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Stabilizing Effect of Intramolecular Lewis Base Toward Racemization of Optically Active Selenoxides

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ABSTRACT: *2-(Methylchalcogenomethyl)diphenyl selenoxides* **1** *and 2-{2′-(N,N-dimethylamino)ethyl}-phenyl alkyl (or aryl) selenoxides* **2**, *which were expected to be stabilized toward racemization by intramolecular coordination, were synthesized and optically resolved into their enantiomers on an optically active column using high-performance liquid chromatography. Relationship between the absolute configurations and the chiroptical properties of the enantiomers was clarified by comparing with those of sulfur analogues. Stabilities toward racemization of optically active selenoxides* **1a** *and* **1b** *were nearly equal to that of 2-{(N,N-dimethylamino)methyl}diphenyl selenoxide and mesityl phenyl selenoxide. The rates of racemization for optically active selenoxides* **2** *were found to be faster than that of 2-{(N,N-dimethylamino)methyl}phenyl alkyl (or aryl) selenoxides.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:301–311, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20299

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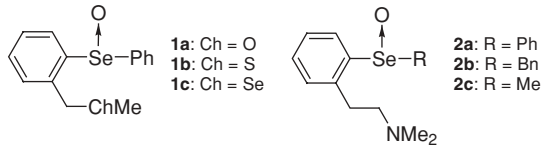
INTRODUCTION

Tricoodinated organosulfur compounds with three different substituents have chirality on the central sulfur atom, and the chiral sulfur compounds have been widely studied. Among tricoodinated organosulfur compounds, many optically active sulfoxides were synthesized and isolated, and their structures and reactions have been studied [1–3]. Moreover, asymmetric reactions utilizing optically active sulfoxide as a chiral source are becoming a very important technique in recent asymmetric synthesis [4,5]. The formation of optically active selenoxides is also proposed as a key intermediate in asymmetric synthesis, e.g. optically active allyl alcohols were synthesized by [2,3] sigmatropic rearrangement via optically active selenoxide by the enantioselective oxidation of corresponding selenide [6–8].

For the past two decades, we and other research groups have succeeded in isolating optically active selenoxides, which were kinetically stabilized by bulky substituents [9–12]. We have also succeeded in isolating optically active selenoxides with 2-(*N*,*N*-dimethylaminomethyl)phenyl group [13], which were stabilized by intramolecular coordination of amino group to the selenium atom (thermodynamic stabilization) [14].

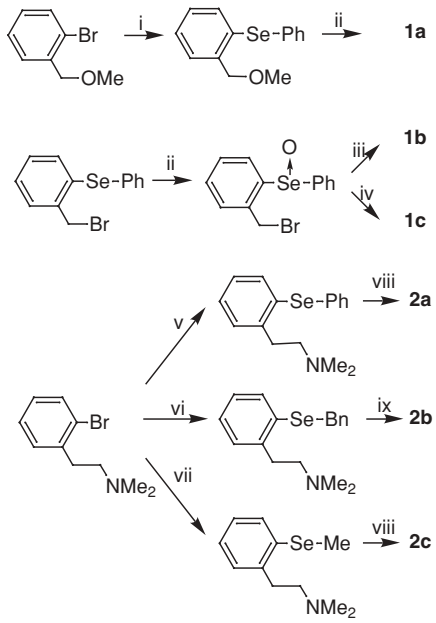
It is of interest to investigate the stabilizing effect of the other intramolecular Lewis base instead of 2-(*N*,*N*-dimethylaminomethyl)phenyl group

toward racemization of optically active selenoxides. We prepared unsymmetric selenoxides with 2-(methylchalcogenomethyl)phenyl group **1a–c** and 2-{2′-(*N*,*N*-dimethylamino)ethyl}phenyl group **2a–c**, which were expected to retard the racemization by intramolecular coordination of the Lewis base to the selenium atom. In this paper, the optical resolution of selenoxides **1** and **2** by HPLC using a chiral column and the stabilizing effect of the intramolecular Lewis base toward racemization of the optically active selenoxides will be described.



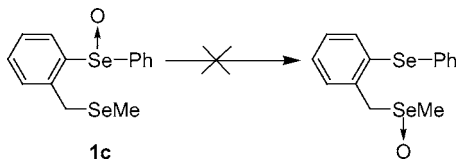
RESULTS AND DISCUSSION

2-(Methoxymethyl)diphenyl selenide was obtained in 69% yield by reacting 2-(methoxymethyl)-phenylmagnesium bromide with diphenyl diselenide (Scheme 1). Racemic selenoxide **1a** was prepared by oxidation of 2-(methoxymethyl)diphenyl selenide with *tert*-butyl hypochlorite in 51% yield (Scheme 1). 2-(Bromomethyl)diphenyl selenoxide was obtained from corresponding selenide in 80% yield. Treatment of 2-(bromomethyl)diphenyl selenoxide with methylthiomagnesium chloride or methylselenomagnesium chloride gave racemic selenoxides **1b** or **1c** in 30 and 35% yields, respectively. Selenides possessing 2-{2′-(*N*,*N*-dimethylamino)ethyl}phenyl group [13] were synthesized by reacting aryl Grignard or lithium reagents with diselenide or selenium atom followed by methyl iodide. Racemic selenoxides **2a–c** were obtained by oxidation of the corresponding selenides with *tert*-butyl hypochlorite or *m*-chloroperbenzoic acid in 34, 24, and 50% yields, respectively.



SCHEME 1 i: Mg, THF then PhSeSePh; ii: *t*-BuOCl, MeOH then $NaOH_{aq}$; iii: MeSMgCl, THF; iv: MeSeMgCl, THF; v: BuLi, THF then PhSeSePh; vi: Mg, THF then BnSeSeBn; vii: BuLi, THF then Se powder, MeI; viii: *t*-BuOCl, MeOH then $NaOH_{aq}$; ix: *m*-CPBA, CH_2Cl_2.

When selenoxide **1a** was subjected to an optically active column packed with amylose carbamate derivative/silica gel (Daicel Chiralpak AS; 4.5 × 250 mm) using high-performance liquid chromatography on an analytical scale with hexane/ethanol (80/20) as eluent, two peaks corresponding to enantiomers of **1a** were observed on the chromatogram, as shown in Fig. 1. Similarly, selenoxides



1b and **2a–c** were also resolved into their enantiomers. However, selenoxide **1c** could not be resolved under similar conditions. It was considered as one of the reason why **1c** was not resolved that a rapid intramolecular oxygen transfer from selenoxide to the selenium atom of methylseleno group in the column. However, no change was observed on the ^{1}H NMR spectrum of the eluate of **1c**. Therefore, it is clarified that no oxygen transfer occurred between two selenium atoms. At the present time, it is not clear why the chiral recognition was very weak by the chiral column in the case of selenoxide **1c**.

The optical resolution of racemic selenoxide **1a** was carried out at a preparative scale using larger column (10 × 250 mm) of the same type with the same eluent. The enantiomer of selenoxide **1a**, which was eluted first, showed a negative specific rotation {(−)-**1a**: ee 100%; $[\alpha]_D$ –59.8 (*c* 0.21, $CHCl_3$)}, and the second-eluted enantiomer of **1a** showed a positive specific rotation {(+)-**1a**: ee 60%; $[\alpha]_D$ + 30.0 (*c* 0.28, $CHCl_3$)}. The optical purities were determined by the HPLC analysis using chiral column. Selenoxide (+)-**1a** could not be obtained as an optically pure form in spite of repeated chromatography, perhaps due to tailing of the first enantiomer on a preparative scale. Similarly, selenoxides (−)-**1b** and (−)-**2a–c** were

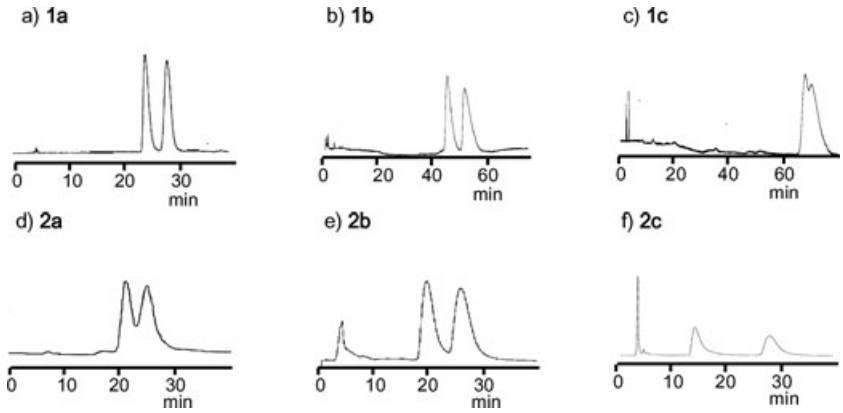
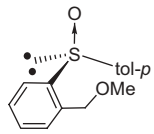


FIGURE 1 Optical resolution of selenoxides **1a–c** and **2a–c** on an optically active column packed with amylose carbamate derivative/silica gel (Daicel Chiralpak AS; 4.6 × 250 mm) by HPLC on an analytical scale at 25°C. (a) hexane/ethanol (80/20), (b) hexane/ethanol (85/15), (c) hexane/ethanol (90/10), (d) hexane/ethanol (75/25), (e) hexane/ethanol (85/15), and (f) hexane/ethanol (75/25).

obtained from the first eluate, and (+)-**1b** and (+)-**2a–c** from the second eluate. Among those selenoxides, (−)-**2a–c** were isolated in pure form. These results are summarized in Table 1.

The absolute configuration of optically pure selenoxide (−)-**1a** or (−)-**2a–c** could not be determined by X-ray analysis, because suitable crystal for X-ray analysis was not obtained. Therefore, the absolute configuration of selenoxide (−)-**1a** was assigned by comparing the specific rotation and circular dichroism spectra with those of optically active sulfoxide (*S*)-(−)-**3** synthesized by Andersen's method [1]. The circular dichroism spectrum of selenoxide (−)-**1a** showed a negative first Cotton effect at 266 nm in acetonitrile, as shown in Fig. 2. On the other hand, selenoxide (+)-**1a** showed a positive first Cotton effect at the corresponding regions. Sulfoxide (*S*)-(−)-**3** showed a negative first Cotton effect at 270 nm (Fig. 2), which corresponded with well that of selenoxide (−)-**1a**. In addition, sulfoxide (*S*)-(−)-**3** was also eluted faster than (*R*)-(+)-**3** on the optically active column in the HPLC analysis. Therefore, the absolute configuration of selenoxide (−)-**1a** was assigned to be *S*-form and (+)-**1a** was *R*-form. Similarly, the absolute configuration of selenoxide (−)-**1b** was *S*-form and (+)-**1b** was *R*-form. In cyclohexane, CD spectra of optically active selenoxides **1a** and **1b** were quite similar to those in acetonitrile, respectively, while difference was observed in the case of sulfoxide **3**.

The circular dichroism spectra of selenoxides (−)-**2a–c** showed a negative first Cotton effects at 260–280 nm, as shown in Fig. 3. These Cotton effects corresponded with those of (*S*)-(−)-**4a–c** [14]. Therefore, the absolute configurations of selenoxides (−)-**2a–c** were assigned to be *S*-form and those of (+)-**2a–c** were *R*-form.



(*S*)-(−)-**3**

Stabilities toward racemization of selenoxides (*S*)-(−)-**1a** and (*S*)-(−)-**1b** were examined. Selenoxides (*S*)-(−)-**1a** and (*S*)-(−)-**1b** did not racemize

TABLE 1 Optical Resolution and Specific Rotation of Selenoxides **1a, 1b**, and **2a–c**[a]

		First Eluted Enantiomer		*Second Eluted Enantiomer*	
Compound	*Ethanol/%*[b]	$[\alpha]_D$ *(c)*[2]	*ee/%*	$[\alpha]_D$ *(c)*[2]	*ee/%*
1a	20	−59.8 (0.21)	100	+30.0 (0.28)	60
1b	15	−31.1 (0.11)	75	+10.8 (0.24)	25
2a	25	−34.2 (0.27)	100	+21.6 (0.57)	60
2b	15	−20.9 (0.33)	100	+13.6 (0.22)	75
2c	25	−117.4 (0.10)	100	+87.7 (0.10)	75

[a]Optical resolution was carried out on an optically active column packed with amylose carbamate derivative/silica gel (Daicel Chiralpak AS; 10 × 250 mm) by HPLC on a preparative scale at 25°C.
[b]Volume percentage of ethanol in hexane used as mobile phase.
[c]Specific rotations were taken in chloroform at 25°C.

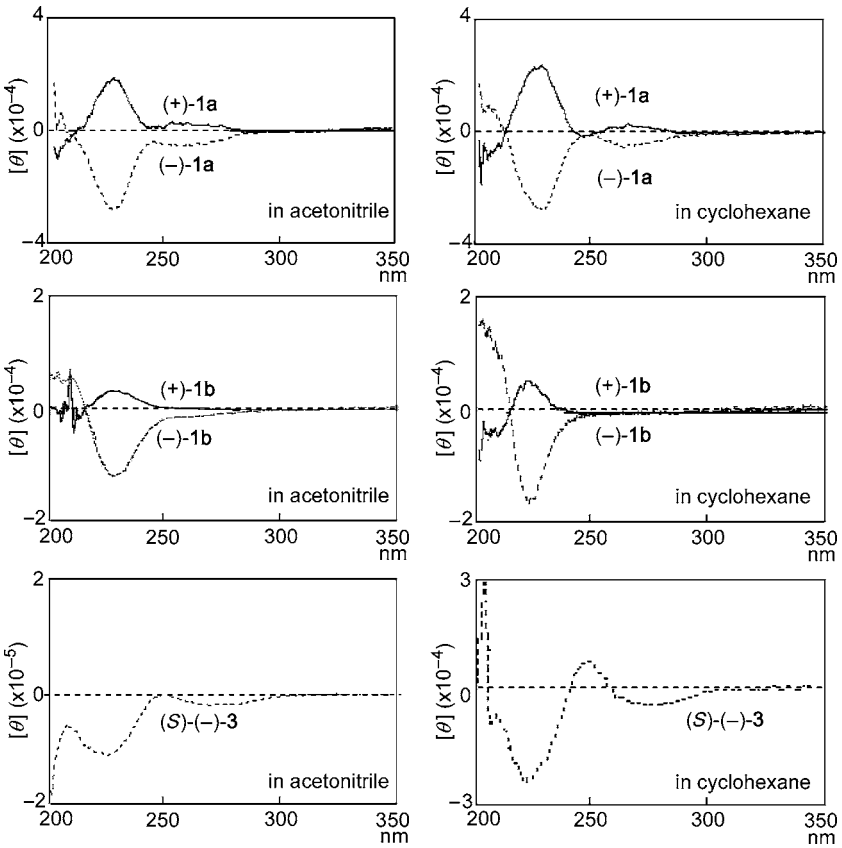
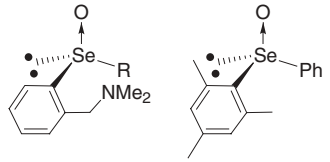


FIGURE 2 Circular dichroism spectra of optically active selenoxides **1a, 1b**, and sulfoxide (*S*)-(−)-**3** in acetonitrile or cyclohexane.

under solvent-free condition for 1 week or in freshly distilled chloroform solution for 3 days. However, selenoxides (*S*)-(−)-**1a** and (*S*)-(−)-**1b** racemized in methanol containing 20 vol% of water. The decrease in the optical purity showed a good linear relationship with the first-order rate plots. The first-order rate constants for racemization of selenoxides (*S*)-(−)-**1a** and (*S*)-(−)-**1b** were 6.10×10^{-5} and 1.70×10^{-4} s^{-1}, respectively. These rate constants were nearly equal to those of selenoxides (*S*)-(−)-**4a** and (*S*)-(−)-**5** ($k_1 = 5.13 \times 10^{-5}$ and 3.34×10^{-5} s^{-1}, respectively) under similar conditions [14,15] (Table 2). These results show that methoxymethyl and methylthiomethyl groups in selenoxides **1** have similar stabilizing effect toward racemization by intramolecular coordination with *N*,*N*-dimethylaminomethyl group of selenoxide **4a**.



(*S*)-(−)-**4a**: R = Ph
(*S*)-(−)-**4b**: R = Bn
(*S*)-(−)-**4c**: R = Me

(*S*)-(−)-**5**

Stabilities toward racemization of selenoxides (*S*)-(−)-**2a–c** were also examined under similar conditions. Selenoxides (*S*)-(−)-**2a–c** did not racemize for 1 week under solvent-free conditions. No racemization of selenoxides (*S*)-(−)-**2a** and (*S*)-(−)-**2b** was also observed in freshly distilled chloroform solution for 3 days. On the other hand, selenoxide (*S*)-(−)-**2c** racemized in freshly distilled chloroform, and the first-order rate constant was determined to be 2.10×10^{-5} s^{-1} (Table 3). Selenoxides (*S*)-(−)-**2a** and (*S*)-(−)-**2b** racemized in methanol containing 20 vol% of water. The rate constants for racemization of selenoxides (*S*)-(−)-**2a** and (*S*)-(−)-**2b** were 1.70×10^{-3} and 5.29×10^{-3} s^{-1}, respectively. On the other hand, selenoxide (*S*)-(−)-**2c** racemized within 1 min under these conditions. Previously, we reported that the rate constants for racemization of selenoxides (*S*)-(−)-**4a–c** were 5.13×10^{-5}, 3.03×10^{-4}, and 1.23×10^{-3} s^{-1}, respectively, in aqueous methanol solution [14]. It was found that the racemization of selenoxides (*S*)-(−)-**2a–c** was faster than selenoxides (*S*)-(−)-**4a–c**. In order to understand the experimental results, the structures of selenoxides **2c** and **4c** were optimized by theoretical calculations (B3LYP/LANL2DZ). Distances between

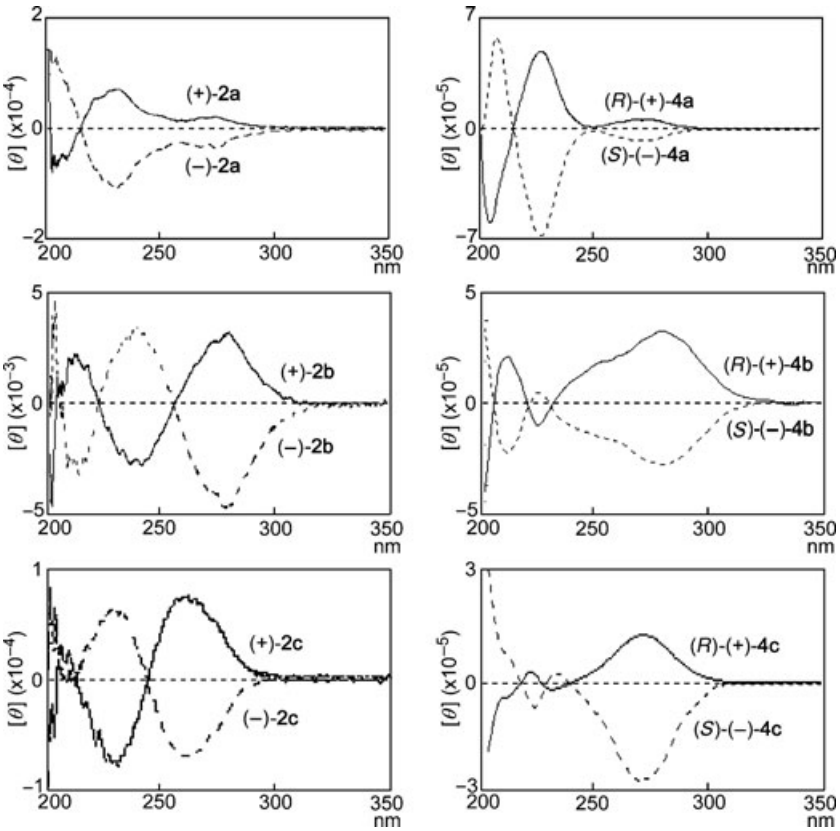


FIGURE 3 Circular dichroism spectra of optically active selenoxides **2a–c** and **4a–c** in cyclohexane.

selenium and nitrogen atoms of the optimized structures of selenoxides **2c** and **4c** were 3.4 and 3.0 Å, respectively. The sum of van der Waals radii of nitrogen and selenium atoms is 3.4 Å. This result indicates that the interaction between selenium and nitrogen atoms of selenoxide **2c** is weaker than that of selenoxide **4c**, and hence thermodynamic stabilization effect by coordination in selenoxide **2c** is less than selenoxide **4c**.

TABLE 2 First-Order Rate Constants and Half-Lives for Racemization of Optically Active Selenoxides (*S*)-(−)-**1a**, (*S*)-(−)-**1b**, (*S*)-(−)-**4a**, and (*S*)-(−)-**5** in the Solution[a]

	$k\ (s^{-1})(t_{1/2}(h))$			
Solvent	*(S)-(−)-**1a***	*(S)-(−)-**1b***	*(S)-(−)-**4a**[b]*	*(S)-(−)-**5**[c]*
$CHCl_3$	A[d]	A	A	A
MeOH/H_2O (4/1)	6.10×10^{-5} (3.15)	1.70×10^{-4} (1.10)	5.13×10^{-5} (3.76)	3.34×10^{-5} (5.76)

[a]In ca. 7 mM solution at 28 ± 1°C.
[b]From [14].
[c]From [15].
[d]A, No racemization was observed even after 3 days.

CONCLUSION

Selenoxides **1a, 1b**, and **2a–c** could be optically resolved into their enantiomers using an optically active column. The absolute configurations of (−)-isomers were assigned to be S-form by comparing their specific rotation, circular dichroism spectra, and behavior in optical resolution with those of the sulfur analogues. Selenoxides **1a** and **1b** were found to be stabilized toward racemization by intramolecular coordination of the chalcogen atoms to selenium atom and also found to be more stable than selenoxides **2a–c**. Thermodynamic stabilization effect toward racemization by coordination of Lewis bases to selenium atom forming five-membered ring in **1** and **4a** is larger than those forming six-membered ring in **2**.

EXPERIMENTAL

Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl before use. Cyclohexane, chloroform, dichloromethane, and hexane were distilled from calcium hydride before use. Methanol and ethanol were distilled from magnesium cake.

TABLE 3 First-Order Rate Constants and Half-Lives for Racemization of Optically Active Selenoxides (*S*)-(−)-**2a–c** and (*S*)-(−)-**4a–c** in the Solution[a]

	$k\ (s^{-1})(t_{1/2}(h))$					
Solvent	*(S)-(−)-**2a***	*(S)-(−)-**2b***	*(S)-(−)-**2c***	*(S)-(−)-**4a**[b]*	*(S)-(−)-**4b**[b]*	*(S)-(−)-**4c**[b]*
$CHCl_3$	A[c]	A	2.10×10^{-5} (9.41)	A	A	A
$MeOH/H_2O$ (4/1)	1.70×10^{-3} (0.11)	5.29×10^{-3} (0.037)	B[d]	5.13×10^{-5} (3.76)	3.03×10^{-4} (0.63)	1.23×10^{-3} (0.16)

[a]In ca. 7 mM solution at 28 ± 1°C.
[b]From [14].
[c]A, No racemization was observed even after 3 days.
[d]B, Racemization was completed within 1 min.

Thin-layer chromatography (TLC) was performed with Merck Art. 5554 DC-Alfolie Kieselgel 60 F_{254}. Column chromatography was performed with Merck 7734 Kieselgel 60. Gel permeation chromatography (GPC) was performed using JAI LC-908 liquid chromatograph with two JAIGEL-1H columns (20 mm × 600 mm), and the products were eluted with chloroform. All reactions were carried out under nitrogen. ^1H, ^{13}C, and ^{77}Se NMR spectra were measured on a JEOL JNM-LA-500 with Me_4Si, Me_4Si, and MeSeMe as internal or external standard, respectively. Elemental analysis was performed by a Perkin-Elmer 240-C. Melting points were determined on a Yamato MP-21 melting point apparatus. UV–VIS spectra were measured on a UV-3100PC UV–VIS–NIR scanning spectrometer. IR spectra were measured on a Perkin-Elmer spectrum GX FT-IR system. Mass spectra (MS) were determined on a Jeol JMS-GCMATE system. Circular dichroism spectra were measured on a Jasco J-725 spectropolarimeter. Specific rotations were measured on a Jasco DIP-140 digital polarimeter.

2-(Methoxymethyl)diphenyl Selenide

To a stirred solution of diphenyl diselenide (3.12 g, 10.0 mmol) in THF (20 mL) was added 2-(methoxymethyl)phenylmagnesium bromide, prepared from 2-(methoxymethyl)bromobenzene (1.85 g, 10.0 mmol) and magnesium (240 mg, 10.0 mmol), dropwise at 0°C. After additional stirring for 18 h at room temperature, the solution was poured into HCl_{aq} (1.0 M, 10 mL) and the product was extracted with ether. The ether solution was washed with brine and dried over magnesium sulfate. After removal of the solvent in vacuo, purification of the remaining residue by silica gel column chromatography (hexane/chloroform = 3/1) gave 2-(methoxymethyl)diphenyl selenide in 69% yield (1.94 g); ^1H NMR (500 MHz, $CDCl_3$) δ 3.40 (s, 3H), 4.57 (s, 2H), 7.15 (ddd, 1H, J = 7.6, 7.4, 0.9 Hz), 7.25–7.28 (m, 4H), 7.33–7.35 (m, 1H), 7.42–7.45 (m, 3H); IR (neat) 3057, 2820, 1578, 1476, 1437, 1380, 1193, 1099, 739, 691 cm^{-1}. MS (EI, 70 ev) m/z: 277 ($M^+ - 1$, ^{80}Se), 275 ($M^+ - 1$, ^{78}Se), 244, 242, 184, 182.

*2-(Methoxymethyl)diphenyl Selenoxide (**1a**)*

To a stirred solution of 2-(methoxymethyl)diphenyl selenide (1.44 g, 5.2 mmol) in methanol (5 mL) and dichloromethane (30 mL) was added dropwise *tert*-butyl hypochlorite (0.60 mL, 5.4 mmol) at −50°C. After additional stirring for 40 min at −50°C, $NaOH_{aq}$ (2.0 M, 5.0 mL) was added to the reaction mixture. The solvent was removed in vacuo, and water was added to the residue. The product was extracted with dichloromethane, washed with brine, and dried over magnesium sulfate. After removal of the solvent in vacuo, purification of the remaining residue by silica gel column chromatography (dichloromethane/methanol = 10/1) gave selenoxide **1a** in 51% yield (753 mg): ^1H NMR (500 MHz, $CDCl_3$) δ 3.36 (s, 3H), 4.39 (d, 1H, J = 12.5 Hz), 4.62 (d, 1H, J = 12.5 Hz), 7.21 (d, 1H, J = 7.4 Hz), 7.39–7.42 (m, 4H), 7.53 (dd, 1H, J = 7.8, 7.6 Hz), 7.70–7.72 (m, 2H), 8.24 (d, 1H, J = 7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 57.7, 73.5, 126.0, 127.0, 127.7, 129.2, 129.3, 130.6, 130.7, 136.8, 142.1, 143.4; ^{77}Se NMR (95 MHz, $CDCl_3$) δ 853; IR (KBr) 3052, 2924, 1629, 1474, 1442, 1385, 1206, 1093, 800, 753, 688 cm^{-1}; UV (cyclohexane) λ_{max} 234 (ε 8.4 × 10^3), 262 (sh, ε 1.7 × 10^3); MS (EI, 30 ev) m/z 277 ($M^+ - O - 1$, ^{80}Se), 275 ($M^+ - O - 1$, ^{78}Se), 244, 242, 184, 182; Anal. Calcd for $C_{16}H_{19}NOSe$: C, 57.35; H, 4.81; N. Found C, 57.15; H, 4.68.

2-(Bromomethyl)diphenyl Selenoxide

To a stirred solution of 2-(bromomethyl)diphenyl selenide (3.31 g, 10.2 mmol) in methanol (2 mL) and dichloromethane (20 mL) was added

dropwise *tert*-butyl hypochlorite (1.20 mL, 10.6 mmol) at 0°C. After additional stirring for 12 h at −50°C, $NaOH_{aq}$ (2.0 M, 10.0 mL) was added to the reaction mixture. The solvent was removed in vacuo, and water was added to the residue. The product was extracted with dichloromethane, washed with brine, and dried over magnesium sulfate. After removal of solvent in vacuo, purification of the remaining residue by silica gel column chromatography (dichloromethane/methanol = 10/1) gave 2-(bromomethyl)diphenyl selenoxide in 80% yield (2.75 g): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.69 (d, 1H, $J = 12.5$ Hz), 4.87 (d, 1H, $J = 12.5$ Hz), 7.21 (d, 1H, $J = 7.4$ Hz), 7.39–7.42 (m, 4H), 7.53 (dd, 1H, $J = 7.8$, 7.6 Hz), 7.70–7.72 (m, 2H), 8.24 (d, 1H, $J = 7.8$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 68.5, 126.2, 127.2, 127.6, 129.1, 129.4, 130.0, 131.7, 136.8, 141.1, 143.4.

*2-(Methylthiomethyl)diphenyl Selenoxide (***1b***)*

To a stirred solution of sulfur (32 mg, 1.0 mmol) in THF (3 mL) was added methylmagnesium chloride solution (2.60 M diethylether solution, 0.50 mL, 1.3 mmol). After additional stirring for 1 h at room temperature, the solution was added 2-(bromomethyl)diphenyl selenoxide (340 mg, 1.0 mmol). After additional stirring for 13 h at room temperature, the solution was poured into HCl_{aq} (1.0 M, 10 mL), and the product was extracted with dichloromethane. The solution was washed with brine and dried over magnesium sulfate. After removal of the solvent in vacuo, purification of the remaining residue by silica gel column chromatography (dichloromethane/methanol = 10/1) gave selenoxide **1b** in 30% yield (87 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.96 (s, 3H), 3.69 (d, 1H, $J = 13.8$ Hz), 3.81 (d, 1H, $J = 13.8$ Hz), 7.24 (dd, 1H, $J = 7.8$, 1.0 Hz), 7.38 (ddd, 1H, $J = 7.8$, 7.3, 1.0 Hz), 7.41–7.45 (m, 4H), 7.76–7.78 (m, 2H), 7.98 (dd, 1H, $J = 7.8$, 1.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6, 36.3, 127.0, 127.4, 128.9, 129.3, 130.0, 130.7, 130.9, 137.4, 142.6, 142.8; ^{77}Se NMR (95 MHz, $CDCl_3$) δ 838; IR (neat) 3053, 2906, 1573, 1473, 1439, 1022, 813, 734, 689 cm^{-1}; UV (cyclohexane) λ_{max} 237 (ε 8.2. × 10^3), 267 (sh, ε 1.8 × 10^3); MS (EI, 30 ev) *m/z* 293 (M^+−O−1, ^{80}Se), 291 (M^+−O−1, ^{78}Se), 278, 276, 244, 242; Anal. Calcd for $C_{16}H_{19}NOSe$: C, 54.37; H, 4.56; N. Found C, 54.41; H, 4.54.

*2-(Methylselenomethyl)diphenyl Selenoxide (***1c***)*

To a stirred solution of selenium powder (78 mg, 1.0 mmol) in THF (3 mL) was added dropwise methylmagnesium chloride solution (2.60 M ether solution, 0.50 mL, 1.3 mmol). After additional stirring for 1 h at room temperature, the solution was added 2-(bromomethyl)diphenyl selenoxide (340 mg, 1.0 mmol). After additional stirring for 11 h at room temperature, the solution was poured into HCl_{aq} (1.0 M, 10 mL) and the product was extracted with dichloromethane. The solution was washed with brine and dried over magnesium sulfate. After removal of the solvent in vacuo, purification of the remaining residue by silica gel column chromatography (dichloromethane/methanol = 10/1) gave selenoxide **1c** in 35% yield (120 mg):^{1}H NMR (500 MHz, $CDCl_3$) δ 1.94 (s, 3H), 3.81 (d, 1H, $J = 12.5$ Hz), 4.01 (d, 1H, $J = 12.5$ Hz), 7.35–7.48 (m, 6H), 7.76–7.80 (m, 2H), 7.89 (t, 1H, $J = 7.4$, 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.6, 36.3, 127.2, 127.5, 127.9, 128.3, 130.4, 130.7, 131.9, 136.4, 141.6, 143.6; ^{77}Se NMR (95 MHz, $CDCl_3$) δ 822, 210; IR (neat) 3040, 2926, 1573, 1468, 1432, 1012, 810, 743, 679 cm^{-1}; UV (cyclohexane) λ_{max} 230 (ε 7.8 × 10^3), 273 (sh, ε 2.0 × 10^3); MS (EI, 30 ev) *m/z* 341 (M^+−O−1, ^{80}Se ^{80}Se), 339 (M^+–O –1, ^{80}Se ^{78}Se), 337 (M^+−O−1, ^{78}Se ^{78}Se), 326, 324, 322; Anal. Calcd for $C_{16}H_{19}NOSe$: C, 47.23; H, 3.96; N. Found C, 46.98; H, 4.24.

2-{2′-(N,N-Dimethylamino)ethyl}diphenyl Selenide

To a stirred solution of 2-{2′-(*N*,*N*-dimethylamino)-ethyl}bromobenzene (1.14 g, 5.0 mmol) in THF (20 mL) was added dropwise butyllithium solution (1.6 M hexane solution, 3.3 mL, 5.3 mmol) at −50°C. After the solution was stirred for 30 min at −50°C, a stirred solution of diphenyl diselenide (1.56 g, 5.0 mmol) in THF (20 mL) was added dropwise to the solution at −30°C, and stirring was continued for an additional 17 h at room temperature. The solution was poured into water, and the product was extracted with ether. The ether solution was washed with brine and dried over magnesium sulfate. After removal of the solvent in vacuo, purification of the remaining residue by silica gel column chromatography (chloroform) gave 2-{2′-(*N*,*N*-dimethylamino)ethyl}diphenyl selenide in 68% yield (1.04 g): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.27 (s, 6H), 2.48–2.51 (m, 2H), 2.95–2.98 (m, 2H), 7.08 (ddd, 1H, $J = 7.5$ Hz, 7.3 Hz, 1.6 Hz), 7.21–7.28 (m, 5H), 7.37–7.39 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.2, 45.2, 60.6, 127.0, 127.1, 128.1, 129.3, 129.9, 131.3, 131.5, 132.4, 134.8, 142.2; IR (neat) 2939, 2816, 2766, 1577, 1435, 1438, 1052, 1021, 737, 690 cm^{-1}; MS (EI, 70 ev) *m/z* 304 (M^+−1, ^{80}Se), 302 (M^+−1, ^{78}Se), 257, 255, 244, 242.

*2-{2′-(N,N-Dimethylamino)ethyl}diphenyl Selenoxide (**2a**)*

To a stirred solution of 2-{2′-(*N*,*N*-dimethylamino)-ethyl}diphenyl selenide (1.04 g, 4.5 mmol) in methanol (60 mL), dropwise *tert*-butyl hypochlorite (0.50 mL, 4.5 mmol) at −50°C was added. After additional stirring for 40 min at −50°C, $NaOH_{aq}$ (2.0 M, 4.5 mL) was added to the reaction mixture. The solvent was removed in vacuo, and water was added to the residue. The product was extracted with dichloromethane, washed with brine, and dried over magnesium sulfate. After removal of the solvent in vacuo, purification of the remaining residue by silica gel column chromatography (methanol) gave selenoxide **2a** in 50% yield (517 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.23 (s, 6H), 2.34–2.39 (m, 1H), 2.50–2.55 (m, 1H), 2.87–2.98 (m, 2H), 7.25–7.26 (m, 1H), 7.41–7.45 (m, 5H), 7.66–7.67 (m, 2H), 7.96–7.98 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.0, 45.4, 60.6, 126.2, 127.1, 128.0, 129.5, 129.8, 131.0, 131.3, 139.5, 142.0, 143.1; ^{77}Se NMR (95 MHz, $CDCl_3$) δ 840; IR (neat) 3053, 2945, 2821, 2780, 1469, 1441, 1052, 825, 747, 689 cm^{-1}; UV (cyclohexane) λ_{max} 223 (ε 7.4×10^3), 251 (sh, ε 1.5×10^3); MS (EI, 30 ev) *m/z* 303 (M^+-O-2, ^{80}Se), 301 (M^+-O-2, ^{78}Se), 257, 255, 244, 242 ; Anal. Calcd for $C_{16}H_{19}NOSe$: C, 60.00; H, 5.98; N, 4.37. Found C, 60.34; H, 6.22; N, 4.59.

Benzyl 2-{2′-(N,N-dimethylamino)ethyl}phenyl Selenide

To a stirred solution of dibenzyl diselenide (1.71 g, 5.0 mmol) in THF (30 mL) was added 2-{2′-(*N*,*N*-dimethylamino)ethyl}phenylmagnesium bromide, prepared from 2-{2′-(*N*,*N*-dimethylamino)ethyl}-bromobenzene (1.14 g, 5.0 mmol) and magnesium (115 mg, 5.0 mmol), dropwise at 0°C. After additional stirring for 16 h at room temperature, the solution was poured into HCl_{aq} (1.0 M, 10 mL). Aqueous layer was washed with ether. $NaOH_{aq}$ (2.0 M, 10 mL) was added to aqueous layer, and the product was extracted with dichloromethane, washed with brine and dried over magnesium sulfate. After removal of the solvent in vacuo, purification of the remaining residue by gel permeation chromatography gave benzyl 2-{2′-(*N*,*N*-dimethylamino)ethyl}phenyl selenide in 24% yield (381 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.27 (s, 6H), 2.37–2.40 (m, 2H), 2.83–2.86 (m, 2H), 4.06 (s, 2H), 7.09–7.25 (m, 8H), 7.49 (d, 1H, $J = 7.7$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.7, 45.4, 49.1, 60.7, 125.8, 127.9, 128.2, 128.6, 129.1, 129.3, 129.8, 130.2, 131.3, 140.0; IR (neat) 3060, 2937, 2856, 2779, 1494, 1263, 1038, 910, 751, 696 cm^{-1}. MS (EI, 70 ev) *m/z*: 318 (M^+-1, ^{80}Se), 316 (M^+-1, ^{78}Se), 275, 273, 245, 243.

*Benzyl 2-{2′-(N,N-dimethylamino)ethyl}phenyl Selenoxide (**2b**)*

To a stirred solution of benzyl 2-{2′′-(*N*,*N*-dimethylamino)ethyl}phenyl selenide (381 mg, 1.2 mmol) in dichloromethane (5 mL) was added by portions *m*-chloroperbenzoic acid (290 mg, 1.8 mmol) at 0°C. After additional stirring for 5 h at room temperature, the reaction mixture was poured into sat. $NaHCO_{3aq}$. The product was extracted with dichloromethane, washed with brine, and dried over magnesium sulfate. After removal of the solvent in vacuo, purification of the remaining residue by gel permeation chromatography gave selenoxide **2b** in 24% yield (85 mg); mp 130–132°C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.20 (s, 6H), 2.20–2.29 (m, 1H), 2.40–2.51 (m, 3H), 3.99 (d, 1H, $J = 11.3$ Hz), 4.20 (d, 1H, $J = 11.3$ Hz), 6.95–6.97 (m, 2H), 7.17–7.27 (m, 4H), 7.39–7.42 (m, 2H), 7.79–7.82 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.7, 45.5, 59.1, 60.7, 125.7, 127.8, 128.1, 128.5, 129.2, 129.7, 130.1, 131.2, 139.8, 139.8; ^{77}Se NMR (95 MHz, $CDCl_3$) δ 866; IR (neat) 2978, 2946, 2778, 1653, 1467, 1454, 1264, 1052, 811, 765, 696 cm^{-1}; UV (cyclohexane) λ_{max} 238 (ε 7.7×10^3), 273 (sh, ε 4.0×10^3); MS (EI, 30 eV) *m/z*: 318 (M^+-O-1, ^{80}Se), 316 (M^+-O-1, ^{78}Se), 275, 273, 245, 243; Anal. Calcd for $C_{17}H_{21}NOSe$: C, 61.17; H, 6.33; N, 4.19. Found: C, 61.09; H, 6.49; N, 4.59.

2-{2′-(N,N-Dimethylamino)ethyl}phenyl Methyl Selenide

To a stirred solution of 2-{2′-(*N*,*N*-dimethylamino)-ethyl}bromobenzene (1.47 g, 6.4 mmol) in THF (30 mL) was added dropwise butyllithium solution (1.60 M hexane solution, 8.2 mL, 13 mmol) at −60°C. After the solution was stirred for an additional 30 min, selenium powder (505 mg, 6.4 mmol) was added by portions to the solution at −40°C. After disappearance of selenium powder, iodomethane (0.40 mL, 6.4 mmol) was added to the solution, and stirring was continued for an additional 4 h at room temperature. The solution was poured into water, and the product was extracted with ether. The ether solution was washed with brine and dried over magnesium sulfate. After removal of the solvent in vacuo, purification of the remaining residue by silica gel column chromatography (ethyl acetate/methanol = 3/1) gave 2-{2′-(*N*,*N*-dimethylamino)ethyl}phenyl methyl selenide in 34% yield (531 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.29 (s, 3H), 2.32 (s, 6H), 2.21–2.54 (m, 2H), 2.89–2.93 (m,

2H) 7.11–7.20 (m, 3H), 7.32–7.35 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.0, 33.9, 45.4, 60.4, 126.2, 127.0, 128.3, 129.3, 129.8, 140.3; IR (neat) 2941, 2766, 1567, 1535, 1463, 1372, 1266, 1144, 1053, 908, 747 cm^{-1}; MS (EI, 70 eV) *m/z*: 242 (M^+-1, ^{80}Se), 240 (M^+-1, ^{78}Se), 198, 196, 168, 166, 105, 91, 77.

*2-{2′-(N,N-Dimethylamino)ethyl}phenyl methyl selenoxide (**2c**)*

To a stirred solution of 2-{2′-(*N*,*N*-dimethylamino)-ethyl}phenyl methyl selenide (531 mg, 2.2 mmol) in a methanol (50 mL) was added dropwise *tert*-butyl hypochlorite (0.35 mL, 2.2 mmol) at −40°C. After additional stirring for 40 min at −40°C, $NaOH_{aq}$ (2.0 M, 3.0 mL) was added to the reaction mixture. The solvent was removed in vacuo, and water was added to the residue. The organic component was extracted with dichloromethane, washed with brine, and dried over magnesium sulfate. After the solvent was removed in vacuo, purification of the remaining residue by silica gel column chromatography (methanol) gave selenoxide **2c** in 34% yield (193 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (s, 6H), 2.44–2.48 (m, 1H), 2.58–2.62 (m, 1H), 2.62 (s, 3H), 2.75–2.78 (m, 1H), 2.88–2.92 (m, 1H), 7.25 (dd, 1H, $J = 7.3$ Hz, 1.2 Hz), 7.43 (ddd, 1H, 8.2 Hz, 6.9 Hz, 1.2 Hz), 7.48 (ddd, 1H, $J = 8.2$ Hz, 7.3 Hz, 1.2 Hz), 8.00 (dd, 1H, $J = 6.9$ Hz, 1.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.3, 37.3, 45.7, 64.1, 125.3, 128.0, 129.5, 131.1, 139.2, 142.5; ^{77}Se NMR (95 MHz, $CDCl_3$) δ 812; IR(neat) 2930, 2786, 1650, 1468, 1441, 1261, 1144, 1051, 803, 762 cm^{-1}; UV (cyclohexane) λ_{max} 214 (ε 1.3×10^4), 260 (sh, ε 5.2×10^3); MS (EI, 30eV) *m/z*: 242 (M^+-O-1, ^{80}Se), 240 (M^+-O-1, ^{78}Se), 199, 197, 169, 167; Anal. Calcd for $C_{11}H_{17}NOSe$: C, 51.17; H, 6.64; N, 5.42. Found: C, 51.09; H, 6.49; N, 5.59.

*(S)-(−)-2-(Methoxymethyl)-4′-methyldiphenyl Sulfoxide ((S)-(−)-**3**)*

To a stirred solution of 2-(*S*)s-(−)-menthyl-(−)-*p*-toluenesufinate (100% ee; 178 mg, 0.60 mmol) in THF (3 mL) was added 2-(methoxymethyl)phenylmagnesium bromide, prepared from 2-(methoxymethyl)bromobenzene (114 mg, 0.72 mmol) and magnesium (16 mg, 0.70 mmol), dropwise at 0°C. After additional stirring for 3 h at room temperature, the mixture was poured into brine. The product was extracted with ether, washed with brine, and dried over magnesium sulfate. After the solvent was removed in vacuo, purification of the remaining residue by gel permeation chromatography gave sulfoxide (*S*)-(−)-**3** in 57% yield (90 mg): colorless oil; 96% ee; CD (cyclohexane): λ_{max} 278 ([θ] -6.9×10^3), 249 ([θ] $+9.8 \times 10^3$), 221 ([θ] -3.6×10^4) nm; CD (acetonitrile): λ_{max} 270 ([θ] -4.0×10^3), 220 ([θ] -1.2×10^4) nm; $[\alpha]_D$ −78.9 (*c* 0.12, $CHCl_3$), $[\alpha]_{435}$−123.3 (*c* 0.12, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.34 (s, 3H), 4.47 (d, 1H, $J = 13.6$ Hz), 4.63 (d, 1H, $J = 13.6$ Hz), 7.24 (d, 2H, $J = 8.0$ Hz), 7.40 (dd, 1H, 7.5 Hz, 1.5 Hz), 7.44 (td, 1H, $J = 7.5$ Hz, 1.5 Hz), 7.49 (td, 1H, $J = 7.5$ Hz, 1.5 Hz), 7.53 (d, 2H, $J = 8.0$ Hz), 7.75 (dd, 1H, $J = 7.5$ Hz, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 43.3, 64.1, 125.6, 128.1, 128.2, 129.5, 130.1, 137.1, 139.2, 142.5; ^{77}Se NMR (95 MHz, $CDCl_3$) δ 812; IR(neat) 2930, 1468, 1441, 1250, 1143, 1051, 820 cm^{-1}; UV (cyclohexane) λ_{max} 206 (ε 4.5×10^4), 240 (sh, ε 1.2×10^4); MS (EI, 30eV) *m/z*: 260 (M^+), 244, 229, 213, 199, 123, 91; Anal. Calcd for $C_{15}H_{16}O_2S$: C, 69.20; H, 6.19. Found: C, 69.31; H, 6.35.

Typical Procedure for Optical Resolution of Racemic Selenoxides by Means of High-Performance Liquid Chromatography Using an Optically Active Column

Racemic selenoxide (20 mg) in eluent (0.3 mL) was applied to an optically active column packed with amylose carbamate derivative/silica gel (Daicel Chiralpak AS; 10 × 250 mm) and eluted with hexane containing 20 (for **1a**), 15 (for **1b**), 25 (for **2a**), 15 (for **2b**), and 25 (for **2c**) vol% ethanol at a flow rate of 1.0 mL min^{-1}. About 5 mg of each optically active selenoxide was collected from the first- and second elutes, respectively. Their optical purities were determined by the HPLC analysis using the same type of chiral column (4.6 × 250 mm) at an analytical scale.

*(S)-(−)-2-(Methoxymethyl)diphenyl Selenoxide {(S)-(−)-**1a**}*. Pale yellow oil; 100% ee; CD (cyclohexane): λ_{max} 266 ([θ] -7.8×10^3), 227 ([θ] -3.6×10^5) nm; CD (acetonitrile): λ_{max} 260 ([θ] -8.1×10^3), 229 ([θ] -3.4×10^5) nm; $[\alpha]_D$ −59.8 (*c* 0.21, $CHCl_3$), $[\alpha]_{435}$−159.8 (*c* 0.21, $CHCl_3$). ^{1}H NMR and UV spectra were similar to that of the racemic one.

*(R)-(+)-2-(Methoxymethyl)diphenyl Selenoxide {(R)-(+)-**1a**}*. Pale yellow oil; 60% ee; CD (cyclohexane): λ_{max} 265 ([θ] $+3.0 \times 10^3$), 227 ([θ]+ 3.0×10^5) nm; CD (acetonitrile): λ_{max} 261 ([θ]+ 2.8×10^3), 228 ([θ]+ 2.8×10^5) nm; $[\alpha]_D$ +30.0 (*c* 0.28, $CHCl_3$), $[\alpha]_{435}$ + 119.8 (*c* 0.28, $CHCl_3$). ^{1}H NMR and UV spectra were similar to that of the racemic one.

*(S)-(−)-2-(Methylthiomethyl)diphenyl Selenoxide {(S)-(−)-**1b**}*. Pale yellow oil; 75% ee; CD (cyclohexane): λ_{max} 227 ($[\theta]$ -1.4×10^4) nm; CD (acetonitrile): λ_{max} 262 ($[\theta] - 3.0 \times 10^3$), 230 ($[\theta]$ -1.1×10^4) nm; $[\alpha]_D - 31.1$ (*c* 0.11, $CHCl_3$), $[\alpha]_{435} - 86.2$ (*c* 0.11, $CHCl_3$). ^{1}H NMR and UV spectra were similar to that of the racemic one.

*(R)-(+)-2-(Methylthiomethyl)diphenyl Selenoxide {(R)-(+)-**1b**}*. Pale yellow oil; 25% ee; CD (cyclohexane): λ_{max} 228 ($[\theta] + 4.6 \times 10^3$) nm; CD (acetonitrile): λ_{max} 228 ($[\theta] + 3.2 \times 10^3$) nm; $[\alpha]_D + 10.8$ (*c* 0.24, $CHCl_3$), $[\alpha]_{435} + 28.8$ (*c* 0.24, $CHCl_3$). ^{1}H NMR and UV spectra were similar to that of the racemic one.

*(S)-(−)-2-{2′-(N,N-Dimethylamino)ethyl}diphenyl Selenoxide {(S)-(−)-**2a**}*. Pale yellow oil; 100% ee; CD (cyclohexane): λ_{max} 275 ($[\theta] - 3.8 \times 10^3$), 231 ($[\theta] - 1.1 \times 10^4$) nm; $[\alpha]_D - 34.2$ (*c* 0.27, $CHCl_3$), $[\alpha]_{435} - 73.5$ (*c* 0.27, $CHCl_3$). ^{1}H NMR and UV spectra were similar to that of the racemic one.

*(R)-(+)-2-{2′-(N,N-Dimethylamino)ethyl}diphenyl Selenoxide {(R)-(+)-**2a**}*. Pale yellow oil; 60% ee; CD (cyclohexane): λ_{max} 274 ($[\theta]$ $+1.8 \times 10^3$), 232 ($[\theta] + 7.0 \times 10^3$) nm; $[\alpha]_D$ +21.6 (*c* 0.57, $CHCl_3$), $[\alpha]_{435}$ +45.1 (*c* 0.57, $CHCl_3$). ^{1}H NMR and UV spectra were similar to that of the racemic one.

*(S)-(−)-Benzyl 2-{2′-(N,N-dimethylamino)ethyl}-phenyl Selenoxide {(S)-(−)-**2b**}*. Colorless crystal, mp 130–132°C; 100% ee; CD (cyclohexane): λ_{max} 279 ($[\theta]$ -4.4×10^3), 238.4 ($[\theta]$ $+3.0 \times 10^3$) nm; $[\alpha]_D$ −20.9 (*c* 0.33, $CHCl_3$), $[\alpha]_{435}$ −56.0 (*c* 0.33, $CHCl_3$). ^{1}H NMR and UV spectra were similar to that of the racemic one.

*(R)-(+)-Benzyl 2-{2′-(N,N-dimethylamino)ethyl}-phenyl Selenoxide {(R)-(+)-**2b**}*. Colorless crystal, mp 130–132°C; 75% ee; CD (cyclohexane): λ_{max} 279 ($[\theta] + 2.8 \times 10^3$), 239 ($[\theta] - 2.6 \times 10^4$) nm; $[\alpha]_D$ +13.6 (*c* 0.22, $CHCl_3$), $[\alpha]_{435}$ +45.1 (*c* 0.22, $CHCl_3$). ^{1}H NMR and UV spectra were similar to that of the racemic one.

*(S)-(−)-2-{2′-(N,N-Dimethylamino)ethyl}phenyl Methyl Selenoxide {(S)-(−)-**2c**}*. Pale yellow oil; 100% ee; CD (cyclohexane): λ_{max} 260 ($[\theta] - 6.5 \times 10^3$), 229 ($[\theta] + 5.2 \times 10^3$) nm; $[\alpha]_D$ −117.4 (*c* 0.10, $CHCl_3$), $[\alpha]_{435}$ −264.8 (*c* 0.10, $CHCl_3$). ^{1}H NMR and UV spectra were similar to that of the racemic one.

*(R)-(+)-2-{2-(N,N-dimethylamino)ethyl}phenyl Methyl Selenoxide{(R)-(+)-**2c**}*. Pale yellow oil; 75% ee; CD (cyclohexane): λ_{max} 260 ($[\theta] + 6.3 \times 10^3$), 229 ($[\theta] - 7.0 \times 10^3$) nm; $[\alpha]_D$ +87.7 (*c* 0.10, $CHCl_3$), $[\alpha]_{435}$+201.6 (*c* 0.10, $CHCl_3$). ^{1}H NMR and UV spectra were similar to that of the racemic one.

Kinetic Studies for Racemization of Optically Active Selenoxides

Kinetic studies on the racemization of optically active selenoxides (*S*)-(−)-1**a**, (*S*)-(−)-**1b**,(*S*)-(−)-**2a**, (*S*)-(−)-**2b**, and (*S*)-(−)-**2c** were examined in chloroform and in methanol/water = 4/1 (ca. 7 mM) at 28°C. The rates of the racemization were calculated based on their specific rotation and plotted according to the first-order rate equation.

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