

## Asymmetric Alkene Epoxidations Catalyzed by Sterically Hindered Salen-Mn(III) Complexes

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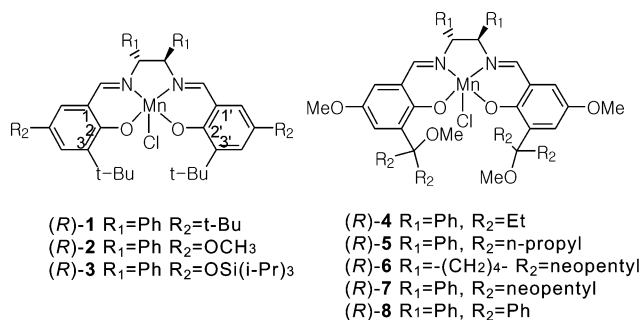
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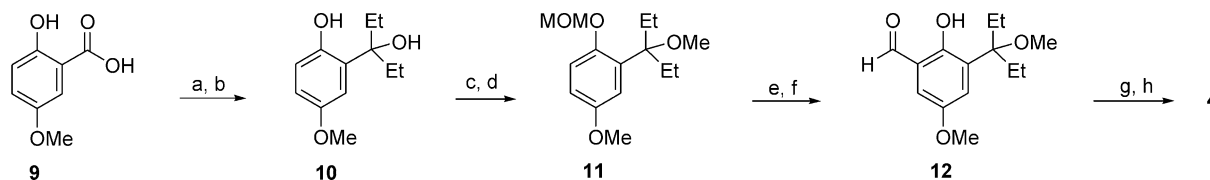
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In recent years, many approaches have been developed for the preparation of enantiomerically pure epoxides.<sup>1</sup> Among these are olefin epoxidations catalyzed by chiral salen-Mn(III) complexes such as **1-3**, which now rank among the most efficient of methods uncovered for the synthesis of chiral epoxides.<sup>2</sup>

It is known that bulky substituents, including *t*-butyl and aryl groups, at the C3 and C3' positions of the ligands are required to obtain high degrees of enantioselectivity in chiral salen-Mn(III) catalyzed epoxidations of alkenes.<sup>3</sup> We have observed similar results in an earlier study with sterically hindered salen ligands.<sup>4</sup> However, salen ligands containing alkyl substituents larger than *t*-butyl at the C3 and C3' positions have not been subjected to detailed investigation thus far.<sup>5</sup> Consequently, we have prepared a series of sterically hindered chiral salen-Mn(III) complexes, such as **4**, and have probed their use in enantioselective epoxidation reactions of alkenes.



The aldehyde **12**, which served as the key intermediate in the synthesis salen complexes **4**, was prepared starting with readily available 4-methoxysalicylic acid (Scheme 1). The sequence involved esterification, double alkylation and formylation.<sup>6</sup> Each step in the route, except for the formylation process, proceeded in greater than 90% yield. Reaction of the aldehyde **12** with chiral diphenylethylenediamine gave



**Scheme 1.** (a) K<sub>2</sub>CO<sub>3</sub>, (CH<sub>3</sub>)<sub>2</sub>SO<sub>4</sub>, acetone, 98%; (b) EtMgBr, THF, 90%; (c) NaH, MOMCl, THF, 98%; (d) KH, MeI, THF, 98%; (e) *t*-BuLi, DMF, THF, 47%; (f) HCl, MeOH, 99%; (g) (1*R*,2*R*)-diphenylethylenediamine, EtOH, reflux, 92%; (h) Mn(OAc)<sub>2</sub>, EtOH, reflux, LiCl, 97%.

the salen ligand, which was metallated with Mn(OAc)<sub>2</sub> and LiCl to yield the salen-Mn(III) complex **4**.<sup>3,7</sup>

The catalytic activity of **4** for epoxidation of alkenes was determined by using Jacobsen's conditions and NaOCl as the oxidant.<sup>8</sup> The results, summarized in Table 1, show that **4** efficiently catalyzed the epoxidation of styrene (entry 2). However, the enantioselectivity of this process (68% ee) is only slightly higher than that obtained by using the Jacobsen's catalyst (entry 1). To evaluate the steric effects of the salen C3 and C3' substituents on the enantioselectivity of the reaction, complexes **5-8** were also prepared by using the general methodology shown Scheme 1 and employing different Grignard reagents. Although active, the catalyst **5** with bis-*n*-propyl substituents at C3 and C3' gave low levels of enantioselectivity (entry 3). Catalysts **6-8**, containing more bulky substitution at these positions, also showed low levels of enantioselectivity as well as low reaction yields (entries 4-6). These results suggest that the C3 and C3' substituents of salen ligand need to be properly tuned in order to obtain the high enantioselectivities.

Interestingly, excellent levels of catalytic activity and enantioselectivity are observed in epoxidation reactions of sterically hindered olefins, catalyzed by salen complex **4**. For example, epoxidation of *cis*- $\beta$ -methylstyrene catalyzed by **4** proceeded with a 98% ee and a *cis/trans* epoxide ratio of 28 (entry 8) that is higher than that obtained in any other NaOCl promoted reaction of this olefin at 0 °C. In contrast, Jacobsen's catalysts **1** and **2** gave respective enantioselectivities of only 85% ee and 83% ee<sup>6</sup> with *cis*- $\beta$ -methylstyrene. Salen complex **4** also displayed an excellent catalytic activity (up to 99% ee) in epoxidation reactions of other alkenes, including indene, 1,2-dihydronaphthalene and 2,2-dimethylchromene (entries 13-22).

LiOCl has been employed frequently in place of NaOCl in Mn(III)-porphyrin catalyzed epoxidations of olefins.<sup>9</sup> As a result, the use of the lithium containing oxidant in epoxid-

**Table 1.** Salen-Mn(III)-Complex Catalyzed NaOCl Epoxidations of Olefins

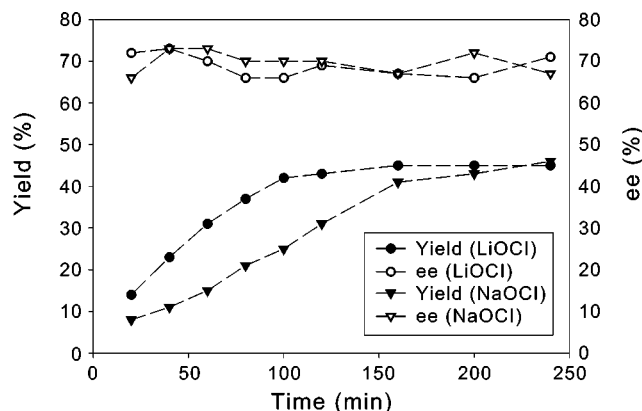
Entry	Alkene	Catalyst	Time (hr)	Yield <sup>a</sup>	% ee <sup>b</sup>	Config. <sup>c</sup>
1	Styrene	(R)-1	4	53	65	(R) <sup>5</sup>
2		(S)-4	2	97	68	(S)
3		(R)-5	4	88	61	(R)
4		(R)-6	8	26	33	(R)
5		(R)-7	8	28	42	(R)
6		(S)-8	8	11	29	(S)
7	Cis- $\beta$ -methylstyrene	(S)-1	4	90	85(17) <sup>d</sup>	(S,R) <sup>5</sup>
8		(S)-4	2	91	98(28) <sup>d</sup>	(S,R)
9		(R)-5	2	58	90(7.0) <sup>d</sup>	(R,S)
10		(R)-6	4	34	93(2.1) <sup>d</sup>	(R,S)
11	Indene	(R)-7	4	22	75(9.6) <sup>d</sup>	(R,S)
12		(R)-1	8	80	84	(R,S) <sup>5</sup>
13		(S)-4	4	63(95) <sup>e</sup>	84(90) <sup>e</sup>	(S,R)
14		(R)-6	4	69	84	(R,S)
15		(R)-7	4	51	89	(R,S)
16		1,2-Dihydronaphthalene	(R)-1	8	62	77
17	(S)-4		3	64(80) <sup>e</sup>	91(95) <sup>e</sup>	(S,R)
18	(R)-5		4	38	95	(R,S)
19	(R)-6		4	52	94	(R,S)
20	3-Chlorostyrene	(R)-7	4	64	76	(R,S)
21		(S)-4	8	71	53	(S)
22	2,2-Dimethylchromene	(S)-4	8	73	99	(R,S)

<sup>a</sup>GC yields (entries 1-11) or isolated yields (entries 12-22). <sup>b</sup>Determined by GC with either Supelco chiral  $\beta$ -dex 325 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu$ m, entries 1-11, 16-20) column and HPLC with either Daicel Chiralcel OJ column (entries 12-15) or OD column (entries 21-22). <sup>c</sup>Absolute configuration was assigned according to the literature procedure. <sup>d</sup>The cis/trans ratio. <sup>e</sup>LiOCl was used instead of NaOCl.

ation reactions catalyzed by the salen complex **4** was investigated. Interestingly, epoxidations of indene and 1,2-dihydronaphthalene were found to occur in high yields (entries 13 and 17) and with slightly higher degrees of enantioselectivity than when NaOCl is used as the oxidant.

To determine the relative reactivities of the two oxidants, LiOCl and NaOCl, reactions of styrene catalyzed by salen complex **4** were studied. As shown in Figure 1, the overall yields of the reactions with both LiOCl and NaOCl after 3 h were ca. 45%, which were lower than that obtained (97%) by using 4 mol % of catalyst **4** (entry 2). This observation indicates that the catalyst becomes inactive after ca. 45 turnovers. However, the enantioselectivities obtained with both LiOCl and NaOCl were the same as that obtained when 4 mol % of the catalyst and NaOCl were used. This result indicates that the level of enantioselectivity is not dependent upon either the amount of catalyst or the type of hypochlorite used. Especially noteworthy is the observation that the rate of the epoxidation reaction using LiOCl, was twice that of the process promoted by NaOCl. The higher rate observed with LiOCl may be due to faster oxygen atom transfer from aqueous LiOCl to the salen-Mn(III) catalyst.

In summary, we have synthesized new chiral salen-Mn(III) complexes **4-8** and shown that they serve as an efficient catalyst for NaOCl-induced epoxidations of olefins. Finally, we have shown that LiOCl could be employed as an oxidant

**Figure 1.** Time course of the yields and enantioselectivities of epoxidation reactions of styrene catalyzed by **4** in the presence of either NaOCl or LiOCl.

in these epoxidation reactions and that the reaction rates with the lithium containing oxidant were higher than those promoted by NaOCl.

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- Analytical data for **12**: <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400MHz)  $\delta$  10.59 (s, 1H), 10.13 (s, 1H), 7.25 (d, *J* = 3.16 Hz, 1H), 7.02 (d, *J* = 3.16 Hz), 3.81 (s, 3H), 3.24 (s, 3H), 2.08 (m, 2H), 1.93 (m, 2H), 0.68 (t, *J* = 7.56 Hz); <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$  193.83, 154.26, 152.13, 131.99, 124.97, 121.46, 111.07, 83.37, 55.76, 48.68, 26.07, 7.66; HRMS (FAB) *m/z* calcd C<sub>14</sub>H<sub>18</sub>O<sub>4</sub> (M+2H)<sup>+</sup> 252.1362, found 252.1368.
- Analytical data for **4**: C<sub>42</sub>H<sub>50</sub>O<sub>6</sub>N<sub>2</sub>MnCl·1/2H<sub>2</sub>O, C, 64.82; H, 6.61; N, 3.61, found C, 64.59; H, 7.14; N, 3.21. mp 210-212 °C.
- The typical procedure used for the epoxidation reactions is as follows: To a stirred solution of 1,2-dihydronaphthalene (0.5 mmol), in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL), catalyst (0.02 mmol) and 4-phenylpyridine-*N*-oxide (4-PPNO, 0.1 mmol) at 0 °C was added pre-cooled buffered bleach (2.5 mmol, buffered to pH 11.3 with Na<sub>2</sub>HPO<sub>4</sub>). The mixture was stirred for 3 h. The organic phase was separated, dried (MgSO<sub>4</sub>) and concentrated in vacuo giving a residue which was subjected to silica gel chromatography.
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