Optical Resolution and Configurational Stability of Selenoxides Stabilized by Intramolecular Coordination

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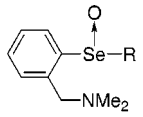
2-((Dimethylamino)methyl)phenyl alkyl (or aryl) selenoxides, configurationally stabilized by intramolecular coordination of an amino group to the selenium atom, were optically resolved into their enantiomeric isomers by means of high-performance liquid chromatography using an optically active column packed with amylosecarbamate derivative/silica gel. This is the first example of the isolation of optically pure selenoxides without bulky substituents and also the first isolation of optically pure alkyl aryl selenoxides. The absolute configuration of the (−)-isomers could be assigned to be the *S*-form by comparison of their specific rotations, circular dichroism spectra, and behavior on the optically active column with those of the sulfur analogue, prepared by Andersen's method. Racemization of the optically active selenoxides was accelerated not only in acidic solution but also in basic media. This result indicates there are two different mechanisms for their racemization in acidic and basic media. The stabilization energy of the selenoxides by the intramolecular coordination of an amino group to the selenium atom was estimated to be ca. 3 kcal mol^{-1} on the basis of variable-temperature ^1H NMR measurements.

Introduction

Recently, we have been interested in chiral tricoordinated selenium and tellurium compounds.[1−3] Among these chiral compounds, optically active selenoxide is well-known to be unstable toward racemization in the presence of water, including even atmospheric moisture. Ever since optically active selenoxide which had bulky substituents and was kinetically stable against racemization via hydration was obtained for the first time in 1983,[4] there have been several reports on the isolation of kinetically stabilized optically active selenoxides[2,3] by various approaches, such as optical resolution of diastereomeric mixtures,[5] chromatographic resolution of racemic selenoxides using optically active columns,[6] and asymmetric oxidation of prochiral selenides.[7,8] Optically active selenoxides have also been extensively studied as key intermediates in asymmetric synthesis.[2,8−10] We have succeeded in isolating an optically pure diaryl selenoxide;[5] however, an optically pure alkyl aryl selenoxide has not been isolated. Isolation of an optically pure alkyl aryl selenoxide is very difficult since it readily undergoes racemization by atmospheric moisture even though the aryl group possesses bulky substituents. Fortunately, there is another method for stabilizing molecular structures, i.e., by coordination, and there are many reports concerning stabilization through the intramolecular coordination of amino groups.[11]

We prepared asymmetric alkyl aryl and diaryl selenoxides **1**, **2**, and **3** which are expected to be stabilized by the intramolecular coordination of an amino group to the selenium atom, and attempted their optical resolution.



1: R = Me
2: R = Bn
3: R = Ph

We report here the isolation of optically pure alkyl aryl and diaryl selenoxides stabilized by intramolecular coordination by means of optical resolution using an optically active column. Their stereochemistries and configurational stabilities were also examined.

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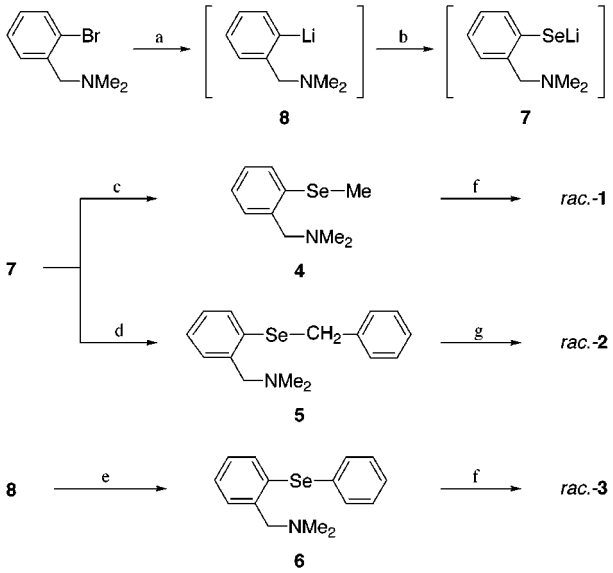
Scheme 1[a]



[a] Key: (a) *n*-BuLi, THF, −20 to −30 °C; (b) Se; (c) MeI; (d) $PhCH_2Br$; (e) PhSeSePh; (f) *t*-BuOCl, MeOH, −30 °C, then NaOH(aq); (g) MCPBA, CH_2Cl_2, 0 °C.

Results and Discussion

Preparation and Optical Resolution of Selenoxides by means of Chromatography Using an Optically Active Column. The precursors, selenides **4** and **5**, were synthesized in yields of 83% and 74%, respectively, by reacting 2-((dimethylamino)methyl)-phenylselenolithium (**7**), prepared from 2-((dimethylamino)methyl)bromobenzene, with methyl iodide or benzyl bromide (Scheme 1). Selenide **6** was prepared in 49% yield by reacting 2-((dimethylamino)methyl)phenyllithium (**8**) with diphenyl diselenide. Racemic selenoxides *rac*-**1**, -**2**, and -**3** were obtained in 74%, 81%, and 79% yields, respectively, by oxidation of the corresponding selenides with *tert*-butyl hypochlorite or *m*-chloroperbenzoic acid.

When *rac*-2-((dimethylamino)methyl)phenyl methyl selenoxide (*rac*-**1**) was subjected to an optically active column (4.6 × 250 mm) packed with amylosecarbamate derivative/silica gel using high-performance liquid chromatography on an analytical scale (hexane/ethanol = 75/25), two peaks corresponding to each enantiomer of **1** were observed on the chromatogram, as shown in Figure 1. Using the same column, *rac*-benzyl 2-((dimethylamino)methyl)phenyl selenoxide (*rac*-**2**) and *rac*-2-((dimethylamino)methyl)diphenyl selenoxide (*rac*-**3**) were also resolved into two peaks corresponding to their enantiomers. In all cases, satisfactory resolutions were observed.

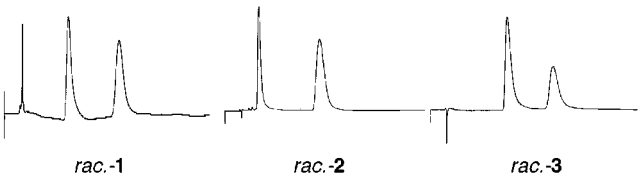


Figure 1. Chromatographic separation of racemic selenodies *rac*-**1**, -**2**, and -**3** on an optically active column (4.6 × 250 mm) packed with amylosecarbamate derivative/silica gel by means of HPLC on an analytical scale (hexane/ethanol = 75/25).

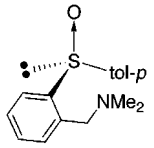
Table 1. Specific Rotations of Optically Active Selenoxides 1, 2, and 3

selenoxide	optical purity[a] (%)	$[\alpha]_D$ ($CHCl_3$)	$[\alpha]_{435}$ ($CHCl_3$)
(−)-**1**	100	−120.8 (*c* 0.32)	−313.2 (*c* 0.32)
(+)-**1**	100	119.8 (*c* 0.23)	296.6 (*c* 0.23)
(−)-**2**	100	−300.4 (*c* 0.50)	−757.4 (*c* 0.50)
(+)-**2**	100	299.2 (*c* 0.50)	791.6 (*c* 0.50)
(−)-**3**	100	−48.1 (*c* 0.26)	−117.8 (*c* 0.26)
(+)-**3**	90	37.2 (*c* 0.17)	86.0 (*c* 0.17)

[a] Optical purity was determined by HPLC analysis.

We attempted to resolve the racemic selenoxides *rac*-**1**, -**2**, and -**3** into their optical isomers on a preparative scale using a larger column (10 × 250 mm) of the same type. In the optical resolution of *rac*-**1**, the enantiomer that was eluted first obtained by repeated resolution (two times) had a negative specific rotation {$[\alpha]_D$ −120.8 (*c* 0.32, $CHCl_3$)} and the enantiomer that was eluted second had a positive specific rotation {$[\alpha]_D$ 119.8 (*c* 0.23, $CHCl_3$)}. Both enantiomers (−)- and (+)-**1** were found to be optically pure by HPLC analysis. Similarly, optical resolution of racemic selenoxides *rac*-**2** and -**3** yielded their optically active isomers. The enantiomers that were eluted first also showed negative specific rotations in both cases, and (−)-**2**, (+)-**2**, and (−)-**3** were confirmed to be optically pure (Table 1). However, optically active selenoxide (+)-**3** could not be obtained as an optically pure form, perhaps due to tailing of the first-eluted enantiomer on a preparative scale despite repeated chromatography.

Circular Dichroism Spectra and Absolute Configuration of Optically Active Selenoxides. Optically active selenoxides **1**, **2**, and **3** with negative specific rotations showed negative first Cotton effects at 270, 279, and 275 nm, respectively, on their circular dichroism spectra in cyclohexane, while (+)-**1**, -**2**, and -**3** showed positive first Cotton effects in the corresponding regions, as shown in Figure 2. However, their absolute configurations could not be determined solely by their specific rotations and CD spectra. We synthesized optically active sulfoxide with similar substituents, (*S*)-(−)-**9**, with inver-



(*S*)-(-)-**9**

sion of configuration from $(S)_S$-(−)-menthyl-(−)-*p*-toluenesulfinate[12,13] according to Andersen's method.[13,14] The CD spectrum of optically active sulfoxide (*S*)-(−)-**9** showed

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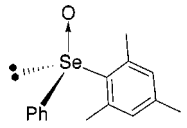
negative first Cotton effects at ca. 284 nm, which corresponded well with those of optically active selenoxides with negative specific rotations, (−)-**1**, -**2**, and -**3**. Furthermore, sulfoxide (*S*)-(−)-**9** was eluted faster than (*R*)-(+)-**9** through the optically active column. Therefore, on the basis of the similarity of the signs of their specific rotations and CD spectra, and their behaviors on the optically active column, the absolute configuration of selenoxides (−)-**1**, -**2**, and -**3** was assigned to be the *S*-form, while that of (+)-**1**, -**2**, and -**3** was the *R*-form.

Configurational Stability of Optically Active Selenoxides. The stability of these optically active selenoxides toward racemization was examined. In a chloroform solution, optically active selenoxides (*S*)-(−)-**1**, -**2**, and -**3** were stable against racemization even after 5 days (Table 2, entry 1). However, racemization was observed in methanol (entry 2), and obeyed good first-order kinetics; half-lives of racemization for (*S*)-(−)-**1**, -**2**, and -**3** were 0.846, 4.20, and 34.5 h, respectively. Addition of water to the methanol solution (entries 3 and 4) accelerated this racemization. These results indicate that the racemization in methanol was caused by a trace amount of water remaining in the solvent despite careful purification. The half-lives of racemization for selenoxide (*S*)-(−)-**3** corresponded well with those[15] for kinetically stabilized selenoxide (*R*)-(+)-**10**. This result indicates that the



(*R*)-(+)-**10**

o-(dimethylamino)methyl group has a stabilizing effect against racemization similar to that of two *o*-methyl groups. A mechanism which involves the formation of an achiral tetracoordinated hydrate was confirmed by examination of the oxygen exchange reaction of selenoxide (*S*)-(−)-**3**. When 30 equiv of $H_2{}^{18}O$ (97 atom % ^{18}O excess) was added to a methanol solution of (*S*)-(−)-**3** (ee 87%) and stirred at room temperature, the mass spectrum showed 8%, 29%, 42%, and 50% ^{18}O-enriched selenoxide at ee's of 79%, 67%, 31%, and 26%, respectively, as shown in Figure 3.

Upon the addition of hydrochloric acid (entry 5), the signals of the selenoxides (*S*)-(−)-**1**, -**2**, and -**3** disappeared from their ^1H NMR spectra, perhaps due to protonation of the amino group, whereas racemization of (*R*)-(+)-**10** was greatly accelerated. However, racemization of (*S*)-(−)-**1**, -**2**, and -**3** was accelerated by the addition of *p*-toluenesulfonic acid (entries 6 and 7). The rates of racemization of (*S*)-(−)-**1**, -**2**, and -**3** were not greatly accelerated until the addition of 1 equiv of *p*-toluenesulfonic acid. However, addition of over 1 equiv of *p*-toluenesulfonic acid accelerated the racemization promptly, as shown in Figure 4. This result may be due to protonation of the amino group. The acid was consumed by the amino group until the addition of 1 equiv of the acid, and the excess acid accelerated racemization via the achiral hydrate[15] formed by protonation of the oxygen atom of the selenoxide followed by hydration. Racemization of selenoxides (*S*)-(−)-**1**, -**2**, and -**3** was also

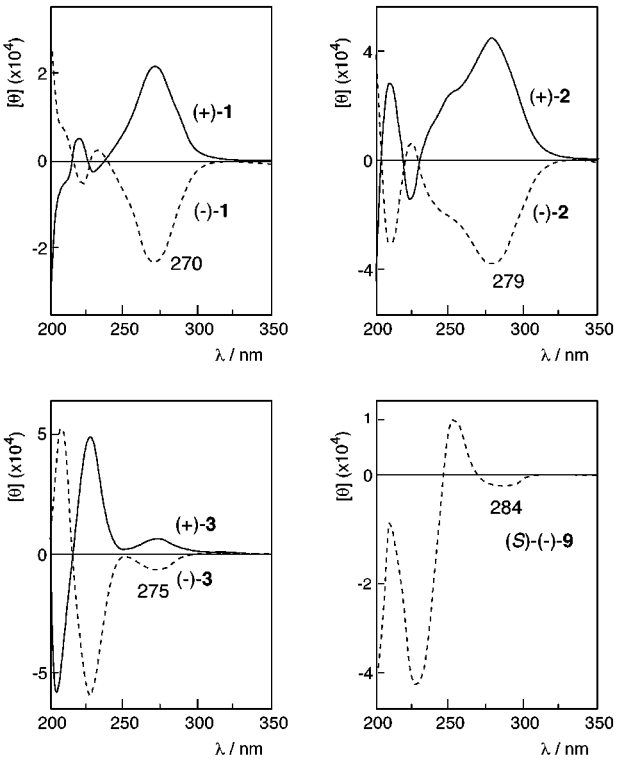


Figure 2. Circular dichroism spectra of optically active selenoxides **1**, **2**, and **3** and sulfoxide (*S*)-(−)-**9** in cyclohexane.

accelerated by the addition of sodium hydroxide, especially in the case of (*S*)-(−)-**1**, whereas the racemization of selenoxide (*R*)-(+)-**10** was not accelerated by the addition of sodium hydroxide (entry 8). These results indicate that the mechanism for racemization of selenoxides (*S*)-(−)-**1**, -**2**, and -**3** in basic solution is not the same as that in acidic media; i.e., racemization in basic media is considered to be caused by the addition of a hydroxide ion to a selenium atom followed by protonation of the oxygen atom to give an achiral hydrate (Scheme 2).

The stabilizing effect of the intramolecular coordination of an amino group to the selenium atom was examined by variable-temperature ^1H NMR measurements (500 MHz). Although methyl protons of the amino group of *rac*-**3** were observed as a singlet signal in acetone-d_6 at room temperature which overlapped with that of acetone, two singlet signals corresponding to the two methyl groups were observed at 188 K, due to coordination of the nitrogen atom to the selenium atom, and ν_{ab} was 359 Hz. The two signals coalesced at 212 K to give a broad singlet, as shown in Figure 5. Similar results were also observed in CD_2Cl_2, and the coalescence temperature was 220 K; the ν_{ab} was 255 Hz at 193 K. On the basis of these observations, the exchange energy of the two methyl groups of *rac*-**3** was estimated[16] to be 9.45 in acetone-d_6 and 9.97 kcal mol^{-1} in CD_2Cl_2. These values include the coordination energy of the amino group to the selenium atom and the rotation energy of the CH_2-N bond or inversion energy on the nitrogen atom.[17] The rotation barrier of the CH_2-N bond (6.7 kcal mol^{-1}) of *N*-cyclohexyl-*N*-methylbenzylamine has been calculated by

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Table 2. First-Order Rate Constants and Half-Lives for Racemization of Optically Active Selenoxides[a]

		$k(s^{-1})$ ($t_{1/2}$ (h))			
entry	conditions	(*S*)-(−)-**1**	(*S*)-(−)-**2**	(*S*)-(−)-**3**	(*R*)-(+)-**10**[b]
1	$CHCl_3$	A[h]	A	A	A
2	MeOH	2.28×10^{-4} (0.846)	4.58×10^{-5} (4.20)	5.58×10^{-6} (34.5)	6.00×10^{-6} (32.1)
3	MeOH + H_2O[c]	2.57×10^{-4} (0.749)	4.96×10^{-5} (3.88)	7.06×10^{-6} (27.3)	6.31×10^{-6} (30.5)
4	MeOH/H_2O (4/1)	1.23×10^{-3} (0.157)	3.03×10^{-4} (0.635)	5.13×10^{-5} (3.76)	3.34×10^{-5} (5.76)
5	MeOH/H_2O (4/1) + HCl[d]	B[i]	B	B	C[j]
6	MeOH/H_2O (4/1) + TsOH[e]	1.59×10^{-3} (0.121)	2.81×10^{-4} (0.685)	6.01×10^{-5} (3.20)	
7	MeOH/H_2O (4/1) + TsOH[f]	C	C	3.57×10^{-3} (0.0539)	
8	MeOH/H_2O (4/1) + NaOH[g]	9.01×10^{-3} (0.021)	5.29×10^{-4} (0.364)	5.49×10^{-5} (3.51)	3.10×10^{-5} (6.21)

[a] In 7 mM solution at 27 °C. [b] Reference 15. [c] H_2O, 30 equiv. [d] HCl, 30 equiv. [e] TsOH, 0.01 equiv. [f] TsOH, 1.4 equiv. [g] NaOH, 30 equiv. [h] A, no racemization was observed even after 5 days. [i] B, selenoxide decomposed. [j] C, racemization was completed within 1 min.

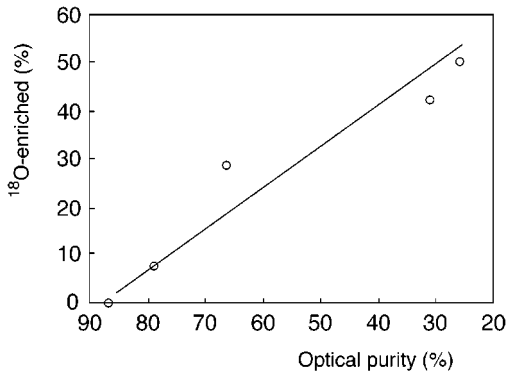


Figure 3. Correlation between optical purity and ^{18}O-labeled selenodies for racemization of selenoxide (*S*)-(−)-**3** in MeOH in the presence of $H_2{}^{18}O$.

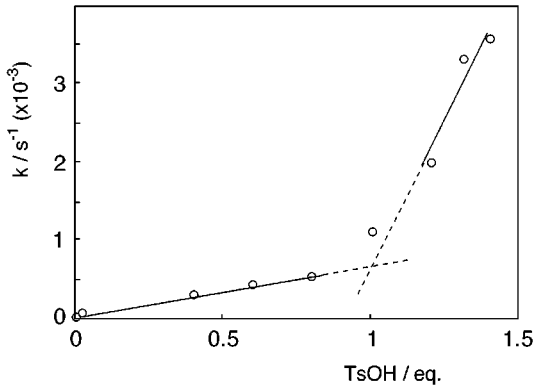


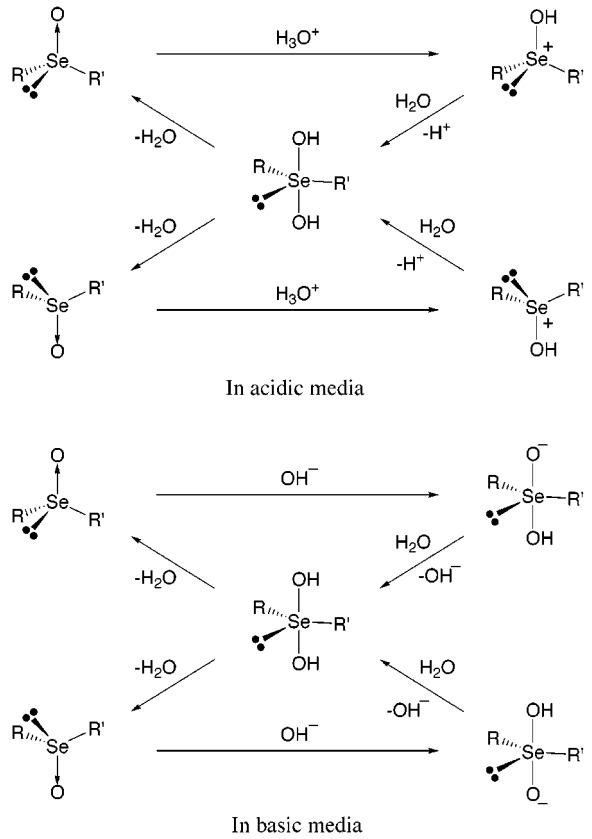
Figure 4. Rate constants for racemization of selenoxide (*S*)-(−)-**3** in MeOH/H_2O (4/1) in the presence of *p*-toluenesulfonic acid.

HF/3-21G to be larger than the inversion energy (3.8 kcal mol^{-1}) on the nitrogen atom.[17] Therefore, the difference between the observed values, obtained from the ^{1}H NMR measurement, and the rotation energy of the CH_2−N bond should represent the coordination energy of the amino group to the selenium atom. Thus, the coordination energy for selenoxide **3** was estimated to be 2.8 kcal mol^{-1} in acetone-d_6 and 3.3 kcal mol^{-1} in CD_2Cl_2. The coordination energy is not so large. Thus, the (dimethylamino)methyl group is considered to be effective at preventing racemization not only thermodynamically but also kinetically.

Conclusion

Asymmetric selenoxides that are configurationally stabilized by intramolecular coordination of an amino group to the selenium atom were optically resolved into their enantiomeric isomers using an optically active column. This is the first example of the isolation of optically pure selenoxides without bulky substituents and also the first example of the isolation of an optically pure alkyl aryl selenoxide. The absolute configuration of the (−)-isomers was assigned to be the *S*-form by comparison of the signs of their specific rotations, their circular dichroism spectra, and their behavior in optical resolution on an optically active column with those of the sulfur analogue. Racemization of optically active selenoxides was accelerated not only in acidic solution but also in basic media. Two different mechanisms for their racemization were proposed in acidic and basic media. The stabilization energy of the selenoxides **3** by intramolecular coordination of an amino group to the selenium atom was estimated to be ca. 3 kcal mol^{-1} on the basis of variable-temperature ^{1}H NMR measurements and ab initio MO calculations.

Scheme 2



Experimental Section

General Procedures. Tetrahydrofuran and hexane were distilled from sodium metal before use. Chloroform and

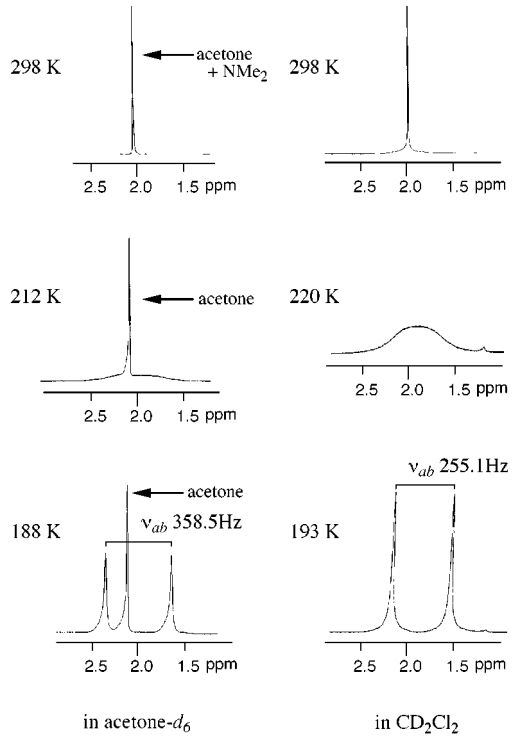


Figure 5. ^{1}H NMR signals of the amino group of variable-temperature NMR spectra for racemic selenoxide *rac*-**3** in acetone-d_6 and in CD_2Cl_2.

dichloromethane were freshly distilled from calcium hydride. Methanol and ethanol were freshly distilled from the magnesium cake. Column chromatography was performed with Merck Kieselgel 60 (70−230 mesh). Gel permeation chromatography (GPC) was performed using JAI LC-08 and LC-908 liquid chromatographs with two JAIGEL-1H columns (20 mm × 600 mm), and the products were eluted with chloroform. All reactions were carried out under nitrogen.^{1}H, ^{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.

2-((Dimethylamino)methyl)bromobenzene. A carbon tetrachloride solution (130 mL) of 2-bromotoluene (40.0 g, 234 mmol) and *N*-bromosuccinimide (50.0 g, 281 mmol) was refluxed for 8.5 h. The solid formed by the reaction was filtered off. After removal of the solvent in vacuo, distillation under reduced pressure gave 2-(bromomethyl)bromobenzene in 94% yield (54.9 g): bp 120−130 °C, 13 mmHg; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.55 (s, 2H), 7.10 (dd, 1H, J = 7.6, 7.6 Hz), 7.24 (dd, 1H, J = 7.6, 7.6 Hz), 7.39 (d, 1H, J = 7.6 Hz), 7.51 (d, 1H, J = 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.4, 124.4, 127.9, 130.0, 131.2, 133.2, 136.9; MS (EI) m/z 248 (M^+), 169, 90. To a benzene solution (250 mL) of 2-(bromomethyl)bromobenzene (20.0 g, 80.6 mmol) and dimethylamine hydrochloride (13.0 g, 159 mmol) was added dropwise triethylamine (18.9 g, 320 mmol), and the solution was refluxed for 19 h. The precipitated solid was filtered off. After removal of the solvent in vacuo, purification by silica gel chromatography (ether/hexane = 2/3) gave 2-((dimethylamino)methyl)bromobenzene in 72% yield (12.3 g): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.29 (s, 6H), 3.51 (s, 2H), 7.09 (dd, 1H, J = 7.6, 7.6 Hz), 7.26 (dd, 1H, J = 7.6, 7.6 Hz), 7.41 (d, 1H, J = 7.6 Hz), 7.52 (d, 1H, J = 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.4, 63.2, 124.6, 127.1, 128.3, 130.9, 132.6, 138.0; MS (EI) m/z 213 (M^+), 169, 135.

2-((Dimethylamino)methyl)phenyl Methyl Selenide (4). To a THF solution (170 mL) of 2-((dimethylamino)methyl)-bromobenzene (9.06 g, 42.3 mmol) was added dropwise *n*-butyllithium solution (1.6 N hexane solution, 52.9 mL, 84.6 mmol) at −20 °C. After the solution was stirred for 10 min, selenium powder (3.34 g, 42.3 mmol) was added by portions to the solution at −20 °C. After the disappearance of selenium powder, methyl iodide (2.64 mL, 42.3 mmol) was added to the solution, and stirring was continued for an additional 7.5 h at −20 °C. 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 by silica gel column chromatography (chloroform) gave selenide **4** in 83% yield (7.97 g): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.21 (s, 6H), 2.24 (s, 3H), 3.45 (s, 2H), 7.10−7.36 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 6.5, 44.8, 64.2, 125.0, 127.7, 128.6, 129.4, 134.7, 139.0; MS (EI) m/z 229 (M^+, ^{80}Se), 214, 170, 134, 91, 58.

***rac*-2-((Dimethylamino)methyl)phenyl Methyl Selenoxide (*rac*-1).** To a methanol solution (380 mL) of selenide **4** (3.91 g, 17.1 mmol) was added dropwise *tert*-butyl hypochlorite (1.90 mL, 17.1 mmol) at −30 °C. After additional stirring for 3 h at −30 °C, the solution was poured into water, and 20 mL of 2 N NaOH solution was added. The solvent was removed in vacuo, and water was added to the residue. The product was extracted with benzene, washed with brine, and dried over magnesium sulfate. After removal of the solvent in vacuo, purification by silica gel column chromatography (dichloromethane/methanol = 5/1) gave the corresponding selenoxide *rac*-**1** in 74% yield (3.09 g): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.23 (s, 6H), 2.62 (s, 3H), 3.41 (d, 1H, J = 13.9 Hz), 3.80 (d, 1H, J = 13.9 Hz), 7.21 (d, 1H, J = 7.4 Hz), 7.40 (dd, 1H, J = 7.4, 7.4 Hz), 7.51 (dd, 1H, J = 7.4, 7.4 Hz), 8.24 (d, 1H, J = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.1, 44.3, 62.8, 125.9, 128.0, 129.0, 130.5, 138.1, 142.6; ^{77}Se NMR (95 MHz, $CDCl_3$) δ 836; IR (neat) ν_{max} 3370, 2950, 2830, 1625, 1460, 1440, 1360, 1240, 1175, 1040, 1030, 840, 790, 760 cm^{-1}; UV (cyclohexane) λ_{max} 219 (ϵ 7.1 × 10^4), 268 (2.3 × 10^4) nm; UV (MeOH) λ_{max} 212 (ϵ 1.0 × 10^4) nm; MS (EI) m/z 245 (M^+, ^{80}Se), 229, 214, 199, 185, 170, 134, 91, 58; HRMS calcd for $C_{10}H_{15}NO^{80}Se$ 245.0319, found 245.0296.

Benzyl 2-((Dimethylamino)methyl)phenyl Selenide (5). To a THF solution (40 mL) of 2-((dimethylamino)methyl)-bromobenzene (2.14 g, 10.0 mmol) was added dropwise *n*-butyllithium solution (1.6 N hexane solution, 12.5 mL, 20.0 mmol) at −30 °C. After the solution was stirred for 10 min, selenium powder (790 mg, 10.0 mmol) was added by portions to the solution at −30 °C. After disappearance of selenium powder, benzyl bromide (1.30 mL, 11.0 mmol) was added to the solution, stirring was continued for 5 h at −20 °C, and the temperature was gradually raised to 10 °C. 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 by silica gel column chromatography (hexane/ethyl acetate = 2/1) gave selenide **5** in 74% yield (2.23 g): mp 46.0−46.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (s, 6H), 3.48 (s, 2H), 4.15 (s, 2H), 7.20−7.58 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.1, 44.7, 64.2, 125.9, 126.6, 127.6, 128.3, 128.8, 129.5, 131.2, 134.3, 138.3, 140.0; MS (EI) m/z 305 (M^+, ^{80}Se), 214, 171, 170, 135, 91, 78, 58.

***rac*-Benzyl 2-((Dimethylamino)methyl)phenyl Selenoxide (*rac*-2).** To a dichloromethane solution (10 mL) of selenide **5** (305 mg, 1.00 mmol) was added by portions *m*-chloroperbenzoic acid (259 mg, 1.50 mmol) at 0 °C. After additional stirring for 30 min at room temperature, the solid formed by the reaction was filtered off, and the filtrate was poured into water. The product was extracted with benzene. The extract was washed with 5% sodium bicarbonate, washed with brine, and dried over magnesium sulfate. After removal of the solvent in vacuo, purification by silica gel column chromatography (ethyl acetate) gave the corresponding selenoxide *rac*-**2** in 81% yield (260 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.29 (s, 6H), 3.31 (d, 1H, J = 13.9 Hz), 3.84 (d, 1H, J = 11.3 Hz), 3.85 (d, 1H, J = 13.9 Hz), 4.19 (d, 1H, J = 11.3 Hz), 7.16−7.79 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.5, 57.6, 63.1, 126.8, 127.9, 128.0, 128.4, 128.6, 130.0, 130.4, 131.5, 138.4, 141.6; ^{77}Se NMR (95 MHz, $CDCl_3$) δ 890; IR (neat) ν_{max} 2340, 1460, 1370, 1250, 1210, 1030, 850, 810, 760, 700 cm^{-1}; UV (cyclohexane) λ_{max} 211 (ϵ 1.3 × 10^4), 276 (2.8 × 10^3) nm; UV (MeOH) λ_{max} 211 (ϵ 1.8 × 10^4), 247 (sh, 7.0 × 10^3) nm; MS (EI)

m/*z* 321 (M^+, ^{80}Se), 230, 214, 135, 91, 78; HRMS calcd for $C_{16}H_{19}NO^{80}Se$ 321.0632, found 321.0590.

2-((Dimethylamino)methyl)diphenyl Selenide (6). To a THF solution (30 mL) of 2-((dimethylamino)methyl)bromobenzene (1.84 g, 8.60 mmol) was added dropwise *n*-butyllithium solution (1.6 N hexane solution, 10.8 mL, 17.2 mmol) at −20 °C. After the solution was stirred for 2 h at −20 °C, a THF solution (10 mL) of diphenyl diselenide (2.68 g, 8.60 mmol) was added dropwise to the solution at −20 °C. The solution was stirred for an additional 21 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 by silica gel column chromatography (chloroform) gave selenide **6** in 49% yield (1.22 g): ^1H NMR (500 MHz, $CDCl_3$) δ 2.23 (s, 6H), 3.51 (s, 2H), 7.02−7.55 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.7, 64.4, 126.0, 127.5, 127.8, 129.2, 129.6, 131.6, 131.9, 134.0, 135.1, 139.5; MS (EI) *m*/*z* 291 (M^+, ^{80}Se), 276, 245, 214, 183, 141, 78, 58.

***rac*-2-((Dimethylamino)methyl)diphenyl Selenoxide (*rac*-3).** To a methanol solution (180 mL) of selenide **6** (2.79 g, 9.60 mmol) was added dropwise *tert*-butyl hypochlorite (1.10 mL, 9.60 mmol) at −30 °C. After additional stirring for 6 h at room temperature, the solution was poured into water, and 20 mL of 2 N NaOH solution was added. The solvent was removed in vacuo, and water was added to the residue. The product was extracted with benzene, washed with brine, and dried over magnesium sulfate. After removal of the solvent in vacuo, purification by silica gel column chromatography (dichloromethane/methanol = 10/1) followed by recrystallization from dichloromethane/hexane gave the corresponding selenoxide *rac*-**3** in 79% yield (2.33 g): mp 132.0−134.0 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.02 (s, 6H), 3.18 (d, 1H, J = 13.9 Hz), 3.58 (d, 1H, J = 13.9 Hz), 7.18−8.46 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.1, 62.8, 127.2, 127.5, 128.3, 128.8, 129.2, 130.5, 130.7, 138.6, 141.5, 144.6; ^{77}Se NMR (95 MHz, $CDCl_3$) δ 879; IR (KBr) ν_{max} 2830, 1610, 1430, 1020, 965, 845, 795, 745, 690 cm^{-1}; UV (cyclohexane) λ_{max} 222 (ϵ 1.4 × 10^4), 261 (3.2 × 10^3) nm; UV (MeOH) λ_{max} 218 (ϵ 1.6 × 10^4), 258 (sh, 4.2 × 10^3) nm; MS (EI) *m*/*z* 307 (M^+, ^{80}Se), 292, 276, 263, 247, 214, 185, 169, 157, 91, 78, 58. Anal. Calcd for $C_{15}H_{17}NOSe$: C, 58.83; H, 4.57; N, 5.59. Found: C, 58.88; H, 4.51; N, 5.66.

Optical Resolution of Racemic Selenoxides by Means of High-Performance Liquid Chromatography Using an Optically Active Column. Optical resolutions of racemic selenoxides *rac*-**1**, -**2**, and -**3** were performed by HPLC using optically active columns packed with amylosecarbamate derivative/silica gel (Daicel Chiralpak AS, 4.6 × 250 mm for an analytical scale and 10 × 250 mm for a preparative scale) eluted by hexane/ethanol (75/25). On a preparative scale, typically, 150 mg of racemic selenoxide was charged to the column. A 50 mg sample of the first-eluted selenoxide and a 50 mg sample of the second-eluted selenoxide were collected, and each of the collected components was charged again to the column, separately. Finally, ca. 10−20 mg of optically pure selenoxides was obtained except for the case of (+)-**3**.

(*S*)-(−)-2-((Dimethylamino)methyl)phenyl Methyl Selenoxide {(*S*)-(−)-1}: 100% ee; $[\alpha]_D$ −120.8 (*c* 0.32, $CHCl_3$); $[\alpha]_{435}$ −313.2 (*c* 0.32, $CHCl_3$); CD (cyclohexane) λ 207 (sh, $[\theta]$ 1.1 × 10^4), 221 (−6.3 × 10^3), 231 (1.8 × 10^3), 270 (−2.4 × 10^4) nm; CD (MeOH) λ 216 ($[\theta]$ 2.6 × 10^3), 234 (−7.3 × 10^3), 247 (−7.0 × 10^3) nm; HRMS calcd for $C_{10}H_{15}NO^{80}Se$ 245.0319, found 245.0315. ^1H NMR, ^{13}C NMR, ^{77}Se NMR, IR, UV, and MS spectra were almost the same as those of the racemic one.

(*R*)-(+)-2-((Dimethylamino)methyl)phenyl Methyl Selenoxide {(*R*)-(+)-1}: 100% ee; $[\alpha]_D$ 119.8 (*c* 0.23, $CHCl_3$); $[\alpha]_{435}$ 296.6 (*c* 0.23, $CHCl_3$); CD (cyclohexane) λ 206 (sh, $[\theta]$ −9.0 × 10^3), 220 (4.7 × 10^3), 229 (−1.5 × 10^3), 270 (2.1 × 10^4) nm; CD (MeOH) λ 214 ($[\theta]$ −4.2 × 10^3), 234 (8.8 × 10^3), 247 (8.5 × 10^3) nm; HRMS calcd for $C_{10}H_{15}NO^{80}Se$ 245.0319, found 245.0292. ^1H NMR, ^{13}C NMR, ^{77}Se NMR, IR, UV, and MS spectra were almost the same as those of the racemic one.

(*S*)-(−)-Benzyl 2-((Dimethylamino)methyl)phenyl Selenoxide {(*S*)-(−)-2}: 100% ee; $[\alpha]_D$ −300.4 (*c* 0.50, $CHCl_3$); $[\alpha]_{435}$ −757.4 (*c* 0.50, $CHCl_3$); CD (cyclohexane) λ 211 ($[\theta]$ −3.0 × 10^4), 225 (8.8 × 10^3), 279 (−3.7 × 10^4) nm; CD (MeOH) λ 205 ($[\theta]$ −1.1 × 10^4), 219 (2.4 × 10^4), 261 (−3.6 × 10^4) nm; HRMS calcd for $C_{16}H_{19}NO^{80}Se$ 321.0632, found 321.0598. ^1H NMR, ^{13}C NMR, ^{77}Se NMR, IR, UV, and MS spectra were almost the same as those of the racemic one.

(*R*)-(+)-Benzyl 2-((Dimethylamino)methyl)phenyl Selenoxide {(*R*)-(+)-2}: 100% ee; $[\alpha]_D$ 299.2 (*c* 0.50, $CHCl_3$); $[\alpha]_{435}$ 791.6 (*c* 0.50, $CHCl_3$); CD (cyclohexane) λ 211 ($[\theta]$ 3.2 × 10^4), 224 (−1.4 × 10^4), 279 (4.3 × 10^4) nm; CD (MeOH) λ 206 ($[\theta]$ 1.9 × 10^4), 220 (−3.1 × 10^4), 265 (4.6 × 10^4) nm; HRMS calcd for $C_{16}H_{19}NO^{80}Se$ 321.0632, found 321.0598. ^1H NMR, ^{13}C NMR, ^{77}Se NMR, IR, UV, and MS spectra were almost the same as those of the racemic one.

(*S*)-(−)-2-((Dimethylamino)methyl)diphenyl Selenoxide {(*S*)-(−)-3}: mp 68.0−69.0 °C; 100% ee; $[\alpha]_D$ −48.1 (*c* 0.26, $CHCl_3$); $[\alpha]_{435}$ −117.8 (*c* 0.26, $CHCl_3$); CD (cyclohexane) λ 208 ($[\theta]$ 5.6 × 10^4), 228 (−6.3 × 10^4), 275 (−7.8 × 10^3) nm; CD (MeOH) λ 208 ($[\theta]$ −1.4 × 10^4), 226 (−6.2 × 10^4), 247 (2.7 × 10^3), 277 (−4.6 × 10^3) nm; HRMS calcd for $C_{15}H_{17}NO^{80}Se$ 307.0475, found 307.0520. ^1H NMR, ^{13}C NMR, ^{77}Se NMR, IR, UV, and MS spectra were almost the same as those of the racemic one.

(*R*)-(+)-2-((Dimethylamino)methyl)diphenyl Selenoxide {(*R*)-(+)-3}: mp 63.0−64.0 °C; 90% ee; $[\alpha]_D$ 37.2 (*c* 0.17, $CHCl_3$); $[\alpha]_{435}$ 86.0 (*c* 0.17, $CHCl_3$); CD (cyclohexane) λ 205 ($[\theta]$ −5.8 × 10^4), 227 (4.9 × 10^4), 276 (5.4 × 10^3) nm; CD (MeOH) λ 208 ($[\theta]$ 1.2 × 10^4), 226 (4.1 × 10^4), 247 (−2.0 × 10^3), 278 (3.1 × 10^3) nm; HRMS calcd for $C_{15}H_{17}NO^{80}Se$ 307.0475, found 307.0500. ^1H NMR, ^{13}C NMR, ^{77}Se NMR, IR, UV, and MS spectra were almost the same as those of the racemic one.

Synthesis of (*S*)-(−)-2-((Dimethylamino)methyl)-4′-methyldiphenyl Sulfoxide {(*S*)-(−)-9}. To an ether solution (125 mL) of $(S)_s$-(−)-menthyl-(−)-*p*-toluenesulfinate (100% ee; 1.47 g, 5.00 mmol)[11,12] was added 2-((dimethylamino)methyl)-phenylmagnesium bromide, prepared from 2-((dimethylamino)methyl)bromobenzene (2.25 g, 10.5 mmol) and magnesium (3.77 g), dropwise at 0 °C.[12,13] After additional stirring for 1 h at room temperature, the mixture was poured into brine. The product was extracted with ether and dried over magnesium sulfate. After removal of the solvent in vacuo, purification by gel permeation chromatography gave (*S*)-(−)-sulfoxide {(*S*)-(−)-**9**} in 90% yield (1.23 g): 91% ee; $[\alpha]_D$ −81.6 (*c* 1.26, $CHCl_3$); $[\alpha]_D$ −105.9 (*c* 1.39, acetone); $[\alpha]_{435}$ −192.9 (*c* 1.26, $CHCl_3$); $[\alpha]_{435}$ −245.3 (*c* 1.39, acetone); CD (cyclohexane) λ 226 ($[\theta]$ −4.2 × 10^4), 252 (1.0 × 10^4), 284 (−2.2 × 10^3) nm; CD (MeCN) λ 226 ($[\theta]$ −7.0 × 10^4), 251 (1.1 × 10^4), 274 (−2.7 × 10^3) nm; CD (MeOH) λ 219 ($[\theta]$ 1.9 × 10^4), 232 (−4.9 × 10^4) nm; ^1H NMR (500 MHz, $CDCl_3$) δ 2.08 (s, 6H), 2.35 (s, 3H), 3.19 (d, 1H, J = 13.3 Hz), 3.70 (d, 1H, J = 13.3 Hz), 7.21 (d, 2H, J = 8.0 Hz), 7.28 (d, 1H, J = 7.6 Hz), 7.38 (dd, 1H, J = 7.6, 7.6 Hz), 7.47 (dd, 1H, J = 7.6, 7.6 Hz), 7.53 (d, 2H, J = 8.0 Hz), 8.06 (d, 1H, J = 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 44.3, 61.1, 125.6, 125.9, 128.5, 129.3, 129.6, 130.4, 137.7, 140.7, 142.9, 144.9; IR (neat) ν_{max} 2930, 1460, 1180, 1040, 820 cm^{-1}; UV (MeCN) λ_{max} 202 (ϵ 4.0 × 10^4), 238 (1.8 × 10^4) nm; UV (MeOH) λ_{max} 206 (ϵ 3.3 × 10^4), 238 (1.9 × 10^4) nm; MS (EI) *m*/*z* 274 ($M^+ + 1$), 213, 134, 91. Anal. Calcd for $C_{16}H_{19}NOS$: C, 70.29; H, 7.00; N, 5.12. Found: C, 70.04; H, 7.05; N, 5.03.

Kinetic Studies for the Racemization of Optically Active Selenoxides. The kinetic studies for racemization of optically active selenoxides **1**−**3** were carried out in 7 mM solution at 27 °C, and the rates of racemization were calculated on the basis of their specific rotations.

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