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Highly Enantioselective Catalytic Oxidation of Alkyl Aryl Sulfides Using Mn-Salen Catalyst

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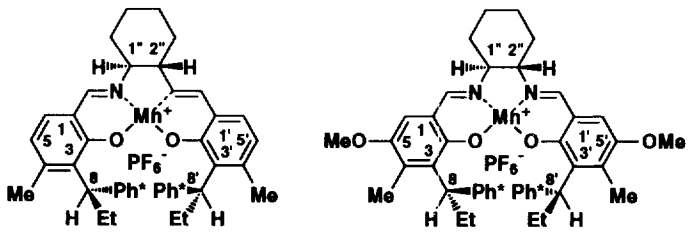
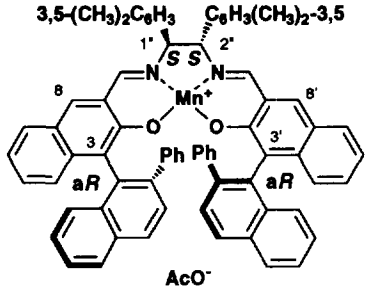
Abstract: Catalytic asymmetric oxidation of sulfides was carried out by using Mn-salen complex (a*S*,*R*)-**4a** as a catalyst and high enantioselectivity up to 94% was achieved. Enantioselectivity of the reaction was affected by the solvent used and the use of acetonitrile, ethyl propionate, or chlorobenzene generally gave good results.

Optically active sulfoxides have various uses as chiral auxiliaries in asymmetric synthesis or as pharmaceuticals.[1] Although many methodologies have been developed for their preparation, asymmetric oxidation of sulfides is the most attractive one from the practical point of view[2] and highly enantioselective stoichiometric oxidation of sulfides has already been reported by using the titanium-tartrate complex modified with water as a catalyst[3] or optically active oxaziridines as chiral oxidants.[4] In contrast to this, catalytic asymmetric oxidation has so far attained a limited success except for a few cases.[5] Uemura *et al.* have reported a highly enantioselective catalytic oxidation of sulfides using titanium-binaphthol complex as a catalyst, wherein the titanium complex catalyzes asymmetric oxidation of sulfides and concomitant kinetic resolution of the resulting sulfoxides.[6] In this method, the optical purity of the sulfoxide obtained by asymmetric oxidation is greatly enhanced (up to 96% ee) by kinetic resolution, at the expense of sulfoxides. Quite recently, Kagan *et al.* reported that the titanium-tartrate complex modified with 2-propanol catalyzed oxidation of sulfides in the presence of molecular sieves in a catalytic and highly enantioselective manner (up to 96% ee).[7] However, 10 mol% of catalyst is still required.[8] In 1986, Fujita *et al.* revealed that optically active (salen)vanadium complex catalyzed asymmetric oxidation of sulfides.[5a] Since then, several metallosalen complexes have been synthesized and used as catalysts for the asymmetric oxidation of sulfides.[5b-e] Especially, oxidation using (salen)manganese(III) complexes (hereafter referred to as Mn-salen complexes) was found to proceed smoothly with lesser amount of catalyst but enantioselectivity remained moderate.[5e] Several years ago, we found that Mn-salen complex bearing chiral centers both at ethylenediamine and salicyl aldehyde moieties were effective catalysts for asymmetric epoxidation[9] and asymmetric oxidation of sulfides.[10] To be interested, however, the best catalyst for asymmetric epoxidation was found not to be identical with the best one for asymmetric oxidation. For example, (8*R*,8'*R*,1"*S*,2"*S*)-**1** is a catalyst of choice for asymmetric epoxidation, while (8*S*,8'*S*,1"*S*,2"*S*)-**2** is the one for asymmetric oxidation



1 Ph*= 4-*t*-BuC$_6$H$_4$ **2**

Fig. 1



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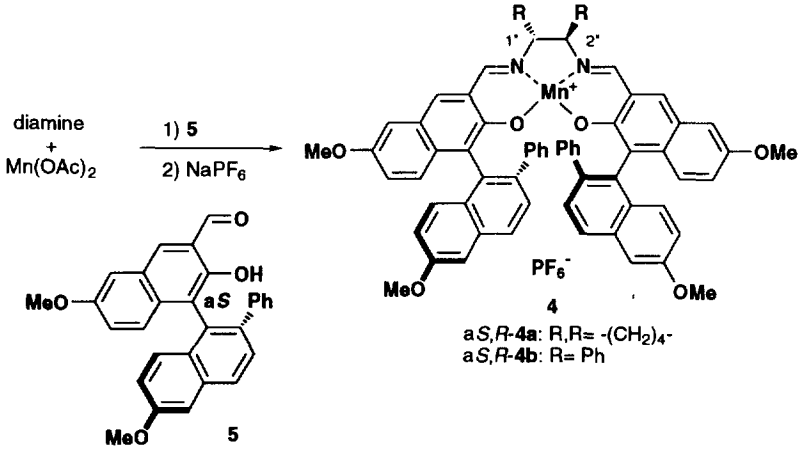
of sulfides (Fig. 1). With **2** as a catalyst, high enantioselectivity up to 90% ee was achieved.[10] However, its scope was limited to methyl aryl sulfides. Recently we further discovered that (a*R*,*S*)-Mn-salen complex **3** bearing binaphthyl group of axial chirality as a chiral element of salicyl aldehyde moiety showed excellent level of enantioselectivity in the epoxidation of conjugated olefins.[9] On the analogy of the previous example, we synthesized (a*S*,*R*)-**4**[11] and examined asymmetric oxidation of sulfides.

Preparation of Mn-Salen Catalyst

Fujita *et al.* have reported that (salen)vanadium complexes with electron-donating aryl substituent(s) show higher asymmetric induction than the complexes without such a substituent.[5a] This is also true for Mn-salen catalyzed asymmetric oxidation.[5e,10] Thus, we synthesized complexes **4** bearing an electron-donating methoxy group. The requisite (a*S*)-aldehyde **5** was prepared according to the reported procedure.[12] Aldehyde **5** was exposed to a solution of (1*R*,2*R*)-1,2-cyclohexanediamine and manganese diacetate in ethanol under aerial conditions to give a (salen)manganese(III) acetate complex. The (salen)manganese(III) acetate complex was further treated with $NaPF_6$ to give cationic Mn-salen complex (a*S*,*R*)-**4a**. Complex (a*S*,*S*)-**4a**, the diastereomer of (a*S*,*R*)-**4a**, was prepared in the same manner as (a*S*,*R*)-**4a** from (1*S*,2*S*)-1,2-cyclohexanediamine. Complex (a*S*,*R*)-**4b** was also prepared in the same manner from (1*R*,2*R*)-1,2-diphenylethylenediamine.



Asymmetric Oxidation of Alkyl Aryl Sulfides

Oxidation of methyl phenyl sulfide was first examined by using 1 mol% of Mn-salen complex (a*S*,*R*)-**4a** as a catalyst and equimolar amount of iodosylbenzene as a terminal oxidant in several solvents (entries 1-3)

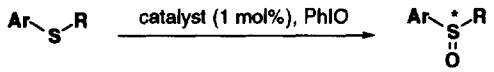


Table 1 Asymmetric oxidation of alkyl aryl sulfides with Mn-salen complexes as catalysts

entry	sulfide(Ar, R)	catalyst	solvent	additive	temp.	time (h)	yield (%)	% ee (confign.)[a]
1	C_6H_5, Me	(a*S*,*R*)-**4a**	CH_3CN	-	r.t.	2	95	67[b] (*S*)
2	"	"	C_6H_6	-	r.t.	2	79	75 (*S*)
3	"	"	C_6H_5Cl	-	r.t.	2	93	77 (*S*)
4	"	"	"	4-PPNO[c]	r.t.	2	98	81 (*S*)
5	"	(a*S*,*S*)-**4a**	"	-	r.t.	2	91	39 (*R*)
6	"	(a*S*,*R*)-**4b**	"	-	r.t.	2	97	71 (*S*)
7	*o*-$O_2NC_6H_4$, Me	(a*S*,*R*)-**4a**	CH_3CN	-	r.t.	2	94	94[d] (-)
8	"	"	"	4-PPNO[c]	r.t.	2	89	81 (-)
9	*p*-$O_2NC_6H_4$, Me	"	"	-	-20 °C	2	49	86[e] (-)
10	"	"	"	4-PPNO[c]	"	2	57	76 (-)
11	*o*-BrC_6H_4, Me	"	"	-	0 °C	2	68	87[f] (-)
12	*p*-BrC_6H_4, Me	"	$C_2H_5CO_2Et$	-	-20 °C	4	49	74[f] (-)
13	"	"	"	4-PPNO[c]	"	2	24	79 (-)
14	*p*-$CH_3OC_6H_4$, Me	"	C_6H_5Cl	4-PPNO[c]	"	4	38	64[g] (*S*)
15	C_6H_5, Et	"	"	-	r.t.	2	89	69[b] (-)
16	"	"	"	4-PPNO[c]	r.t.	2	63	75 (-)
17	*o*-$O_2NC_6H_4$, Et	"	CH_3CN	-	r.t.	4	40	89[b] (-)
18	"	"	C_6H_5Cl	-	r.t.	2	28	86 (-)
19	"	"	"	4-PPNO[c]	r.t.	2	50	72 (-)

a) Determined by comparison of the specific rotation (see experimental).
b) Determined by HPLC analysis (DAICEL CHIRALCEL OD, hexane/*i*-PrOH = 9/1).
c) 4-PPNO= 4-phenylpyridine *N*-oxide.
d) Determined by HPLC analysis (DAICEL CHIRALPAK AD, hexane/*i*-PrOH = 9/1).
e) Determined by HPLC analysis (DAICEL CHIRALPAK AD, hexane/*i*-PrOH = 15/1).
f) Determined by HPLC analysis (DAICEL CHIRALCEL OB-H, hexane/*i*-PrOH = 4/1).
g) Determined by HPLC analysis (DAICEL CHIRALCEL OB-H, hexane/*i*-PrOH = 1/1).

and it was found that the best enantioselectivity of 77% ee was achieved in chlorobenzene (entry 3). In this solvent, we also examined the oxidation of methyl phenyl sulfide with complexes (a*S*,*S*)-**4a** and (a*S*,*R*)-**4b** as catalysts. Complex (a*S*,*S*)-**4a** exhibited considerably lower enantioselectivity as compared with (a*S*,*R*)-**4a** in accord with our previous report (entry 5).[10] Complex (a*S*,*R*)-**4b** also showed a slightly diminished enantioselectivity (entry 6). We have already reported that the enantioselectivity of Mn-salen catalyzed epoxidation is often improved by the addition of a donor ligand in the reaction medium.[13] Thus, we examined the oxidation of methyl phenyl sulfide with (a*S*,*R*)-**4a** in the presence of 4-phenylpyridine *N*-oxide and enantioselectivity was found to further enhance up to 81% ee (entry 4). Based on this finding, we also examined oxidation of other sulfides with (a*S*,*R*)-**4a** as a catalyst. However, the best solvent varied with the sulfides used. In general, acetonitrile, ethyl propionate, and chlorobenzene gave good results. To be interested, however, the reaction in acetonitrile showed better asymmetric induction in the absence of donor ligand (entries 7 and 8), while the reaction in ethyl propionate or chlorobenzene exhibited better asymmetric induction in the presence of a donor ligand such as 4-phenylpyridine *N*-oxide (entries 12 and 13) except for the reaction of ethyl *o*-nitrophenyl sulfide (entry 19). Under the optimized conditions, moderate to excellent level of enantioselectivity was realized in all the oxidations examined. In accord with other Mn-salen catalyzed oxidations,[5e,10] oxidation of alkyl aryl sulfides bearing electron-withdrawing group with (a*S*,*R*)-**4a** generally shows better enantioselectivity than that of sulfides bearing electron-donating group. This seems different from oxidation using the modified titanium-tartrate catalyst[7] or vanadium catalyst.[5j] For example, the

oxidation of methyl *o*-nitrophenyl sulfide and methyl *p*-methoxyphenyl sulfide with (a*S*,*R*)-**4a** showed enantioselectivity of 94 and 64% ee (entries 7 and 14) respectively, while oxidation of these two sulfides with titanium-tartrate catalyst modified with 2-propanol showed enantioselectivity of 75 and 92% ee, respectively.[7] Furthermore, distinct from our previous catalyst **2**, (a*S*,*R*)-**4a** can be applied to oxidation of sulfides other than aryl methyl sulfides. Oxidation of aryl ethyl sulfides showed moderate to good enantioselectivity (entries 15-19).

In conclusion, we could show that Mn-salen complexes are effective catalysts for asymmetric oxidation of sulfides as well as for the epoxidation of conjugated olefins, though there is a room for further improvement.

Experimental

NMR spectra were recorded at 270 MHz on a JEOL EX-270 instrument. All signals were expressed as ppm down field from tetramethylsilane used as an internal standard (δ-value in $CDCl_3$). IR spectra were obtained with a SHIMADZU FTIR-8600 instrument. Optical rotation was measured with a JASCO DIP-360 automatic digital polarimeter. High resolution mass spectra were recorded on a JEOL JMS-SX/SX 102A instrument. Column chromatography was conducted on Silica Gel BW-820MH, 70-200 mesh ASTM, available from FUJI SILYSIA CHEMICAL LTD. Preparative thin layer chromatography was performed on 0.5 mm x 20 cm x 20 cm E. Merck silica gel plate (60 F-254). Solvents were dried and distilled shortly before use. Reactions were carried out under an atmosphere of nitrogen if necessary. HPLC analysis of enantiomeric excess was carried out using Hitachi L-4000 equipped with an appropriate optically active column, as described in the footnote of Table 1.

(Salen)manganese(III) complex (a*S*,*R*)-4a

$Mn(OAc)_2 \cdot 4H_2O$ (18.0 mg, 74 μmol) was added to a solution of (1*R*,2*R*)-1,2-cyclohexanediamine (8.4 mg, 74 μmol) in ethanol (5 ml) and stirred for 3 h at room temperature. To this solution was added aldehyde **5** (64.3 mg, 0.15 mmol) and the mixture was stirred for 4 h at 50 °C under aerial conditions, then allowed to cool to room temperature. To this solution was added a solution of $NaPF_6$ (124 mg, 0.74 mmol) dissolved in minimum water and stirred for 3h. The mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel (dichloromethane:methanol = 1:0-10:1) to give (a*S*,*R*)-**4a** (89.3 mg, quant.) as a solid. (a*S*,*R*)-**4a**; IR (KBr): 2930, 1624, 1585, 1493, 1391, 1350, 1329, 1269, 1169, 1126, 1030, 847, 698, 557 cm^{-1}. Calcd. for $C_{64}H_{52}N_2O_6MnPF_6 \cdot 2CH_3OH$: C, 5.00; H, 65.56; N, 2.32%. Found: C, 5.07; H, 65.45; N, 2.30%.

(Salen)manganese(III) complex (a*S*,*S*)-4a

Salen complex (a*S*,*S*)-**4a** was synthesized from **5** and (1*S*,2*S*)-1,2-cyclohexanediamine in the same procedure as described for the synthesis of (a*S*,*R*)-**4a**. (a*S*,*S*)-**4a**; IR (KBr): 2936, 1624, 1585, 1493, 1348, 1327, 1271, 1217, 1169, 1128, 1030, 849, 698, 559 cm^{-1}. HRFABMS m/z. Calcd. for $C_{64}H_{52}N_2O_6Mn$: 999.3206. Found 999.3218(M+)

(Salen)manganese(III) complex (a*S*,*R*)-4b

Aldehyde **5** (26.0 mg, 60 μmol) was added to a solution of (1*R*,2*R*)-1,2-diphenylethylenediamine (6.4 mg, 30 μmol) in ethanol (1 ml) and stirred for 8 h at room temperature. The mixture was concentrated to dryness *in vacuo* and diluted with deairated acetonitrile (1.5 ml). This solution was transferred by canula into the flask containing $Mn(OAc)_2 \cdot 4H_2O$ (7.4 mg, 30 μmol) and the resulting mixture was stirred for 4 h at room temperature. To this mixture was added a solution of ferricenium hexafluorophosphate (10.0 mg, 30 μmol) in acetonitrile (1.5 ml) dropwise. The mixture was concentrated to dryness and washed with hexane to remove the side product, ferrocene. The residue was purified on silica gel column chromatography (dichloromethane: methanol = 1:0-10:1) to give (a*S*,*R*)-**4b** (28.2 mg, 76%) as a solid. (a*S*,*R*)-**4b**; IR (KBr): 2934, 2835, 1585,

1495, 1329, 1273, 1223, 1169, 1128, 1032, 849, 704, 559 cm^{-1}. HRFABMS m/z. Calcd. for $C_{72}H_{54}N_2O_6Mn$: 1097.3362. Found 1097.3344(M+).

General procedure for asymmetric oxidation using complex (a*S*,*R*)-4a as a catalyst

(The reaction in acetonitrile without 4-phenylpyridine *N*-oxide)

Methyl *o*-nitrophenyl sulfide (16.9 mg, 0.1 mmol) was added to a solution of complex **4a** (1.1 mg, 1 μmol) in acetonitrile (1.0 ml). To this solution was added iodosylbenzene (22.0 mg, 0.1 mmol) at room temperature. The whole mixture was stirred for 2 h and filtrated through a pad of Celite. No sulfone formation was detected by TLC analysis of the filtrate. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica gel (hexane:ethyl acetate = 3:7) to give methyl *o*-nitrophenyl sulfoxide (17.5 mg, 94%). The enantiomeric excess of the sulfoxide was determined to be 94% ee by HPLC analysis using DAICEL CHIRALPAK AD (hexane:*i*-PrOH = 9:1).

(The reaction in chlorobenzene with 4-phenylpyridine *N*-oxide)

Methyl phenyl sulfide (11.7 μl, 0.1 mmol) was added to a solution of complex **4a** (1.1 mg, 1 μmol) and 4-phenylpyridine *N*-oxide (1.7 mg, 0.01 mmol) in chlorobenzene (1.0 ml). To this solution was added iodosylbenzene (22.0 mg, 0.1 mmol) at room temperature and the whole mixture was stirred for 2h. The mixture was filtrated through a pad of Celite. No sulfone formation was detected by TLC analysis of the filtrate. The filtrate was concentrated and the residue was chromatographed on silica gel (hexane:ethyl acetate = 3:7) to give methyl phenyl sulfoxide (13.7 mg, 98%). The enantiomeric excess of the sulfoxide was determined to be 81% ee by HPLC analysis using DAICEL CHIRALCEL OD (hexane:*i*-PrOH = 9:1).

Spectroscopic data of the sulfoxides obtained

All the sulfoxides obtained except for ethyl phenyl sulfoxide, gave the same spectroscopic data as described in reference 8b. Accordingly only the values of specific rotation of the sulfoxides are given below. Spectroscopic data of ethyl phenyl sulfoxide are also given below.

(*S*)-Methyl phenyl sulfoxide (81% ee); $[\alpha]_D^{25}$ -131.0° (*c* 0.53, $CHCl_3$).[14]

Methyl *o*-nitrophenyl sulfoxide (94% ee); $[\alpha]_D^{25}$ -122.7° (*c* 0.15, $CHCl_3$). Lit.[10b] (90% ee); $[\alpha]_D^{21}$ +116.5° (*c* 0.57), $CHCl_3$).

Methyl *p*-nitrophenyl sulfoxide (86% ee); $[\alpha]_D^{25}$ -130.5° (*c* 0.33, $CHCl_3$). Lit.[3a] (99.3% ee); $[\alpha]_D$ -156.9° (*c* 0.75, $CHCl_3$).

***o*-Bromophenyl methyl sulfoxide** (87% ee); $[\alpha]_D^{25}$ -232.4° (*c* 0.21, $CHCl_3$). Lit.[10b] (88% ee); $[\alpha]_D^{21}$ +241.9° (*c* 0.48, $CHCl_3$).

***p*-Bromophenyl methyl sulfoxide** (79% ee); $[\alpha]_D^{25}$ -105.2° (*c* 0.44, $CHCl_3$). Lit.[10b] (75% ee); $[\alpha]_D^{21}$ +101.9° (*c* 0.39, $CHCl_3$).

(*S*)-*p*-Methoxyphenyl methyl sulfoxide (64% ee); $[\alpha]_D^{25}$ -108.2° (*c* 0.13, $CHCl_3$). Lit.[3a] (99.5% ee); $[\alpha]_D$ +165.9° (*c* 0.38, $CHCl_3$). Lit.[4] (*S*)-isomer (83% ee); $[\alpha]_D^{20}$ -113.8° (*c* 3.09, $CHCl_3$).

Ethyl phenyl sulfoxide (75% ee); $[\alpha]_D^{25}$ -273.2° (*c* 0.13, $CHCl_3$). IR (neat): 3055, 2978, 2934, 1477, 1443, 1088, 1045, 1022, 748, 692 cm^{-1}. ^1H NMR ($CDCl_3$): 7.63-7.60 (m, 2H), 7.59-7.46 (m, 3H), 2.98-2.71 (m, 2H), 1.20 (t, *J* =7.43 Hz, 3H).

Ethyl *o*-nitrophenyl sulfoxide (89% ee); $[\alpha]_D^{25}$ -204.2° (*c* 0.33, $CHCl_3$). Lit.[10b] (8.5% ee); $[\alpha]_D^{24}$ +66.7° (*c* 0.15, $CHCl_3$).

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References and Notes

1. a) Barbachyn, J. D.; Johnson, C. R. In *Asymmetric Synthesis*; Morrison, J. D.; Scott, J. W. Eds; Academic Press: New York, 1983; Vol 4, pp227-261. b) Posner, G. H. In *Asymmetric Synthesis*, ed by Morrison, J. D. Ed.; Academic Press: New York, 1983; Vol. 2, Chapter, 8, pp225-241. c) Pitchen, P. *Chem. Ind.* **1994**, 15 Aug, p636-639.
2. Kagan, H. B. In *Catalytic Asymmetric Synthesis*, ed by Ojima, I. VCH, New York, 1993, pp203-226.
3. a) Brunel, J.-M.; Diter, P.; Duetsch, M.; Kagan, H. B. *J. Org. Chem.* **1995**, *60*, 8086-8088. b) Pitchen, P. Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188-8193. c) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1-299.
4. Davis, F. A.; Reddy, R. T.; Han, W.; Carroll, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 1428-1437.
5. a) Nakajima, K.; Kojima, K.; Fujita, J. *Chem. Lett.* **1986**, 1483-1486. b) Colombo, A.; Matsurano, G.; Passini, A. *Gazz. Chim. Ital.* **1986**, *116*, 35-40. c) Colonna, S.; Manfredi, A.; Spadoni, M.; Casella, L.; Gulotti, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 71-73. d) Sasaki, C.; Nakajima, K.; Kojima, M.; Fujita, J. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1318-1324. e) Palucki, M.; Hanson, P.; Jacobsen, E. N. *Tetrahedron Lett.* **1992**, *33*, 7111-7114. f) Ando, W.; Tajima, R.; Takata, T. *Tetrahedron Lett.* **1982**, *23*, 1685-1688. g) Groves, J. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628-3634. h) Naruta, Y.; Tani, F.; Maruyama, K. *Tetrahedron: Asymmetry* **1991**, *2*, 533-542. i) Halterman, R. L.; Jan, S.-T.; Nimmons, H. L. *Synlett* **1991**, 791-792. j) Bolm, C.; Bienewald, F. *Angew. Chem. Int. Ed. Eng.* **1995**, *34*, 2640-2642. k) Page, P. C. B.; Heer, J. P.; Collington, E. W.; Andrews, D. M. *Synlett* **1995**, 773-775.
6. a) Komatsu, N.; Nishibayashi, Y.; Sugita, T.; Uemura, S. *Tetrahedron Lett.* **1992**, *33*, 5391-5394. b) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 4529-4533.
7. Brunel, J. M.; Kagan, H. B. *Synlett* **1996**, 404-406.
8. Alkyl hydroperoxides oxidize sulfides without catalyst. Fujita *et al.* have reported that this uncatalyzed reaction makes highly catalytic asymmetric oxidation of sulfides with Ti-salen complex difficult (reference 5d).
9. For the recent review of Mn-salen catalyzed epoxidation, see: a) Katsuki, T. *J. Synth. Org. Chem., Jpn.* **1995**, *53*, 940-951. b) Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189-214.
10. a) Noda, K.; Hosoya, N.; Yanai, K.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **1994**, *35*, 1887-1890. b) Noda, K.; Hosoya, Irie, R.; Yamashita, Y.; Katsuki, T. *Tetrahedron* **1994**, *50*, 9609-9618.
11. Although the axial chiralities of the salicyl aldehyde moieties of complexes **3** and **4** are identical, their nomenclatures are opposite to each other due to the sequence rule of IUPAC nomenclature.
12. Hamada, T.; Fukuda, T.; Imanishi, H.; Katsuki, T. *Tetrahedron* **1996**, *52*, 515-530.
13. Irie, R.; Ito, Y.; Katsuki, T. *Synlett* **1991**, 265-266.
14. The specific rotation $[\alpha]_D^{21}$ +130.3° reported by us for (*S*)-methyl phenyl sulfoxide of 63% ee seems too large (reference 10b). Thus we correct the specific rotation of (*S*)-methyl phenyl sulfoxide as described in this text.

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