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Asymmetric Ring Opening Reactions of Symmetrical N-Acylaziridines with Thiols Catalyzed by Chiral Dialkyl Tartrate–Diethylzinc Complexes

Masahiko Hayashi, Kazuyuki Ono, Haruhisa Hoshimi and Nobuki Oguni*

Department of Chemistry, Faculty of Science, Yamaguchi University, Yamaguchi, 753, Japan

Abstracts: The asymmetric ring opening reaction of 1,2-(N-acylimino)cyclohexanes (*N*-acylaziridines) with some thiols proceeded in the presence of chiral zinc complexes prepared from diethylzinc and dialkyl L-(+)-tartrate to afford *trans* 2-(*N*-acylamino)-1-arylthiocyclohexane in up to 93% ee. The enantioselectivity is highly influenced by the molar ratio of the reactants and the nature of chiral dialkyl tartrate. The chemical structure of dialkyl L-(+)-tartrate-zinc complex is discussed on their ¹H NMR spectra and molecular weight. Copyright © 1996 Elsevier Science Ltd

Introduction

The asymmetric synthesis of optically active organic compounds from symmetrical precursors has attracted much attention these days, and various biological¹ and chemical² methods have been reported in this field. Among those, in particular, the enantioselective ring opening of symmetrical epoxides with some nucleophiles in the presence of chiral catalysts has become attractive synthetic methods, because this method offers the opportunity to generate two chiral centers with a single operation (eq. 1). Mukaiyama first reported



the asymmetric ring opening reaction of cyclohexene oxide with some thiols by the use of a heterogeneous chiral catalyst.³ After that report, several asymmetric ring opening reactions of symmetrical epoxides with some heteroatom nucleophiles have been reported.⁴

On the other hand, the asymmetric ring cleavage of symmetrical N-substituted aziridines with nucleophiles has not been reported so far.⁵ This paper deals with the first report on the highly enantioselective ring opening reaction of the symmetrical N-acylaziridines with arenethiols catalyzed by dialkyl L-(+)-tartrate-diethylzinc complexes and the study on the structure of zinc compounds in solution (eq. 2).⁶



Results and Discussion

Asymmetric Ring Opening Reaction of 1,2-[N-(p-Nitrobenzoyl)imino]cyclohexane (1a) with*p-tert*-Butylbenzenethiol. First, we investigated the reactions of 1a with*p-tert*-butylbenzenethiol in the presence of an equimolar amount of chiral zinc complexes prepared from diisopropyl L-(+)-tartrate (DIPT) and diethylzinc in dichloromethane (eq. 3). During the screening of a variety of reaction conditions, we found that the enantioselectivity was much influenced by the molar ratio of the reactants. As shown in Table 1, the highest enantioselectivity was achieved when the reaction was carried out by using 1:3:1:4.8 molar ratio of 1a:diethylzinc:L-(+)-DIPT:thiol. Under these conditions, the ring opening product, 1-(*p-tert*-butylphenylthio)-2-[N-(*p*-nitrobenzoyl)amino]cyclohexane (2a) was obtained in 88% ee and 98% yield (entry 8).

	molar ratio			product		
entry	Et ₂ Zn	L-(+)-DIPT	thiol	% yield ^b	% eec,d	
1	1	1	1	83	22	
2	1	1	2	95	66	
3	2	1	2	96	12	
4	2	- 1	3	96	70	
5	2	1	3.6	97	82	
6	2	1	4	97	67	
7	3	1	3	90	29	
8	3	1	4.8	98	88	
9	3	1	5	98	85	
10	3	1	5.2	98	85	
11	3	1	6	94	69	

Table 1. Effect of Molar Ratio on Enantioselectivity in the Reaction of 1a with *p*-tert-Butylbenzenethiol Promoted by L-(+)-DIPT-Et₂Zn Complex^a

^a All reactions were carried out in dichloromethane at 0 °C for 14-96 h. ^b Isolated yield after column chromatography. ^c HPLC analysis (SUMIPAX OA-4000). ^d Absolute configuration of the product was (1*S*, 2*S*).

For the purpose to achieve higher enantioselectivity, we have investigated the effects of the nature of solvents and of the alkyl groups in dialkyl tartrate on the enantioselectivity of the reaction. The results obtained in solvent other than dichloromethane were as follows: toluene (98% yield, 85% ee), chloroform (98% yield, 80% ee), 1,2-dichloroethane (98% yield, 63% ee), and THF (75% yield, 33% ee). Among the various alkyl esters of L-(+)-tartaric acid, such as diethyl tartrate (DET), dicyclohexyl tartrate (DCHT), and di-*tert*-butyl tartrate (DTBT) the highest enantioselectivity (93% ee) was attained when the reaction was undertaken in toluene using L-(+)-DCHT (entry 4 in Table 2). The reaction using 1,2-(N-benzoylimino)cyclohexane (1b) instead of 1a as a substrate gave the ring opening product in 81% ee under the same condition using L-(+)-DCHT.

		produ	ct
entry	dialkyl L-(+)-tartrate ^b	% yield ^c	% eed
1	L-(+)-DET	98	90
2	L-(+)-DIPT	98	85
3	L-(+)-DIBT	98	89
4	L-(+)-DCHT	98	93
5	L-(+)-DTBT	98	65
3 4 5	L-(+)-DIBT L-(+)-DCHT L-(+)-DTBT	98 98 98	89 93 65

Table 2. Effect of the Nature of Dialkyl L-(+)-Tartrate on Enantioselectivity in Toluene^a

^a All reactions were carried out in toluene at 0 °C for 14 h. ^b DET = diethyl tartrate. DIPT = diisopropyl tartrate. DIBT = diisobutyl tartrate. DCHT = dicyclohexyl tartrate. DTBT = di-*tert*-butyl tartrate. ^c Isolated yield. ^d HPLC analysis.

The ee of the ring opening product 2a was determined by HPLC analysis on chiral stationary phase (SUMIPAX OA-4000). The absolute configuration of 2a was determined as (1*S*, 2*S*), which was confirmed by the correlation of the optical rotation value after derivatizing to *trans-2-(p-tert-butylphenylthio)cyclohexanol* whose absolute configuration was known.³

Reaction of 1a with a Variety of Thiols. Then we examined the reactions of 1a with a variety of thiols using the catalyst system composed of diethylzinc and L-(+)-DCHT in toluene. The results are summarized in Table 3. Generally, the arenethiols react with 1a smoothly to give the ring opening products in moderate to high optical yield. Among the arenethiols we examined, *p-tert*-butylbenzenethiol gave the highest enantioselectivity (93% ee), whereas the reaction of 1a with benzenethiol afforded the product 3 in low level of enantioselectivity (45% ee). When benzenethiol derivatives possessing methyl or methoxy group at 3 or 4 position were employed, the ring opening products were obtained in high optical yield (79–89% ee). In all cases, the ee of the products was determined by HPLC analysis using chiral stationary phase (SUMIPAX OA-4000 or CHIRALCED OD). The absolute configurations of the products were also determined by the correlation of the optical rotation value and retention time of HPLC analysis after derivatizing to *trans*-2-

thiocyclohexanols. It should be noted that the reactions of 1a with the alkanethiols, such as *n*-butanethiol and benzyl mercaptan proceeded in a non-enantioselective manner (entries 7 and 8).

$$\begin{array}{c}
 \mathbb{R}^{1} \\
 \overline{C}=O \\
 \mathbb{N} \\
 \mathbb{E}_{2}Zn-dicyclohexyl L-(+)-tartrate \\
 \mathbb{N} \\$$

Table 3. Asymmetric Ring Opening Reactions of 1a with a Variety of Thiolsa

			F		
entry	thiol	time/h	% yield ^b	% ee ^c	[α]D ^{24d}
1	<i>p</i> -(CH3)3CC6H4SH	14	98	93	+48.69
2	C6H5SH	24	99	45	+26.38
3	m-CH3C6H4SH	24	92	7 9	+39.07
4	p-CH3C6H4SH	24	91	89	+70.19
5	p-CH3OC6H4SH	23	81	80	+96.23
6	β-naphtharenethiol	24	88	76 ^e	+50.82
7	C ₆ H ₅ CH ₂ SH	96	53	2	_
8	<i>n</i> -C4H9SH	96	68	1	_

^a All reactions were carried out in toluene using 1:3:1:4.8 molar ratio of $1a:Et_2Zn:L-(+)$ -DCHT:thiol. ^b Isolated yield. ^c HPLC analysis (Sumipax OA 4000) unless otherwise noted. ^d Measured in CHCl₃ (c 1.0). ^e CHIRALCEL OD was used.

Catalytic Reactions. The reaction with a small amount of the catalyst induced the decrease of enantioselectivity in comparison with that of the equimolar reaction, although the yield of the reaction was highly independent of the amount of catalyst (Table 4). The products of 78 and 17% ee were obtained by the use of 50 and 20 mol% of catalyst, respectively.

			product		
entry	catalyst/mol%	time/h	% yield ^b	% ee ^c	
lq	100	14	98	93	
2 ^e	50	16	95	78	
3ſ	20	96	93	17	

Table 4. Catalytic Reaction of 1a with p-tert-Butylbenzenethiola

^a All reactions were carried out in toluene at 0 °C. ^b Isolated yield after column chromatography. ^c HPLC analysis (SUMIPAX OA-4000). ^d **1a**:L-(+)-DCHT:Et₂Zn:thiol = 1:1:3:4.8. ^e **1a**:L-(+)-DCHT:Et₂Zn:thiol = 1:0.5:1:3. f **1a**:L-(+)-DCHT:Et₂Zn:thiol = 1:0.2:0.4:3.

Reaction of Other *N*-Acylaziridines. The reactions of *N*-acylaziridines other than 1,2-[N-(p-nitrobenzoyl)imino]cyclohexane with thiols were examined. The reaction of <math>1,2-[N-(p-nitrobenzoyl)imino]cyclopentane (1c) with*p-tert*-butylbenzenethiol gave the ring opening product in 85% ee in 89% yield.



The reaction of p-nitrobenzoyl-cis-2,3-diphenylaziridine (1d) with p-tert-butylbenzenethiol gave also the ring opening product in 84% ee and in 94% yield. However, when p-methylbenzenethiol or p-methoxybenzenethiol was reacted, the ring opening products were obtained in low level of enantioselectivity (eq. 5 and Table 5). These observations were common features as the reaction of 1 c.

			product		
entry	thiol	time/h	% yield ^b	% ee ^c	
1	4-(CH3)3CC6H4SH	14	94	84	
2	4-CH3C6H4SH	24	83	22	
3	4-CH3OC6H4SH	24	82	30 ^d	

Table 5. Asymmetric Ring Opening Reactions of 1d with Thiols^a

^a All reactions were carried out in toluene using 1:3:1:4.8 molar ratio of 1d:Et₂Zn:L-(+)-DCHT:thiol. ^b Isolated yield. ^c HPLC analysis (Sumichiral OA 4600) unless otherwise noted. ^d CHIRALCEL OD was used.

Structure of the catalyst. In order to obtain the information on the solution structure of the dialkyl L-(+)-tartrate--diethylzinc complexes, we measured the ¹H NMR spectrum of the reaction product of diethylzinc and L-(+)-DIPT (molar ratio of 1:1) in chloroform-d.⁷ As shown in Figure 1, the proton peaks assigned to ethyl group of diethylzinc and hydroxy group of L-(+)-DIPT disappeared. This would indicate the formation of zinc alkoxide complex A with the evolution of ethane according to eq. 6. The complexity of the peaks in the region of methyl (1.0–1.5 ppm) and methine (4–5.4 ppm) suggests that the complex A exists in a oligometric form in solution. Indeed, the molecular weight measurement of 1:1 mixture of diethylzinc and L-(+)-DIPT indicated that the complex A exists as aggregates in solution. The degree of association proved to be dependent on the concentration of the reactants (Table 6).

entry	ω ^b	ΔT ^c	Kf ^d	MWe	AN. ^f	-
1	8.6	0.04	6.2	1437	4.8	
2	10.8	0.07	6.2	1008	3.4	
3	11.7	0.07	6.2	1034	3.5	
4	15.0	0.03	6.2	3315	11.2	
5	19.0	0.04	6.2	3188	10.8	
6	37.1	0.07	6.2	3434	11.6	
7	41.0	0.08	6.2	3099	10.4	

 Table 6.
 Molecular Weight Determination of the Reaction Product of Et₂Zn and L-(+)-DIPT

 (1:1 Molar Ratio) by Cryoscopic Method in Benzene^a

^a The procedure for molecular weight determination is described in experimental section. ^b Weight (g) of solute in 1000 g of benzene. ^c Depression (°C). ^d Molar depression of the solvent (benzene). ^e Molecular weight. ^f AN = association number, MW = 297 (n = 1 for complex A).



However, it was found that the addition of *p*-tert-butylbenzenethiol into a chloroform-d solution of complex A dramatically brought about the change of the ¹H NMR spectrum due to the ligand exchange of zinc complexes. The change of structure began by the addition of 0.5 equiv. (per zinc atom) of *p*-tert-butylbenzenethiol as shown in Figure 2(a), and the ligand exchange was accomplished completely by the addition of 2 equiv. of thiol (Figure 2(c)). In this process, the peaks assignable to free L-(+)-DIPT, tert-butyl (0.9–1.3 ppm) and aromatic protons (6.4–7.6 ppm) were observed, in which only the peaks based on L-(+)-

DIPT appeared as sharp signals. Furthermore, the addition of 3 equiv. of thiol increased the peak intensity of free *p-tert*-butylbenzenethiol (Figure 2(d)). These results would indicate that two thiolate groups could combine on one zinc atom.



Figure 2. 'H NMR of $Et_2Zn-L-(+)$ -DIPT (1:1) + n p-(CH₃)₃CC₆H₄SH (n = 0.5, 1, 2, 3)

Based on these observations, the structure of chiral zinc-thiolate complex formed by the reaction of complex A with 2 equiv. of *p*-tert-butylbenzenethiol will be estimated as the four coordinated zinc complex B (eq. 7).



The clear signal of doublet resonanced at 3.2 and 4.5 ppm (the proton peak of hydroxy and methine group of L-(+)-DIPT, respectively) in Figure 2(c) would be reasonably assignable to the intramolecular hydrogen bonding between the carbonyl oxygen of esters and the proton of hydroxy group. It should be noted that the order of the addition of the reagents had no effect on the formation of complex **B**. That is, the addition of diethylzinc into a mixture of *p-tert*-butylbenzenethiol and L-(+)-DIPT (2:1 ratio) also would lead to the formation of complex **B**, which was confirmed by ¹H NMR spectra. These phenomena would be due to the strong affinity of zinc to sulfur atom.

The ¹H NMR spectra of 2:1 mixture of diethylzinc and L-(+)-DIPT were also measured (eq. 8 and Figure 3). In this case, the presence of ethyl group attached to zinc atom was observed (complex C). Interestingly, the spectrum obtained by the addition of 4 equiv. of *p-tert*-butylbenzenethiol to the solution of complex C was



quite similar to the one observed in the formation of complex **B** (Figure 4). This result means the same zinc thiolate complexes were formed by the reaction of 2 equiv. of thiol with 1:1 complex of diethylzinc-L-(+)-DIPT and 4 equiv. of thiol with 2:1 complex of diethylzinc-L-(+)-DIPT. In the latter case, one equivalent of $Zn(SR)_2$ (R = p-NO₂C₆H₄) complex also produced in addition to complex **B** (eq. 9). On the basis of the above spectroscopic results, we assume the complex **B** to be the main active species in solution regardless of

the molar ratio of the reactants. The reaction would proceed via several types of competitive reaction paths, and be very complicated.



Conclusion

Highly enantioselective ring opening reaction of symmetrical *N*-acylaziridines with some arenethiols has been realized by the promotion of chiral zinc complexes composed of dialkyl L-(+)-tartrate-diethylzinc complexes to give *trans* 2-(*N*-acylamino)-1-arylthioalkanes in high chemical and optical yield.

Experimental Section

General. All melting points were measured by using a Yanaco MP-500D apparatus and were uncorrected. ¹H NMR spectra (250 MHz) were measured on Hitachi R-250 Fourier Transfer NMR spectrometer using chloroform-d as a solvent and recorded in ppm relative to internal tetramethylsilane standard.

J Values are given in Hz. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; m, multiplet; br, broad peak. High resolution mass spectra (HRMS) were measured on a Hitachi M-2500 (EI, 4 kV). IR spectra were obtained with a Hitachi 270-50. Elemental analyses were performed at UBE Scientific Analysis Laboratory Inc. Optical rotations were measured on a JASCO DIP-4 digital polarimeter for solutions in a 5 dm cell. Preparative silica-gel column chromatography was carried out on a Wacogel-200 column. HPLC analyses were carried out on a JASCO PU-980 liquid chromatography with a JASCO UV-970 detector. Dichloromethane was distilled from P4O10. Toluene, diethyl ether and benzene were distilled from sodium benzophenone ketyl under argon. All experiments were carried out under an argon atmosphere.

1,2-[N-(p-Nitrobenzoyl)imino]cyclohexane (1a): To a mixture of 1,2-iminocyclohexane (20.1 g, 0.207 mmol) and triethylamine (28.9 mL, 0.207 mol) in diethyl ether (200 mL) was added p-nitrobenzoyl chloride (35.5 g, 0.207 mol) in diethyl ether (200 mL) at room temperature, and the whole was stirred for 1 h at this temperature. After filtration, the solid was recrystallized from ethanol to give 1a (30.7 g, 60%) as pale yellow crystals. m.p. 118–122 °C. IR (KBr) v_{max} : 2936, 1670, 1606, 1522, 1356, 1344, 1292, 722 cm⁻¹. ¹H NMR (CDCl₃) δ 1.3–1.4 (m, 2H), 1.4–1.6 (m, 2H), 1.9–2.1 (m, 4H), 2.8 (t, J = 1.2 Hz, 2H), 8.13 (d, J = 8.5 Hz, 2H), 8.30 (d, J = 8.5 Hz, 2H). Anal. Calcd for C1₃H14N₂O₃; C, 63.40; H, 5.73; N, 11.38: Found; C, 63.40; H, 5.62; N, 11.35.

1,2-(*N*-Benzoylimino)cyclohexane (1b): To a mixture of 1,2-iminocyclohexane (5 g, 0.05 mol) and diethyl ether (50 mL) was added 20% aqueous NaOH solution (125 mL) at 0 °C, and the mixture was stirred for 30 min at this temperature. Benzoyl chloride (7 g, 0.05 mol) in diethyl ether was added to the above mixture. After being stirred for 1 h, the mixture was filtered. The obtained solid was silicagel column chromatographed (eluent, hexane:ethyl acetate 12:1) to give 1b (7.35 g, 71%) as a colorless crystal. m.p. 79–80 °C (lit.⁸ 70–72 °C). IR (KBr) v_{max} : 2932, 1670, 1452, 1412, 1314, 1294, 736 cm⁻¹. ¹H NMR (CDCl₃) δ 1.3–1.5 (m, 2H), 1.5–1.6 (m, 2H), 1.8–2.0 (m, 2H), 2.0–2.2 (m, 2H), 2.76 (d, *J* = 1.8 Hz, 2H), 7.4–7.6 (m, 3H), 8.0 (d, *J* = 6.7 Hz, 2H). Anal. Calcd for C_{13H15}NO; C, 77.58; H, 7.51; N, 6.96: Found; C, 77.57; H, 7.57; N, 7.06.

1,2-[*N*-(*p*-Nitrobenzoyl)imino]cyclopentane (1c): To a mixture of 1,2-iminocyclopentane⁵ (6.9 g, 83 mmol) and triethylamine (11.6 mL, 83 mmol) in diethyl ether (150 mL) was added *p*-nitrobenzoyl chloride (15.4 g, 83 mmol) in diethyl ether (50 mL) at 0 °C, and the whole was stirred for 1 h at room temperature. After filtration, the solid was recrystallized from ethanol to give 1c (3.18 g, 17%) as pale yellow crystals. m.p. 112–114 °C. IR (KBr) v_{max}: 2960, 1660, 1652, 1602, 1384, 1334, 1316, 1284 cm⁻¹. ¹H NMR (CDCl₃) δ 1.3–1.8 (m, 4H), 2.1–2.2 (m, 2H), 3.25 (s, 2H), 8.12 (d, *J*=9.2 Hz, 2H), 8.29 (d, *J* = 9.2 Hz, 2H). Anal. Calcd for C₁₂H₁₂N₂O₃; C, 62.06; H, 5.21; N, 12.06: Found; C, 62.32; H, 5.18; N, 12.05.

p-Nitrobenzoyl-*cis*-2, 3-diphenylaziridine (1d): To a mixture of *cis*-2,3-diphenylaziridine (4.0 g, 21 mmol), triethylamine (2.1 g, 21 mmol), and diethyl ether (50 mL) was added *p*-nitrobenzoyl chloride (3.8 g, 21 mmol) at 0 °C. The mixture was stirred for 15 h at room temperature. After this, the brine (50 mL) was added, then extracted with ethyl acetate (50 mL x 3). The organic layer was concentrated, and the obtained residue was recrystallized from ethanol to give 1d (3.88 g, 55%) as a colorless crystal. m.p. 156–158 °C. IR (KBr) ν_{max} : 1688, 1524, 1320, 1308, 1288, 720 cm⁻¹. ¹H NMR (CDCl₃) δ 4.12 (s, 2H), 7.2 (m, 10H), 8.2–8.3 (m 4H). Anal. Calcd for C₂₁H₁₆N₂O₃; C, 73.24; H, 4.68; N, 8.13: Found; C, 73.51; H, 4.63; N, 8.18.

General Procedure for the Asymmetric Ring Opening Reaction of 1,2-[N-(p-Nitrobenzoyl)imino]cyclohexane (1a) with Thiols. In a Schlenk tube were placed dialkyl L-(+)-tartrate (2.0 mmol) and dry toluene (30 mL). The mixture was cooled to 0 °C and diethylzinc (0.62 mL, 6.0 mmol) was added slowly. After being stirred for 1 h at room temperature, thiol (9.6 mmol) and then 1a (2.0 mmol) in toluene (10 mL) were added at 0 °C, and the above mixture was stirred for 14 h at this temperature. The brine (100 mL) was added to the mixture, and stirred vigorously for 30 min at room temperature. The mixture was filtered through a pad of Celite, then extracted with ethyl acetate (50 mL x 3). The combined organic layer was dried over anhydrous Na2SO4. After evaporation, the obtained residue was chromatographed on silica-gel (eluent, CHCl3) to afford*trans*2-(N-acylamino)-1-arylthiocyclohexane.

(15, 2S)-1-(p-tert-Butylphenylthio)-2-[N-(p-nitrobenzoyl)amino]cyclohexane (2a). 820 mg (98%). m.p. 66–68 °C. $[\alpha]D^{25}$ +48.91 (c 1.0, CHCl3). IR (KBr) v_{max}: 3316, 2932, 1642, 1528, 1344 cm⁻¹; ¹H NMR (250 MHz, CDCl3) δ 1.28 (s, 9H), 1.3–1.5 (m, 4H), 1.7–1.8 (m, 2H), 2.2–2.3 (m, 1H), 2.3–2.4 (m, 1H), 3.0–3.1 (m, 1H), 3.9–4.0 (m, 1H), 6.4 (m, 1H), 7.27 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 9.2 Hz, 2H), 7.83 (d, J = 9.2 Hz, 2H), 8.22 (d, J = 9.2 Hz, 2H). Anal. Calcd for C₂₃H₂₈N₂O₃S; C, 66.96; H, 6.85; N, 6.79: Found: C, 67.04; H, 7.01; N, 6.68. The ee of the reaction product was determined as 93% ee by HPLC analysis. $r_{\rm R}$ of (1*R*,2*R*)-isomer: 13 min; $r_{\rm R}$ of (1*S*,2*S*)-isomer: 14 min [column; SUMIPAX OA-4000, eluent; hexane–ethanol (97:3), 1.0 mL/min, 254 nm].

(1S,2S)-2-(N-Benzoylamino)1-(p-tert-butylphenylthio)cyclohexane (2b). 760 mg (98%). m.p. 160–165 °C. [α]D²⁵ +48.69 (c 1.0, CHCl3). IR (KBr) ν_{max} : 3308, 2960, 2936, 1636, 1546, 1492 cm⁻¹; ¹H NMR (250 MHz, CDCl3) δ 1.29 (s, 9H), 1.2–1.4 (m, 4H), 1.7–1.8 (m, 2H), 2.1–2.2 (m, 1H), 2.3–2.4 (m, 1H), 2.9–3.0 (m, 1H), 3.9 (m, 1H), 6.2–6.3 (m, 1H), 7.3–7.5 (m, 7H), 7.7 (m, 2H). Anal. Calcd for C₂₃H₂₉NOS; C, 75.16; H, 7.95; N, 3.81: Found: C, 75.28; H, 8.07; N, 3.80. The ee of the reaction product was determined as 81% ee by HPLC analysis. $r_{\rm R}$ of (1*R*,2*R*)-isomer: 9 min; $r_{\rm R}$ of (1*S*,2*S*)-isomer: 15 min [column; CHIRALCEL OD, eluent; hexane–ethanol (97:3), 1.0 mL/min, 254 nm].

(15,25)-1-Phenylthio-2-[N-(p-nitrobenzoy])amino]cyclohexane (3). 720 mg (99%). m.p. 133–136 °C. $[\alpha]D^{25}$ +26.38 (c 1.0, CHCl3). IR (KBr) ν_{max} : 3320, 2936, 1652, 1604, 1556, 1354, 1316 cm⁻¹; ¹H NMR (250 MHz, CDCl3) δ 1.3--1.5 (m, 4H), 1.7-1.8 (m, 2H), 2.1-2.2 (m, 1H), 2.3-2.4 (m, 1H), 3.0-3.1 (m, 1H), 3.9-4.0 (m, 1H), 6.2-6.3 (m, 1H), 7.2-7.3 (m, 3H), 7.4-7.5 (m, 2H), 7.76 (d, J = 9.2 Hz, 2H), 8.23 (d, J = 8.5 Hz, 2H). Anal. Calcd for C19H20N2O3S; C, 64.02; H, 5.66; N, 7.86: Found: C, 64.00; H, 5.68; N, 7.87. The ee of the reaction product was determined as 45% ee by HPLC analysis. r_{R} of (1*R*,2*R*)-isomer: 19 min; r_{R} of (1*S*,2*S*)-isomer: 22 min [column; SUMIPAX OA 4000, eluent; hexane-ethanol (97:3), 1.0 mL/min, 254 nm].

 $(15, 25) - 1 - (m-Methylphenylthio) - 2 - [N - (p-nitrobenzoyl) amino] cyclohexane (4). 700 mg (92%). m.p. 141–143 °C. [<math>\alpha$]D²⁵ +39.07 (c 1.0, CHCl3). IR (KBr) ν_{max} : 3308, 2940, 1640, 1602, 1548, 1522, 1346 cm⁻¹; ¹H NMR (250 MHz, CDCl3) δ 1.2–1.6 (m, 4H), 1.7–1.9 (m, 2H), 2.2–2.4 (m, 2H), 2.25 (s, 3H), 3.0–3.2 (m, 1H), 3.9–4.0 (m, 1H), 6.2–6.3 (m, 1H), 7.0–7.1 (m, 1H), 7.1–7.3 (m, 3H), 7.73 (d, J = 8.5 Hz, 2H), 8.20 (d, J = 8.5 Hz, 2H). Anal. Calcd for C₂₀H₂₂N₂O₃S; C, 64.84; H, 5.99; N, 7.56: Found: C, 64.59; H, 5.94; N, 7.56. The ee of the reaction product was determined as 79% e.e. by HPLC analysis. t_{R} of (1*R*,2*R*)-isomer: 16 min; t_{R} of (1*S*,2*S*)-isomer: 18 min [column; SUMIPAX OA 4000, eluent; hexane–ethanol (97:3), 1.0 mL/min, 254 nm].

(15,25)-1-(*p*-Methylphenylthio)-2-[*N*-(*p*-nitrobenzoyl)amino]cyclohexane (5). 680 mg (91%). m.p. 181–183 °C. $[\alpha]D^{25}$ +70.19 (*c* 1.0, CHCl₃). IR (KBr) v_{max}: 3336, 2940, 1640, 1538, 1520, 1494, 1352, 1328 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 1.2–1.5 (m, 4H), 1.7–1.8 (m, 2H), 2.1–2.2 (m, 1H), 2.31 (s, 3H), 2.3–2.4 (m, 1H), 2.9–3.0 (m, 1H), 3.8–3.9 (m, 1H), 6.2–6.3 (m, 1H), 7.07 (d, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.80 (d, *J* = 8.5 Hz, 2H), 8.23 (d, *J* = 8.5 Hz, 2H). Anal. Calcd for C₂₀H₂₂N₂O₃S; C, 64.84; H, 5.99; N, 7.56: Found: C, 64.87; H, 6.07; N, 7.23. The ee of the reaction product was determined as 89% ee by HPLC analysis. *r*_R of (1*R*,2*R*)-isomer: 16 min; *r*_R of (1*S*,2*S*)-isomer: 19 min [column; SUMIPAX OA 4000, eluent; hexane–ethanol (97:3), 1.0 mL/min, 254 nm].

(15, 25)-1-(p-Methoxylphenylthio)-2-[N-(p-nitrobenzoyl)amino]cyclohexane (6). 620 mg (81%). m.p. 179–182 °C. $[\alpha]D^{25}$ +96.23 (*c* 1.0, CHCl₃). IR (KBr) v_{max} : 3308, 2940, 1640, 1602, 1594, 1548, 1522, 1496, 1346 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 1.3–1.5 (m, 4H), 1.7–1.8 (m, 2H), 2.1–2.2 (m, 1H), 2.3–2.4 (m, 1H), 2.8–2.9 (m, 1H), 3.77 (s, 3H), 3.8–3.9 (m, 1H), 6.1–6.2 (m, 1H), 6.80 (d, J = 9.2 Hz, 2H), 7.36 (d, J = 9.2 Hz, 2H), 7.88 (d, J = 8.5 Hz, 2H), 8.28 (d, J = 9.2 Hz, 2H). HRMS (EI) *m*/*z* Calcd for C₂₀H₂₂N₂O4S (M⁺): 386.1317. Found: 386.1303. The ee of the reaction product was determined as 80% ee by HPLC analysis. *r*_R of (1*R*,2*R*)-isomer: 28 min; *r*_R of (1*S*,2*S*)-isomer: 31 min [column; SUMIPAX OA 4000, eluent; hexane–ethanol (97:3), 1.0 mL/min, 254 nm].

(15,25)-1-(β-Naphthylthio)-2-[N-(p-nitrobenzoyl)amino]cyclohexane (7). 720 mg (88%). m.p. 160–161 °C. [α] D^{25} +50.82 (c 1.0, CHCl3). IR (KBr) v_{max}: 3308, 2928, 1640, 1600, 1548, 1524, 1344, 1328, 852 cm⁻¹; ¹H NMR (250 MHz, CDCl3) δ 1.3–1.6 (m, 4H), 1.7–1.8 (m, 2H), 2.2–2.4 (m, 2H), 3.2–3.3 (m, 1H), 4.0–4.1 (m, 1H), 6.0–6.1 (m, 1H), 7.4–7.6 (m, 6H), 7.73 (d, J = 8.5 Hz, 2H), 7.85 (s, 1H), 7.96 (d, J = 8.5 Hz, 2H). Anal. Calcd for C₂₃H₂₂N₂O₃S; C, 67.95; H, 5.46; N, 6.89: Found: C, 68.09; H, 5.47; N, 6.93. The ee of the reaction product was determined as 76% ee by HPLC analysis. $r_{\rm R}$ of (1*R*,2*R*)-isomer: 20 min; $r_{\rm R}$ of (1*S*,2*S*)-isomer: 26 min [column; CHIRALCEL OD, eluent; hexane–ethanol (95:5), 1.0 mL/min, 254 nm].

trans 2-[*N*-(*p*-Nitrobenzoyl)amino]-1-(α -toluenethio)cyclohexane (8). 400 mg (53%). m.p. 150–151 °C. IR (KBr) v_{max}: 3304, 2928, 1638, 1600, 1550, 1526, 1344, 1334, 704 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 1.2–1.6 (m, 4H), 1.6–1.8 (m, 2H), 2.2–2.3 (m, 1H), 2.3–2.4 (m, 1H), 2.4–2.6 (m, 1H), 3.7–3.9 (m, 3H), 6.0–6.1 (m, 1H), 7.2–7.4 (m, 5H), 7.81 (d, *J* = 8.5 Hz, 2H), 8.26 (d, *J* = 8.5 Hz, 2H). Anal. Calcd for C₂₀H₂₂N₂O₃S; C, 64.84; H, 5.99; N, 7.56: Found: C, 64.80; H, 5.98; N, 7.55. The ee of the reaction product was determined as 2% ee by HPLC analysis. *t*_R 34 min, 38 min [column; SUMIPAX OA 4000, eluent; hexane–ethanol (97:3), 0.5 mL/min, 254 nm].

trans 1-*n*-Butylthio-2-[*N*-(*p*-nitrobenzoyl)amino]cyclohexane (9). 460 mg (68%). m.p. 157–159 °C. IR (KBr) v_{max} : 3288, 2928, 1640, 1602, 1554, 1522, 1352 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 0.88 (t, *J* = 7.3 Hz, 3H), 1.3–1.7 (m, 8H), 1.8–1.9 (m, 2H), 2.1–2.2 (m, 1H), 2.4–2.5 (m, 1H), 2.54 (t, *J* = 7.3 Hz, 2H), 2.6–2.7 (m, 1H), 3.8–3.9 (m, 1H), 6.3–6.4 (m, 1H), 7.94 (d, *J* = 8.5 Hz, 2H), 8.30 (d, *J* = 8.5 Hz, 2H). Anal. Calcd for C17H24N2O3S; C, 60.69; H, 7.19; N, 8.33: Found: C, 60.59; H, 7.21; N, 8.33. The ee of the reaction product was determined as 1% ee by HPLC analysis. *t*_R 25 min, 28 min [column; SUMIPAX OA 4000, eluent; hexane–ethanol (97:3), 0.5 mL/min, 254 nm].

trans 1-(*p-tert*-Butylphenylthio)-2-[*N*-(*p*-nitrobenzoyl)amino]cyclopentane (10). 720 mg (88%). m.p. 43–46 °C. $[\alpha]D^{25}$ +50.28 (*c* 1.0, CHCl₃). IR (KBr) v_{max}: 3288, 2960, 1640, 1602, 1530, 1348 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 1.26 (s, 9H), 1.5–1.6 (m, 1H), 1.7–1.8 (m, 3H), 2.2–2.3

(m, 1H), 2.3-2.4 (m, 1H), 3.3-3.4 (m, 1H), 4.1-4.2 (m, 1H), 6.0-6.1 (m, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 7.77 (d, J = 8.5 Hz, 2H), 8.24 (d, J = 8.5 Hz, 2H). Anal. Calcd for C22H26N2O3S; C, 66.31; H, 6.58; N, 7.03: Found: C, 66.48; H, 6.71; N, 7.01. The ee of the reaction product was determined as 85% ee by HPLC analysis. $t_{\rm R}$ of minor-isomer: 17 min; $t_{\rm R}$ of major-isomer: 19 min [column; SUMIPAX OA-4000, eluent; hexane-ethanol (97:3), 1.0 mL/min, 254 nm].

trans 2-(*p*-*tert*-Butylphenylthio)-3-[*N*-(*p*-nitrobenzoyl)amino]-2, 3-diphenylethane (11). 980 mg (94%). m.p. 155–157 °C. $[\alpha]D^{25}$ +33.43 (*c* 1.0, CHCl₃). IR (KBr) ν_{max} : 3296, 2960, 1644, 1602, 1530, 1490, 1348 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 1.25 (s, 9H), 4.68 (d, *J* = 7.9 Hz, 1H), 5.62 (dd, *J* = 7.9 Hz, *J* = 7.9 Hz, 1H), 7.02 (d, *J* = 7.9 Hz, 1H), 7.1–7.2 (m, 14 H), 7.87 (d, *J* = 9.2 Hz, 2H), 8.25 (d, *J* = 9.2 Hz, 2H). HRMS (EI) *m/z* Anal. Calcd for C₂₁H₁₇N₂O₃ (M⁺-SC₆H₄C₄H₉): 345.1239. Found: 345.1212. The ee of the reaction product was determined as 84% ee by HPLC analysis. *t*R of major-isomer: 20 min; *t*R of minor-isomer: 22 min [column; SUMICHIRAL OA-4600, eluent; hexane—ethanol (97:3), 1.0 mL/min, 254 nm].

trans 2-(*p*-Methylphenylthio)-3-[*N*-(*p*-nitrobenzoyl)amino]-2,3-diphenylethane (12). 800 mg (83%). m.p. 86–89 °C. $[\alpha]D^{25}$ +13.31 (*c* 1.0, CHCl3). IR (KBr) v_{max}: 3264, 1640, 1602, 1526, 1492, 1350 cm⁻¹; ¹H NMR (250 MHz, CDCl3) δ 2.26 (s, 3H), 4.66 (d, *J* = 8.5 Hz, 1H), 5.59 (dd, *J* = 7.9 Hz, 8.5 Hz, 1H), 6.98 (d, *J* = 7.9 Hz, 1H), 7.0–7.2 (m, 14 H), 7.86 (d, *J* = 8.5 Hz, 2H), 8.22 (d, *J* = 8.5 Hz, 2H). HRMS (EI) *m/z* Anal. Calcd for C₂₁H₁₇N₂O₃ (M*-SC₆H₄CH₃): 345.1239. Found: 345.1210. The ee of the reaction product was determined as 22% ee by HPLC analysis. *r*_R of major-isomer: 24 min; *r*_R of minor-isomer: 27 min [column; CHIRALCEL-OD, eluent; hexane–ethanol (97:3), 1.0 mL/min, 254 nm].

trans 2-(*p*-Methoxylphenylthio)-3-[*N*-(*p*-nitrobenzoyl)amino]-2,3-diphenylethane (13). 800 mg (82%). m.p. 60–63 °C. $[\alpha]_D^{2.5}$ +14.82 (*c* 1.0, CHCl₃). IR (KBr) ν_{max} : 2928, 2856, 1640, 1600, 1532, 1496, 1350, 1288, 1248 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 3.74 (s, 3H), 4.54 (d, *J* = 8.5 Hz, 1H), 5.58 (dd, *J* = 7.9 Hz, 8.5 Hz, 1H), 6.71 (d, *J* =7.9 Hz, 1H), 7.0–7.2 (m, 14 H), 7.93 (d, *J* = 9.2 Hz, 2H), 8.30 (d, *J* = 9.2 Hz, 2H). HRMS (EI) *m/z* Anal. Calcd for C₂₁H₁₇N₂O₃ (M⁺-SC₆H₄OCH₃): 345.1239. Found: 345.1227. The ee of the reaction product was determined as 30% ee by HPLC analysis. *t*R of minor-isomer: 35 min; *t*R of major-isomer: 40 min [column; CHIRALCEL-OD, eluent; hexane–ethanol (95:5), 1.0 mL/min, 254 nm].

Determination of Absolute Configurations. The absolute configuration of the ring opening product 2a and 5 was determined as (1S, 2S), which was confirmed by the correlation of the optical rotation value after derivatizing to *trans*-2-(*p*-tert-butylphenylthio)cyclohexanol whose absolute configuration was known (eq. 10).³ The procedure is as follows: In a three-necked flask were placed *trans* 1-thio-2-[*N*-(*p*-nitrobenzoyl)amino]cyclohexane and THF. To this mixture was added LiAlH4 in THF. The mixture was refluxed for 18 h. Usual aqueous workup afforded *trans* 2-amino-1-(*p*-tert-butylphenylthio)cyclohexane. This aminothiol was converted to *trans* 1-hydroxy-2-(*p*-tert-butylbenzenethio)cyclohexane by the treatment with NaNO2 in acetic acid. For other products (3, 4, 6, and 7), the absolute configurations of the corresponding 1-hydroxy-2-thiocyclohexane were unknown. Therefore, further derivatization to (*S*)-(-)-2-cyclohexene-1-ol



by oxidation of 1-hydroxy-2-thiocyclohexane with *m*-chloroperbenzoic acid (*m*-CPBA) and successive thermal decomposition of the resulting S-oxides (S)-(-)-2-cyclohexene-1-ol proved to be the absolute configurations of



3, 5, 6, and 7 were (1S, 2S) (eq. 11). The absolute configurations of 10, 11, 12, and 13 were assumed as (1S, 2S) by comparison with the sign of optical rotation values and the retention time in HPLC analysis.

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