Asymmetric Ring Opening of Meso Epoxides with Thiols: Enantiomeric Enrichment Using a Bifunctional Nucleophile

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Introduction

The desymmetrization of meso epoxides via nucleophilic ring opening is a powerful strategy for establishing two contiguous stereogenic centers in a single event.[1] Our contributions to this area began with the discovery that the (salen)Cr(III) complex **1** catalyzes the addition of $TMSN_3$ to meso epoxides with high enantioselectivity.[2] This methodology has been successfully applied to the kinetic resolution of terminal epoxides[3] and to the synthesis of a variety of biologically important compounds containing the β-amino alcohol motif.[4] We now report extension of the (salen)Cr-catalyzed asymmetric ring opening (ARO) technology[5] to include alkanethiols as nucleophiles. In particular, we demonstrate the use of a bifunctional thiol to afford doubly ring opened products in good yield and high enantiomeric excess.

Results and Discussion

An important breakthrough in thiol addition to meso epoxides was achieved recently by Shibasaki through the use of a gallium−lithium heterobimetallic binaphthoxide system.[6] Using 10 mol % of the catalyst and 4 Å molecular sieves, this system was found to effect the addition of *tert*-butyl thiol to cyclic and acyclic meso epoxides in 82−98% enantiomeric excess (ee). Our own screen of several transition metal−salen complexes using *tert*-butyl thiol as the nucleophile and cyclohexene oxide as the electrophile revealed that Cr catalyst **1** was highly efficient but only poorly enantioselective (10% ee). After evaluating a wide range of thiol structures, we identified

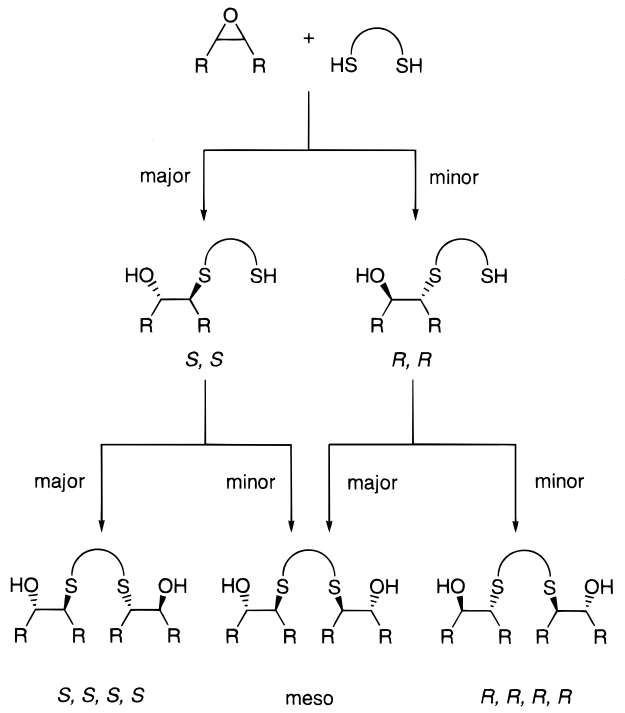
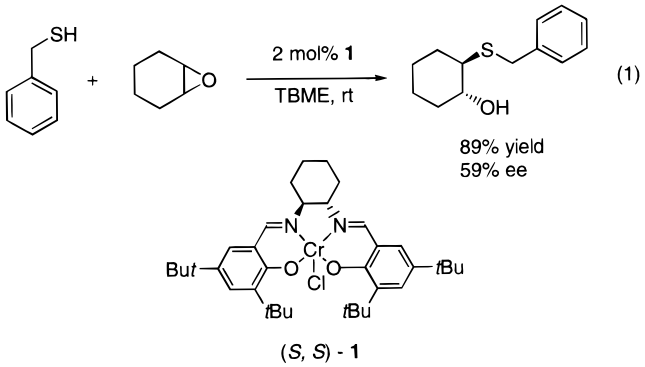


Figure 1. Double ARO strategy using a dithiol nucleophile.

that benzyl mercaptan afforded the ring-opened product in highest ee (eq 1).[7]



Unfortunately, modification of the steric and electronic properties of the ligand substituents did not lead to any further improvement in enantioselectivity beyond the moderate level of 59% ee. We reasoned that the use of a dithiol would result in addition of 2 equiv of epoxide to afford mixtures of chiral and meso bis-adducts (Figure 1). Assuming no diastereoselection in the second ring-opening event, a reaction with a monofunctional thiol reagent that affords a $[x:(1-x)]$ ratio of enantiomers will provide an improved enantiomer ratio of $[x^2:(1-x)^2]$ with a bifunctional nucleophile, along with $2x(1-x)$ of the meso product. This concept has been applied previously, primarily as a means to improve the optical purity of partially enriched mixtures of enantiomers via derivatization with a bifunctional acylating reagent.[8]

(1) (a) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 1461. (b) Paterson, I.; Berrisford, D. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1179.

(2) Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897.

(3) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420.

(4) (a) Schaus, S. E.; Jacobsen, E. N. *Tetrahedron Lett.* **1996**, *37*, 7937. (b) Wu, M. H.; Jacobsen, E. N. *Tetrahedron Lett.* **1997**, *38*, 1693.

(5) For asymmetric ring-opening reactions catalyzed by the corresponding Co(salen) complex, see: (a) Jacobsen, E. N.; Kakiuchi, F.; Konsler, R. G.; Larrow, J. F.; Tokunaga, M. *Tetrahedron Lett.* **1997**, *38*, 773. (b) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

(6) (a) Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 4783. For other examples, see: (b) Fukuzawa, S.; Kato, H.; Ohtaguchi, M.; Hayashi, Y.; Yamazaki, H. *J. Chem. Soc., Perkins Trans. 1* **1997**, 3059. (c) Yamashita, H.; Mukaiyama, T. *Chem. Lett.* **1987**, 525.

(7) The absolute configuration of this product was determined by comparison of optical rotation values reported in ref 6c. All other assignments were made by analogy.

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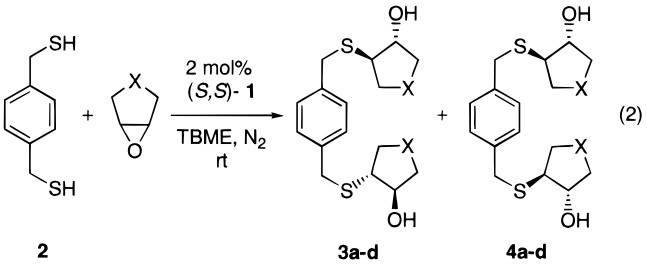
Table 1. Asymmetric Ring Opening of Meso Epoxides by Dithiol 2 Catalyzed by (*S,S*)−(salen)Cr Complex 1

entry	X	time, h	yield,[a] %	C_2:meso[b]	ee of C_2, %
a	CH_2CH_2	24	95	1.8:1	85
b	*N*-BOC	72	84	2.1:1	89
c[c]	O	96	69	2.2:1	91
d	CH_2	24	95	2.8:1	93

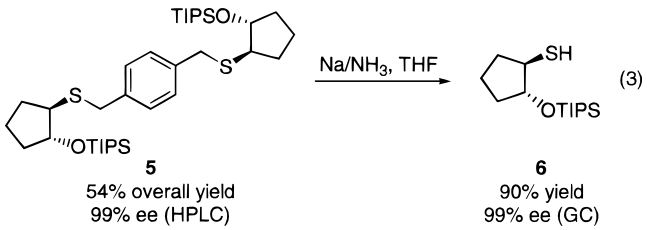
[a] Isolated yield of all stereoisomers after chromatography. [b] Diastereomeric and enantiomeric ratios were determined by HPLC (see Experimental Section). [c] A 1:1 TBME/THF solvent mixture was used with 10 mol % 1.

Given the relative success attained with benzyl mercaptan in the ARO with **1**, we chose the *p*-xylene dithiol **2**[9] as the dithiol derivative to evaluate in the double ARO strategy. Cyclohexene oxide underwent reaction with **2** in the presence of catalyst **1** to afford the corresponding bishydroxysulfide in 85% ee and excellent yield. Careful exclusion of air from the reaction medium was found to be critical, as trace amounts led to the formation of disulfide byproducts. Smaller carbocyclic and heterocyclic meso epoxides also proved to be effective substrates, with the ring opening of cyclopentene oxide affording product in highest ee (Table 1). The chiral cyclopentyl bishydroxysulfide **3d** could be efficiently separated from the meso diastereomer by means of preparative HPLC, and the optically pure bishydroxysulfide was obtained by following a single recrystallization in 54% overall yield.



(2)

The cyclopentene oxide derived ring-opening product **3d** was readily transformed into the free thiol by dissolving metal reduction of the silyl ether **5** (eq 3). This straightforward deprotection strategy allows the synthesis of enantiopure β-hydroxy thiols, which can serve as conformationally constrained chiral scaffolds for the synthesis of compounds of potential biological interest or as ligands for asymmetric catalysis.[10]



(3)

Through the use of a bifunctional thiol, very good levels of enantiomeric purity are attainable in the (salen)Cr-catalyzed ring opening of cyclopentene oxide and related meso epoxides. The ability of (salen)M(III) complexes to catalyze highly enantioselective processes ranging from asymmetric oxidations[11] to nucleophile/electrophile reactions[2,5] and cycloaddition reactions[12] is certainly striking, and it remains a focus of our continued research efforts.

Experimental Section

Representative Procedure for the Asymmetric Ring Opening of Epoxides by 2. Compounds 3a and 4a. A 50-mL Schlenk flask equipped with stir bar was charged with 1.19 g (7.0 mmol, 0.35 equiv) of dithiol **2**, and this white solid was then dissolved in 25 mL of TBME. Under an N_2 atmosphere, 2.02 mL (20.0 mmol, 1.00 equiv) of cyclohexene oxide was added via syringe. Solid Catalyst **1** (0.263 g, 0.40 mmol, 0.02 equiv) was then added in one portion to afford a brown, homogeneous solution that was quickly degassed by three freeze−pump−thaw cycles. The reaction was then allowed to stir under an atmosphere of N_2 for 24 h, during which time the reaction became heterogeneous. At this stage, solvent was removed in vacuo, and the resulting brown oil was loaded directly onto a silica column (7.5 cm × 12 cm). Elution with 10% EtOAc in CH_2Cl_2 afforded 2.42 g (6.61 mmol, 95% yield) of **3a** and **4a** as a mixture that solidified upon solvent removal: mp 99−100 °C; α^{23}_D = −33.9° (c = 1.0, CH_2Cl_2); IR (KBr) 3350 (b), 2932, 2853 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.27 (4H, s), 3.76 (4H, m), 3.29 (2H, m), 2.76 (2H, m), 2.47 (2H, m), 2.01−2.07 (4H, m), 1.66−1.71 (4H, m), 1.41−1.45 (2H, m), 1.21−1.27 (6H, m); ^{13}C NMR ($CDCl_3$) 138.0, 129.0, 72.2, 53.0, 34.4, 33.8, 32.6, 26.1, 24.3; exact mass (CI) calcd for $C_{20}H_{30}O_2S_2$ $[M + NH_4]^+$ 384.2031, found 384.2031. The stereoisomers were analyzed by HPLC using two (*R,R*) Whelko columns in tandem, eluting with 3% EtOH in hexanes at 1 mL/min [t_R 55.4, 61.2 (meso), 66.0 min]. Analysis of the reaction mixture showed a C_2:meso ratio of 1.8:1, with the chiral products present in 85% ee.

Compounds 3b and 4b. Flash chromatography (20−60% EtOAc/CH_2Cl_2, 5 cm × 10 cm) afforded **3b** and **4b** in 84% overall yield: mp 166−170 °C; α^{23}_D = −32.6° (c = 0.5, CH_2Cl_2); IR (KBr) 3245 (b), 2976, 2932, 1670 cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 7.31 (4H, s), 4.13 (2H, m), 3.82 (4H, m), 3.40−3.61 (4H, m), 3.19−3.30 (4H, m), 3.00−3.09 (2H, m), 1.44 (18H, s); ^{13}C NMR (MeOH-d_4, 318 K) 154.5, 137.3, 129.1, 79.8, 74.8, 52.1, 50.1, 48.9, 35.9, 28.4; exact mass (FAB) calcd for $C_{24}H_{40}N_2O_6S_2$ $[M + Na]^+$ 563.2226, found 563.2223. The stereoisomers were analyzed as the bis(4-nitrobenzoate) esters by HPLC using a Chiracel OD column, eluting with 20% IPA/hexane at 1.2 mL/min [t_R 36.3, 42.4 (meso), 54.1 min].

Compounds 3c and 4c. Flash chromatography (60−100% EtOAc/CH_2Cl_2, 5 cm × 12 cm) afforded **3c** and **4c** in 69% overall yield: mp 129−130 °C; α^{23}_D = +41.0° (c = 1.0, MeOH); IR (KBr) 3374 (b), 2943, 2880 cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 7.30 (4H, s), 4.19 (2H, m), 4.11 (dd, 2H, J = 9.2, 6.4 Hz), 3.93 (dd, 2H, J = 9.5, 4.4 Hz), 3.81 (4H, AB quartet, J = 13.6 Hz), 3.64 (d, 2H, J = 9.5 Hz), 3.52 (dd, 2H, J = 9.3, 4.0 Hz), 3.07 (2H, m); ^{13}C NMR (MeOH-d_4) 138.6, 130.2, 78.2, 75.1, 73.3, 51.5, 36.6; exact mass (CI) calcd for $C_{16}H_{22}O_4S_2$ $[M + NH_4]^+$ 360.1303;, found 360.1294. The stereoisomers were analyzed as the bisacetate esters by HPLC using an (*R,R*) Whelko column, eluting with 15% EtOH in hexanes at 1 mL/min [t_R 27.0, 29.3 (meso), 34.0 min].

Purification of 3d. Flash chromatography (10−20% EtOAc/CH_2Cl_2, 7.5 cm × 12 cm) afforded **3d** and **4d** in 95% yield. The *d,l*/meso mixture could be separated by preparative HPLC (Zorbax silica column, 21.2 mm × 25 cm) eluting with 2% EtOH/hexanes at 20 mL/min (t_R 78.7, 102.4 min). Purification of a 0.25 g (0.74 mmol) sample of **3d**/**4d** afforded 0.16 g of **3d** which was then recrystallized from benzene/ligroin to afford 0.14 g (0.43 mmol, 54% overall yield from epoxide) of **3d** as fine white needles: mp 90 °C; α^{23}_D = −36.7° (c = 1.0, CH_2Cl_2); IR (KBr) 3367 (b), 2963, 2907, 2863 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 (4H,

(8) (a) D′Arrigo, P.; Feliciotti, L.; Pedrocchi-Fantoni, G.; Servi, S. *J. Org. Chem.* **1997**, *62*, 6394. (b) Soai, K.; Inoue, Y.; Takahashi, T.; Shibata, T. *Tetrahedron* **1996**, *52*, 13355. (c) Fleming, I.; Ghosh, S. K. *J. Chem. Soc., Chem. Commun.* **1994**, 99.

(9) Houk, J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1987**, *109*, 6825.

(10) For examples, see: (a) Spencer, J.; Gramlich, V.; Häusel, R.; Togni, A. *Tetrahedron: Asymmetry* **1996**, *7*, 41. (b) Chelucci, G.; Cabras, M. A. *Ibid* **1996**, *7*, 965.

(11) Jacobsen, E. N. In *Comprehensive Organometallic Chemistry II*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Hegedus, L. S., Eds.; Pergamon: New York, 1995; Vol. 12, Chapter 11.1.

(12) Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403.

s), 3.92 (2H, m), 3.76 (4H, m), 2.72 (2H, m), 2.12 (2H, m), 1.96 (2H, m), 1.96 (2H, s) 1.69 (4H, m), 1.52 (4H, m); ^{13}C NMR ($CDCl_3$) 137.6, 129.1, 78.9, 51.3, 35.9, 33.3, 31.3, 21.8; exact mass (EI) calcd for $C_{18}H_{26}O_2S_2$ $[M]^+$ 338.1374, found 338.1377. The stereoisomers were analyzed by HPLC using a Chiracel OD column, eluting with 12% EtOH in hexanes at 1 mL/min [t_R 8.9, 13.9 min]. The purified sample was shown to be present in 99% ee and was diastereomerically pure.

Compound 4d. The meso diastereomer **4d** displayed physical properties indistinguishable from those of **3d** in all respects except for the following: mp 95 °C; ^{13}C NMR ($CDCl_3$) 137.7, 129.1, 79.0, 51.4, 36.0, 33.3, 31.3, 21.8.

Compound 5. A 10 mL round-bottom flask was charged with 0.060 g (0.17 mmol) of **3d**, and the white solid was dissolved in 2 mL of CH_2Cl_2. 2,6-Lutidine (0.12 mL, 1.0 mmol, 6.0 equiv) was added via syringe, and the solution was cooled to −78 °C. Syringe additon of TIPSOTf (0.12 mL, 0.44 mmol, 2.5 equiv) afforded a homogeneous solution that was warmed to room temperature over 1.5 h. The reaction was diluted with 30 mL of EtOAc and then washed with 30 mL portions of saturated NH_4Cl, $NaHCO_3$, and NaCl. The organic layer was dried with $NaSO_4$, filtered, and concentrated in vacuo. Flash chromatography (0−2% EtOAc in hexanes) afforded 0.11 g (0.17 mmol, 95% yield) of **5** as a colorless oil: $\alpha^{23}_D = -44.0°$ ($c = 0.5$, CH_2Cl_2); IR (neat) 2943, 2866 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.25 (4H, s), 4.18 (2H, m), 3.74 (4H, m), 2.90 (2H, m), 2.10−2.16 (2H, m), 1.91−1.97 (2H, m), 1.52−1.76 (10H, m), 1.02 (42H, m); ^{13}C NMR ($CDCl_3$) 137.0, 128.9, 79.5, 52.0, 36.0, 34.5, 30.9, 21.2, 18.1, 18.0, 12.2. Anal. Calcd for $C_{36}H_{66}O_2S_2Si_2$: C, 66.40; H, 10.22; S, 9.85; Si, 8.63. Found: C, 66.16; H, 10.07; S, 9.67; Si, 8.84.

(1*R*,2*R*)-2-Triisopropylsiloxy-1-mercaptocyclopentane (6). A THF solution of **5** (0.10 g, 0.15 mmol) was added to approximately 20 mL of liquid ammonia at −78 °C. To this solution was added 0.014 g of sodium metal (0.61 mmol, 4.0 equiv) that dissolved within 5 min to form a deep blue solution. The reaction was allowed to stir at −78 °C for 5 min and then warmed to −33 °C for 1.5 h. The excess sodium was then quenched with solid NH_4Cl, and then the ammonia was evaporated over 5 h under a steady stream of N_2. The white residue was then dissolved in 1.0 M $NaHSO_4$ and extracted with 40 mL of EtOAc. The organic layer was washed with brine, dried over $NaSO_4$, filtered, and concentrated in vacuo. Flash chromatography (2.5 × 10 cm silica, hexanes) afforded 0.077 g (0.28 mmol, 92% yield) of **6** that contained 2% (by ^{1}H NMR) of a dixylene contaminant. Further chromatography afforded an analytically pure sample for characterization: $\alpha^{23}_D = -44.0°$ ($c = 1.0$, CH_2Cl_2); IR (neat) 2943, 2866 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.08 (1H, m), 3.08 (1H, m), 2.23 (1H, m), 2.05 (1H, m), 1.70−1.81 (2H, m), 1.59 (1H, d, $J = 5.7$ Hz), 1.48−1.61 (2H, m), 1.05 (21H, m); ^{13}C NMR ($CDCl_3$) 82.5, 46.2, 33.5, 33.0, 21.4, 18.0, 12.2; exact mass (CI) calcd for $C_{14}H_{30}OSSi$ $[M + NH_4]^+$ 292.3130, found 292.2117. Analysis of the bisacetate ester by GC (γ-TA column, 120 °C isothermal, $t_R = 7.28$, 8.54 min) confirmed the product to be 99% ee.

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Supporting Information Available: Chromatographic analyses of racemic and enantiomerically enriched hydroxysulfides, as well as ^{1}H NMR spectra of all new compounds (13 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.

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