21	43
5	$C_6H_5CH_3$	3	34
6	CH_3CN	No Reaction	-

a) All the reactions were carried out for 5 h using 0.02 equiv. of **6**, 0.4 equiv. of **11**, and 1 equiv. of iodosylbenzene at 0 °C.

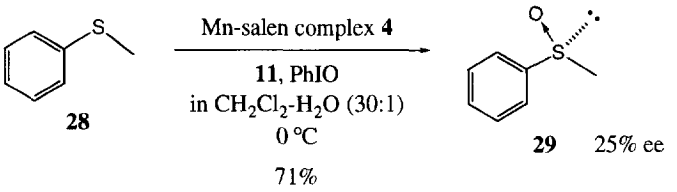
Table 3. Asymmetric epoxidation of other conjugated olefins with complex **4** as a catalyst[a)]

Entry	Olefin	Solvent	Product(s)	Yield (%)	Ee (%)	Absolute confign.
1	 **9**	CH_2Cl_2	 **10**	11	60	(3*R*,4*R*)
2		CH_2Cl_2-H_2O (30:1)		6	73	(3*R*,4*R*)
3	 **13**	CH_2Cl_2	 **20**	10	47	(3*R*,4*R*)
4		CH_2Cl_2-H_2O (30:1)		5	58	(3*R*,4*R*)
5	 **14**	CH_2Cl_2	 **21**	3	52	(3*R*,4*R*)
6		CH_2Cl_2-H_2O (30:1)		5	64	(3*R*,4*R*)
7	 **15**	CH_2Cl_2	 **22**	6	50	(3*R*,4*R*)
8		CH_2Cl_2-H_2O (30:1)		8	70	(3*R*,4*R*)
9	 **16**	CH_2Cl_2	 a mixture of *cis*- and *trans*-isomers, **23** and **24**	23 (cis:trans 1:2)	57 (cis) 52 (trans)	-[b)] -[b)]
10		CH_2Cl_2-H_2O (30:1)		11 (cis:trans 1:1.4)	72 (cis) 54 (trans)	-[b)] -[b)]
11	 **17**	CH_2Cl_2	 **25**	14	21	(1*R*,2*S*)
12	 **18**	CH_2Cl_2	 **26**	16	30	(1*R*,2*S*)
13	 **19**	CH_2Cl_2	 **27**	19	7	(*R*)

a) All the reactions were carried out for 5 h using 0.02 equiv. of **4**, 0.4 equiv. of **11**, and 1 equiv. of iodosylbenzene.
b) The absolute configuration has not been determined.

such as acetonitrile and ethyl acetate gave poor results and dichloromethane was found to be the best solvent. The other achiral Mn-salen complexes showed various levels of asymmetric induction of 4% ee (**1**), 18% ee (**2**), 23% ee (**3**), 60% ee (**4**), 34% ee (**5**), 2% ee (**7**) in the same optimized reaction conditions. Interestingly, addition of water to the reaction was found to improve enantioselectivity further. The asymmetric induction was increased to 73% ee with **4**, while the chemical yield was depressed to a considerable extent (Table 3, entries 1 and 2). Under the optimized conditions, the epoxidation of other olefins was carried out. As shown in Table 3, aryl substituted olefins were oxidized to give optically active epoxides or diols.

The above mentioned new catalyst system was also found to be applicable to the asymmetric oxidation of sulfide. Methyl phenyl sulfide was oxidized to the corresponding sulfoxide of 25% ee as described in Scheme 2. The absolute configuration of the sulfoxide was determined to be *S* by comparison with authentic sample using HPLC analysis.[12] The sense of asymmetric induction in the present oxidation of sulfide was consisted with that predicted from the related asymmetric epoxidation (*vide supra*), suggesting that olefins and sulfides follow the same approaching pathway to oxo Mn-salen species.



Scheme 2

Although we mentioned that the equilibrium of the enantiomeric conformers of achiral oxo Mn-salen complex would be shifted to one side by coordination of an optically active ligand, it does not seem reasonable to consider that the sterically congested nitrogen atom(s) of **11** directly coordinate to the manganese ion centered in the salen complex. Direct coordination of **11** would cause severe non-bonding interaction with the salen ligand. A question how compound **11** induces the chirality in the salen ligand may be answered by taking the positive effect of addition of water on the asymmetric induction into account. Compound **11** is considered to bind to Mn-salen complex through water which is hydrogen-bonding to the nitrogen atoms of **11** as described in Figure 3.

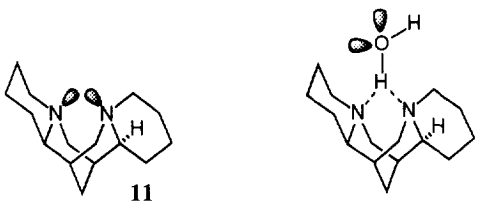
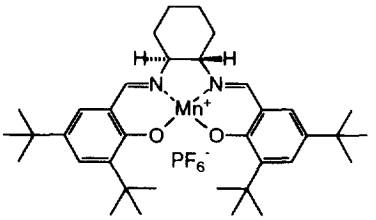
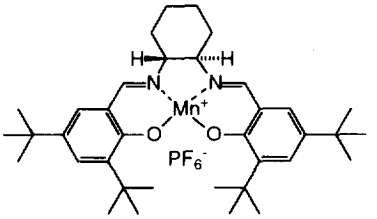


Figure 3

As mentioned above, the conformation of the ligand of chiral Mn-salen complexes is dictated by the chirality of the ethylenediamine moiety. This was supported by the experiment using racemic-**30** (racemic Jacobsen's catalyst). Epoxidation of **17** with racemic-**30** in the presence of **11** showed poor enantioselectivity (<5% ee) as shown in Table 4, entries 1 and 2. Furthermore, epoxidations with optically active (*S,S*)- and (*R,R*)-**30** provided enantiomeric epoxides of almost the same enantiomeric excess (entries 5 and 7), suggesting also that coordination of optically active ligand did not influence on the conformation of the salen framework.



(*S,S*)-**30**



(*R,R*)-**30**

Table 4. Asymmetric epoxidation of **17**[a)]

Entry	Mn-salen	Equivalent of **11**	Solvent	Yield (%)	Ee (%)	Absolute confign.
1	*dl*-**30**	0.4	CH_2Cl_2	8	3	(1*R*,2*S*)
2	*dl*-**30**	0.4	CH_2Cl_2-H_2O	27	4	(1*R*,2*S*)
3	**4**	0.4	CH_2Cl_2-H_2O	14	21	(1*R*,2*S*)
4	(*S,S*)-**30**	0	CH_2Cl_2-H_2O	32	59	(1*S*,2*R*)
5	(*S,S*)-**30**	0.4	CH_2Cl_2-H_2O	21	68	(1*S*,2*R*)
6	(*R,R*)-**30**	0	CH_2Cl_2-H_2O	48	58	(1*R*,2*S*)
7	(*R,R*)-**30**	0.4	CH_2Cl_2-H_2O	16	71	(1*R*,2*S*)

a) All the reactions were carried out for 5 h using 0.02 equiv. of Mn-salen complex and 1 equiv. of iodosylbenzene.

In this study, we were able to demonstrate that an achiral catalyst can be used as a chiral catalyst, if the ligand-conformation of the catalyst is controlled by the addition of optically active compound. It has already been reported that a racemic catalyst serves as a chiral catalyst in the presence of an optically active agent which selectively depresses the catalytic activity of one enantiomer of the catalyst.[13)] This type of optically active agent is called as chiral poison. Recently, the concept of chiral drugging which further activates catalytic activity of a chiral catalyst has been presented.[14)] Our present study provides another new concept of chiral actualizer. A latent chirality of achiral catalyst is incarnated by optically active agent, chiral actualizer. As described here, new concept for asymmetric epoxidation was realized by using a combination of achiral Mn-salen complex and the chiral actualizer **11**. This concept may have the potential to open a new avenue for the

practical catalytic asymmetric reaction. Further studies on this approach are underway in our laboratory.

Experimental

Melting points were uncorrected. Measurements of optical rotations were performed with a JASCO DIP-360 automatic digital polarimeter. ^{1}H NMR spectra were measured with a JEOL EX-270 instrument (270 MHz). All signals were expressed as ppm down field from tetramethylsilane used as an internal standard (δ-value in $CDCl_3$). IR spectral measurements were carried out with a JASCO IR-77 instrument. High resolution mass spectra (HRMS) were taken with a JOEL JMS-SX/SX 102A instrument. HPLC analyses were carried out with a Hitachi L-6000 pump, L-4000 UV detector (λ=254 nm) and appropriated chiral stationary phase column (purchased from Daicel Chemical Industries, Ltd.). Column chromatography was conducted on a Silica Gel BW-820-MH (70-230 mesh) available from Fuji Silysia Chemical Ltd. Preparative thin layer chromatography was performed on 0.25 mm x 20 cm x 20 cm silica gel plate (Merck, $60F_{254}$). Solvents were dried and distilled shortly before use. Ethylenediamine, trimethylenediamine, manganese(II) acetate tetrahydrate, and salicylaldehyde were purchased from Nacalai Tesque Inc. (1*S*,2*S*)-1,2-Diaminocyclohexane, (±)-*trans*-1,2-diaminocyclohexane, and sodium hexafluorophosphate were purchased from Aldrich Chemical Co., Inc. (1*R*,2*R*)-Diaminocyclohexane was purchaced from Wako Pure Chemical Ind., Ltd. 3,5-Di-*tert*-butylsalicylaldehyde[15], 3-*tert*-butyl-5-triisopropylsiloxysalicylaldehyde,[16] 2,3-Diamino-2,3-dimethylbutane[17] were prepared according to the literature methods. 6-Acetamido-2,2-dimethyl-7-nitrochromene (**9**) was provided from Nissan Chemical Industries Ltd. Cationic Mn-salen complex **1** was prepared according to Kochi's procedure.[4] This procedure could not be applied to the preparation of another cationic Mn-salen complex **4** at our hand and complex **4** was prepared with a modified procedure which is described in this section. Complexes (**6**, **7**, and ***dl*-30**) were also prepared with the modified procedure. Mn-salen acetates (**2**, **3**, and **5**) were prepared according to the reported procedure.[18] 2,2-Dimethylchromene (**13**)[19], 6-cyano-2,2-dimethylchromene (**14**)[20], 6-acetyl-5-methoxychromene (**15**)[21], and 6,6-dimethylnaphtho(1',2':2,3)pyran (**16**)[22] were prepared according to the reported methods. 1,2-Dihydronaphthalene (**17**) was purchased from Aldrich Chemical Co., Inc. Indene (**18**) and styrene (**19**) were purchased from Nacalai Tesque Inc. and Kishida Chemical Co., Ltd. respectively and employed after distillation. The analytical data of (3*R*,4*R*)-3,4-epoxy-2,2-dimethylchromene (**20**), (1*R*,2*S*)-1,2-epoxy-1,2,3,4-tetrahydronaphthalene (**25**), (1*R*,2*S*)-1,2-epoxyindan (**26**) have been reported already and their descriptions are omitted.[3,23] Optically active styrene oxide (**27**) is commercially avairable from Aldrich Chemical Company, Inc., and the absolute configuration and optical purity of the epoxidation product of styrene was determined by comparing the retention time of the sample with that of authentic sample in HPLC.[24]

Typical procedure for preparing (salen)manganese(III) complexes: [*N*,*N*'-Bis(3,5-di-*tert*-butylsalicylidene)-2,3-dimethyl-2,3-butylenediaminato]manganese(III) hexafluorophosphate (4). To a solution of 3,5-di-*tert*-butylsalicylaldehyde (879 mg, 3.75 mmol) in EtOH (26 ml) was added 2,3-diamino-2,3-dimethylbutane (218 mg, 1.88 mmol), and the mixture was stirred for 24 h at room temparature. The yellow crystals were separated from the solution and collected by filtration (891 mg, 86%). The crystals (785 mg, 1.43 mmol) were dissolved in EtOH (20 ml) and, to the solution, was added $Mn(OAc)_2 \cdot 4H_2O$ (351 mg, 1.43 mmol). After stirring in air for 1 day at room temparature, the mixture was added $NaPF_6$ (2.4 g, 14.3 mmol) in water (8 ml) and left overnight. The brown precipitate was filtrated, washed with water, and

recrystallized from hexane and dichloromethane to give **4** (741 mg, 69%) as dark brown crystals. IR (KBr): 3474, 2957, 2907, 2870, 1599, 1537, 1466, 1429, 1393, 1362, 1308, 1273, 1254, 1254, 1202, 1178, 1148, 839, 781, 750, 588, 559, 542 cm^{-1}. Anal. Calcd. for $C_{36}H_{54}F_6MnN_2O_2P$: H, 7.29; C, 57.90; N, 3.75%. Found: H,7.48; C, 58.38; N, 3.73%. This elementary analysis suggested that this sample was contaminated by a small amount (~5%) of complex **5**, though the presence of **5** in the sample could not be detected spectroscopically. Anal. Calcd. for a 95:5 mixture of **4** and **5**: H, 7.35; C, 58.40; N, 3.77%. However, as further recrystallization of this sample did not improve the analytical data, it was used for the present study.

[*N*,*N*'-Bis(3,5-di-*tert*-butylsalicylidene)-*cis*-1,2-cyclohexanediaminato]manganese(III) acetate (3). Dark brown crystals. IR (KBr): 3447, 2955, 2907, 2868, 1611, 1558, 1537, 1464, 1431, 1410, 1388, 1362, 1308, 1271, 1250, 1200, 1175, 843, 781, 750, 565, 546 cm^{-1}. Anal. Calcd. for $C_{38}H_{55}MnN_2O_4 \cdot 3/2\ H_2O$: H, 8.52; C, 66.55; N, 4.08%. Found.: H, 8.29; C, 66.86; N, 3.97%.

[*N*,*N*'-Bis(3,5-di-*tert*-butylsalicylidene)-2,3-dimethyl-2,3-butylenediaminato]manganese(III) acetate (5). Dark brown crystals. IR (KBr): 3447, 2959, 2361, 2341, 1601, 1558, 1539, 1394, 1256 cm^{-1}. Anal. Calcd. for $C_{38}H_{57}MnN_2O_4 \cdot 1/2\ CH_2Cl_2$: H, 8.31, C, 65.75, N, 3.98%. Found: H, 8.47, C, 65.74, N, 3.83% (After recrystallization from CH_2Cl_2-hexane).

[*N*,*N*'-Bis[3-*tert*-butyl-5-(triisopropylsilyloxy)salicylidene]-2,3-dimethyl-2,3-butylenediaminato]manganese(III) hexafluorophosphate (6). Dark brown crystals. IR (KBr): 3445, 2947, 2868, 2893, 1618, 1541, 1410, 1342, 1292, 1232, 1205, 1159, 1038, 1009, 959, 870, 687, 559 cm^{-1}. Anal. Calcd. for $C_{46}H_{78}F_6MnN_2O_4PSi_2$: H, 8.03, C, 56.42, N, 2.86%. Found: 8.09, 56.66, 2.80%.

[*N*,*N*'-Bis(3,5-di-*tert*-butylsalicylidene)-1,3-propylenediaminato]manganese(III) hexafluorophosphate (7). Dark brown crystals. IR (KBr): 3447, 2959, 2909, 2870, 1612, 1541, 1458, 1437, 1394, 1364, 1273, 1256, 1178, 847, 559 cm^{-1}. Anal. Calcd. for $C_{33}H_{48}F_6MnN_2O_2P \cdot C_2H_5OH$: H, 7.25, C, 56.00, N, 3.73%. Found: 7.44, 55.95, 3.78%.

[*N*,*N*'-Bis(3,5-di-*tert*-butylsalicylidene)-*trans*-1,2-cyclohexanediaminato]manganese(III) hexafluorophosphate (*dl*-30). Dark brown crystals. IR (KBr): 3474, 2957, 1612, 1537, 1340, 1312, 1271, 1252, 1177, 847, 578, 559 cm^{-1}. Anal. Calcd. for $C_{36}H_{52}F_6MnN_2O_2P \cdot 3/2\ H_2O$: H, 7.18, C, 56.03, N, 3.63%. Found: H, 7.19, C, 55.92, N, 3.44%.

General procedure for asymmetric epoxidation: (3*R*,4*R*)-6-Acetamido-3,4-epoxy-2,2-dimethyl-7-nitrochromene (10). Complex **4** (3.1 mg, 4.2 μmol) was added to a solution of 6-acetamido-2,2-dimethyl-7-nitrochromene (**9**) (54.4 mg, 0.207 mmol) in dichloromethane (1 ml) and the mixture was cooled to 0 °C. Water (37.4 μl, 2.08 mmol), a stock solution of **11** in dichloromethane (0.20 ml, 0.415 M, 83 μmol), and iodosylbenzene (45.7 mg, 0.208 mmol) were added to the solution at the same temparature. After stirring for 5 h, the mixture was chromatographed on slica gel (hexane/AcOEt 1:1) to afford **10** (3.6 mg, 6%) as an orange solid. $[\alpha]_D^{20}$ -17.2° (73% ee, *c* 0.25, $CHCl_3$).[3] ^1H NMR: δ 10.09 (br s, 1H), 8.79 (s, 1H), 7.64 (s, 1H), 3.97 (d, *J*=4.3 Hz, 1H), 3.55 (d, *J*=4.3 Hz, 1H), 2.28 (s, 3H), 1.27 (s, 3H). IR (KBr): 3369,

2974, 1697, 1587, 1504, 1448, 1344, 1292, 1240, 1202, 1167, 1040, 999, 905, 872, 822, 752 cm^{-1}. The optical purity of this sample was determined to be 73% ee by HPLC (DAICEL CHIRALCEL OJ, hexane/2-propanol 1:1. Flow rate: 0.5 ml/min, retention time: 38min for (3*R*,4*R*)-isomer, 52 min for (3*S*,4*S*)-isomer).

(3*R*,4*R*)-6-Cyano-3,4-epoxy-2,2-dimethylchromene (21). Colorless oil. $[\alpha]_D^{20}$ +53.8° (64% ee, *c* 0.16, $CHCl_3$).[21] ^1H NMR: δ 7.65 (d, *J*=2.0 Hz, 1H), 7.53 (dd, *J*=2.0 and 8.6 Hz, 1H), 6.87 (d, *J*=8.6 Hz, 1H), 3.91 (d, *J*=4.3 Hz, 1H), 3.54 (d, *J*=4.3 Hz, 1H), 1.60 (s, 3H), 1.30 (s, 3H). IR (KBr): 2927, 2855, 2228, 1616, 1495, 1279, 1163, 1134, 1101, 1040, 959, 868, 816, 768, 725, 633, 525 cm^{-1}. FAB HRMS calcd for $C_{12}H_{12}NO_2$ $(M+H)^+$ m/z 202.0868, found: 202.0868. The optical purity was determined by HPLC (DAICEL CHIRALCEL OJ, hexane/2-propanol 1/1, flow rate: 0.5 ml/min, retention time: 16min for (3*R*,4*R*)-isomer and 25 min for (3*S*,4*S*)-isomer).

(3*R*,4*R*)-6-Acetyl-3,4-epoxy-5-methoxychromene (22). Colorless oil. $[\alpha]_D^{20}$ +95.8° (70% ee, *c* 0.33, $CHCl_3$).[21] ^1H NMR: δ 7.66 (d, *J*=8.9 Hz, 1H), 6.64 (d, *J*=8.9 Hz, 1H), 4.32 (d, *J*=4.6 Hz, 1H), 3.92 (s, 3H), 3.52 (d, *J*=4.6 Hz, 1H), 2.62 (s, 3H), 1.59 (s, 3H), 1.30 (s, 3H). IR (neat): 2980, 2934, 2374, 2322, 1670, 1597, 1578, 1460, 1358, 1259, 1070 cm^{-1}. FAB HRMS calcd for $C_{14}H_{17}O_4$ $(M+H)^+$ m/z 249.1127, found: 249.1125. The optical purity was determined by HPLC (DAICEL CHIRALCEL OJ, hexane/2-propanol 9/1, flow rate: 0.5 ml/min, retention time: 30 min for (3*R*,4*R*)-isomer and 36 min for (3*S*,4*S*)-isomer).

4,5-*cis*-Dihydroxy-6,6-dimethylnaphto(1',2':2,3)pyran (23). Colorless solid. $[\alpha]_D^{20}$ -10.3° (49% ee, *c* 0.23, $CHCl_3$). ^1H NMR: δ 8.21-8.24 (m, 1H), 7.76-7.79 (m, 1H), 7.60 (d, *J*=8.6 Hz, 1H), 7.45-7.51 (m, 3H), 4.94 (d, *J*=4.3 Hz, 1H), 3.82 (d, *J*=4.3 Hz, 1H), 2.68 (br, 1H), 2.09 (br, 1H), 1.62 (s, 3H), 1.37 (s, 3H). The coupling constant ($J_{4,5}$= 4.3 Hz) supports a gauche arrangement of 4H and 5H and, therefore, the cis configuration of **23**. IR (KBr): 3331, 2972, 2909, 1574, 1508, 1466, 1437, 1414, 1396, 1367, 1309, 1261, 1211, 1151, 1107, 1074, 1016, 945, 920, 797, 773 cm^{-1}. FAB HRMS calcd for $C_{15}H_{16}O_3$ (M^+) m/z 244.1099,.found: 244.1099. The optical purity was determined by HPLC (DAICEL CHIRALCEL OD, hexane/2-propanol 15/1, flow rate: 0.5 ml/min, retention time: 33 min for major isomer and 37 min for minor isomer).

4,5-*trans*-Dihydroxy-6,6-dimethylnaphto(1',2':2,3)pyran (24). Colorless solid. $[\alpha]_D^{20}$ -15.0° (40% ee, *c* 0.18, $CHCl_3$). ^1H NMR: δ 8.19-8.23 (m, 1H), 7.75-7.79 (m, 1H), 7.43-7.55 (m, 4H), 4.72 (d, *J*=8.3 Hz, 1H), 3.75 (d, *J*=8.3 Hz, 1H), 2.49 (br s, 1H), 2.10 (br s, 1H), 1.63 (s, 3H), 1.31 (s, 3H). The large coupling constant ($J_{4,5}$= 8.3 Hz) supports an antiperiplanar arrangement of 4H and 5H and, therefore, the trans configuration of **24**. IR (KBr): 3504, 3404, 3356, 3184, 2980, 2910, 1634, 1601, 1578, 1509, 1458, 1436, 1385, 1369, 1269, 1207, 1142, 1105, 1065, 1032, 912, 822, 799, 770, 750, 664, 642 cm^{-1}. FAB HRMS calcd for $C_{15}H_{16}O_3$ (M^+) m/z 244.1099, found: 244.1099. The optical purity was determined by HPLC (DAICEL CHIRALCEL OD, hexane/2-propanol 15/1, flow rate: 0.5 ml/min, retention time: 24 min for minor isomer and 28 min for major isomer).

Asymmetric oxidation of sulfide: (*S*)-Methyl phenyl sulfoxide (29). Compound **4** (1.9 mg, 2.5

μmol) was added to a solution of thioanisole **28** (14.7 μl, 125 μmol) in dichloromethane (0.6 ml) and the mixture was cooled to 0 °C. Water (22.5 μl, 1.25 mmol), a stock solution of **11** in dichloromethane (0.12 ml, 0.415 M, 50 μmol), and iodosylbenzene (27.5 mg, 125 μmol) were added at the same temparature, and the whole mixture was stirred for 5 h. The mixture was readly chromatographed on slica gel (hexane/AcOEt 1:9) to afford **29** (12.5 mg, 71%) as a colorless oil. $[\alpha]_D^{20}$ -46.3° (25% ee, *c* 0.63, $CHCl_3$).[12] ^1H NMR: δ 7.51-7.68 (m, 5H), 2.74 (s, 3H). The optical purity of this sample was determined to be 25% ee by HPLC (DAICEL CHIRALCEL OD, hexane/2-propanol 9:1), flow rate: 0.5 ml/min, retention time: 21min for (*R*)-isomer and 27 min for (*S*)-isomer.

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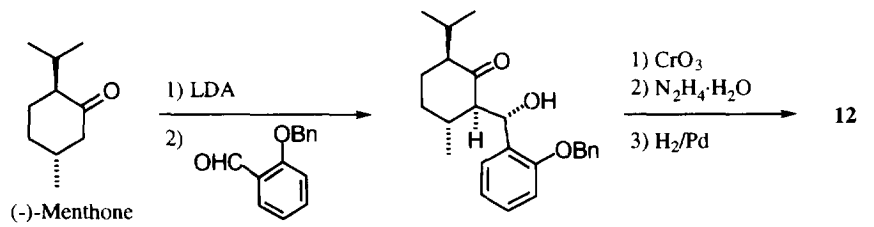
11) Compound **12** was prepared from (-)-menthone as described below.



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23) HPLC data of **20**, **25** and **26** are as follows. **20**: DAICEL CHIRALCEL OB-H, hexane/2-propanol 9/1, flow rate: 0.5 ml/min, retention time: 13 min for (3*S*,4*S*)-isomer and 22 min for (3*R*,4*R*)-isomer. **25**: DAICEL CHIRALCEL OB-H, hexane/2-propanol 9/1, flow rate: 0.5 ml/min, retention time: 15 min for (1*S*,2*R*)-isomer and 18 min for (1*R*,2*S*)-isomer. **26**: DAICEL CHIRALCEL OJ, hexane/2-propanol 4/1, flow rate: 0.5 ml/min, retention time: 19 min for (1*S*,2*R*)-isomer and 23 min for (1*R*,2*S*)-isomer.
24) HPLC data of **27** are as follows. DAICEL CHIRALCEL OD, hexane/2-propanol 400/1, flow rate: 0.4 ml/min, retention time: 23 min for (*S*)-isomer and 26 min for (*R*)-isomer).

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