Effect of Chiral Quaternary Ammonium Salts on (salen)Mn-Catalyzed Epoxidation of cis-Olefins. A Highly Enantioselective, Catalytic Route to Trans-Epoxides

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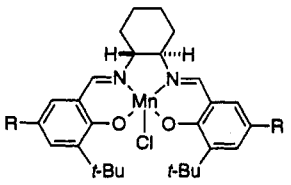
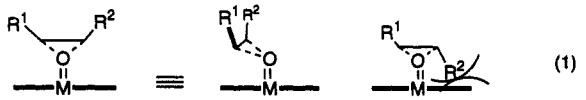
The design of catalysts that exhibit high enantioselectivity with broad substrate generality constitutes one of the most significant challenges in asymmetric synthesis. In principle, greatest substrate generality may be attained with systems that can exert high stereoinduction without requiring any specific functionality on the substrate for catalyst precoordination.[2] In this context, we have reported that chiral (salen)Mn complexes such as **1** and **2** catalyze highly enantioselective epoxidation of unfunctionalized cis-disubstituted olefins and trisubstituted olefins.[3] However, the



1: R = *t*-Bu
2: R = OSi*i*-Pr$_3$

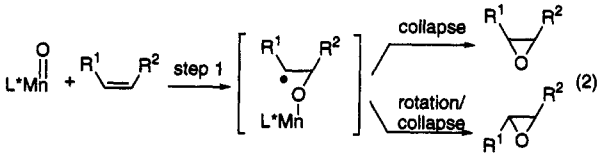
(salen)Mn-catalyzed epoxidation has provided only a partial solution to the problem of asymmetric alkene epoxidation, because it was found that trans-disubstituted olefins were epoxidized with low enantioselectivity with these systems (e.g., *trans*-stilbene undergoes epoxidation with **1** with 27% ee).[4] Limited success has also been obtained in the epoxidation of trans-olefins using other oxo-transfer catalysts bearing salen or porphyrin ligands;[5] in fact, heme-containing monooxygenases and peroxidases generally do not even accept these compounds as substrates.[6] To account for these observations, a transition-state model has been advanced for olefin epoxidation by heme-containing proteins and their mimics involving side-on approach of olefin to a metal–oxo intermediate (eq 1),[7]and this model (or slight variants thereof[3f])



(1)

has recently gained broad acceptance.[8] If the side-on approach mechanism is correct and general, it is possible that trans-olefins will always be poor substrates for catalysts bearing salen, porphyrin, and related tetradentate ligands.

An alternate, direct route to trans-epoxides is provided via the direct, nonstereospecific epoxidation of cis olefins. The generation of both cis- and trans-epoxides as primary products from acyclic cis-olefins is a common feature of oxo–transfer catalysis[9] and is attributable to stepwise C–O bond formation via radical or a polar intermediates (e.g., eq 2).[10] In epoxidations catalyzed by

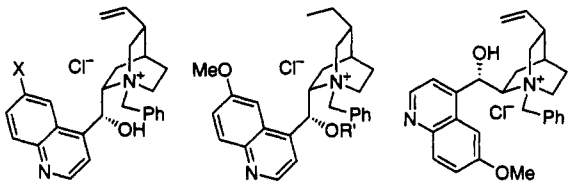


(2)

chiral (salen)manganese complexes, aryl- and alkyl-disubstituted cis-olefins afford cis-epoxides as major products, with cis/trans ratios ranging from >99:1 to 3:1.[4] Enhancement of the trans pathway for these substrates could provide a synthetically viable and highly enantioselective route to trans-epoxides, because good enantiofacial selectivity is attainable in the initial addition of cis-olefins to the metal–oxo intermediate (eq 2, step 1). We describe here the successful attainment of this goal, through the unexpected observation that certain chiral quaternary ammonium salts induce a dramatic reversal in epoxidation diastereoselectivity by (salen)Mn complexes. This finding provides the first method for the direct catalytic synthesis of trans-epoxides with high (>80%) enantioselectivity.

Epoxidation of *cis*-β-methylstyrene was studied under a variety of conditions in order to identify factors that influence cis/trans selectivity. As shown in Table 1, epoxidation with catalyst **1** in dichloromethane led to high (>10:1) selectivity for the cis product, whereas lower cis selectivity was obtained with catalyst **2** in the same solvent (entries 1 and 2). Reactions in aromatic solvents such as chlorobenzene afforded slightly higher proportions of trans product, with a cis/trans ratio of 6:4 obtained with catalyst **2** in this solvent. Thus, although minor changes to the cis/trans partitioning could be induced by simply varying the (salen)Mn catalyst and the solvent, in all cases the cis epoxide was the predominant product.

In contrast, the addition of cinchona alkaloid-derived salts **3–7** was found to promote a dramatic reversal in the diastereoselectivity of (salen)Mn-catalyzed epoxidation of *cis*-β-methylstyrene. For



3: X = OMe
4: X = H

5: R' = Me
6: R' = 9-phenanthryl

7

example, trans-epoxide was generated in 90% de (95:5 trans/cis) in the presence of the quinine-derived salt **3** in chlorobenzene solvent (entry 4). Almost identical results were obtained with quinine-, cinchonidine-, and quinidine-derived salts, **3**, **4**, and **7** (entries 4, 7, and 10). Ephedrine-derived **8** also induced a preference for trans-epoxide formation, ruling out the possibility that the additive effect is due to coordination of quinoline nitrogens

(1) University of Illinois, Urbana, IL.
(2) See, e.g.: Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 4.4.
(3) (a) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063. (b) Lee, N. H.; Muci, A. R.; Jacobsen, E. N. *Tetrahedron Lett.* **1991**, *32*, 5055. (c) Lee, N. H.; Jacobsen, E. N. *Tetrahedron Lett.* **1991**, *32*, 6533. (d) Deng, L.; Jacobsen, E. N. *J. Org. Chem.* **1992**, *57*, 4320. (e) Chang, S.; Lee, N. H.; Jacobsen, E. N. *J. Org. Chem.* **1993**, *58*, 6939. (f) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martínez, L. E. *Tetrahedron* **1994**, *50*, 4323. (g) Chang, S.; Heid, R. M.; Jacobsen, E. N. *Tetrahedron Lett.* **1994**, *35*, 669. (h) Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939. (i) Brandes, B. D.; Jacobsen, E. N., submitted.
(4) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 4.2.
(5) (a) Sakaki, H.; Irie, R.; Katsuki, T. *Synlett.* **1993**, 300. (b) Halterman, R. L.; Jan, S.-T. *J. Org. Chem.* **1991**, *56*, 5253. (c) Groves, J. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628. (d) Collman, J. P.; Lee, V. J.; Zhang, X.; Ibers, J. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1993**, *115*, 3834.
(6) Allain, E. A.; Hager, L. P.; Deng, L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 4415.
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(10) (a) Srinivasan, K.; Perrier, S.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309. (b) Zhang, W.; Lee, N. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 425.

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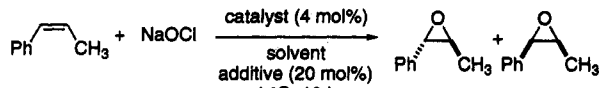
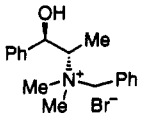
Table 1



entry	catalyst	solvent[a]	additive	trans-epoxide/ cis-epoxide
1	1	CH_2Cl_2	none	8:92
2	2	CH_2Cl_2	none	29:71
3	2	PhCl	none	39:61
4	2	PhCl	3	95:5
5	2	PhF	3	96:4
6	2	PhH	3	92:8
7	2	PhCl	4	94:6
8	2	PhCl	5	84:16
9	2	PhCl	6	86:14
10	2	PhCl	7	93:7
11	2	PhCl	8	91:9

[a] The initial concentration of substrate was 0.05 M in all runs.

in 3–7 to the (salen)Mn catalyst. Simple tetraalkylammonium



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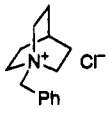

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salts such as $Et_3NBn^+Br^-$ and the quinuclidinium salt **9** exerted a negligible effect on the diastereoselectivity of epoxidation, indicating that the enhancement of the trans pathway by **3–8** is not due to a phase-transfer catalysis effect alone. *O*-Alkylated or *O*-arylated derivatives **5** and **6** also induced a preference for formation of the trans-epoxide, although the effect was attenuated relative to additives bearing a free hydroxyl group.

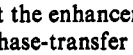
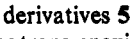
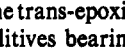
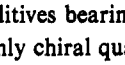
Thus far, only chiral quaternary ammonium salts have been found to induce high selectivity for formation of trans-epoxide, yet these salts do not appear to exert any influence on the enantioselectivity of epoxidation. Epoxidations with achiral (salen)Mn catalysts in the presence of **3** afforded only racemic epoxide products. In each case, the enantiomeric composition of the trans-epoxide was similar (80–85% ee) in reactions using the (salen)Mn complex **2**, and the absolute configuration of the major epoxide product depended only on the stereochemistry of **2**. Neither cis-olefin nor cis-epoxide was observed to undergo isomerization under the conditions of epoxidation.

At this stage, no clear mechanism that accounts for the selective formation of trans-epoxides from cis-olefins in the presence of salts such as **3–8** has been ascertained. It is possible that the ammonium salts are interacting with the intermediate in eq 2 in a manner that extends its lifetime, thus permitting free rotation of the C–C single bond in this species and selective collapse to the trans product. Alternatively, the ammonium salt additives may be giving rise to a new manganese-based oxidant that effects epoxidation via an unusually trans-selective pathway. This oxidant may be either absent or present as a minor component in epoxidations carried out in the absence of such additives.[9]

While the mechanistic basis for the role of added chiral quaternary ammonium salts in epoxidation remains unclear, the synthetic utility of the trans pathway enhancement may be immediately realized (Table 2). In all cases examined thus far, cis-disubstituted olefins have been found to undergo selective oxidation to the trans-epoxides with good enantioselectivity. Notable examples include cis-1,2-dialkyl-substituted olefins, which have been proposed previously to undergo epoxidation by (salen)Mn catalysts via a concerted mechanism.[11] trans-Epoxides

(11) Fu, H.; Look, G. C.; Zhang, W.; Jacobsen, E. N.; Wong, C.-H. *J. Org. Chem.* **1991**, *56*, 6497.

Table 2. Epoxidation of cis-Olefins in the Presence of **2** (4 mol %) and **3** (25 mol %)[a]

entry	substrate	solvent ([alkene]$_0$, M)	trans-epoxide/ cis-epoxide	ee of trans-epoxide, % (config)[b]
1		PhCl (0.1)	95:5	81 (*S,S*)
2		PhH (0.1)	69:31	84 (n.d.)
3		PhCl (0.05)	>96:4	90 (*S,S*)
4		PhCl (0.1)	89:11	86 (*S,S*)

[a] Reactions were carried out using NaOCl as oxidant according to the procedure described in ref 12. [b] Enantiomeric excesses were determined directly by GC or by HPLC analysis (see supplementary material). n.d., not determined.

are generated selectively from these substrates in the presence of salts such as **3** (e.g., entry 2). The epoxidation of *cis*-stilbene is also intriguing (entry 3), since it constitutes an example of an enantioselective reaction of an olefin bearing formally homotopic faces. The synthetically useful epoxide *trans*-stilbene oxide was isolated in good yield and in enantio- and diastereomerically pure form by a single recrystallization of the product mixture.[12]

Cinchona alkaloid derivatives have a venerable history in the field of asymmetric catalysis,[13] and this work introduces a new role for this readily available class of compounds. Our current efforts are directed toward further refining the design of these catalyst systems to enhance selectivity and toward elucidating the mechanistic basis for the unexpected effect of chiral quaternary ammonium salts on (salen)Mn-catalyzed epoxidations.

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Supplementary Material Available: Chromatographic analyses of racemic and enantiomerically enriched epoxides from Table 2 (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(12) The following procedure for the epoxidation of *cis*-stilbene is representative. To a solution of *cis*-stilbene (0.54 g, 3.0 mmol) in chlorobenzene (60 mL) was added *N*-benzylquininium chloride (Fluka, 0.34 g, 0.75 mmol), and the suspension was cooled to 4 °C. An unbuffered, undiluted solution of commercial NaOCl (13% w/w, 8.0 mL, 12 mmol) was added, and the resulting mixture was stirred for 5 min. The (salen)Mn complex (*R,R*)-**2** (0.10 g, 0.12 mmol) was then added as a solid, and the reaction was stirred under N_2 for 10 h at 4 °C. The mixture was extracted with Et_2O (2 × 50 mL), and the combined organic phases were washed with H_2O (2 × 50 mL) and brine (50 mL) and then dried over Na_2SO_4. Solvent evaporation under reduced pressure afforded a crude mixture of *trans*- and *cis*-stilbene oxides in 80% yield and in a ratio of ≥96:4, with the *trans*-epoxide present in 90% ee. Recrystallization from ligroin provided 0.35 g (60% yield) of pure (–)-(*S,S*)-*trans*-stilbene oxide (>99% ee, >99% purity by GC analysis), mp 69.5–70 °C.

(13) (a) Helder, R.; Hummelen, J. C.; Laane, R. W. P. M.; Wiering, J. S.; Wynberg, H. *Tetrahedron Lett.* **1976**, 1831. (b) Wynberg, H. In *Tropics in Stereochemistry*; Eliel, E. L., Wilen, S., Allinger, N. L., Eds.; Wiley: New York, 1986; Vol. 16 p 87. (c) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263. (d) Jacobsen, E. N.; Markó, I. E.; Mungall, W. S.; Schröder, G. W.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. (e) Dolling, U.-H.; Hughes, D. L.; Bhattacharya, A.; Ryan, K. M.; Karady, S.; Weinstock, L. M.; Grabowski, E. J. J. In *Phase Transfer Catalysis*. Starks, C. M., Ed.; ACS Symposium Series 326; ACS: Washington, DC, 1987; p 67. (f) O'Donnell, M. J. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 8.