A Practical Method for the Large-Scale Preparation of [*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2−)]manganese(III) Chloride, a Highly Enantioselective Epoxidation Catalyst

Jay F. Larrow and Eric N. Jacobsen*

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

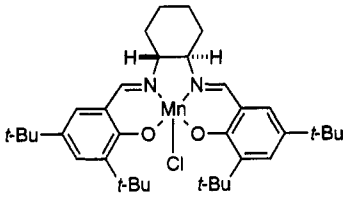
Yun Gao,* Yaping Hong, Xiaoyi Nie, and Charles M. Zepp

Sepracor Inc., 33 Locke Drive, Marlborough, Massachusetts 01752

Received November 9, 1993

Introduction

The use of catalytic asymmetric reactions for the synthesis of highly enantiomerically enriched chiral compounds is of growing importance in organic chemistry and in the chemical industry at large.[1] The practical utility of a catalytic asymmetric method is closely tied to the accessibility of the catalyst and can be severely undermined if the process for preparation of the catalyst proves too costly or technically-difficult for large-scale production. The chiral Mn(III)–Schiff base complex 1 has recently emerged as the most enantioselective catalyst uncovered to date for the epoxidation of a wide variety of olefins.[2] Herein we describe an efficient, highly-optimized procedure for the preparation of both enantiomers of 1 which is practical both on the laboratory scale and at the multihundred kilogram level.[3] The ready accessibility of 1 is likely to facilitate its incorporation into a variety of laboratory and commercial applications.

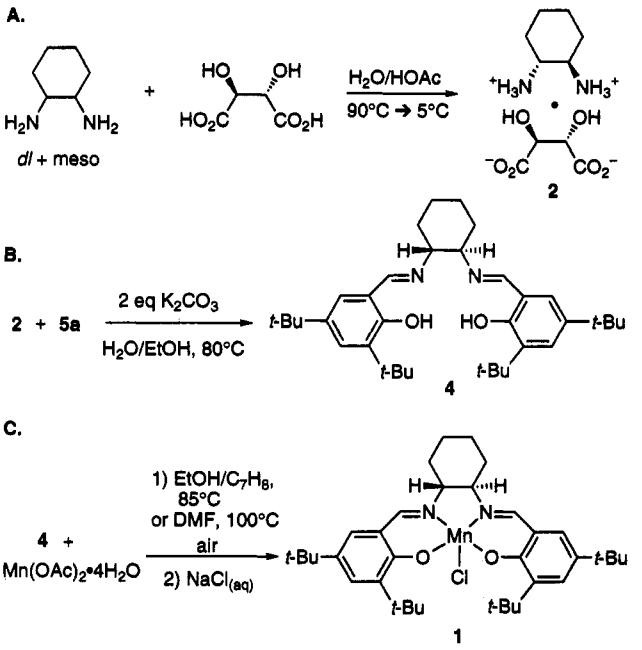


(*R,R*)-1

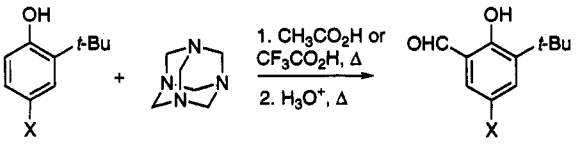
Results and Discussion

The synthesis of catalyst 1 outlined in Schemes 1 and 2 involves three linear and four total steps from inexpensive precursors. Two key improvements have been effected over previously reported (salen)Mn catalyst syntheses.[2d,4]

Scheme 1



Scheme 2



3a: X=*t*-Bu
3b: X=CH_3
3c: X=OCH_3
3d: X=Cl
3e: X=Br

5a-e

The most important modification from the perspective of large-scale production is the application of the Duff reaction[5] to the formylation of 2,4-di-*tert*-butylphenol (**3a**, Scheme 2). This procedure offers significant advantages over $SnCl_4$-mediated formylation[2d,6] or the Reimer–Tiemann reaction,[4a,7] each of which involve toxic reagents and require special handling. Although the Duff reaction is generally recognized as being low-yielding,[8] the required salicylaldehyde derivative **5a** was obtained in pure, crystalline form in 40–50% yield under optimized reaction conditions. This yield was considered quite acceptable given that all of the reagents are very economical and easy to manipulate.

The second significant improvement affecting the catalyst synthesis was tied to the resolution of 1,2-diaminocyclohexane.[9] The monotartrate salt **2** was obtained in high diastereomeric purity from either the racemic trans-diamine or the commercial mixture of racemic trans- and cis-isomers. Precipitation from aqueous acetic acid and application of a series of methanol

(1) (a) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993. (b) Nugent, W. A.; RajanBabu, T. V.; Burk, M. J. *Science* **1993**, *259*, 479.

(2) (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*, in press.

(3) Catalyst 1 has been prepared in 75–100 kg batches at two toll-manufacturing facilities under contract from Sepracor, Inc. according to method B (see Experimental Section).

(4) (a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2296.

(5) Duff, J. C.; Bills, E. J. *J.Chem. Soc.* **1934**, 1305.

(6) Casiraghi, G.; Casnati, G.; Puglia, G.; Sartori, G.; Terenghi, G. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1862.

(7) (a) Reimer, K. *Ber.* **1876**, *9*, 423. (b) Reimer, K.; Tiemann, F. *Ber.* **1876**, *9*, 824. (c) Reimer, K.; Tiemann, F. *Ber.* **1876**, *9*, 1268. (d) Reimer, K.; Tiemann, F. *Ber.* **1876**, *9*, 1285.

(8) (a) Ferguson, L. N. *Chem. Rev.* **1946**, *38*, 227. (b) Fieser, M.; Fieser, L. F. *Reagents for Organic Synthesis*; Wiley: New York, 1974; Vol. 4, p. 243.

(9) Gasbøl, F.; Steenbøl, P.; Sørensen, B. S. *Acta Chem. Scand.* **1972**, *26*, 3605.

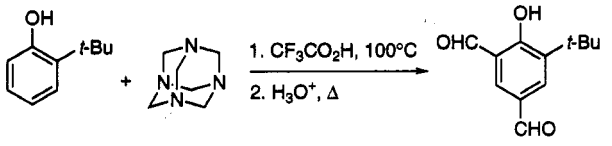
0022-3263/94/1959-1939$04.50/0

Table 1

phenol	solvent	temp, °C	product[a]	isolated yield[b]
3a	CH_3CO_2H	130	5a	40–50%
3b	CF_3CO_2H	100	5b	35%
3c	CH_3CO_2H	110	5c	45%
3d	CF_3CO_2H	110	5d	27%
3e	CF_3CO_2H	115	5e	27%
3f	CF_3CO_2H	100	6	25%

[a] The major reaction product, as determined by ^1H NMR of the crude reaction mixture. [b] The yields of 5b–e and 6 are unoptimized.

Scheme 3



3f 6

washes to the filtered salt effectively removed traces of the unwanted isomer, thereby eliminating the need for recrystallization of the salt.

The condensation of salicylaldehyde **5a** with resolved *trans*-1,2-diaminocyclohexane was effected using the tartrate salt **2** directly (Scheme 1B) which avoided isolation of the water-soluble and moderately air-sensitive free diamine. Incorporation of Mn(III) into the Schiff base ligand **4** was greatly facilitated by bubbling air through a hot suspension of $Mn(OAc)_2$. Isolation of **1** as a brown air- and water-stable powder was achieved most conveniently on laboratory scale by partial evaporation of a 50:50 CH_2Cl_2/heptane solution, followed by filtration. On multi-kilogram scale, precipitation of **1** was best effected by addition of water to a DMF solution of the catalyst.

The application of the Duff reaction to other phenols provided a series of related 3,5-substituted salicylaldehydes in 25–45% yield (Table 1). The product yield was found to be very sensitive to the temperature profile of the reaction. Significantly diminished product yields were obtained if the temperature was raised too slowly or if the prescribed temperature was exceeded. The use of trifluoroacetic acid[10] in place of acetic acid effectively increased reaction yields in certain cases by 10–15%,[11] and this proved especially valuable for the sluggishly-reacting halogenated phenols (**3d,e**). Interestingly, the monosubstituted phenol **3f** underwent double formylation to generate the dialdehyde **6** as the major product (Scheme 3). The general effectiveness of the Duff reaction in the formylation of 2,4-disubstituted phenols allows for the large-scale production of various salicylaldehyde derivatives. These, in turn, are readily incorporated into the protocol of Scheme 1 for the preparation of a variety of chiral (salen)Mn(III) derivatives.

Experimental Section

General. Unless otherwise indicated, all materials were obtained from commercial sources and were used without further purification. The instrumentation and common chromatographic techniques employed in this study have been described elsewhere.[2f] FAB samples were dissolved in CH_2Cl_2 and added to a matrix of 3-nitrobenzyl alcohol. High resolution experiments were performed at 3500 resolution using PFK internal standard. HPLC analysis was performed using a Pirkle L-Leucine column (Regis).

Representative Procedure for Formylation Reaction: 3,5-Di-*tert*-butyl-2-hydroxybenzaldehyde (5a). The procedure of Duff and Bills[5] was followed with modifications. With mechanical stirring, 2,4-di-*tert*-butylphenol (125 g, 0.61 mol, 1.0 equiv), hexamethylenetetramine (HMT, 170 g, 1.21 mol, 2.0 equiv), and glacial acetic acid (300 mL) were combined in a 2-L, three-necked, round-bottomed flask. The homogeneous mixture was heated to 130 °C over a period of 60 min or less and was maintained at this temperature (±5 °C) for 2 h. The mixture was cooled to 75 °C and 33% (w/w) aqueous H_2SO_4 (300 mL) was added. The stirred mixture was heated at reflux (105–110 °C) for 60 min before heating and stirring were discontinued. The mixture was allowed to cool to 75 °C and then transferred to a separatory funnel preheated to 75 °C with electrical heating tape. The phases were allowed to separate for 30 min at this temperature before the lower aqueous layer was removed. The organic layer was transferred to an Erlenmeyer flask and allowed to cool to 50 °C before methanol (100 mL) was added. The crude product crystallized from this mixture upon external cooling to 5 °C and was collected by vacuum filtration. Recrystallization from methanol[12] (1:1 w/v) afforded the desired compound as a free-flowing yellow solid (56–71 g, 40–50% yield) in ≥98% purity as determined by GC: mp 53–56 °C (lit.[13] mp 58–60 °C); ^1H NMR δ 11.65 (s, 1 H), 9.87 (s, 1 H), 7.59 (d, J = 2.4 Hz, 1 H), 7.35 (d, J = 2.4 Hz, 1 H), 1.43 (s, 9 H), 1.33 (s, 9 H); ^{13}C NMR δ 197.2, 159.2, 141.7, 137.8, 131.9, 127.8, 120.2, 35.1, 34.3, 31.4, 29.4; HRMS (EI) m/z 234.1628 (calcd for M^+ 234.1619). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.98; H, 9.35.

3-*tert*-Butyl-2-hydroxy-5-methylbenzaldehyde (5b). The modification of the Duff reaction developed by Smith[10] was followed with modifications. A stirred mixture containing 2-*tert*-butyl-4-methylphenol (6.69 g, 40 mmol, 1.0 equiv), HMT (11.33 g, 80 mmol, 2.0 equiv) and trifluoroacetic acid (TFA, 40 mL) was heated at 100 °C (±5 °C) for 4 h. The reaction mixture was hydrolyzed as described for **5a**, and the resulting mixture was allowed to cool to room temperature and extracted with diethyl ether (100 mL). The extract was washed with water (6 × 100 mL) and brine (100 mL) and then dried over Na_2SO_4. The solvent was removed *in vacuo* to yield an oil (24.3 g) contaminated with TFA. The crude product was purified by flash chromatography (EtOAc/hexanes 5:95) to yield **5b** as a yellow solid (2.70 g, 35% yield): mp 69–71 °C (lit.[4b] mp 74–76 °C); ^1H NMR δ 11.61 (s, 1 H), 9.83 (s, 1 H), 7.33 (d, J = 1.2 Hz, 1 H), 7.18 (s, 1 H), 2.32 (s, 3 H), 1.43 (s, 9 H); ^{13}C NMR δ 197.0, 159.2, 138.1, 135.4, 131.4, 128.2, 120.5, 34.8, 29.3, 20.5; IR (KBr) ν 2962, 2914, 1649, 1618; HRMS (EI) m/z 192.1157 (calcd for M^+ 192.1149).

3-*tert*-Butyl-2-hydroxy-5-methoxybenzaldehyde (5c). A stirred mixture of 2-*tert*-butyl-4-methoxyphenol (7.36 g, 40 mmol, 1.0 equiv), HMT (11.33 g, 80 mmol, 2.0 equiv), and acetic acid (40 mL) was heated at 110 °C (±5 °C) for 2 h. The mixture was extracted with diethyl ether (100 mL) following hydrolysis, and the extract was washed with water (3 × 100 mL) then brine (100 mL). The organic layer was dried over Na_2SO_4, and solvent removal yielded the crude product as a dark oil (6.80 g). Purification by flash chromatography (EtOAc/hexanes 10:90) yielded **5c** as a yellow oil (3.75 g, 45% yield): ^1H NMR δ 11.52 (s, 1 H), 9.84 (s, 1 H), 7.17 (d, J = 2.7 Hz, 1 H), 6.81 (s, J = 2.7 Hz, 1 H), 3.81 (s, 3 H), 1.41 (s, 9 H); ^{13}C NMR δ 196.5, 156.2, 148.8, 146.2, 123.8, 119.9, 55.8, 35.0, 29.1; IR (neat, NaCl) ν 2958, 2914, 1657, 1651, 1614, 1605; HRMS (EI) m/z 208.1102 (calcd for M^+ 208.1099).

3-*tert*-Butyl-5-chloro-2-hydroxybenzaldehyde (5d). A stirred mixture of 2-*tert*-butyl-4-chlorophenol[14] (7.62 g, 40 mmol, 1.0 equiv), HMT (11.33 g, 80 mmol, 2.0 equiv) and TFA (40 mL) was heated at 110 °C (±5 °C) for 4 h. Hydrolysis and workup yielded a light brown oil (18.8 g) contaminated with TFA. Flash chromatography (EtOAc/ hexanes 5:95) yielded a gummy yellow solid (4.35 g) which contained an impurity as detected by GC

(10) Smith, W. E. *J. Org. Chem.* **1972**, *37*, 3972.
(11) Optimal yields of **5a** were obtained using acetic acid, however.
(12) If undissolved solids remained after stirring with methanol at 55 °C for 30 min, the warm mixture was filtered prior to recrystallization.
(13) Claus, P.; Schilling, P.; Gratzl, J. S.; Kratzl, K. *Monatsch. Chem.* **1972**, *103*, 1178.
(14) This material was prepared by chlorination of 2-*tert*-butylphenol with SO_2Cl_2. Zhang, W. Ph D. Dissertation, University of Illinois at Urbana—Champaign, 1991.

analysis. The product was suspended in warm methanol (10 mL) and a white powder[15] (1.4 g, mp 155–157 °C) was separated by vacuum filtration. The filtrate was concentrated and the desired product was crystallized at −20 °C to yield a crystalline yellow solid (2.29 g, 27% yield): mp 56–58 °C; ^{1}H NMR δ 11.72 (s, 1 H), 9.81 (s, 1 H), 7.45 (d, J = 2.4 Hz, 1 H), 7.37 (s, J = 2.4 Hz, 1 H), 1.40 (s, 9 H); ^{13}C NMR δ 196.0, 159.8, 140.8, 134.3, 130.4, 124.0, 121.0, 35.1, 29.0; IR (KBr) ν 2970, 2958, 1657, 1607; HRMS (EI) m/z 212.0593 (calcd for M^+ 212.0603).

5-Bromo-3-*tert*-butyl-2-hydroxybenzaldehyde (5e). A stirred mixture of 4-bromo-2-*tert*-butylphenol[16] (10.0 g, 40 mmol, 1.0 equiv), HMT (11.33 g, 80 mmol, 2.0 equiv) and TFA (40 mL) was heated at 115 °C (±5 °C) for 6 h. After hydrolysis, the mixture was extracted with diethyl ether (100 mL). The extract was washed with water (3 × 100 mL), neutralized with saturated aqueous $NaHCO_3$ (2 × 100 mL), and then washed with water and brine (100 mL each). The organic layer was dried (Na_2SO_4) and the solvent was removed to yield a green oil (12.9 g) which was taken up in warm methanol (10 mL). A solid product was recovered in two crops, and these were combined and resuspended in warm methanol (10 mL). A white solid[17] (0.7 g, mp 177–180 °C) was separated from the warm solution by vacuum filtration. The filtrate yielded **5e** in two crops as a yellow solid (3.33 g, 33% yield) which contained a minor impurity as indicated by GC analysis. The crops were combined and recrystallized from methanol (8 mL) to yield the desired product as yellow needles (2.75g, 27% yield): mp 63.3–65.5 °C; ^{1}H NMR δ 11.73 (s, 1 H), 9.81 (s, 1 H), 7.58 (d, J = 2.4 Hz, 1 H), 7.51 (d, J = 2.4 Hz, 1 H), 1.40 (s, 9 H); ^{13}C NMR δ 195.9, 160.2, 141.3, 137.0, 133.6, 124.5, 121.8, 35.2, 29.1; IR (KBr) ν 2968, 2956, 1660, 1657, 1605; HRMS (EI) m/z 256.0090 (calcd for M^+ 256.0098).

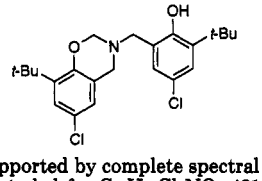
5-*tert*-Butyl-4-hydroxyisophthalaldehyde (6). A stirred mixture of 2-*tert*-butylphenol (6.07 g, 40 mmol, 1.0 equiv), HMT (11.33 g, 80 mmol, 2.0 equiv) and TFA (40 mL) was heated at 100 °C (±5 °C) for 4 h. Workup was carried out as described for **5e** to yield an orange oil (6.90 g). Purification by flash chromatography (EtOAc/hexanes 15:85) afforded **6** as a yellow solid (2.43 g, 29% yield): mp 49.5–51.5 °C; ^{1}H NMR δ 12.42 (s, 1 H), 10.00 (s, 1 H), 9.94 (s, 1 H), 8.08 (d, J = 2.0 Hz, 1 H), 8.01 (d, J = 2.0 Hz, 1 H), 1.46 (s, 9 H); ^{13}C NMR δ 196.8, 189.9, 166.1, 139.9, 135.3, 133.8, 128.5, 120.3, 35.1, 29.0; IR (KBr) ν 2960, 2869, 1699, 1649; HRMS (FAB) m/z 207.1028 (calcd for (M + H)$^+$ 207.1020).

Resolution of *cis*/*trans*-1,2-Diaminocyclohexane. This procedure is a modification of that reported by Galsbøl et al.[9] A 1-L beaker equipped with an overhead stirrer was charged with L-(+)-tartaric acid (150 g, 0.99 mol) and distilled water (400 mL). The mixture was stirred at room temperature until complete dissolution occurred, at which point a mixture of *cis*- and *trans*-1,2-diaminocyclohexane (240 mL, 1.94 mol)[18] was added at a rate such that the reaction temperature just reached 70 °C. To the resulting solution was added glacial acetic acid (100 mL, 1.75 mol) at a rate such that the reaction temperature just reached 90 °C. A white precipitate formed immediately upon addition of the acid, and the slurry was vigorously stirred as it was cooled to room temperature over 2 h. The mixture was then cooled to ≤5 °C in an ice bath for 2 h and the precipitate was collected by vacuum filtration. The wet cake was washed with 5 °C water (100 mL) and then rinsed with methanol (5 × 100 mL).[19] The solid was dried by drawing air through the filter cake for 1 h and then was analyzed for enantiomeric purity as the corresponding bis-*m*-toluoyl amide.[20] The product was then dried at 40 °C under reduced pressure to yield (*R,R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt (**2**) as a white solid (160 g, 99% yield) in ≥99% enantiomeric excess.[21]

Ligand Preparation: (*R,R*)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine (4). A 2-L, three-necked flask equipped with a mechanical stirrer, a reflux condenser, and an addition funnel was charged with **2** (29.7 g, 0.112 mol), K_2CO_3 (31.2 g, 0.225 mol), and distilled water (150 mL). The mixture was stirred until dissolution was achieved, and then ethanol (600 mL) was added. The resulting cloudy mixture was heated to reflux (75–80 °C), and a solution of 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (**5a**) in ethanol (53.7 g, 0.225 mol in 250 mL) was added in a steady stream over 30 min. The funnel was rinsed with ethanol (50 mL), and the yellow slurry was stirred at reflux for 2 h before heating was discontinued. Water (150 mL) was added and the stirred mixture was cooled to ≤5 °C over 2 h and maintained at that temperature for 1 additional hour. The product was collected by vacuum filtration and washed with ethanol (100 mL). The crude solid was redissolved in CH_2Cl_2 (500 mL) and washed with water (2 × 300 mL) and brine (100 mL). After drying over Na_2SO_4, the solvent was removed under vacuum, and **4** was isolated as a yellow powder (58.2–60.6 g, 95–99% yield): mp 200–203 °C;[22] ^{1}H NMR δ 13.76 (s, 2 H), 8.34 (s, 2 H), 7.34 (d, J = 2.2 Hz, 2 H), 7.02 (d, J = 2.2 Hz, 2 H), 3.70–3.31 (m, 2 H), 2.0–1.4 (m, 6 H), 1.45 (s, 20 H), 1.27 (s, 18 H); ^{13}C NMR δ 165.9, 158.1, 139.9, 136.4, 126.8, 126.1, 117.9, 72.4, 35.0, 34.1, 33.3, 29.5, 24.4; $[\alpha]^{20}_D$ = −315° (c 1, CH_2Cl_2); IR (KBr) ν 2960, 2869, 1631, 1595. Anal. Calcd for $C_{36}H_{54}N_2O_2$: C, 79.07; H, 9.95; N, 5.12. Found: C, 79.12; H, 9.97; N, 5.12.

[(*R,R*)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2−)]manganese(III) Chloride (1): Method A. A 2-L, three-necked flask equipped with a mechanical overhead stirrer, a reflux condenser, and an addition funnel was charged with $Mn(OAc)_2 \cdot 4H_2O$ (67.2 g, 0.27 mol, 3.0 equiv) and ethanol (600 mL). The stirred solution was heated to reflux (80–85 °C) with a heating mantle, and a solution of ligand **4** in toluene[23] (50.0 g, 0.091 mol, 1.0 equiv in 250 mL) was added in a slow stream over 45 min. The addition funnel was rinsed with toluene (50 mL), and the mixture was stirred at reflux for 2 h. The addition funnel was replaced with a gas dispersion tube and air was bubbled through the reaction mixture for 1 h at a rate of 10–30 mL/min. The reaction was monitored by TLC (EtOAc/hexanes 1:4; **4** R_f = 0.85; 1 R_f = baseline) until complete ligand disappearance was observed. At this point, heating and air addition were discontinued and saturated aqueous NaCl (100 mL) was added. The mixture was cooled to room temperature and rinsed into a separatory funnel with toluene (200 mL). The

(15) This side product was determined to have the following structure:



This structure was supported by complete spectral data and by HRMS (FAB): m/z 421.1573 (calcd for $C_{23}H_{29}Cl_2NO_2$ 421.1574). See: Komissarova, N. L.; Belostotskaya, I. S.; Shubina, O. V.; Ershov, V. V.; Voznesenskii, V. N.; Chervin, I. I. *Bull. Acad. Sci., U.S.S.R. Chem. Sci. (Eng. Transl.)* **1988**, *88*, 1966. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1988**, *9*, 2186.

(16) This material was prepared by bromination of 2-*tert*-butylphenol with bromine in diethyl ether. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry, 5th Ed.*; Longman Scientific and Technical: London, 1989; pp 980–1.

(17) This side product was determined to have a structure analogous to that reported for ref 15, as was supported by HRMS (FAB) m/z 511.0548 (calcd for $C_{23}H_{29}Br_2NO_2$ 511.0546).

(18) The compound is available as a ≈60/40 (trans:cis) mixture of isomers from Aldrich or DuPont and is substantially less expensive than the pure racemic trans diastereomer. The same procedure should be followed if the pure trans isomer is used.

(19) The opposite enantiomer of the diamine can be isolated from the aqueous filtrates as the bis(tartrate) salt by the addition of more tartaric acid (see ref 10).

(20) The enantiomeric purity of the diamine was determined by combining 25 mg of the diammonium salt, 1.5 mL of CH_2Cl_2, and 0.5 mL of 4 N NaOH. *m*-Toluoyl chloride (50 μL) was added with efficient mixing, and 250 μL of the (lower) organic layer was diluted to 10 mL with 2-propanol. The resulting solution was then analyzed by HPLC by injecting 10 μL and eluting with 2-propanol/hexane (1:9) at 1 mL/min. If the enantiomeric excess of the diamine was found to be <99% or if the difference between the top and bottom of the cake was >0.2%, the cake was washed with additional portions of methanol. Failure to obtain product with ≥ 99% ee required the recrystallization of the product from water (≈1:10 w/v) by heating to 90 °C to dissolve the salt then cooling to 5 °C overnight (typical recovery 60–70%).

(21) The opposite enantiomer of the diamine was obtained using this procedure by substituting D-(−)-tartaric acid for the L-form. This allowed for ready preparation of either enantiomer of the catalyst and the tartaric acid could be recovered in the synthesis of ligand **4**.

(22) If the product was of insufficient purity, it was crystallized in two crops from acetone (1:20 w/v; typical recovery 86–93%).

(23) Complete dissolution of the ligand often required gentle heating and/or sonication.

brown organic layer was washed with water (3 × 500 mL) and brine (500 mL) and then dried over Na_2SO_4. Solvent removal *in vacuo* yielded a brown solid which was redissolved completely in CH_2Cl_2 (300 mL). To this solution was added heptane (300 mL), and the resulting mixture was concentrated by rotary evaporation to a volume of ≈300 mL. The mixture was cooled in an ice bath for 1 h and the precipitated brown solid was collected by vacuum filtration. The catalyst was dried under high vacuum at 50–60 °C for 12 h to yield the desired product (54.9–57.2 g, 95–99% yield): mp 324–326 °C;[24] $[\alpha]^{23}_D$ = 580° (*c* 0.01, EtOH); IR (KBr) ν 2958–2950, 2912, 1612, 1535; MS (FAB) *m/z* 599 $(M - Cl)^+$. Anal. Calcd for $C_{36}H_{52}ClMnN_2O_2$: C, 67.05; H, 8.31; Cl, 5.22; Mn, 8.09; N, 4.12. Found: C, 67.05; H, 8.34; Cl, 5.48; Mn, 8.31; N, 4.28.

[(*R,R*)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2−)]manganese(III) Chloride (1): Method B. A 12-L, three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a gas dispersion tube was charged with $Mn(OAc)_2 \cdot 4H_2O$ (300 g, 1.22 mol, 2.0 equiv), ligand **2** (332 g, 0.61 mol, 1.0 equiv) and DMF (3.0 L). The vigorously stirred mixture was heated to 100–105 °C over 60 min and maintained at that temperature for 1.5 h. The addition of air was begun via the dispersion tube at a rate of ≈300 mL/min for a period of 1 h at a temperature of 90–100 °C. The reaction was monitored for ligand disappearance by TLC (EtOAc/hexanes 1:4; **4** R_f = 0.85, **1** R_f = baseline). Upon complete consumption of the ligand, saturated aqueous NaCl (300 mL) was added over 30 min with continued sparging. Heating and sparging were discontinued and the reaction mixture was cooled to 5–10 °C with external cooling over 60 min. Ambient temperature water (3.0 L) was added over 30 min with vigorous stirring, and the resulting slurry was stirred for an additional 30 min while maintaining the temperature below 5 °C. The brown precipitate was collected by vacuum filtration and was washed with hot (50 °C) water (2 × 800 mL). The solid was dried on the filter for 2 h and then under vacuum (50–100 mmHg) at 60–70 °C for 12 h. The yield of **1** was in the range of 300–400 g (77–103%) in 95–97% purity.[25]

(24) Generally, a melting point above 320 °C indicated product of acceptable purity.

Acknowledgment. We thank Professor W. H. Pirkle and Dr. C. Welsh for helpful discussions, and Mr. R. Feinberg and Ms. S. Witchwoot for technical assistance. The work carried out at Harvard University was supported by the National Institutes of Health (GM-43214). We thank the National Science Foundation PYI program (CHE-9057740), the Packard Foundation, the Camille and Henry Dreyfus Teacher-Scholar program, and the Sloan Foundation for awards to E.N.J.

Supplementary Material Available: ^1H NMR spectra of compounds **5a–e** and **6** (6 pages). This material is contained in 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.

(25) Due to the presence of variable amounts of DMF in the product, the melting point of the catalyst produced with this procedure varied greatly. However, DMF had no detrimental effect on the performance of the catalyst in epoxidation reactions.