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Enantioselective epoxidation of olefins catalyzed by new sterically hindered salen–Mn(III) complexes

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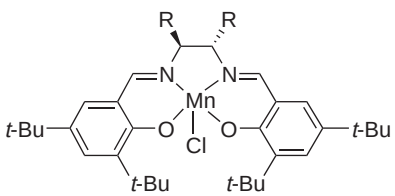
Abstract—New, sterically hindered chiral salen–Mn(III) complexes, **5** and **6**, were prepared from an aldehyde derived from BINOL. These substances catalyze efficient, enantioselective NaOCl-promoted epoxidations of olefins and enantioselectivities as high as 96–99% ee are observed in epoxidations of *cis*-β-methylstyrene and 2,2-dimethylchromene.

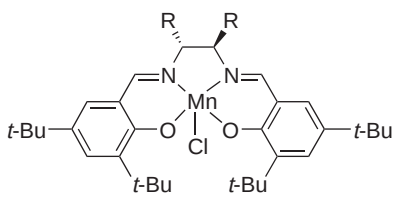
Optically active epoxides are important starting materials in the synthesis of a wide variety of biologically and pharmaceutically important compounds.[1] Epoxidations of unfunctionalized olefins, catalyzed by chiral salen–Mn(III) complexes (e.g. **1**–**3**), initially developed by Jacobsen[2] and Katsuki,[3] have emerged as practical methods for the synthesis of optically active epoxides. In addition, various epoxidation strategies utilizing homogeneous[4,5] and supported[6,7] salen–Mn(III) complexes and a host of oxidants,[8,9] including the economical NaOCl,[10] have been developed to improve the enantioselectivities of these reactions. Epoxidations promoted by the Katsuki catalyst **3**, which contains two additional (compared to the Jacobsen catalysts) stereogenic axes at the C3 and C3′ positions of the salen ligand,[11] are noteworthy owing to the exceptionally high levels of enantioselectivity observed with a variety of alkenes.

Our interest in preparing novel ligands for transition metal catalyzed asymmetric reactions grew out of recent investigations in which we developed a new method for efficient resolution of BINOL.[12] We believed that salen–Mn(III) complexes related to **5** would be worthy targets of our continuing efforts since these complexes might be more easily prepared than the Katsuki catalyst **3**. Furthermore, we felt that the presence of polar ester groups at R_2 in **5** would enhance the rate of transfer of the oxidant between the phases in the aqueous/alkene biphasic reaction system and, as a result, increase turn over frequencies in the epoxidation reactions would be expected. Below, we describe the preparation of the new salen–Mn(III) complexes **5** and **6** and their use as efficient catalysts for enantioselective epoxidations of unfunctionalized olefins.

The chiral aldehyde **11** serves as the key intermediate in synthetic routes to **5** and **6**. This substance is prepared from bis-MOM-protected BINOL **9** by a sequence (Scheme 1) involving mono-formylation and deprotection (→**10**, 65%) and sterically controlled mono-esterification with pivaloyl chloride (89%).[13a] Reaction of **11**



(*S*)-**1** R = Ph
(*S*)-**2** R = -$(CH_2)_4$-



(*R*)-**1** R = Ph
(*R*)-**2** R = -$(CH_2)_4$-

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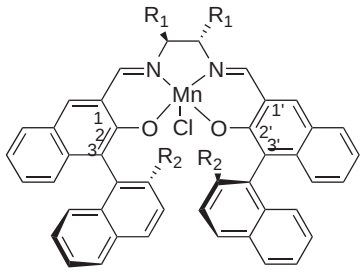
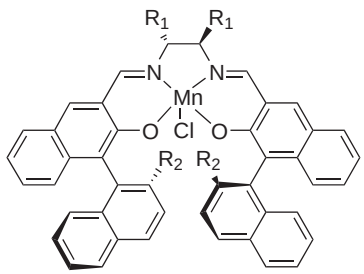




3 R_1 = Ph R_2 = Ar
(*R,S*)-**5** R_1 = Ph R_2 = -OOC-*t*-Bu
(*R,S*)-**6** R_1 = -$(CH_2)_4$- R_2 = -OOC-*t*-Bu

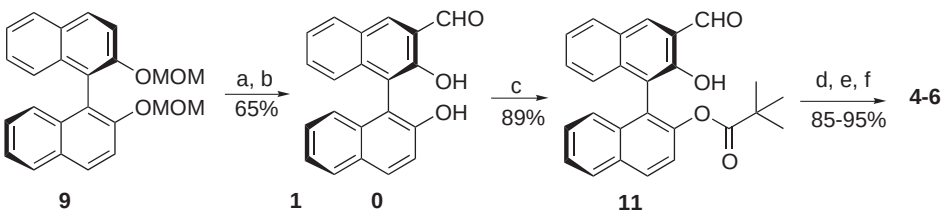
4 R_1 = H R_2 = -OOC-*t*-Bu
(*R,R*)-**5** R_1 = Ph R_2 = -OOC-*t*-Bu
(*R,R*)-**6** R_1 = -$(CH_2)_4$- R_2 = -OOC-*t*-Bu
(*R,R*)-**7** R_1 = Ph R_2 = -$OOCCH_3$
(*R,R*)-**8** R_1 = Ph R_2 = -$OSiPh_2$(*t*-Bu)

with ethylenediamines gives salen ligands, which are metallated with $Mn(OAc)_2$ and LiCl to yield the salen–Mn(III) complexes **4**–**6**.[13]

The catalytic activities of **4**–**6**, along with those of the Jacobsen catalysts **1**–**2**, for epoxidation of alkenes were determined by using Jacobsen's conditions and NaOCl as the oxidant.[14] The results, summarized in Table 1, show that **4**–**6** efficiently catalyze the epoxidation of styrene (entries 3–6, Table 1). However, the levels of enantioselectivity (25–62% ee) are similar to those obtained by using the Jacobsen catalysts (entries 1–2). The high epoxidation yields observed with **4**–**6** may be due to the predicted high transfer rates of oxidant between the aqueous and organic phases.[15] The two layers are well-mixed in reactions with **4**–**6** as compared to those employing **1**–**2**. The comparatively low 25% ee (entry 3) associated with reactions employing catalyst **4**, which contains stereogenic centers at only C3 and C3′ of the salen ligand, suggests that chirality in the diamine moiety is a requirement for high levels of enantioselectivity. Also, as seen by comparing the results of epoxidations catalyzed by (*R,R*)-**5** and (*R,S*)-**5** (entries 4 and 5), the absolute configuration of the styrene oxide product is determined by chirality in the diamine bridge and not by the absolute configuration at C3 and C3′ in the BINOL unit. To evaluate the steric effects of the salen R_2-substituent on these reactions, salen–Mn(III) complexes **7** and **8** were prepared and tested as styrene epoxidation catalysts. Although active, both catalysts give low levels of enantioselectivity (entries 7 and 8).

Epoxidations of *cis*- and *trans*-β-methylstyrenes, indene, 2,3-dihydronaphthalene, 2,2-dimethylchromene and 6-cyano-2,2-dimethylchromene, catalyzed by **5** and **6**, occur with exceptionally high enantioselectivities (up to 99% ee). Especially noteworthy is the (*R,S*)-**5** catalyzed epoxidation of *cis*-β-methylstyrene, which proceeds with 96% ee and yields a *cis*/*trans* epoxide ratio of 15 (entry 11) that is higher than that obtained in any other NaOCl promoted reaction at 0°C. The absolute configuration of the epoxides obtained in these processes is again governed by the chirality of the diamine group in the salen ligand (entries 10 and 11). However, the % ee is strongly influenced by the chirality at C3 and C3′. For example, epoxidations of sterically hindered acyclic and cyclic alkenes such as *cis*-β-methylstyrene, 2,2-dimethylchromene and 6-cyano-2,2-dimethylchromene catalyzed by (*R,S*)-**5** uniformly give higher levels of enantioselectivity as compared to those promoted by (*R,R*)-**5**. In contrast, (*R,R*)-**5** was found to give higher selectivities in epoxidations of *trans*-β-methylstyrene,[16] indene and 2,3-dihydronaphthalene.

In summary, we have synthesized new chiral salen–Mn(III) complexes, **5**–**6** and shown that they serve as efficient catalysts for NaOCl-induced epoxidations of olefins. Moreover, epoxidation reactions, catalyzed by these substances, yield chiral epoxides with exceptionally high levels of enantioselectivity.



Scheme 1. (a) *t*-BuLi, DMF, THF, −78°C; (b) HCl, EtOH; (c) NaH, pivaloyl chloride, THF; (d) diamine, EtOH, reflux; (e) $Mn(OAc)_2$, EtOH, reflux, O_2; (f) LiCl, EtOH.

Table 1. Salen–Mn(III) complex catalyzed NaOCl epoxidations of olefins

Entry	Alkene	Catalyst	Yield[a]	% Ee[b]	Config.[c]
1	Styrene	(*R*)-**1**	53	65	*R*
2		(*R*)-**2**	76	46	*R*
3		**4**	97	25	*R*
4		(*R*,*R*)-**5**	87	62	*R*
5		(*R*,*S*)-**5**	95	55	*S*
6		(*R*,*R*)-**6**	>99	41	*R*
7		(*R*,*R*)-**7**	97	52	*R*
8		(*R*,*R*)-**8**	25	43	*R*
9	*cis*-β-Methylstyrene	(*S*)-**1**	90	85(17)[d]	(*S*,*R*)
10		(*R*,*R*)-**5**	62	87(8)[d]	(*R*,*S*)
11		(*R*,*S*)-**5**	87(16)[e]	96(90[e], 15[d])	(*S*,*R*)
12	*trans*-β-Methylstyrene	(*R*)-**1**	59	28	(*S*,*S*)
13		(*R*)-**2**	75	23	(*S*,*S*)
14		(*R*,*R*)-**5**	38	57	(*S*,*S*)
15		(*R*,*S*)-**5**	95	30	(*R*,*R*)
16		(*R*,*R*)-**6**	35	63	(*S*,*S*)
17	Indene	(*R*)-**1**	80	84	(*R*,*S*)
18		(*R*,*R*)-**5**	57	94	(*R*,*S*)
19		(*R*,*S*)-**5**	55(55)[e]	88(98)[e]	(*S*,*R*)
20		(*R*,*R*)-**6**	63	90	(*R*,*S*)
21	2,3-Dihydronaphthalene	(*R*)-**1**	62	77	(*R*,*S*)
22		(*R*,*R*)-**5**	65	95	(*R*,*S*)
23		(*R*,*S*)-**5**	60(78)[e]	87(98)[e]	(*S*,*R*)
24		(*R*,*R*)-**6**	62	95	(*R*,*S*)
25	2,2-Dimethylchromene	(*R*)-**1**	85	99	(3*R*,4*R*)
26		(*R*,*R*)-**5**	60	85	(3*R*,4*R*)
27		(*R*,*S*)-**5**	80(75)[e]	99(99)[e]	(3*S*,4*S*)
28		(*R*,*R*)-**6**	62	98	(3*R*,4*R*)
29	6-Cyano-2,2-dimethylchromene	(*R*)-**2**	92	96	(3*R*,4*R*)
30		(*R*,*R*)-**5**	77	78	(3*R*,4*R*)
31		(*R*,*S*)-**5**	87	92	(3*S*,4*S*)

[a] GC yield (entries 1–16) or isolated yield (entries 17–31).
[b] Determined by GC with either Supelco chiral β-dex 325 (30 m×0.25 mm×0.25 μm, entries 1–16) or β-dex 120 (30 m×0.25 mm×0.25 μm, entries 21–24) column and HPLC with either Whelk-O1 (5 μm, 4.5×250 mm with CN guard, entries 17–20) or Daicel Chiralcel OJ column (entries 25–31).
[c] Absolute configuration was assigned according to the literature procedure.[2,3,9–11]
[d] The *cis*/*trans* ratio.
[e] Results obtained with Katsuki's catalyst.[11b]

Acknowledgements

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13. (a) To a mixture of **10** (120 mg, 0.38 mmol) and NaH (23 mg, 0.96 mmol) in THF (7 mL) at 0°C was added pivaloyl chloride (46 mg, 0.38 mmol). After 2 h at room temperature, water was added. Product was extracted with ethyl acetate, and the organic phase was dried over $MgSO_4$ and concentrated. Flash chromatography (hexane/ethyl acetate = 4/1) provided **11** (134 mg, 89%). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.79 (s, 9H), 7.22–8.01 (m, 9H), 8.05 (d, J = 8.90 Hz, 1H), 8.33 (s, 1H), 10.21 (s, 1H), 10.48 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.42, 38.61, 117.01, 121.75, 122.06, 123.06, 124.47, 125.45, 125.58, 125.62, 126.73, 127.29, 128.35, 129.51, 129.61, 130.54, 131.76, 133.19, 137.47, 138.06, 147.18, 153.48, 176.31, 196.57; HRMS (EI) m/z calcd $C_{26}H_{22}O_4$ (M^+) 398.1518, found 398.1521; (b) A solution of **11** (100 mg, 0.25 mmol) and (1*R*,2*R*)-1,2-diphenylethylenediamine (28 mg, 0.13 mmol) in EtOH (4 mL) was heated to reflux for 2 h before the addition of manganese(II) acetate (42 mg, 0.24 mmol). The mixture was heated to reflux for an additional 2 h and cooled to room temperature. Saturated aqueous LiCl was added. The product was extracted with ethyl acetate, and the organic phase was dried over $MgSO_4$ and concentrated. Flash chromatography ($MeOH/CH_2Cl_2$ = 1/9) provided (*R*,*R*)-**5** (93 mg, 85%): IR (KBr) ν 2968, 2928, 1745, 1608, 1584, 1556; HRMS (FAB), m/z calcd $C_{66}H_{55}N_2O_6Mn$ $(M-Cl+H)^+$ 1026.3441, found 1026.3439; (c) Analytical data for (*R*,*R*)-**6**: HRMS (FAB), m/z calcd $C_{58}H_{53}N_2O_6Mn$ $(M-Cl+H)^+$ 928.3284, found 928.3278.
14. The general procedure used for the epoxidation reactions is as follows: To a stirred solution of olefin (0.5 mmol) in CH_2Cl_2 (2.5 mL), catalyst (0.02 mmol) and 4-phenylpyridine-*N*-oxide (4-PPNO, 0.1 mmol) at 0°C is added pre-cooled buffered bleach (2.5 mmol, buffered to pH 11.3 with Na_2HPO_4). The mixture is stirred for either 4 h (entries 1–16) or 8 h (entries 17–31). The organic phase is separated, dried ($MgSO_4$) and concentrated in vacuo giving a residue which is subjected to silica gel chromatography.
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