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Enantioselective ring opening of *meso*-epoxides with thiols catalyzed by a chiral (salen)Ti(IV) complex

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Abstract

A chiral (salen)Ti(IV) complex was an efficient catalyst in the asymmetric ring opening of *meso*-epoxides **1** with thiols **2** in high yields and good ee.

1. Introduction

The enantioselective ring opening of symmetrical epoxides is an attractive and quite powerful method in asymmetric synthesis and a number of products can be obtained when a variety of reagents are used as nucleophiles.[1,2] To date, there are only a few reports about the desymmetrization reaction of *meso*-epoxides by using RSH as a nucleophile.[3,4] Yamashita and Mukaiyama reported the catalytic asymmetric ring opening of epoxides with thiols using a zinc tartrate catalyst.[3] However the reaction time was too long and the catalyst was unsatisfactory in terms of broad specificity. Recently, Shibasaki reported the catalytic asymmetric ring opening of epoxides with *t*-BuSH using the gallium·lithium·bis(binaphthoxide) (GaLB) complex as catalyst in excellent ee, although the nucleophile was limited to *t*-BuSH.[4a] Jacobsen et al. have also reported that (salen)Cr(III) complex is effective at promoting similar reactions.[4b] However, as a program aimed at the synthesis of epoxides and aziridines and their applications in organic synthesis,[5] we studied the ring-opening reactions of epoxides and aziridines and found that the desymmetrization reaction of epoxides with anilines was carried out in the presence of a catalytic amount of chiral Yb–binol complex.[6] Herein, we provide another example of an enantioselective ring opening reaction of epoxides with various thiols using a chiral (salen)Ti(IV) complex as the catalyst.

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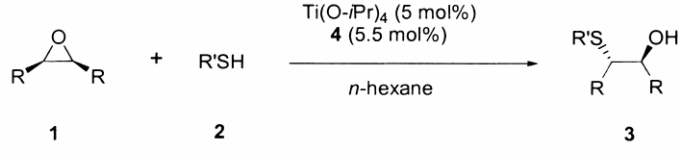
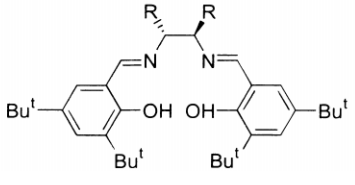
2. Results and discussion

Ti(O–^{i}Pr)$_4$-promoted ring opening of epoxides with thiols was reported by Sharpless in 1985.[7] A stoichiometric amount of Ti(O–^{i}Pr)$_4$ was necessary to allow the reaction to proceed. However, we found that salen–**4**[8] was an efficient ligand in the ring opening reaction of *meso*-epoxides **1** with thiophenol **2**. After several ligands had been examined, a high yield and good ee were obtained when a catalytic amount of salen–**4** and Ti(O–^{i}Pr) were used (Scheme 1). On the other hand, salen–**5** and Ti(O–^{i}Pr)$_4$ can catalyze the reaction of cyclohexene oxide **1a** with thiophenol **2a** effectively, but the ee is only 18%. In the reaction of cyclohexene oxide **1a** with thiophenol **2a**, the solvent effect was conspicuous. Reaction in non-polar solvents gave a better result than those in polar solvents. When CH_3CN was used as the solvent, the ee dropped to 3% although the yield was high (97% yield), while when using *n*-hexane as the solvent, 52% ee and 96% yield were obtained. In addition, the temperature also had a large influence on the reactivity and selectivity of this reaction. When the reaction of cyclohexene oxide **1a** with thiophenol **2a** was carried out at room temperature, it was complete in 10 min and hydroxy sulfide was afforded in 96% yield and 52% ee. However the same reaction run at −78°C was seriously retarded, and only a trace amount of product was detected even after 24 h. When the temperature was elevated from −25 to −40°C, the reaction was complete in 4 h and 93% yield of ring opening product was provided in 63% ee. The addition of 4A molecular sieves did not improve the reactivity or selectivity for this reaction. Based on these results, we examined the reactions of symmetrical epoxides with various thiols at −25 to −40°C in *n*-hexane. The results are shown in Table 1.



1a R, R = -$(CH_2)_4$-; **2a** R' = Ph;
1b R, R = -$(CH_2)_3$-; **2b** R' = *p*-$CH_3C_6H_4$;
1c R, R = -$(CH_2)_6$-; **2c** R' = *p*-ClC_6H_4;
1d R = -$(CH_2CH_2CH{=})_2$-; **2d** R' = *p*-$(CH_3)_3CC_6H_4$;
1e R = CH_3. **2e** R' = $PhCH_2$.



4 R = -$(CH_2)_4$-
5 R = Ph

Scheme 1.

From Table 1 it can be found that all reactions proceeded smoothly under these conditions to afford the desired β-hydroxy sulfides except in the case of cyclooctene oxide **1c** (entry 9) and 1,5-cyclooctdiene monooxide **1d** (entry 10) which failed to give products even when reacted with thiophenol **2a** at room temperature for 24 h. In this reaction, moderate to good enantioselectivities were observed and the highest ee was 63% for cyclohexene oxide **1a** with thiophenol **2a** (entry 1). In the reaction of cyclohexene oxide **1a** with a thiol having an electron-withdrawing group or an electron-donating group in the *para*-position, no significant influence was observed. Reaction of epoxide **1a** with benzylmercaptan only delivered a trace amount of product at −25 to −40°C. However, the yield increased if the reaction was carried out at room temperature (36% yield, 42% ee) (entry 5). It was also found that the results obtained by using

Table 1
Asymmetric ring opening of *meso*-epoxides with thiols[a]

entry	epoxide	thiol	time (h)	product	yield (%)[b]	ee (%)[c]	$[\alpha]_D$	Config.[e]
1	**1a**	**2a**	4	**3aa**	93	63	51.0	1S, 2S
2	**1a**	**2b**	4	**3ab**	70	62	42.7	(1S, 2S)
3	**1a**	**2c**	2	**3ac**	87	59	40.6	(1S, 2S)
4	**1a**	**2d**	6	**3ad**	90	58	36.0	(1S, 2S)
5[d]	**1a**	**2e**	24	**3ae**	36	42	22.9	(1S, 2S)
6	**1b**	**2a**	4	**3ba**	95	46	11.4	(1S, 2S)
7	**1b**	**2b**	12	**3bb**	60	44	8.2	(1S, 2S)
8	**1b**	**2d**	6	**3bd**	87	39	5.1	(1S, 2S)
9[d]	**1c**	**2a**	24	**3ca**	/	/	/	
10	**1d**	**2a**	24	**3da**	/	/	/	
11	**1e**	**2a**	4	**3ea**	82	49	26.0	(2S, 3S)
12	**1e**	**2b**	6	**3eb**	86	57	25.6	(2S, 3S)
13	**1e**	**2d**	8	**3ed**	82	49	17.1	(2S, 3S)

[a]Ti(O-*i*Pr)$_4$ (5 mol%)/**4** (5.5 mol%) in n-hexane at -25 - -40°C. [b]Isolated yield. [c]The ee values were determined by chiral HPLC. [d]The reaction was carried at room temperature. [e]Compared with the authentic specfic rotation in ref. 5. The Configuration in the parenthesis is estimated by analogy with (1S,2S)-2-(phenylthio)cyclohexanol.

thiophenol **2a** are better than those derived from the reaction of epoxides with other thio derivatives. On the other hand, when **1e** reacted with *p*-methylthiophenol **2b**, the ee value was enhanced compared with the reaction in which thiophenol **2a** was used (entries 11 and 12). All reactions in Table 1 were complete in a reasonable time period. For example, the reaction of **2d** with **1a** was complete in 6 h at −25°C in 90% yield and 58% ee (entry 4). The same reaction using zinc tartrate catalyst was complete in 120 h at 25°C in 98% yield and 52% ee.[3]

In conclusion, a facile and convenient method to synthesize the chiral β-hydroxy sulfide compounds has been developed through the (salen)Ti(IV)-catalyzed desymmetrization of *meso*-epoxides with thiols. Extension of this methodology to other racemic compounds and ring opening reactions using other classes of nucleophiles are under investigation.

3. Experimental

3.1. General method

All reactions were performed under a nitrogen atmosphere using oven-dried glassware. Solvents were treated prior to use according to the standard method. The commercially available reagents were used as received without further purification. Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Brucker AMX-300 (300 MHz) spectrometer in $CDCl_3$ at room temperature. Chemical shifts are given in parts per million downfield from tetramethylsilane. Optical rotations were measured using a Perkin–Elmer 241 MC polarimeter with a thermally jacketed 10 cm cell at 20°C (concentration c given as g/100 mL). IR spectra were measured in cm^{-1}, using a Shimadzu IR-440 infrared spectrophotometer. Mass spectra and high-resolution mass spectra were taken using HP 5989A and Finnigan MAT mass spectrometers, respectively. Elemental analyses were performed on a Foss–Heraeus Vario EL instrument. The ee values were determined by chiral HPLC on a Chiralcel OD column or a Chiralpak AD column.

3.2. General procedure

To a stirred solution of (1*R*,2*R*)-**4** (30 mg, 0.055 mmol) in *n*-hexane (3.0 mL) under nitrogen was added $Ti(O\text{–}^iPr)_4$ (0.015 mL, 0.05 mmol). The resulting mixture was stirred at room temperature for 1 h, then cooled to between −25°C and −40°C, and epoxide (1.0 mmol) and thiol (1.0 mmol) added. The reaction mixture was stirred at between −25°C and −40°C to completion, then filtered through a plug of silica gel, and washed with 20 mL of CH_2Cl_2. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography to furnish the corresponding product. The enantiomeric purity was determined by HPLC analysis using a chiral column.

3.3. (1S,2S)-2-(Phenylthio)cyclohexanol ***3aa***[3a]

Colorless liquid; 193 mg, yield: 93%; ee: 63%; $[\alpha]_D^{20}$=51.0 (c 1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.15–1.45 (m, 4H), 1.60–1.85 (m, 2H), 2.00–2.20 (m, 2H), 2.70 (br, 1H), 2.75–2.90 (m, 1H), 3.30–3.40 (m, 1H), 7.25–7.40 (m, 3H), 7.45–7.60 (m, 2H).

3.4. (1S,2S)-2-(4-Methylphenylthio)cyclohexanol ***3ab***[3a]

Colorless liquid; 155 mg, yield: 70%; ee: 62%; $[\alpha]_D^{20}$=42.7 (c 0.75, CH_2Cl_2); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.10–1.40 (m, 4H), 1.60–1.80 (m, 2H), 2.00–2.20 (m, 2H), 2.10 (s, 3H), 2.60–2.80 (m, 2H), 3.20–3.30 (m, 1H), 7.10–7.20 (d, J=7.89 Hz, 2H), 7.30–7.40 (d, J=8.10 Hz, 2H); EIMS (relative intensity): 223 (MH^+, 15), 222 (M^+, 100), 205 (8), 137 (7), 124 (49), 91 (17).

3.5. (1S,2S)-2-(4-Chlorophenylthio)cyclohexanol ***3ac***[3a]

White solid; mp: 49–51°C; 210 mg, yield: 87%; ee: 59%; $[\alpha]_D^{20}$=40.6 (c 1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.10–1.40 (m, 4H), 1.55–1.75 (m, 2H), 2.00–2.20 (m, 2H), 2.55 (br, 1H), 2.70–2.80 (m, 1H), 3.25–3.40 (m, 1H), 7.25–7.35 (m, 2H), 7.40–7.50 (m, 2H); EIMS (relative intensity): 245 (MH^+, 4, ^{37}Cl), 244 (M^+, 25, ^{37}Cl), 243 (MH^+, 11, ^{35}Cl), 242 (M^+, 69, ^{35}Cl), 224 (2), 222 (24), 144 (100), 124 (23), 81 (46).

3.6. (1S,2S)-2-(4-tert-Butylphenylthio)cyclohexanol **3ad**[3a]

Colorless liquid; 237 mg, yield: 90%; ee: 58%; $[\alpha]_D^{20}$=36.0 (c 1.35, CH_2Cl_2); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.20–1.50 (m, 13H), 1.55–1.75 (m, 2H), 2.05–2.20 (m, 2H), 2.60–2.80 (m, 2H), 3.25–3.45 (m, 1H), 7.25–7.35 (m, 2H), 7.35–7.50 (m, 2H); EIMS (relative intensity): 265 (MH^+, 10), 264 (M^+, 57), 249 (36), 166 (21), 151 (100), 123 (7).

3.7. (1S,2S)-2-(Phenylmethylthio)cyclohexanol **3ae**[3b]

Colorless liquid; 80 mg, yield: 36%; ee: 42%; $[\alpha]_D^{20}$=22.9 (c 1.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.20–1.60 (m, 4H), 1.65–1.80 (m, 2H), 1.90–2.20 (m, 2H), 2.05–2.25 (m, 2H), 3.25–3.45 (m, 1H), 3.70–3.90 (m, 2H), 7.20–7.40 (m, 5H); EIMS (relative intensity): 223 (MH^+, 13), 222 (M^+, 36), 205 (25), 123 (40), 91 (100), 65 (9).

3.8. (1S,2S)-2-(Phenylthio)cyclopentanol **3ba**[9]

Colorless liquid; 184 mg, yield: 95%; ee: 46%; $[\alpha]_D^{20}$=11.4 (c 1.65, CH_2Cl_2); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.50–1.70 (m, 2H), 1.70–1.90 (m, 3H), 2.00–2.15 (m, 1H), 2.20–2.30 (m, 1H), 3.30–3.50 (m, 1H), 4.10–4.20 (m, 1H), 7.20–7.30 (m, 3H), 7.35–7.50 (m, 2H); EIMS (relative intensity): 195 (MH^+, 13), 194 (M^+, 100), 177 (6), 166 (13), 123 (12), 110 (91), 84 (24).

3.9. (1S,2S)-2-(4-Methylphenylthio)cyclopentanol **3bb**[3b]

Colorless liquid; 124 mg, yield: 60%; ee: 44%; $[\alpha]_D^{20}$=8.2 (c 1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.50–1.70 (m, 2H), 1.70–1.90 (m, 3H), 1.95–2.05 (m, 1H), 2.10–2.25 (m, 1H), 2.30 (s, 3H), 3.25–3.35 (m, 1H), 4.00–4.15 (m, 1H), 7.10 (d, J=7.80 Hz, 2H), 7.30 (d, J=8.13 Hz, 2H); EIMS (relative intensity): 209 (MH^+, 13), 208 (M^+, 100), 191 (6), 180 (8), 137 (8), 124 (44), 91 (14).

3.10. (1S,2S)-2-(4-tert-Butylphenylthio)cyclopentanol **3bd**

Colorless liquid; 217 mg, yield: 87%; ee: 39%; $[\alpha]_D^{20}$=5.1 (c 1.35, CH_2Cl_2); IR (neat): 3317 (br), 2964 (s); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.30 (s, 9H), 1.50–1.70 (m, 2H), 1.75–1.85 (m, 3H), 2.00–2.15 (m, 1H), 2.20–2.30 (m, 1H), 3.30–3.40 (m, 1H), 4.10–4.20 (m, 1H), 7.30–7.40 (m, 4H); EIMS (relative intensity): 251 (MH^+, 11), 250 (M^+, 62), 235 (78), 233 (7), 207 (9), 151 (100), 123 (15), 91 (9); HRMS: calcd for $C_{15}H_{22}OS$: 250.1391; found: 250.1400.

3.11. (2S,3S)-3-(Phenylthio)-2-butanol **3ea**[10]

Colorless liquid; 150 mg, yield: 82%; ee: 49%; $[\alpha]_D^{20}$=26.0 (c 1.15, CH_2Cl_2); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.25 (d, J=6.26 Hz, 3H), 1.30 (d, J=6.92 Hz, 3H), 2.30 (br, 1H), 3.00–3.20 (m, 1H), 3.60–3.75 (m, 1H), 7.20–7.30 (m, 3H), 7.35–7.50 (m, 2H); EIMS (relative intensity): 183 (MH^+, 17), 182 (M^+, 100), 165 (37), 137 (96), 123 (11), 109 (20), 77 (6).

3.12. (2S,3S)-3-(4-Methylphenylthio)-2-butanol **3eb**[3b]

Colorless liquid; 168 mg, yield: 86%; ee: 57%; $[\alpha]_D^{20}$=25.6 (c 1.35, CH_2Cl_2); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.20 (d, J=6.29 Hz, 3H), 1.25 (d, J=6.96 Hz, 3H), 2.30 (s, 3H), 2.45 (br, 1H), 2.90–3.00 (m, 1H), 3.50–3.60 (m, 1H), 7.10 (d, J=7.79 Hz, 2H), 7.35 (d, J=8.12 Hz, 2H); EIMS (relative intensity): 197 (MH^+, 18), 196 (M^+, 100), 179 (47), 151 (93), 123 (13), 91 (18).

3.13. (2S,3S)-3-(4-tert-Butylphenylthio)-2-butanol **3ed**

Colorless liquid; 196 mg, yield: 82%; ee: 49%; $[\alpha]_D^{20}$=17.1 (c 1.20, CH_2Cl_2); IR (neat): 3406 (br), 2964 (s); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.25 (d, J=6.17 Hz, 3H), 1.30 (d, J=6.99 Hz, 3H), 1.35 (s, 9H), 2.25 (br, 1H), 2.95–3.05 (m, 1H), 3.55–3.70 (m, 1H), 7.30–7.40 (m, 4H); EIMS (relative intensity): 239 (MH^+, 11), 238 (M^+, 65), 223 (10), 221 (4), 193 (100), 179 (40), 151 (54) 137 (51); HRMS: calcd for $C_{14}H_{22}OS$: 238.1391; found: 238.1396.

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