Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 23, pp. 3927–3933, 1997

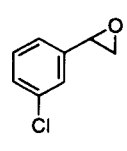
Printed in Great Britain
PII: S0957-4166(97)00568-5
0957-4166/97 $17.00 + 0.00

Synthesis of enantiopure 3-chlorostyrene oxide via an asymmetric epoxidation–hydrolytic kinetic resolution sequence †

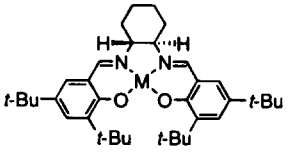
Bridget D. Brandes and Eric N. Jacobsen *
Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, USA

Abstract: 3-Chlorostyrene oxide was prepared in >99% ee employing the (salen)Co-catalyzed hydrolytic kinetic resolution (HKR) reaction. The HKR was performed successfully on both racemic and enantiomerically enriched epoxides, the latter was obtained via (salen)Mn-catalyzed asymmetric epoxidation reactions. © 1997 Elsevier Science Ltd. All rights reserved.

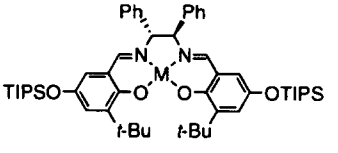
Styrene oxide derivatives are important chiral building blocks for the synthesis of a variety of pharmaceutically significant compounds.[1] One derivative in particular, 3-chlorostyrene oxide **1**, is a key intermediate for the preparation of several β-3-adrenergic compounds that exhibit antiobesity and antidiabetic therapeutic properties.[2] As might be expected for such an important target, several different approaches have been documented for its synthesis in enantiomerically enriched form. Reduction of 2,3′-dichloroacetophenone using an oxazaborolidine-based catalyst afforded the chlorohydrin precursor to the epoxide in 85% ee and 36% overall yield from commercially available 3′-chloroacetophenone.[2b] Asymmetric dihydroxylation of 3-chlorostyrene followed by a stereospecific dehydrative ring closure afforded **1** in 98% ee and good yield.[2e] Enzymatic resolution of racemic **1** has also yielded enantiopure **1**, albeit in less than 5% yield.[3] Unfortunately, the most straightforward route to enantiopure **1** — asymmetric epoxidation (AE) of 3-chlorostyrene — has not been developed in a practical manner.[4]



1



2: M = Co(OAc)(H_2O)
3: M = MnCl

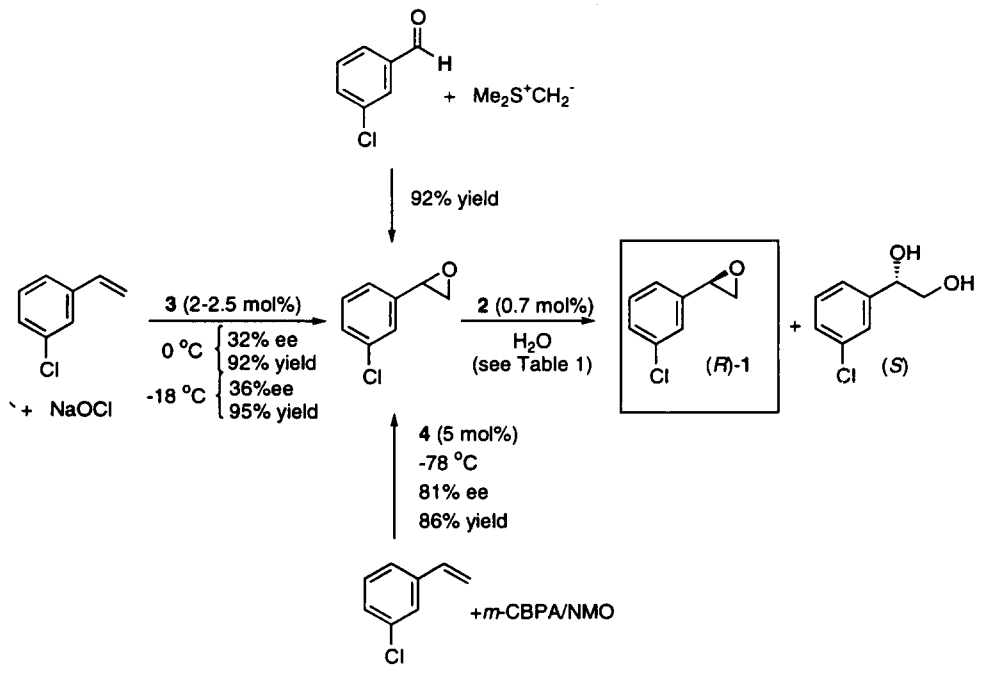


4: M = MnCl

The recently discovered hydrolytic kinetic resolution (HKR) using (salen)Co-catalyst **2** presents a highly attractive method for accessing terminal epoxides in high enantiomeric purity.[5] The HKR uses water as the only reagent, no solvent, and low loadings of a readily available and recyclable catalyst.[6] In principle, kinetic resolution strategies are especially viable when the racemic starting material is inexpensive, readily available and when the enantiopure material is relatively difficult to access. In the case of **1**, the latter criterion is clearly met, but racemic **1** is not easily obtained from commercial sources.[7] We have evaluated several approaches to **1**, including racemic synthesis, preparation in moderate enantiomeric excess via highly practical epoxidation with NaOCl and the commercial catalyst **3**,[8] and low temperature asymmetric epoxidation with *m*-CPBA and catalyst **4** under conditions devised to afford optimal enantioselectivity.[9] Herein we report the successful application of these different epoxidation strategies in connection with the HKR for the synthesis of enantiopure **1**.

† Dedicated to Professor H. C. Brown on the occasion of his 85th birthday.
* Corresponding author. Email: jacobsen@chemisty.harvard.edu

Given the substantially lower cost of 3-chlorobenzaldehyde compared with 3-chlorostyrene, we chose to carry out the synthesis of racemic **1** by means of sulfur ylide addition to the aldehyde rather than epoxidation of the alkene (Scheme 1).



Scheme 1. Synthesis of enantiopure **1**.

Enantiomerically enriched epoxide was accessed from 3-chlorostyrene using 3 different sets of epoxidation conditions (Scheme 1). As noted previously,[9] the attainment of high enantioselectivity in the epoxidation of terminal styrene derivatives with (salen)Mn-catalysts and related monooxygenase mimics requires both high enantiofacial selectivity in the first C–O bond-forming step and high diastereoselectivity in the second, ring-closure step. Both selectivity factors improve at lower temperature, and as a result enantioselectivities in epoxidations of these substrates display a strong temperature dependence. Epoxidation of 3-chlorostyrene under standard NaOCl conditions using the commercial catalyst **3** proceeded in only 32% ee but very good yield. Enantioselectivity was improved slightly by carrying out the reaction at −18°C (36% ee), but lower temperatures were not accessible with this aqueous oxidant.[10] Epoxidation employing the recently developed homogenous low temperature protocol (*m*-CPBA/*N*-methylmorpholine *N*-oxide (NMO)/catalyst **4**)[9] afforded epoxide **1** in excellent yield and 81% ee.

The HKR of **1** was carried out using epoxide prepared by the four different methods outlined above, with the amount of water in the HKR adjusted to correspond to 1.1 equivalents relative to the minor epoxide enantiomer (Table 1). Reactions on 1 g (6.9 mmol) of epoxide were complete within 2 days using 0.7 mol% (*R,R*)-**2**, and afforded enantiopure **1** in nearly quantitative yield. Entries 1 and 3 were also carried out on a 6 g (38.9 mmol) scale under the same conditions with consistent results.[11] After the resolution was complete, epoxide was isolated by partitioning the products between pentane and water. The pentane phase contained epoxide and catalyst while the diol remained in the aqueous layer. Phase separation and solvent removal followed by distillation of each product afforded both enantiomerically enriched epoxide (99% ee, *R*) and diol (up to 91% ee, *S*). In all cases, an excellent correlation can be seen between overall yields of enantiopure **1** and the theoretical yields obtainable based on the ee of

Table 1. HKR of 3-chlorostyrene oxide with 0.7 mol% (*R,R*)-**2**

	Starting Epoxide	HKR Conditions	HKR Epoxide		HKR Diol	
Entry	Ee (%) (*R*)	H_2O (Equiv.)	Ee (%)	Yield (%)[a]	Ee (%)	Yield (%)[a]
1	0	0.55	99	45	91	45
2	32	0.38	99	61	88	31
3	36	0.35	99	64	87	30
4	81	0.11	99	87	67	8

[a] Yield based on starting epoxide.

the starting material. While (*R*)-**1** is the desired epoxide in most applications,[2] the epoxidation/HKR sequence allows access to either enantiomer of **1** by simply switching the enantiomers of the catalyst.

The determination of which of the above described methods is most practical for the preparation of enantiopure **1** will clearly depend on the reaction scale and starting material costs. If 3-chlorobenzaldehyde is the most viable starting material, then a racemic epoxidation/HKR sequence is probably the most attractive alternative. If 3-chlorostyrene is employed as the starting material, epoxidation with NaOCl and catalyst **3** is competitive on a practical level with the best racemic methods such as peracid epoxidation, and the catalytic method affords a non-trivial overall yield advantage (61% yield of enantiopure **1** for the two step sequence from the alkene using the −18°C epoxidation conditions). Low temperature epoxidation with the more exotic catalyst **4** is clearly less attractive for large scale applications, but it affords the highest overall yield (75%) from the corresponding olefin and thus might prove useful for very precious substrates.

Experimental section

Materials

3-Chlorostyrene, 4-phenylpyridine *N*-oxide (4-PPNO), and (*R*)-(+)-3-chlorostyrene oxide were obtained from Aldrich and used as received.[12] 3-Chlorobenzaldehyde was purchased from Avocado and also used as received. Complex **3** is available from a variety of commercial sources or it can be conveniently prepared.[13] The (salen)Co-complex **2** can be made from commercially available ligand as described in the literature,[6] or it is available commercially from ChiRex Ltd (Dudley, UK). Complex **4** was synthesized as described below.

Methods

Flash chromatography was performed using packed glass columns of EM silica gel 60 (230–400 mesh). Gas chromatography analyses were performed on a Hewlett–Packard 5890 Series II instrument equipped with an FID detector using a Hewlett Packard 30 m×0.32 mm i.d. HP-5 capillary column. High performance liquid chromatography was used for the enantiomeric excess analyses of the epoxide and diol. Whelk-O (0.25% isopropyl alcohol in hexane, 1.0 mL/min, λ=220 nm) was used for determination of enantiomeric excess for 3-chlorostyrene oxide. Chiralcel OD (3% isopropyl alcohol/hex., 1 mL/min, λ=220 nm) was used for ee determination of 1-(3-chlorophenyl)-ethane-1,2-diol. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer. Chemical shifts are reported downfield from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform, δ 7.26 and 77.06 ppm respectively). Infrared spectra were recorded on a Mattson Galaxy FTIR 3000 spectrometer. The optical rotations were measured on a Jasco DIP 370 digital polarimeter. Mass spectra were performed by the Harvard University Mass Spectrometry Laboratory on a Jeol AX-505 or SX-102 high resolution magnetic sector mass spectrometers.

Chloro-(R,R)-[[2,2''-[(1,2-diphenyl-1,2-ethanediyl)bis(nitrilo-methylidyne)]-bis[4-triisopropylsiloxy-6-(1,1-dimethylethyl)phenolato]]-N,N''O,O''] manganese(III) 4

To a solution of diphenylethylenediamine (0.244 g, 1.15 mmol) in 90 mL of EtOH was added 3-*t*-butyl-5-triisopropylsilyloxysalicylaldehyde[14] (0.800 g, 2.30 mmol). The resulting yellow solution was heated to reflux for 25 min before the addition of a solution of $Mn(OAc)_2 \cdot 4H_2O$ (0.564 g, 2.30 mmol) in 5 mL H_2O. The resulting brown solution was heated to reflux for 30 min, after which air was bubbled through the solution via a needle for an additional 30 min. Brine (5 mL) was added, and the mixture was further heated at reflux for 30 min before being cooled to ambient temperature. The solvent volume was reduced to ca. 15 mL under vacuum, and CH_2Cl_2 (100 mL) and water (100 mL) were added. The organic phase was separated, washed with brine (100 mL), and dried over Na_2SO_4. After solvent removal, the residue was purified by chromatography (SiO_2, 5% EtOH/CH_2Cl_2) to afford 0.854 g of product (77% yield), mp 280–280.8°C. IR (CH_2Cl_2) 2947, 2868, 1600, 1535, 1464, 1409, 1343, 1230, 1041, 1010, 963, 882, 869 cm^{-1}; HRMS (FAB) *m/z*: calcd ($C_{54}H_{78}ClMnN_2O_4Si_2$) 929.4881 ($[M-Cl]^+$), found 929.4914.

Racemic 1

(A) Synthesis of trimethylsulfonium hydrogen sulfate:[15] to dimethyl sulfate[16] (10.0 mL, 1.05×10^{-1} mol) at 0°C was added dimethyl sulfide (10.4 mL, 1.42×10^{-1} mol). After stirring rapidly at 0°C for 30 minutes, the reaction was slowly warmed to room temperature yielding a crystalline solid, trimethylsulfonium methyl sulfate. After 3 hours, distilled water (20 mL) was added to form a clear solution of trimethylsulfonium sulfate.

(B) Synthesis of (±)-**1**: the aqueous solution of trimethylsulfonium sulfate (20 mL, 1.05×10^{-1} mol) was added slowly to a biphasic mixture of 50% NaOH (100 mL), 3-chlorobenzaldehyde (7.03 g, 5.00×10^{-2} mol), tetrabutylammonium bromide (0.126 g, 3.91×10^{-4} mol), and CH_2Cl_2 (132 mL). The reaction was heated at 50°C for 13 hours and then cooled to room temperature. The reaction was diluted carefully with brine (250 mL) and diethyl ether (350 mL), then filtered to remove the solids. The aqueous layer was extracted with diethyl ether (3×350 mL), and the combined organic layers were washed with brine (200 mL) and dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a pale yellow liquid. Bulb-to-bulb distillation (70°C, 0.6 mmHg) from CaH_2 afforded **1** (7.12 g, 92%) as a colorless liquid. ^1H NMR ($CDCl_3$); δ 7.27 (m, 3H), 7.17 (m, 1H), 3.83 (dd, *J*=2.5, 4.1 Hz, 1H), 3.15 (dd, *J*=4.1, 5.5 Hz, 1H), 2.76 (dd, *J*=2.5, 5.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$); δ 139.9, 134.7, 129.9, 128.4, 125.6, 123.8, 51.8, 51.3. IR (thin film, cm^{-1}); 3057, 2994, 2920, 1603, 1576, 1080. CIHRMS calcd for $(C_8H_7ClO+NH_4)^+$=172.0529, found 172.0527.

(R)-1 (32% ee)

A 2-necked round-bottom flask equipped with a water-cooled overhead stirrer was charged with 3-chlorostyrene (5.01 g, 3.61×10^{-2} mol), CH_2Cl_2 (45 mL), (*R,R*)-**3** (0.578 g, 9.10×10^{-4} mol), and 4-PPNO (0.924 g, 5.40×10^{-3} mol). The solution was cooled to 0°C, and precooled buffered bleach (0.6 M, 75 mL, 4.50×10^{-2} mol, Clorox®, buffered to pH=11.3 with 0.05 M Na_2HPO_4 and 1M NaOH) was added. The biphasic system was stirred vigorously, and the course of the reaction was monitored by GC. Upon complete consumption of starting olefin (<6 h),[17] the reaction mixture was filtered through a plug of Celite on a coarse glass frit and washed with CH_2Cl_2 (75 mL). The organic layer of the filtrate was washed with distilled water (2×25 mL), and the aqueous layers were extracted with CH_2Cl_2 (2×25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Removal of the catalyst was effected by elution through a pad of SiO_2 (30 g) using pentane and CH_2Cl_2 (1:1). The eluent was concentrated *in vacuo*, and subsequent bulb-to-bulb distillation (70°C, 0.6 mmHg) from CaH_2 afforded (*R*)-3-chlorostyrene oxide (5.15 g, 92%) as a pale yellow liquid in 32% ee.

(R)-1 (36% ee)

A 2-necked round-bottom flask equipped with an overhead stirrer was charged with 3-chlorostyrene (4.00 g, 2.89×10^{-2} mol), CH_2Cl_2 (35 mL), (*R,R*)-**3** (0.361 g, 5.68×10^{-4} mol), 4-PPNO (0.724 g, 4.23×10^{-3} mol), and 4.00 g ground NaCl.[18] The solution was cooled to −18°C while stirring vigorously and precooled 13% bleach (19.5 mL, Acros) was added down the side of the flask to allow for further cooling. The course of the reaction was monitored by GC. Upon complete consumption of the starting olefin (<27 h), the reaction mixture was filtered through a plug of Celite using CH_2Cl_2 as the eluent, and the filtrate was treated as described above to afford (*R*)-3-chlorostyrene oxide (4.24 g, 95%) as a colorless liquid in 36% ee.

(R)-1 (81% ee)

A round-bottom flask equipped with an overhead stirrer was charged with 3-chlorostyrene (1.00 g, 7.22×10^{-3} mol), CH_2Cl_2 (78 mL), (*R,R*)-**4** (0.349 g, 3.61×10^{-4} mol), and NMO (4.22 g, 3.62×10^{-2} mol). The solution was cooled to −78°C before solid *m*-CPBA[19] (2.51 g, 1.46×10^{-2} mol) was added in portions over 1.5 minutes. The reaction was monitored by GC. On completion (3 h), the reaction was quenched by the addition of a solution of dimethyl sulfide (6 mL) in CH_2Cl_2 (25 mL) precooled to −78°C. The solution was stirred for an additional 10 minutes at −78°C before removal of the cold bath and addition of 2 N NaOH (20 mL) and CH_2Cl_2 (20 mL). The phases were separated and the aqueous layer was washed with CH_2Cl_2 (2×50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Removal of the catalyst was effected by elution through a pad of SiO_2 (10 g) using pentane and CH_2Cl_2 (1:1). The eluent was concentrated *in vacuo*, and subsequent bulb-to-bulb distillation from CaH_2 afforded (*R*)-3-chlorostyrene oxide (0.963 g, 86%) as a colorless liquid in 81% ee.

Hydrolytic kinetic resolution of (R)-1

To (*R*)-**1** (6.00 g, 3.88×10^{-2} mol, 36% ee) and (*R,R*)-**2** (0.192 g, 2.82×10^{-4} mol) was added water (245 mL, 1.36×10^{-2} mol, 0.35 eq) and the mixture was stirred at room temperature for 48 h. Pentane (2×100 mL) was added, and the resulting mixture was stirred vigorously for 5 minutes. The solution was separated from the solid residue by decantation. The residue was stirred with a 1:1 pentane:water mixture (2×100 mL) and filtered through glass wool. The layers were separated and the aqueous layer was washed with pentane (3×100 mL) until no color remained. All the pentane layers were combined and dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Bulb-to-bulb distillation from CaH_2 afforded (*R*)-**1** (3.78 g, 63%, clear, pale yellow liquid) in 99% ee. The aqueous layer was also concentrated and after bulb-to-bulb distillation[20] afforded (1*S*)-1-(3-chlorophenyl)-ethane-1,2-diol (1.83 g, 27%) in 87% ee. Diol: ^{1}H NMR ($CDCl_3$); δ 7.34 (m, 1H), 7.26 (m, 2H), 7.18 (m, 1H), 4.74 (dd, *J*=3.3, 8.3 Hz, 1H), 3.70 (dd, *J*=3.3, 11.5 Hz, 1H), 3.57 (dd, *J*=8.3, 11.5 Hz, 1H), 3.29 (bs, 2H). ^{13}C NMR ($CDCl_3$); δ 142.5, 134.4, 129.8, 128.0, 126.2, 124.1, 74.0, 67.8. IR (thin film, cm^{-1}); 3376, 2928, 1431, 1196, 1076, 1030. CIHRMS calcd for $(C_8H_9ClO_2+NH_4)^+$=190.0635, found 190.0637. $[\alpha]_D^{26}$=+21.2 (c=2.9, EtOH); lit.[21] $[\alpha]_D$=+24.05 (c=1.24, EtOH, 95% ee material).

Acknowledgements

This work was supported by a grant from the National Institutes of Health (GM-43214).

References

1. (a) 3-Benzyloxy: Britten, A. Z. *Chemistry and Industry* **1968**, 771–772. (b) 4-Benzyloxy-3-nitro: Hett, R.; Fang, Q. K.; Gao, Y.; Hong, Y.; Butler, H. T.; Nie, X.; Wald, S. A. *Tetrahedron Lett.* **1997**, *38*, 1125–1128. (c) 4-Chloro: Nankai, M.; Nicholas, C.; Fage, D.; Carter, C. *Br. J. Pharmacol.* **1994**, *112*; PU142: Di Fabio, R.; Pietra, C.; Thomas, R. J.; Ziviani, L. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 551–554. (d) 3,4-Dichloro: Solladié-Cavallo, A.; Diep-Vohuule, A. *J. Org. Chem.* **1995**, *60*, 3494–3498 (also 2-naphthal). (e) 4-Fluoro: Nieduzak, T. R.; Margolin, A. L. *Tetrahedron:*

Asymmetry **1991**, *2*, 113–122. (f) 3-Nitro: Wierenga, W.; Harrison, A. W.; Evans, B. R.; Chidester, C. G. *J. Org. Chem.* **1984**, *49*, 438–442. (g) 4-Nitro: Marmo, E.; Caputi, A. P.; Rossi, F.; Lampa, E.; Vacca, C.; Brita, G.; Saini, R.-K.; Di Nola, R. *Agressologie* **1976**, *17*, 279–295. Pedragosa-Moreau, S.; Morisseau, C.; Baratti, J.; Zylber, J.; Archelas, A.; Furstoss, R. *Tetrahedron* **1997**, *53*, 9707–9714. (h) Unsubstituted: Mitchell, D.; Koenig, T. M. *Synth. Commun.* **1995**, *25*, 1231–1238. Coote, S. J.; Davies, S. G.; Middlemiss, D.; Naylor, A. S. *J. Chem. Soc., Perkins Trans 1* **1989**, 2223–2228. (i) Various: Atkins, R. K.; Frazier, J.; Moore, L. L.; Weigel, L. O.; *Tetrahedron Lett.* **1986**, *27*, 2451–2454. Pfeiffer, F. R.; Wilson, J. W.; Weinstock, J.; Kuo, G. Y.; Chambers, P. A.; Holden, K. G.; Hahn, R. A.; Wardell, J. R.; Tobia, A. J.; Setler, P. E.; Sarau, H. M. *J. Med. Chem.* **1982**, *25*, 352–358.

2. (a) Arch, J. R. S.; Ainsworth, A. T.; Cawthorne, M. A.; Piercy, V.; Sennitt, M. V.; Thody, V. E.; Wilson, C.; Wilson, S. *Nature* **1984**, *309*, 163–165. (b) Bloom, J. D.; Dutia, M. D.; Johnson, B. D.; Wissner, A.; Burns, M. G.; Largis, E. E.; Dolan, J. A.; Claus, T. H. *J. Med. Chem.* **1992**, *35*, 3081–3084. (c) Badone, D.; Guzzi, U. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1921–1924. (d) Cecchi, R.; Croci, T.; Boigegrain, R.; Boveri, S.; Baroni, M.; Boccardi, G.; Guimbard, J. P.; Guzzi, U. *Eur. J. Med. Chem.* **1994**, *29*, 259–267. (e) Hattori, K.; Nagano, M.; Kato, T.; Nakanishi, I.; Imai, K.; Kinoshita, T.; Sakane, K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2821–2824. General yields (81–95% yield) reported for several substrates which included 3-chlorostyrene oxide. (f) Sher, P. M.; Fisher, L. G.; Skwish, S.; Michel, I. M.; Seiler, S. M.; Washburn, W. N.; Dickinson, K. E. J. *Med. Chem. Res.* **1997**, *7*, 109–115.
3. Matsuyama, A.; Kobayashi, Y. European Patent 0 611 826 A2, 1994.
4. (a) Xylene oxygenase two-liquid phase culture (96±2% ee, no yield), reaction with 3-chlorostyrene as 1% (v/v) of the organic phase; Wubbolts, M. G.; Hoven, J.; Melgert, B.; Witholt, B. *Enzyme Microb. Technol.* **1994**, *16*, 887–894. (b) M(salen) and PhIO (46% ee, 60% Y); Ho, C.-W.; Cheng, W.-C.; Cheng, M.-C.; Peng, S.-M.; Cheng, K.-F. and Che, C.-M. *J. Chem. Soc., Dalton Trans.* **1996**, 405–414. (c) Ru(II) Schiff base complex and iodosylbenzene (72% ee, 48% conv.); Kureshy, R. I.; Khan, N. H.; Abdi, S. H. R. *J. Mol. Cat. A–Chem.* **1995**, *96*, 117–122. (d) Chloroperoxidase and *t*-BuOOH (62% ee (*R*), 34% Y); Colonna, S.; Gaggero, N.; Casella, L; Carrea, G.; Pasta, P. *Tetrahedron: Asymmetry* **1993**, *4*, 1325–1330 (e) Co complexes and PhIO (up to 13% ee, 65% Y); Ozaki, S.; Mimura, H.; Yasuhara, N.; Masui, M.; Yamagata, Y.; Tomita, K.; Collins, T. J. *J. Chem. Soc., Perkins Trans 2* **1990**, 353–360.
5. Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936–938.
6. Pettman, R. B. *Speciality Chemicals* **1997**, 118–120.
7. Two commercial suppliers of racemic **1** are listed in *Chem Sources International* (1996); however, both companies informed us that they did not maintain stocks of that material.
8. Jacobsen, E. N. In *Comprehensive Organometallic Chemistry II*, Wilkinson, G.; Stone, F. G. A.; Abel, E. W.; Hegedus, L. S. Ed.; Pergamon Press: New York, 1995; Vol. 12, Chapter 11.1.
9. (a) Palucki, M.; Pospisil, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 9333–9334. (b) Palucki, M.; McCormick, G. J.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5457–5460.
10. A 23% NaCl solution freezes at −20.5°C. *The Merck Index*; Budavari, S. Ed.; Merck and Co. Inc.: Rahway, NJ USA 1996 no. 8742.
11. Racemic **1** provided epoxide in 99% ee and 45% yield, and diol in 90% ee and 44% yield; 36% ee **1** provided epoxide in 99% ee and 63% yield, and diol in 87% ee and 27% yield.
12. (*R*)-(+)-3-Chlorostyrene oxide, Aldrich catalog 44,086-8, $[\alpha]_D^{20}$=+21 (neat).
13. (*R,R*) or (*S,S*)- *N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-manganese(III) chloride. Literature synthesis: Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939–1942. Larrow, J. F.; Jacobsen, E. N. *Organic Synth.*, in press.
14. Pospisil, P. J.; Carsten, D. H.; Jacobsen, E. N. *Chem. Eur. J.* **1996**, *2*, 974–980.
15. Procedure modified from (a) Ray, F. E.; Farmer, J. L. *J. Org. Chem.* **1943**, *8*, 391–396. (b) Haridas, K.; Dev, S. *Indian J. Chem.* **1987**, *26B*, 1018–1020. (c) Kaufman, T. *Synthetic Commun.* **1993**, *23*,

473–486. (d) Merz, A.; Märkl, G. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 845–846 (phase transfer conditions).
16. CAUTION!: very toxic cancer-suspect reagent. Use extreme caution in handling.
17. The reaction rate is dependent largely on the rate of stirring. More vigorous stirring leads to shorter reaction times and no deleterious effects on yield or enantioselectivity.
18. The amount of NaCl was not optimized, but was added simply to lower the melting point of the aqueous bleach phase and therefore allow the use of lower reaction temperatures.
19. *m*-CPBA was purified prior to use according to the method of Bortolini *et al.*, with the sole modification that CH_2Cl_2 was used for recrystallization (rather than CH_2Cl_2/Et_2O). Bortolini, O.; Campestrini, S.; DiFuria, F.; Modena, G. *J. Org. Chem.* **1987**, *52*, 5093–5095.
20. Boiling point of diol 189–191°C at 5 mmHg.
21. Hudlicky, T.; Boros, E. E.; Boros, C. H. *Tetrahedron: Asymmetry* **1993**, *4*, 1365–1368.

(Received 3 October 1997; accepted 7 November 1997)