Highly Enantioselective, Low-Temperature Epoxidation of Styrene

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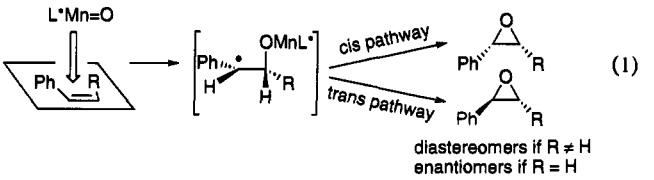
Styrene is one of the chemical industry's most important prochiral olefins,[1] and its derived epoxide is an extremely useful building block for the synthesis of chiral organic compounds.[2] However, despite recent progress in the development of asymmetric epoxidation catalysts based on salen and porphyrin ligands,[3] no methods for direct, highly enantioselective epoxidation of terminal olefins such as styrene have yet been devised.[4,5] Catalysts bearing chiral salen ligands have been developed for the epoxidation of conjugated cis-disubstituted and trisubstituted olefins with >90% ee,[6] but styrene undergoes epoxidation with only 50–70% ee using these and related oxo-transfer catalysts.[7] This difference may be attributed to two separate factors: first, terminal olefins such as styrene may simply undergo addition by known chiral epoxidation catalysts with lower enantiofacial selectivity than cis-disubstituted and trisubstituted olefins; second, asymmetric epoxidation of terminal olefins is subject to a special type of enantiomeric "leakage" pathway. Epoxidation via oxo-transfer catalysis has been demonstrated to proceed, either partially or entirely,[8] via stepwise, nonstereospecific mechanisms.[9] As illustrated in eq 1, the trans pathway results in a decrease in enantioselectivity with terminal olefins, since with these substrates the cis and trans products are enantiomeric.



(1)

Assuming that all steps represented in eq 1 are irreversible,[10] the detrimental effect of the trans pathway on the observed enantioselectivity of epoxidation of styrene (ee_{obs}) can be expressed quantitatively (eqs 2 and 3):[11]

$$ee_{obs} = (ee_{cis} \times \%cis) + (ee_{trans} \times \%trans) \quad (2)$$

$$ee_{obs} = ee_{fac} - 2(ee_{trans} \times \%trans) \quad (3)$$

where ee_{fac} is the enantiofacial selectivity in the first step of the epoxidation. The attainment of high enantioselectivity in the epoxidation of styrene and related terminal olefins thus requires not only high facial selectivity in the first C–O bond-forming step but also high diastereoselectivity in the epoxide ring closure step.

Studies on the epoxidation of styrene and of one of its deuterium-labeled derivatives with (salen)Mn catalysts indeed confirmed that both factors are responsible for low product enantioselectivity with this catalyst system. Epoxidation of styrene with catalyst **3** at 23 °C using NaOCl as the stoichiometric oxidant afforded styrene oxide with 59% ee by GC analysis. The ^{1}H NMR spectrum of the product of epoxidation of *cis*-β-deuteriostyrene (Figure 1a) indicated the formation of both *cis*- and *trans*-β-deuteriostyrene oxides (cis/trans = 10.4:1). Chiral shift analysis ($Eu(hfc)_3$) afforded separation of all three oxirane ring proton resonances, thus revealing the composition of both the cis (69% ee) and the trans (40% ee) epoxides (Figure 1b). All of the parameters on the right side of eq 2 were therefore determined directly; the value for ee_{obs} was thus calculated to be 59%, matching the experimental value exactly. Similarly, the enantiofacial selectivity of the first step, ee_{fac}, was calculated to be 66%. Thus, the 59% enantioselectivity obtained in the epoxidation of styrene using catalyst **3** reflects a trans-pathway-induced 7% reduction of the already modest enantiofacial selectivity.

We reasoned that reducing the epoxidation reaction temperatures might provide a straightforward approach toward both minimizing the trans pathway and improving the enantiofacial selectivity in the first step. Sodium hypochlorite has been developed as the terminal oxidant of choice for (salen)Mn-catalyzed asymmetric epoxidation reactions;[12] however, the temperature window available for reactions with such aqueous oxidant systems is limited by the high freezing temperature of water. Evaluation of nonaqueous terminal oxidant systems revealed that various reagents, including Oxone, magnesium monoperoxyphthalate (MMPP), *tert*-butylhydroperoxide (TBHP), and *m*-chlorobenzoic acid (*m*-CPBA), can induce epoxidation of styrene in organic solvents such as CH_2Cl_2 in the presence of (salen)Mn catalysts. Of these, both MMPP and *m*-CPBA effected epoxidation of styrene at –78 °C in the presence of catalysts **1**–**3** (Table 1). Whereas reactions using MMPP were impractically slow (entry 7), epoxidations with *m*-CPBA were remarkably rapid even at –78 °C, with complete and essentially quantitative conversion of styrene to the corresponding epoxide occurring within 30 min (entries 6 and 8). Enantioselectivities were also improved significantly at –78 °C, exceeding 80% in the presence of catalysts **2** or **3**.[13]

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(3) Recent reviews: (a) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 4.2. (b) Collman, J. P.; Zhang, X.; Lee, V. J.; Uffelman, E. S.; Brauman, J. I. *Science* **1993**, *261*, 1404.

(4) Naruta and Maruyama have reported exceptionally high enantioselectivity in the epoxidation of 3,5-dinitrostyrene (96% ee) and 2-nitrostyrene (89% ee) employing an electron-rich binaphthyl-strapped iron porphyrin complex. However, this extraordinary selectivity is restricted to styrene derivatives bearing nitro substituents, and it is apparently due to specific π-stacking interactions between substrate and catalyst. In general, enantioselectivities in the epoxidation of terminal olefins with the Naruta-Maruyama catalysts are typical of those observed with the best chiral porphyrin- and salen-based catalysts (e.g., 56% ee with styrene). Naruta, Y.; Ishihara, N.; Tani, F.; Maruyama, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 158.

(5) For indirect routes to enantioenriched styrene oxide employing asymmetric catalysts, see: (a) Kolb, H.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515. (b) Chen, X.-J.; Archelas, A.; Furstoss, R. *J. Org. Chem.* **1993**, *58*, 5528. (c) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1993**, *34*, 5227. (d) Chan, T. H.; Chen, L. M.; Wang, D.; Li, L. H. *Can. J. Chem.* **1993**, *71*, 60.

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(9) Epoxidations of conjugated olefins catalyzed by (salen)Mn complexes proceed via radical intermediates. See: (a) Srinivasan, K.; Perrier, S.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309. (b) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martínez, L. E. *Tetrahedron* **1994**, *50*, 4323.

(10) Zhang, W.; Lee, N. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 425.

(11) Derivation of eqs 2 and 3 is provided in the supplementary material.

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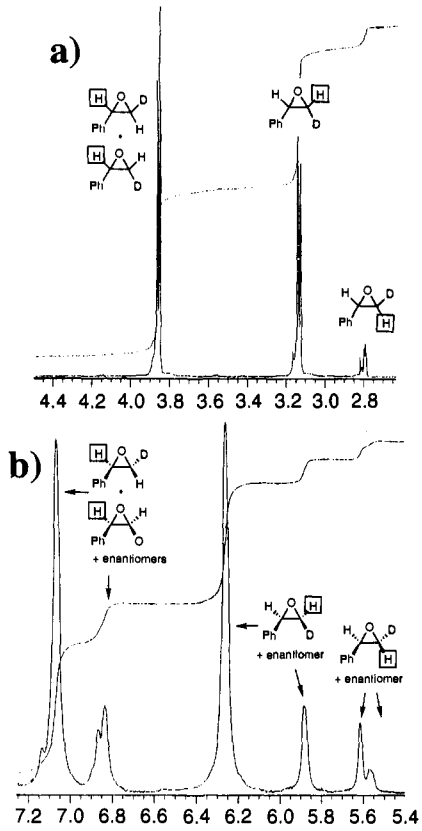
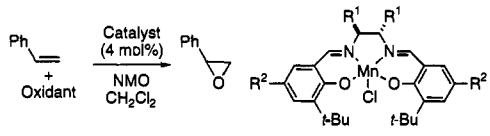


Figure 1.

Table 1. Enantioselective Epoxidation of Styrene under Nonaqueous Conditions[a]



1: R^1 =-(C_4H_8)-, R^2 = t-Bu
2: R^1 =Ph, R^2 =Me
3: R^1 =Ph, R^2 =OSi(i-Pr)$_3$

entry	catalyst	oxidant	time	T (°C)	ee (%)[b]	yield (%)[c]
1	1	m-CPBA	<15 min	0	46	97
2	2	m-CPBA	<15 min	0	65	98
3	2	MMPP	1 h	0	70	70
4	3	m-CPBA	<15 min	0	63	53
5	1	m-CPBA	30 min	-78	59	94
6	2	m-CPBA	30 min	-78	83	99
7	2	MMPP	150 h	-78	80	75
8	3	m-CPBA	30 min	-78	86	88[d]

[a] Experimental details are provided in ref 13. [b] Determined by capillary GC using a commercial Cyclodex-B chiral column (J&W Scientific). [c] Yields determined by capillary GC integration against an internal quantitative standard (dodecane) unless otherwise noted. [d] Isolated yield.

The use of excess *N*-methylmorpholine *N*-oxide (NMO) as an additive in these epoxidation reactions was observed to be critical to the attainment of high enantioselectivities. Although the uncatalyzed reaction between *m*-CPBA and styrene leading to racemic epoxide proceeds within hours at 23 °C, in the presence of excess NMO this pathway was shut down completely. In CH_2Cl_2, a 1:1 salt is generated between NMO and *m*-CPBA[14] which is unreactive toward olefins yet which appears to oxidize the (salen)Mn catalysts with high efficiency even at low temperature. In the absence of NMO, *m*-CPBA epoxidation of styrene in the presence of **2** produced racemic epoxide. No epoxidation was observed using NMO in the absence of an additional stoichiometric oxidant.

(13) The following procedure is representative. A solution of styrene (100 mg, 0.96 mmol), NMO (562 mg, 4.80 mmol), and (salen)Mn complex **3** (37 mg, 0.038 mmol) in 8 mL of CH_2Cl_2 was cooled to -78 °C. Solid *m*-CPBA (343 mg, 1.92 mmol) was added as a solid in four roughly equal portions over a 2 min period. The reaction mixture was stirred for 45 min at -78 °C, and then 10 mL of 1 N NaOH was added. The organic phase was separated and washed with brine (1 × 10 mL). The aqueous phases were then combined and washed with CH_2Cl_2 (2 × 10 mL), and the combined organic phases were then dried over Na_2SO_4 and concentrated to approximately 2 mL. Residual catalyst was removed by filtration through a small pad of silica gel. Complete removal of the solvent from the resulting filtrate provided styrene oxide that was >99% pure by GC and ^{1}H NMR analysis.

Table 2. Epoxidation of *cis*-β-Deuteriostyrene at Various Temperatures[a]

entry	catalyst	T (°C)	ee_{obs} (%)[b]	cis/trans[c]	ee_{cis} (%)[c]	ee_{trans} (%)[c]	ee_{fac} (%)[d]
1	2	23	62	16	73	54	72
2	2	0	65	19	74	59	74
3	2	-40	74	24	82	64	82
4	2	-60	79	28	85	81	85
5	2	-78	83	36	88	83	88
6	3	-78	86	31	91	85	91

[a] Reaction conditions were analogous to those described in ref 13. [b] Determined by GC analysis (see Table 1). [c] Determined by integration of the appropriate ^{1}H NMR resonances (see Figure 1). [d] Calculated according to eq 3.

The increase in enantioselectivity in the low-temperature epoxidation of styrene could be due to a combination of higher cis/trans partitioning and/or increased ee_{fac} (eq 3). The relative contributions of these two parameters were evaluated by examining the epoxidation of *cis*-β-deuteriostyrene at various temperatures (Table 2). These data clearly demonstrate that, at reduced temperatures, the enantiofacial selectivity in the first C–O bond-forming step of epoxidation is enhanced and the trans pathway in the second C–O bond-forming step is suppressed.

The data in Table 2 allow estimation of the relative entropic and enthalpic contributions to the kinetic selectivities in the first C–O bond-forming step of styrene epoxidation. A plot of $1/T$ vs $R\ \ln(k_{major}/k_{minor})$ (calculated from ee_{fac}) was strictly linear over the entire temperature range examined.[15] From this plot, the following activation parameters for the enantiofacial selectivity-determining step were deduced: $\Delta\Delta H^{\ddagger} = 1.10 \pm 0.04$ kcal·mol^{-1}, $\Delta\Delta S^{\ddagger} = -0.16 \pm 0.19$ eu. Thus, enantiofacial selectivity is controlled almost entirely by differences in enthalpy of activation, consistent with the notion that enantiofacial selectivity is directly dependent on the position of the transition state (i.e., the extent of C–O bond formation) in the first step.[16]

The discovery of a protocol for rapid, quantitative catalytic olefin epoxidation at low temperatures and under homogeneous conditions provides a powerful new tool for the study of metal-mediated oxidations. Precise kinetic data for these and related catalytic oxidation reactions are now accessible over a wide temperature range, and the enhanced stereoselectivities obtainable at low temperatures may be extended to other substrate classes and other types of oxidation reactions. Finally, the attainment of high enantioselectivity with terminal olefins extends the scope of the (salen)Mn-catalyzed epoxidation reaction to this most important substrate class.

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Supplementary Material Available: Derivation of eqs 2 and 3, and plots of $1/T$ vs $R\ \ln$(cis/trans) and of $1/T$ vs $R\ \ln(k_{major}/k_{minor})$ based on the data in Table 2 (3 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.

(14) ^{1}H NMR ($CDCl_3$): δ 10.7 (s, br, 1H), 8.02 (s, 1H), 7.92 (d, 1H, J = 7.4 Hz), 7.43 (d, 1H, J = 7.7 Hz), 7.33 (t, 1H, J = 7.6 Hz), 4.38 (t, 2H, J = 11.8 Hz), 3.85 (d, 2H, J = 12.6 Hz), 3.70 (d, 1H, J = 11.8 Hz), 3.53 (s, 3H), 3.37 (dt, 2H, J = 11.5, 2.6 Hz; IR (CH_2Cl_2) $\nu_{C=O}$ 1681 cm^{-1}; MS (FAB) m/z 235 ($\{NMO\}_2H^+$).

(15) This plot is provided in the supplementary material.

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