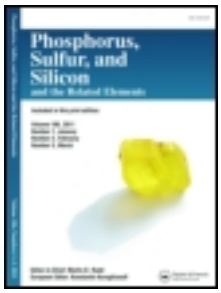

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Asymmetric Ring-Opening of Cyclohexene Oxide with Mercaptan (Thiophenols) Catalyzed by Chiral Schiff Base/Ti(OPr-i)4 or (-)-(S)-Binaphthol/Ti(OPr-i)4

Zhenghong Zhou [a], Zhaoming Li [a], Kangying Li [a], Zhuohong Yang [a], Guofeng Zhao [a], Lixin Wang [a], Qilin Zhou [a] & Chuchi Tang [a]

[a] State Key Laboratory of Elemento-Organic Chemistry, Tianjin, China

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ASYMMETRIC RING-OPENING OF CYCLOHEXENE OXIDE WITH MERCAPTAN (THIOPHENOLS) CATALYZED BY CHIRAL SCHIFF BASE/Ti(OPr-*i*)$_4$ OR (−)-(S)-BINAPHTHOL/Ti(OPr-*i*)$_4$

Zhenghong Zhou, Zhaoming Li, Kangying Li, Zhuohong Yang, Guofeng Zhao, Lixin Wang, Qilin Zhou, and Chuchi Tang
State Key Laboratory of Elemento-Organic Chemistry, Tianjin, China

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New chiral Schiff base ligands ***1–4*** *were synthesized starting from (+)-camphor and (+)-1-(4-nitrophenyl)-2-amino-1,3-propanediol, and their application in asymmetric ring-opening of cyclohexene oxide using mercaptan (thiophenols) as nucleophiles was investigated. The aymmetric ring-opening of cylohexene oxide catalyzed respectively by chiral Schiff bases* ***1–4*** */Ti(OPr-*i*)$_4$ and (−)-(S)-1,1′-binaphthalene-2,2′-diol* ***5*** */Ti(OPr-*i*)$_4$ complex afforded the corresponding chiral β-hydroxysulfides* ***6–10*** *in lower to good yield with lower to moderate ee values. Moreover, the using of (−)-(S)-1,1′-binaphthalene-2,2′-diol as ligand led to better chiral induction effect.*

Keywords: Asymmetric ring opening; binaphthol; chiral Schiff base; cyclohexane epoxide; thiophenols (mercaptan)

The stereoselective ring-opening of *meso*-epoxides with various nucleophiles is an important transformation in organic synthesis because it is a powerful strategy for the formation 1,2-bifunctionalized systems, and at the same time establishes two contiguous stereogenic centers. A wide variety of nucleophiles are used in the aforementioned ring-opening reaction.[1,2] Among them, sulfur nucleophiles are important and the most reported sulfur nucleophiles are alkane- and arene-thiols. This asymmetric ring-opening of *meso*-epoxides with mercaptan or

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Address correspondence to Chuchi Tang, State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P.R. China. E-mail: c.c.tang@eyou.com

thiophenols catalyzed by a chiral metal reagent affrods the corresponding chiral β-hydroxysulfides. Yamashita has realized the enantioselective ring-opening of epoxides with mercaptans catalyzed by Metal(II) *d*-tartarate.[3] However, this suffered from long reaction time and harsh reaction conditions as well as the low enantioselectivity. Although high enantioselectivity was obtained by Shibasaki and Jacobsen using Ga/Li bis(binaphthoxide) complex and salen(Cr) as the catalysts, respectively, the ring-opening reagents were limited to *tert*-butyl mercaptan[4] and dimercapto compounds.[5] Hou has investigated salen Ti(IV) catalyzed ring-opening of epoxides with mercaptan or thiophenol. The corresponding ring-opening products were obtained only with moderate ee values.[6]

Herein, we report the asymmetric ring-opening of cyclohexene oxide with mercaptan (thiophenol) catalyzed by 4 recently synthesized Schiff bases **1–4** and (d)-(S)-1,1′-binaphthalene-2,2′-diol **5** in the presence of Ti(OPr-*i*)$_4$.

EXPERIMENTAL

^{1}H and ^{31}P NMR were recorded in $CDCl_3$ as solvent on a Brucker AC-P200 instrument using TMS as internal standard for ^{1}H NMR and 85% H_3PO_4 as external standard for ^{31}P NMR. Elemental analyses were conducted on MT-3 CHN automatic analyzer. Melting points were determined on XT-4 apparatus. Specific rotations were measured on a Perkin Elmer 241MC polarimeter. All the temperatures were uncorrected. All the solvents were dried and redistilled according to the literature. Ti(OPr-*i*)$_4$ was Fluka reagent.

Preparation of Chiral Schiff Base

(+)-cis-1,2,2,-Trimethylcyclopentane-1,3-dicarboxylic Acid[7]

A mixture of (1R)-(+)-camphor (19.0 g, 0.125 mmol), $FeSO_4 \cdot 7H_2O$ (1.2 g, 0.0036 mmol), HNO_3 (180 mL, 65–68%) and 85 mL of water was refluxed at 100–105°C for 30 h, then the resulting was cooled to room temperature, the white solid precipitate was collected by filteration and washed twice with water to give desired product 12.2 g, yield: 49%, m.p. 202–205°C, $[\alpha]_D^{25} = +44$ (c 10, EtOH).

(+)-cis-1,2,2-Trimethylcyclopentane-1,3-diamine[7]

To a mixture of (+)-*cis*-1,2,2,-trimethylcyclopentane-1,3-dicarboxylic acid (20.3 g, 0.1 mmol), concentrated H_2SO_4 (60 mL) and 200 mL of chloroform was added NaN_3 (18.6 g, 0.286 mmol) at intervals until gas

evolution ceased. The resulting solution was cooled to room temperature and adjusted to pH > 14 with saturated NaOH. The solution was deposited overnight and filtered, and washed with $CHCl_3$ (2 × 30 mL). The organic phase was separated and the aqueous layer was extracted with $CHCl_3$ (2 × 30 mL). The combined organic phase was dried over anhydrous $MgSO_4$, then the solvent was removed under reduced pressure to afford crude product 12.2 g, yield: 86%.

Preparation of Compound 1 (Typical Procedure)[7]

A mixture of salicylaldehyde (2.44 g, 20 mmol), (+)-*cis*-1,2,2-trimethylcyclopentane-1,3-diamine (1.42 g, 10 mmol), *p*-toluenesulfonic acid (0.01 g) and 40 mL of toluene was stirred under reflux for 2 h. After removal of solvent, the crude product was recrystallized from ethyl acetate to give 2.80 g of **1** as yellow solid. M.p. 159–161°C; $[\alpha]_D^{25} = +34$ (c 2, $CHCl_3$); ^{1}H NMR (δ, ppm): 0.95 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 2.15 (m, 4H, $2CH_2$), 3.71 (t, 1H, CH, J = 6.84 Hz), 7.11 (m, 8H, Ar-H), 8.45 (s, 2H, OH). Elemental analysis calculated for $C_{22}H_{26}N_2O_2$: C, 75.36; H, 7.49; N, 7.99. Found: C, 75.15; H, 7.50; N, 7.88.

Preparation of Compound 2

Yellow solid, 80% yield, m.p. 137–139°C; $[\alpha]_D^{25} = +41.9$ (c 1.5, $CHCl_3$); ^{1}H NMR (δ, ppm): 0.96 (s, 6H, CH_3), 1.32 (s, 3H, CH_3), 1.35 (s, 9H, Bu-H), 1.45 (s, 9H, Bu-H), 2.28 (m, 7H, CH_3 and $2CH_2$), 3.54 (t, 1H, CH, J = 7.26 Hz), 7.20 (m, 4H, Ar-H), 8.34 (s, 1H, OH), 13.24 (s, 1H, OH). Elemental analysis calculated for $C_{32}H_{46}N_2O_2$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.14; H, 9.36; N, 5.45.

Preparation of Compound 3

Yellow solid, 77% yield, m.p. 237–240°C; $[\alpha]_D^{25} = +37.7$ (c 1, $CHCl_3$); ^{1}H NMR (δ, ppm): 0.95 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 2.04 (m, 4H, $2CH_2$), 3.68 (t, 1H, CH, J = 7.02 Hz), 7.29 (m, 4H, Ar-H), 8.24 (s, 2H, OH). Elemental analysis calculated for $C_{22}H_{22}Cl_4N_2O_2$: C, 54.12; H, 4.54; N, 5.74. Found: C, 54.13; H, 4.28; N, 5.73.

Preparation of Compound 4

A mixture of salicylaldehyde (1.20 g, 20 mmol), (+)-1-(4-nitrobenzyl)-2-amino-1,3-propanediol (2.10 g, 10 mmol), *p*-toluenesulfonic acid (0.01 g) and 30 mL of toluene was stirred under reflux for 7 h. After cooling to room temperature, the precipitate formed was collected by filtration and washed with ether to give 3.00 g of the desired Schiff base **4**. 97% yield, m.p. 184–186°C; $[\alpha]_D^{25} = +308.4$ (c 2, $CHCl_3$); ^{1}H NMR

(δ, ppm): 3.63 (m, 3H, CH_2 and CH), 5.19 (s, 1H, CH), 6.84 (d, 2H, Ar-H, J = 7.87 Hz), 7.25 (d, 2H, Ar-H, J = 3.17 Hz), 7.69 (d, 2H, Ar-H, J = 8.55 Hz), 8.15 (d, 2H, Ar-H, J = 4.47 Hz), 8.32 (s, 1H, OH). Elemental analysis calculated for $C_{16}H_{16}N_3O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.70; H, 4.95; N, 8.75.

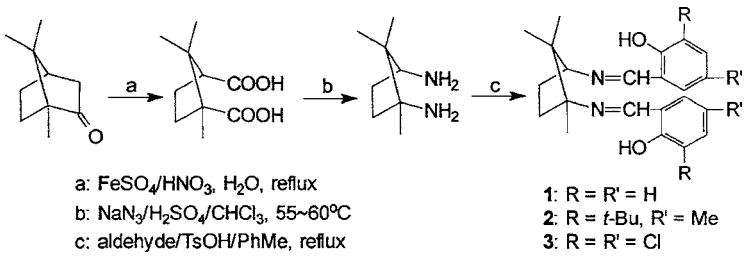
Asymmetric Ring-Opening Reaction of Cyclohexane Epoxide with Mercaptans (Or Thiophenols)

To a 10 mL anhydrous flask was added 2 mL of solvent, 0.3–1 mmol of chiral ligands (1:1 of Schiff base or (S)-binaphthol/Ti(OPr-*i*)$_4$) under a nitrogen atomosphere. The mixture was stirred at room temperature for 1 h, then 1 mmol of mercaptan (or thiophenols) and 1 mmol of cyclohexane epoxide were introduced. The resulting mixture was stirred at room temperature monitored by TLC. After removal of the solvent, the crude product was purified by thin layer chromatography on silica gel (300–400 mesh, petroleum ether/ethyl acetate as eluent) to afford ring-opening products **6–10**. (See Table III for data for compounds **6–10**).

RESULTS AND DISCUSSION

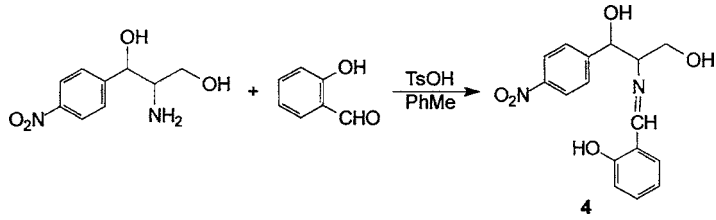
The Synthesis of Chiral Schiff Base

The chiral Schiff bases **1–3** were synthesized by successive oxidation, aminaton, and imination of (+)-camphor according to the method reported by our group.[7] Because (+)-*cis*-1,2,2-trimethylcyclopentane-1,3-diamine was difficult to purify, it was used directly in the reaction with salicylaldehyde or its derivatives to produce desired ligands **1–3**.



(+)-1-(4-nitrobenzyl)-2-amino-1,3-propanediol was an easily available by-product in the manufacture of chloromycetin. It was reacted with salicylaldehyde catalyzed by *p*-toluenesulfonic acid to afford Schiff

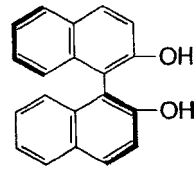
base **4** in excellent yield.



4

(−)-(S)-1,1′-Binaphthalene-2,2′-diol 5

Highly enantiomeric pure **5** could be obtained with high yield according to our recently reported method using L-menthol as resolving agent via the cyclic phosphite.[8]



5

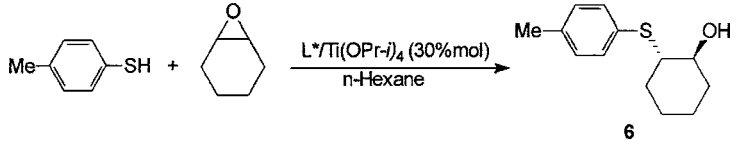
Ring-Opening Reaction of Epoxides Catalyzed by Chiral Schiff Base 1–5/Ti(OPr-*i*)$_4$

The asymmetric ring-opening of cyclohexene epoxide with 4-methylthiophenol catalyzed by 30 mol% of 4 chiral Schiff bases in n-hexane was investigated. All the results are summarized in Table I.

As shown in Table I, the reaction temperature had a modest influence on the enantioselectivity and yield of the ring-opening reaction. The enantioselectivity and yield at −20°C (entry 1) were lower than those at 0°C. Similarly, the catalytic effect at 20°C was slightly decreased compared with that at 0°C. Therefore, the optimal reaction temperature was 0°C.

The structure of the catalysts also was found to by an essential factor to the enantioselectivity and yield of the reaction. The best catalyst was the Schiff base which has bulky group substituted at the *ortho*-position of the hydroxy in the benzene ring. For example, because of the bulky tert-butyl group the catalytic effect of ligand **2** was much better than those of ligands **3**, **4**, **1**, which have only small groups, such as hydrogen, chloro substituted at the *ortho*-position. The yield and enantioselectivity of ligand **2** were 78% and 36% ee respectively. However, the latter had only 45–34% yield and 11–3% ee.

TABLE I Ring-Opening of Cylohexene Oxide Catalyzed by Chiral Schiff Bases **1–4**/Ti(OPr-*i*)$_4$



6

Entry	Ligands	Temp. (°C)	Yield (%)[a]	$[\alpha]_D^{25}$ (c 1, CH_2Cl_2)	ee%[b]	ee%[c]
1	**2**	−20	72	+17.3	25	26
2	**2**	0	78	+22.2	32	36
3	**2**	20	75	+22.1	32	
4	**1**	0	35	+6.1	9	
5	**3**	0	34	+2.0	3	3
6	**4**	0	45	+7.1	10	11

[a]Isolated yield.
[b]Determined by the comparison of sepecific rotation values, $[\alpha]_D^{20}$ +42.7 (*c* 0.75, CH_2Cl_2) with 62%ee.[6]
[c]Determined by HPLC with chiral column (Chiralcel OD).

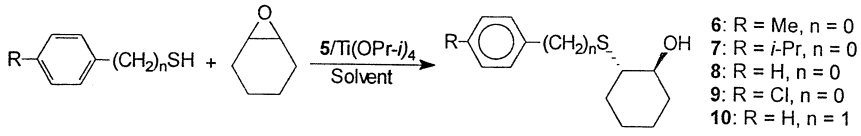
Comparison of specific rotation value with those reported in literature,[3b] the absolute configuration of ring-opening products 6 could be determined as 1S,2S. (Other data of compounds **6** are shown in Table III).

Ring-Opening Reaction of Epoxides Catalyzed by (−)-(S)-Binaphthol 5/Ti(OPr-*i*)$_4$

The catalytic effect of (−)-(S)-binaphthol/Ti(OPr-*i*)$_4$ was examined using benzyl mercaptan or substituted thiophenols as ring-opening reagents and cyclohexene epoxide as substrate. All the results are summarized in Table II.

As shown in Table II, the amount of catalyst had a modest influence on the enantioselectivity and yield. Thus, the use of 50 mol% of catalyst led to the expected product in high yield with ee of 35% (entry 3), while the use of 30 mol% and 100 mol% of catalyst gave lower enantioselectivity (entry 1, 22% ee; entry 2, 32% ee). Therefore, the optimal amount of catalyst was 50 mol%. Moreover, the solvent also was found to a important factor to this reaction. The yield and enantioselectivity in polar solvent (THF, entry 4) were lower than those in less polar solvent (toluene, entry 6) or nonpolar solvent (n-hexane, entry 3). Although good yield was obtained in CH_2Cl_2, the enantioselectivity was dramatically

TABLE II Ring-Opening of Cylohexene Oxide Catalyzed by (−)-(S)-**5**/Ti(OPr-*i*)$_4$



Entry	R	n	Amount of Catalyst (mol%)	Solvent	Temp. (°C)	$[\alpha]_D^{25}$ (*c* 1, CH_2Cl_2)	Products	Yield (%)[a]	e.e.%[b]	e.e.%[c]
1	Me	0	30	n-hexane	0	+15	**6**[6]	30	22	
2	Me	0	100	n-hexane	0	+22	**6**	55	32	
3	Me	0	50	n-hexane	0	+24	**6**	45	35	41
4	Me	0	50	THF	0	+19	**6**	27	28	32
5	Me	0	50	CH_2Cl_2	0	+15	**6**	45	22	22
6	Me	0	50	toluene	0	+27	**6**	45	40	43
7	Me	0	50	toluene	25	+17	**6**	50	25	
8	Me	0	50	toluene	−20	+22	**6**	35	30	38
9	i-Pr	0	50	toluene	0	+22	**7**	48		37
10	H	0	50	toluene	0	+28	**8**[6]	53	35	38
11	Cl	0	50	toluene	0	+15	**9**[6]	57	22	
12	H	1	50	toluene	0	+13	**10**[9]	46	24	18

[a]Isolated yield.

[b]Determined by the comparison of sepecific rotation values: product **6**, $[\alpha]_D^{20}$ + 42.7 (*c* 0.75, CH_2Cl_2) with 62%ee[6]; product **8**, $[\alpha]_D^{20}$ + 51.0 (*c* 1, CH_2Cl_2) with 63%ee; product **9**, $[\alpha]_D^{20}$ + 40.6 (*c* 1, CH_2Cl_2) with 59%ee[6]; product **10**, $[\alpha]_D^{20}$ + 22.9 (*c* 1.2, CH_2Cl_2) with 42%ee.[9]

[c]Determined by HPLC with chiral column (Chiralcel OD).

decreased (entry 5). The optimal reaction temperature was 0°C. The enantioselectivity and yield were both decreased (entry 8) when the reaction was carried out at lower temperature. At higher temperature, although the yield was increased a little the enantioselectivity was decreased markedly (entry 7). The enantioselectivity was also influenced by the nature of the ring-opening reagents. The enantioselectivities of thiophenols (entry 6, 9–11) were higher than that of mercaptan (entry 12). Furthermore, better enantioselectivities were obtained when there was electron-donating substituent in the benzene ring of thiophenols (entry 6, 9, 11).

The ring-opening products **6**, **8–10** are known compounds, and by comparison of the specific rotation value their absolute configuration could be determined as 1S,2S according to the literature.[3b] As for the unknown compound **7**, we preliminarily determined its absolute

TABLE III Experimental Data of Ring-Opening Products **6–10**

Products	m.p. (°C)	^{1}H NMR	Elemental Analysis (Calc./Found)	
6	Thick	1.26 (m, 4H), 1.67 (m, 2H), 2.10 (m, 2H), 2.34 (s, 3H), 2.62 (m, 1H), 2.91 (s, 1H), 3.28 (m, 1H), 7.14 (d, 2H), 7.36 (d, 2H)	70.23/70.30	8.16/8.20
7	Thick	1.14–1.33 (m, 10H), 1.66 (m, 2H), 2.07 (m, 2H), 2.50 (m, 1H), 2.66 (m, 1H), 3.11 (s, 1H), 3.27 (m, 1H), 7.16 (d, 2H), 7.39 (d, 2H)	71.95/71.68	8.86/8.65
8	Thick	1.29 (m, 4H), 1.66 (m, 2H), 2.06 (m, 2H), 2.74 (m, 1H), 2.97 (s, 1H), 3.29 (m, 1H), 7.24–7.47 (m, 5H)	69.18/69.19	7.76/7.60
9	44–46	1.26 (m, 4H), 1.66 (m, 2H), 2.05 (m, 2H), 2.85 (m, 1H), 2.99 (s, 1H), 3.26 (m, 1H), 7.24 (d, 2H), 7.36 (d, 2H)	59.37/59.25	6.23/6.10
10	Thick	1.17 (m, 4H), 1.25 (m, 2H), 1.99 (m, 2H), 2.14 (m, 1H), 2.41 (s, 1H), 3.30 (m, 1H), 3.80 (m, 2H), 7.27 (m, 5H)	70.21/70.30	8.18/8.15

configuration as 1S,2S by comparison of the specific rotation value with the analogues. The experimental data of the products **6–10** are summarized in Table III.

In conclusion, moderate enantioselectivity was obtained in the Schiff base/Ti(OPr-*i*)$_4$ catalyzed ring-opening reaction of epoxides with mercaptan or thiophenols, which was consistent with the literature results. Furthermore, better results were obtained using (−)-(S)-binaphthol as the ligand. These studies will give helpful information to further designing of ligands containing two hydroxy groups.

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