# JOC*Article*

Optically Active Seleninamides: Isolation, Absolute Configuration, and Racemization Mechanism

Yusuke Nakashima, Toshio Shimizu,* Kazunori Hirabayashi, and Nobumasa Kamigata*

Department of Chemistry, Graduate School of Science, Tokyo Metropolitan University, Minami-ohsawa, Hachioji, Tokyo 192-0397, Japan

kamigata-nobumasa@c.metro-u.ac.jp

R = *t*-Bu, 1-Ad, 2,4,6-Me$_3$C$_6$H$_2$,
2,4,6-*i*-Pr$_3$C$_6$H$_2$
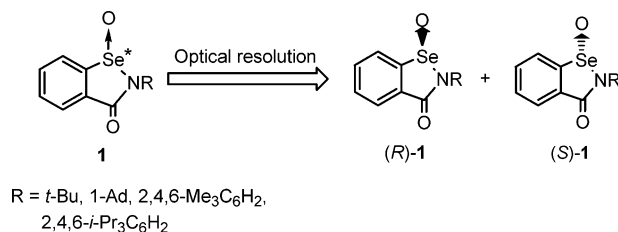
Optically active seleninamides were obtained for the first time by chromatographic resolution on an optically active column. The absolute configurations of the optically active seleninamides were determined by comparing their chiroptical properties with those of analogous sulfinamides, the stereochemistry of which was determined by transformation into chiral sulfoxides of known configurations. The optically active seleninamides were found to racemize in solution. Kinetic studies of the racemization and theoretical studies clarified that the racemization of the optically active seleninamides in solution proceeds via hypervalent hydrates formed by the reaction with water.

Introduction

Many optically active tricoordinated selenium and tellurium compounds, such as oxides, onium salts, ylides, and imides, have been isolated and their properties were determined.[1] Recently, we have isolated optically active chalcogenic acids and clarified their properties. Optically active areneseleninic acids[2,3] and an arenetellurinic acid[4] were obtained by chromatographic resolution on optically active columns, whereas chiral methaneseleninic acid was obtained by chiral crystallization.[5] Chalcogeninamides, which are the derivatives of chalcogenic acids, are also tricoordinated chalcogen compounds and have chiral centers on the chalcogen atoms. Many reports on the isolation and properties of optically active sulfinamides have been published.[6] However, there is no report on the chiral selenium analogues. Moreover, there are few reports on the preparation of racemic acyclic seleninamides.[7] The scarcity seems to be due to their instability toward hydrolysis. By contrast, cyclic seleninamides having electron-withdrawing substituents are known to be more stable toward hydrolysis.[8]

We examined the optical resolution of cyclic seleninamides by means of liquid chromatography on an optically active column and succeeded in obtaining optically active seleninamides for the first time. The absolute configurations of the chiral seleninamides were determined. We describe herein the first isolation of optically active seleninamides together with their absolute configurations and stability toward racemization.

* Address correspondence to this author. Phone: +81 (426) 77-2556. Fax: +81 (426) 77-2525.

(1) For reviews, see: (a) Shimizu, T.; Kamigata, N. *Rev. Heteroatom Chem.* **1998**, *18*, 11. (b) Shimizu, T.; Kamigata, N. *Org. Prep. Proced. Int.* **1997**, *29*, 603.

(2) Shimizu, T.; Watanabe, I.; Kamigata, N. *Angew. Chem.*, *Int. Ed.* **2001**, *40*, 2460.

(3) Shimizu, T.; Nakashima, Y.; Watanabe, I.; Hirabayashi, K.; Kamigata, N. *J. Chem. Soc.*, *Perkin Trans. 1* **2002**, 2151.

(4) Nakashima, Y.; Shimizu, T.; Hirabayashi, K.; Kamigata, N. *Org. Lett.* **2004**, *6*, 2575.

(5) Nakashima, Y.; Shimizu, T.; Hirabayashi, K.; Kamigata, N.; Yasui, M.; Nakazato, M.; Iwasaki, F. *Tetrahedron Lett.* **2004**, *45*, 2301.

(6) For books, see: (a) Reid, D. H. *Organic Compounds of Sulfur, Selenium, and Tellurium*; The Chemical Society Burlington House: London, UK, 1973;Vol. 2. (b) *The Chemistry of Sulphinic Acids, Esters and their Derivatives*; Patai, S., Ed.; John Wiley & Sons: Chichester, England, UK, 1990.

(7) (a) Banks, C. K.; Hamilton, C. S. *J. Am. Chem. Soc.* **1940**, *62*, 1859. (b) Davis, F. A.; Kluger, E. W. *J. Am. Chem. Soc.* **1976**, *98*, 302.

(8) (a) Kamigata, N.; Iizuka, H.; Izuoka, A.; Kobayashi, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2179. (b) Kamigata, N.; Takata, M.; Matsuyama, H.; Kobayashi, M. *Sulfur Lett.* **1986**, *5*, 1. (c) Kloc, K.; Mlochowski, J.; Syper, L. *Liebigs Ann. Chem.* **1989**, 811. (d) Mlochowski, J.; Kloc, K.; Syper, L.; Inglot, A. D.; Piasecki, E. *Liebigs Ann. Chem.* **1993**, 1239. (e) Reich, H. J.; Jasperse, C. P. *J. Am. Chem. Soc.* **1987**, *109*, 5549.

SCHEME 1

1a: R = *t*-Bu
1b: R = 1-Ad
1c: R = 2,4,6-Me$_3$C$_6$H$_2$
1d: R = 2,4,6-*i*-Pr$_3$C$_6$H$_2$
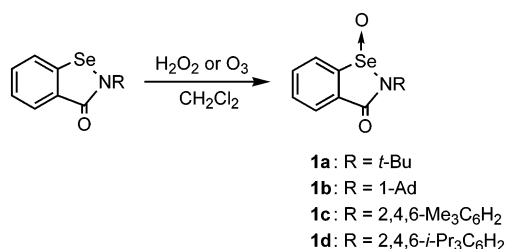
Results and Discussion

Preparation and Optical Resolution of Seleninamides. Seleninamides **1a–d** having various bulky substituents were prepared from corresponding selenenamides by oxidation with hydrogen peroxide or ozone in yields of 70%, 92%, 94%, and 73%, respectively (Scheme 1).

When a racemic sample of seleninamide **1a** was subjected to chromatography on a chiral column (4.6 × 250 mm) packed with amylose carbamate derivative-silica gel at an analytical scale with hexane/2-propanol (3/1) as the eluent, two peaks corresponding to two enantiomers were observed on the chromatogram (Figure 1).
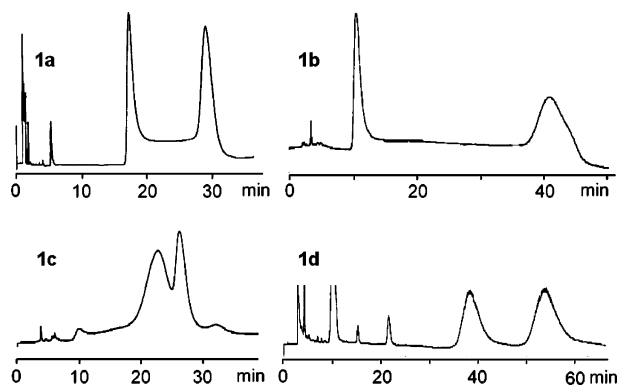

FIGURE 1. Chromatographic resolution of racemic seleninamides **1a–d** on an optically active column (Daicel Chiralpak AS) by means of HPLC at an analytical scale. Eluent: hexane/2-propanol (3/1) for **1a–c**; hexane/ethanol (99/1) for **1d**.

Similarly, two separate enantiomers were observed on the chromatograms of seleninamides **1b–d**. In the case of **1a** and **1b**, the intensities between the two peaks were not reduced to the baseline on the chromatograms, indicating that resolution and racemization of the seleninamides occurred competitively in the column. In the case of **1d** that had a particularly bulky substituent, satisfactory separation was observed, indicating that the racemization of seleninamide may be suppressed by the bulky substituent.

The optical resolution of the seleninamides at a preparative scale was examined on a larger column of the same type (10 × 250 mm). Seleninamide **1d** was subjected to chromatography on the column, and the first and second fractions containing each enantiomer were collected and the solvents were removed under reduced pressure. The enantiomeric excess of each enantiomer was determined by HPLC analysis. As a result, optically pure seleninamide (−)-**1d** {[α]$_D^{29}$ −103 (*c* 0.091, dichloromethane); [α]$_{435}^{29}$ −202 (*c* 0.091, dichloromethane)}
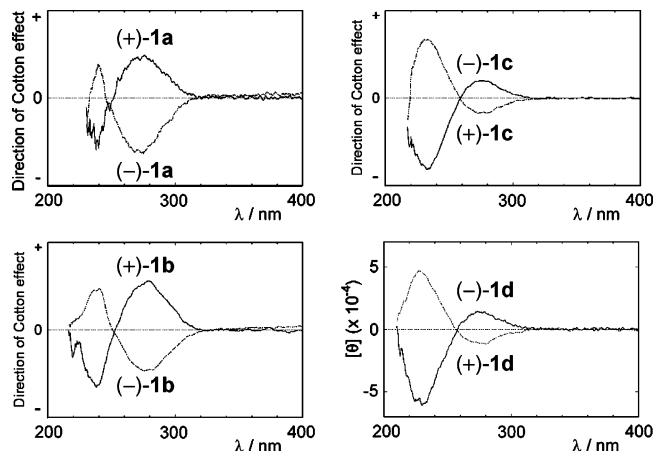

FIGURE 2. Circular dichroism spectra of optically active seleninamides **1a–c** in hexane/2-propanol (3/1) and **1d** in 2-propanol.

was obtained from the first-eluted fraction and (+)-**1d** was obtained from the second-eluted fraction in 68% ee, and the enantiomeric excess could be improved to 82% {[α]$_D^{29}$ +69.6 (*c* 0.116, dichloromethane); [α]$_{435}^{29}$ +158 (*c* 0.116, dichloromethane)} by repeated chromatography. Similarly, seleninamides **1a–c** were also resolved by chromatography, and eluates that showed positive and negative optical rotations were obtained. The enantiomers of seleninamides **1a–c** racemized rapidly in solution and concentration of the eluates caused the racemization. On the other hand, the enantiomers of seleninamide **1d** did not racemize during concentration of the eluates. Therefore, the optical purities of the enantiomers of seleninamides **1a–c** could not be determined.

Chiroptical Properties and Absolute Configurations of Optically Active Seleninamides. Each first-eluted enantiomer of **1a** and **1b**, which have alkyl substituents on the nitrogen atoms, showed positive optical rotation and each second-eluted enantiomer showed negative optical rotation. On the other hand, the first-eluted enantiomers of **1c** and **1d** with aryl substituents showed negative optical rotations and the second-eluted enantiomers showed positive optical rotations. In the circular dichroism spectra, the first-eluted optically active seleninamides (+)-**1a**, (+)-**1b**, (−)-**1c**, and (−)-**1d** showed positive first Cotton effects at around 270 nm and negative second Cotton effects at around 230 nm, and (−)-**1a**, (−)-**1b**, (+)-**1c**, and (+)-**1d** obtained from respective second fractions showed negative first Cotton effects and positive second Cotton effects in the corresponding regions, as shown in Figure 2.

If the optically active seleninamides **1** could be transformed into chiral selenoxides of known configurations, the absolute configurations of **1** would be determined. However, this is difficult because the optically active selenoxides are generally unstable toward racemization.[9] Thus, the absolute configurations of the seleninamides were determined by comparing their chiroptical properties with those of the enantiomers of sulfinamides **2a** and **2b**, which have alkyl and aryl substituents, respectively.

(9) (a) Davis, F. A.; Billmers, J. M.; Stringer, O. D. *Tetrahedron Lett.* **1983**, *24*, 3191. (b) Davis, F. A.; Stringer, O. D.; McCauley, J. P. *Tetrahedron* **1985**, *41*, 4747. (c) Shimizu, T.; Kobayashi, M.; Kamigata, N. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3761.

TABLE 1. Chiroptical Properties and Absolute Configurations of Optically Active Seleninamides (1a−d) and Sulfinamides (2a, 2b)

| compd	order of elution	ee (%)	$[\alpha]_{435}$	Cotton effect/nm (sign)	absolute configuration
1a	first[a]		$+^c$	276 (+), 237 (−)[c]	R
	second[a]		$-^c$	275 (−), 238 (+)[c]	S
1b	first[a]		$+^c$	279 (+), 237 (−)[c]	R
	second[a]		$-^c$	279 (−), 238 (+)[c]	S
1c	first[a]		$-^c$	275 (+), 231 (−)[c]	R
	second[a]		$+^c$	274 (−), 230 (+)[c]	S
1d	first[a]	100	-103 (c 0.091)[d]	273 ($[\theta]$ 1.45×10^4), 230 ($[\theta]$ -6.06×10^4)[e]	R
	second[a]	82	$+158$ (c 0.116)[d]	273 ($[\theta]$ -1.16×10^4), 228 ($[\theta]$ 4.70×10^4)[e]	S
2a	first[b]	100	$+133$ (c 0.050)[e]	284 ($[\theta]$ 2.31×10^4), 248 ($[\theta]$ -3.90×10^4)[e]	R
2b	first[a]	54	$+9.3$ (c 0.037)[e]	277 ($[\theta]$ -1.76×10^4), 232 ($[\theta]$ 3.58×10^4)[e]	S

[a] Chiralpak AS column was used. [b] Chiralcel OD column was used. [c] In hexane/2-propanol (3/1). [d] In dichloromethane. [e] In 2-propanol.

TABLE 2. First-Order Rate Constants and Half-Lives for Racemization of Optically Active Seleninamides 1a−d[a]

run	seleninamide	solvent	$10^5 c$ (mol L^{-1})	$10^5 k_1$ (s^{-1})	$t_{1/2}$ (min)
1	(R)-(+)-**1a**	hexane/2-propanol (3/1)	2.13	50.6	22.8
2	(R)-(+)-**1b**	hexane/2-propanol (3/1)	8.22	58.9	19.6
3	(R)-(−)-**1c**	hexane/2-propanol (3/1)	4.98	37.7	30.6
4	(R)-(−)-**1d**	hexane/2-propanol (3/1)	3.31	9.47	122
5	(R)-(−)-**1d**	hexane/2-propanol (3/1)	1.36	10.5	110
6	(R)-(−)-**1d**	dichloromethane	2.45	—[b]	—[b]
7	(R)-(−)-**1d**	chloroform	7.55	0.301	3840
8	(R)-(+)-**1b**	hexane/2-propanol/H$_2$O (73/24/3)	4.28	378	3.05
9	(R)-(+)-**1b**	hexane/2-propanol/D$_2$O (73/24/3)	4.21	132	8.76

[a] At 26 ± 2 °C. [b] No racemization was observed after 2 days.

Optically active sulfinamides (+)-**2a** {100% ee; $[\alpha]_D^{27}$ +72.8 (c 0.138, 2-propanol); $[\alpha]_{435}^{26}$ +133 (c 0.050, 2-propanol)} and (+)-**2b** {54% ee; $[\alpha]_D^{29}$ +2.2 (c 0.037, 2-propanol); $[\alpha]_{435}^{29}$ +9.3 (c 0.037, 2-propanol)} were obtained by chromatographic resolution of the racemic samples on chiral columns. The reactions of (+)-**2a** and (+)-**2b** with


2a: R = 1-Ad
2b: R = 2,4,6-Me$_3$C$_6$H$_2$

3a: R = 1-Ad
3b: R = 2,4,6-Me$_3$C$_6$H$_2$
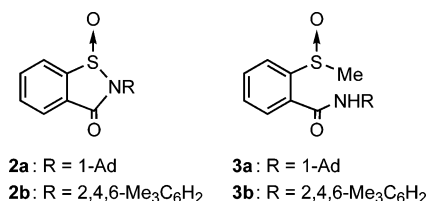
methylmagnesium chloride afforded corresponding optically active sulfoxides (+)-**3a** {99% ee; $[\alpha]_D^{26}$ +70 (c 0.24, ethanol)} and (−)-**3b** {52% ee; $[\alpha]_D^{26}$ −56 (c 0.018, ethanol)}, respectively. Mislow and co-workers reported that (R)-methyl p-tolyl sulfoxide showed positive specific rotation in ethanol.[10] Therefore, the absolute configurations of sulfoxides (+)-**3a** and (−)-**3b** were determined to be R and S, respectively, on the basis of the specific rotations. This result indicates that the absolute configurations of (+)-**2a** and (+)-**2b** are R and S, respectively, because the sulfoxides are obtained from sulfinamides with inversion of the stereochemistry.[11] Sulfinamides (R)-(+)-**2a** showed a positive first Cotton effect at 284 nm and (S)-(+)-**2b** showed a negative first Cotton effect at 277 nm in the circular dichroism spectra. These first Cotton effects corresponded well with those of the opti-

(10) Mislow, K.; Green, M. M.; Laur, P.; Melillo, J. T.; Simmons, T.; Ternay, A. L., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 1958.
(11) Colonna, S.; Giovini, R.; Montanari, F. *Chem. Commun.* **1968**, 865.

cally active seleninamides **1**. Thus, the absolute configurations of the optically active seleninamides **1** were determined as shown in Table 1 on the basis of the relationship between the absolute configurations and chiroptical properties of the optically active sulfinamides **2**; seleninamides (+)-**1a**, (+)-**1b**, (−)-**1c**, and (−)-**1d** were determined to be R and (−)-**1a**, (−)-**1b**, (+)-**1c**, and (+)-**1d** were determined to be S.

Stability of Optically Active Seleninamides. When optically pure (R)-(−)-**1d** was stored in powdered form under nitrogen at room temperature, its optical purity was decreased to 88% ee after 3 days, although no decomposition was observed. This means that the racemization of (R)-(−)-**1d** occurred. Seleninamide (R)-(−)-**1d** was stable toward racemization in dichloromethane at room temperature, whereas (R)-(−)-**1d** gradually racemized in chloroform at 26 °C or in hexane/2-propanol (3/1) at 25 °C, and the rate of the racemization showed a good linear relationship with first-order rate plots ($k_1 = 3.01 \times 10^{-6}$ and 9.47×10^{-5} s^{-1}, respectively). Then, the kinetics of the racemization of the optically active seleninamides **1a−d** was examined to clarify the racemization mechanism. The racemization of the optically active seleninamides was observed under various conditions and showed a good linear relationship with first-order rate plots in all cases. The first-order rate constants and the half-lives for the racemization of the seleninamides are summarized in Table 2. The rate constant of (R)-(−)-**1d**, which has a particularly bulky substituent, is smaller than those of seleninamides **1a−c** in the same solvent (runs 1−4). Little difference was observed between the rate constant of (R)-(−)-**1d** at high concentration and that at low concentration (runs 4 and 5), indicating that intermolecular reaction does not take place in the racemization under the given conditions. The

SCHEME 2. Racemization Mechanism of Optically Active Seleninamides in Solution

SCHEME 3

$\Delta G = 26.0$ kcal mol^{-1} for **5**
= 13.0 kcal mol^{-1} for **4**

5: Ch = S
4: Ch = Se
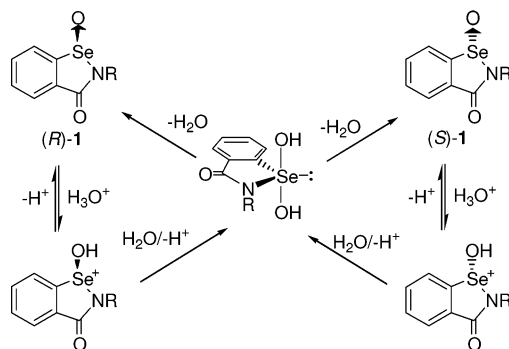
rate constant $(3.78 \times 10^{-3} \text{ s}^{-1})$ of (R)-(+)-**1b** in hexane/2-propanol/H$_2$O (73/24/3) is much larger than that in hexane/2-propanol (3/1) $(5.89 \times 10^{-4} \text{ s}^{-1})$ (runs 2 and 8). These results show that a small amount of water causes the racemization of the optically active seleninamides. Moreover, the rate constant of (R)-(+)-**1b** in hexane/2-propanol/H$_2$O (73/24/3) is approximately three times as large as that in hexane/2-propanol/D$_2$O (73/24/3) (runs 8 and 9), indicating that there is a primary kinetic isotope effect in the racemization and the rate-controlling step is the protonation to seleninamides by water. Vertex inversion is also the first-order racemization mechanism of tricoordinated optically active chalcogen compounds.[12] However, the barrier for vertex inversion of a model molecule, seleninamide **4**, was estimated to be 69 kcal mol^{-1} by MO calculation (MP2[13]/LANL2DZ[14]), which is too high for the racemization to occur at room temperature. Therefore, the racemization of the optically active seleninamides is concluded to proceed via an achiral hypervalent hydrate (selenurane) that is formed by the addition of water to seleninamide (Scheme 2). The difference between the stability of (R)-(−)-**1d** in dichloromethane and that in chloroform is probably due to the

4
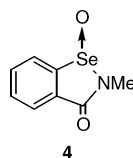
presence of a small amount of hydrogen chloride in chloroform, which causes the protonation of (R)-(−)-**1d** and accelerates the racemization. The racemization of the
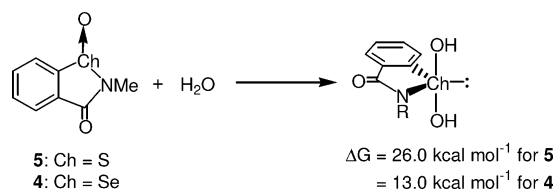
(R)-(−)-**1d** powder is probably due to residual water that could not be removed under reduced pressure. Residual water was detected in the ^{1}H NMR spectrum of the sample.

By contrast, optically active sulfinamide (R)-(+)-**2a** was stable toward racemization both in the solid state and in 2-propanol/H$_2$O (4/1) solution at room temperature. The difference in stability between the optically active sulfinamides and the seleninamides is explained by the ability to form the hypervalent chalcogenurane form, which is the intermediate for the racemization. The energy changes involved in the addition of water to the model molecules of sulfinamide **5** and seleninamide **4** to give hypervalent chalcogenuranes were estimated to be 26.0 and 13.0 kcal mol^{-1}, respectively, by MO calculations (MP2/LANL2DZ) (Scheme 3). These results show that the seleninamide forms an achiral selenurane more readily than the sulfinamide.

Conclusion

The isolation of optically active seleninamides was accomplished for the first time by chromatographic resolution on an optically active column and their absolute configurations were determined. It was found that the optically active seleninamides are unstable toward racemization, in contrast with the high stability of the optically active sulfinamides. It was also found that steric protection by bulky substituents is effective in suppressing the racemization. Kinetic studies of the racemization and theoretical studies clarified that the racemization of the optically active seleninamides in solution proceeds via hypervalent hydrates formed by the reaction with a small amount of water in the solvents. The difference in stability between the optically active sulfinamides and the seleninamides is due to the ability to form the hypervalent chalcogenurane form.

Experimental Section

General. Tetrahydrofuran (THF) and ether were distilled from sodium benzophenone ketyl before use. Dichloromethane, chloroform, hexane, and 2-propanol were distilled from CaH$_2$ before use.

General Procedure for Preparation of Selenenamides. To an ether (6 mL) solution of amine (2 mmol) and triethylamine (4 mmol) was slowly added an ether (6 mL) solution of 2-(chloroseleno)benzoyl chloride[8a] (2 mmol) over 30 min, and the mixture was stirred for an additional 3 h. In the case of using 2,4,6-triisopropylaniline as amine, the mixture was refluxed for an additional 4 h. The solvent was removed under

(12) (a) Andersen, K. K.; Folly, J. W.; Perkins, T. I.; Gaffield, W.; Papanikolau, N. E. *J. Am. Chem. Soc.* **1964**, *86*, 5637. (b) Zhao, S.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135. (c) Darwish, D.; Tomilson, R. L. *J. Am. Chem. Soc.* **1968**, *90*, 5938. (d) Campbell, S. J.; Darwish, D. *Can. J. Chem.* **1974**, *52*, 2953. (e) Moriyama, M.; Oae, S.; Numata, T.; Furukawa, N. *Chem. Ind.* **1976**, 163. (f) Andersen, K. K.; Caret, R. L.; Ladd, D. L. *J. Org. Chem.* **1976**, *41*, 3096. (g) *The Chemistry of the Sulphonium Group*; Stirling, C. J., Patai, S., Eds.; Wiley: New York, 1981. (h) Day, J.; Cram, D. J. *J. Am. Chem. Soc.* **1965**, *87*, 4398. (i) Moriyama, M.; Yoshimura, T.; Furukawa, N.; Numata, T.; Oae, S. *Tetrahedron* **1976**, *32*, 3003. (j) Kamigata, N.; Taka, H.; Matsuhisa, A.; Matsuyama, H.; Shimizu, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2257. (k) Kamigata, N.; Taka, H.; Matsuhisa, A.; Shimizu, T. *J. Phys. Org. Chem.* **1995**, *8*, 139. (l) Shimizu, T.; Seki, N.; Taka, H.; Kamigata, N. *J. Org. Chem.* **1996**, *61*, 6013. (m) Shimizu, T.; Matsuhisa, A.; Kamigata, N.; Ikuta, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1805. (n) Shimizu, T.; Kamigata, N. *Rev. Heteroatom Chem.* **1998**, *18*, 11. (o) Shimizu, T.; Kamigata, N.; Ikuta, S. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1469.

(13) (a) Moeller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618. (b) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab initio Molecular Orbital Theory*; Wiley: New York, 1986; Chapter 2.9.3.

(14) (a) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284. (b) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270.

reduced pressure and the residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate = 4/1).

2-*tert*-Butyl-1,2-benzisoselenazol-3(2*H*)-one.[8d] Yield 93%; mp 137−138 °C (pale orange needles from dichloromethane/ethyl acetate); ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.68 (9H, s), 7.40 (1H, dd, *J* = 7.90, 6.40 Hz), 7.53−7.60 (2H, m), 7.96 (1H, d, *J* = 7.96 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 28.9, 58.6, 123.2, 125.7, 128.1, 129.8, 131.3, 136.9, 166.8; ^{77}Se NMR (95 MHz, CDCl$_3$) δ 860; MS (EI, 70 eV) *m/z* 255 (M$^+$, [80]Se), 198 (M$^+$ − ^{t}Bu, [80]Se), 196 (M$^+$ − ^{t}Bu, [78]Se); IR (KBr) 1589 (C=O), 1442, 1342 cm^{-1}. Anal. Calcd for C$_{11}$H$_{13}$NOSe: N, 5.51; C, 51.98; H, 5.15. Found: N, 5.59; C, 51.84; H, 5.15.

General Procedure for Preparation of Seleninamides 1a and 1b. To a dichloromethane (3 mL) solution of selenenamide (2 mmol) was added 30% hydrogen peroxide (2.4 mmol) at 0 °C, and the mixture was stirred for an additional 2 h. The precipitated product was filtered off and dried under reduced pressure.

2-*tert*-Butyl-1,2-benzisoselenazol-3(2*H*)-one 1-Oxide (1a).[8d] Yield 70%; mp 114−115 °C (colorless needles from acetonitrile); ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.76 (9H, s), 7.73 (1H, dd, *J* = 7.33, 7.00 Hz), 7.66 (1H, dd, *J* = 7.33, 7.00 Hz), 7.81 (1H, d, *J* = 7.00 Hz), 7.97 (1H, d, *J* = 7.00 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 29.9, 59.0, 126.4, 127.7, 132.2, 132.7, 133.6, 142.7, 168.0; ^{77}Se NMR (95 MHz, CDCl$_3$) δ 1081; MS (EI, 30 eV) *m/z* 270 (M$^+$ − 1, [80]Se), 268 (M$^+$ − 1, [78]Se), 255 (M$^+$ − O, [80]Se), 253 (M$^+$ − O, [78]Se), 199; IR (KBr) 1625 (C=O), 1567, 1459, 1340, 1219, 827 (Se=O), 744, 669 cm^{-1}; UV (hexane/2-propanol = 3/1) λ_{max} 274 (sh, ε 2.64 × 10^3), 232 (sh, ε 1.11 × 10^4), 201 (ε 3.32 × 10^4) nm.

General Procedure for Preparation of Seleninamides 1c and 1d. Ozone was bubbled into a dichloromethane (40 mL) solution of selenenamide (1 mmol) at −20 °C for 30 min, and removal of the solvent under reduced pressure afforded the product.

2-{2,4,6-Trimethylphenyl}-1,2-benzisoselenazol-3(2*H*)-one 1-Oxide (1c). Yield 94%; mp 121 °C (colorless powder; dec); ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.14 (3H, s), 2.31 (3H, s), 2.32 (3H, s), 6.97 (1H, s), 7.01 (1H, s) ,7.82−7.88 (2H, m), 8.13−8.16 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ 18.5, 18.6, 21.0, 127.8, 128.6, 129.2, 129.5, 129.8, 129.9, 133.3, 134.5, 136.0, 139.0, 139.3, 144.4, 166.8; ^{77}Se NMR (95 MHz, CDCl$_3$) δ 1102; MS (EI, 30 eV) *m/z* 333 (M$^+$, [80]Se), 317 (M$^+$ − O, [80]Se), 300, 298, 133; IR (KBr) 2908, 1686 (C=O), 1316, 1294, 853 (Se=O), 745 cm^{-1}; UV (hexane/2-propanol = 3/1) λ_{max} 270 (ε 3.30 × 10^3), 215 (ε 2.43 × 10^4) nm; HRMS (30 eV) *m/z* 333.0279 (C$_{16}$H$_{15}$NO$_2$[80]Se requires 333.0268).

Optical Resolution of Seleninamide 1a−d. A racemic sample of **1a−d** (10−20 mg) in eluent (0.5 mL) was charged to a chiral column packed with amylase carbamate derivative silica gel (Daicel Chiralpak AS; 10 × 250 mm) and eluted with hexane containing 25 (for **1a−c**) and 2 (for **1d**) vol % of 2-propanol at a flow rate of 1.5 mL min^{-1}. The eluates containing about 3−5 mg of optically active seleninamides were collected from the first eluted portions and second portions, respectively. In the case of **1d**, the specific rotations and the circular dichroism spectra were measured after removal of the solvents under reduced pressure. In the case of **1a−c** the optical rotations and the circular dichroism spectra were measured in the eluates because concentration of the eluates caused racemization. The chemical structures of **1a−c** were confirmed by ^{1}H NMR spectra after concentration.

Compound (*R*)-(−)-1d. 100% ee; mp 223 °C (colorless powder; dec); [α]$_D^{29}$ −103 (*c* 0.091, dichloromethane); [α]$_{435}^{29}$ −202 (*c* 0.091, dichloromethane); CD (2-propanol) 273 ([θ] 1.45 × 10^4), 230 ([θ] −6.06 × 10^4) nm. ^{1}H, ^{13}C NMR, MS, and IR spectra were almost the same as those of the racemic sample.

Compound (*S*)-(+)-1d. 82% ee; mp 201 °C (colorless powder; dec); [α]$_D^{29}$ +69.6 (*c* 0.116 dichloromethane); [α]$_{435}^{29}$ +158 (*c* 0.116 dichloromethane); CD (2-propanol) 273 ([θ]

−1.16 × 10^4), 228 ([θ] 4.70 × 10^4) nm. ^{1}H, ^{13}C NMR, MS, and IR spectra were almost the same as those of the racemic sample.

N,N′-Bis(1-adamantyl)-2,2′-dithiodibenzamide. To a dichloromethane (20 mL) solution of 1-adamantanammonium chloride (1.32 g, 7.00 mmol) and triethylamine (1.96 mL, 14.0 mmol) was slowly added a dichloromethane (50 mL) solution of 2,2′-dithiodibenzoyl chloride[15] (1.03 g, 3.00 mmol) over 15 min. After the mixture was stirred for 5.5 h, solvent was evaporated and 1 M HCl (50 mL) was added to the residue, then the mixture was stirred for 1 h. The product precipitated was filtered, washed with water, and dried in vacuo (3.68 g). Yield 98%; mp 162 °C (colorless needles from acetone/ethyl acetate; dec); ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.72 (3H, d, *J* = 12.9 Hz), 1.74 (3H, d, *J* = 12.9 Hz), 2.14 (9H, s), 5.76 (1H), 7.19 (1H, dd, *J* = 7.95, 7.60 Hz), 7.31 (1H, dd, *J* = 7.60, 7.65 Hz), 7.43 (1H, d, *J* = 7.65 Hz), 7.73 (1H, d, *J* = 7.95 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 29.5, 36.3, 41.6, 52.9, 126.3, 127.3, 127.7, 130.7, 136.0, 136.3, 166.9; MS (EI, 30 eV) *m/z* 570 (M$^+$ − 2), 285, 135; IR (KBr) 3314 (NH), 2904, 1627 (C=O), 1541, 1307, 741 cm^{-1}.

2-{1-Adamantyl}-1,2-benzisothiazol-3(2*H*)-one. To a dichloromethane (20 mL) solution of N,N′-bis(1-adamantyl)-2,2′-dithiodibenzamide (573 mg, 1.00 mmol) was slowly added a dichloromethane (3 mL) solution of bromine (0.052 mL, 1.0 mmol) and the solution was stirred for an additional 15 h. To the reaction mixture was added activated basic alumina (4 g) followed by 3 h of stirring. The solvent was evaporated, and the residue was purified by alumina column chromatography (chloroform) (478 mg). Yield 84%; mp 174−175 °C (colorless prisms from acetone); ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.74 (3H, d, *J* = 11.8 Hz), 1.80 (3H, d, *J* = 11.8 Hz), 2.21 (3H, s), 2.46 (6H, s), 7.35 (1H, dd, *J* = 7.95, 7.00 Hz), 7.50 (1H, d, *J* = 7.90 Hz), 7.56 (1H, dd, *J* = 7.90, 7.00 Hz), 7.95 (1H, d, *J* = 7.95 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 29.9, 36.1, 40.5, 59.7, 119.7, 124.9, 126.0, 127.1, 131.1, 139.8, 165.3; MS (EI, 30 eV) *m/z* 285 (M$^+$), 151, 135; IR (KBr) 2908, 1647 (C=O), 1448, 1301, 748 cm^{-1}. Anal. Calcd for C$_{17}$H$_{19}$NOS: N, 4.91; C, 71.54; H, 6.71. Found: N, 4.88; C, 71.11; H, 6.70.

2-{1-Adamantyl}-1,2-benzisothiazol-3(2*H*)-one 1-Oxide (2a). Ozone was bubbled into a dichloromethane (30 mL) solution of 2-{1-adamantyl}-1,2-benzisoselenazol-3(2*H*)-one (114 mg, 0.40 mmol) at −20 °C for 8 min. Removal of the solvent under reduced pressure afforded **2a** (104 mg). Yield 86%; mp 172−173 °C (colorless prisms from dichloromethane/hexane); ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.74 (3H, d, *J* = 12.2 Hz), 1.81 (3H, d, *J* = 12.2 Hz), 2.21 (3H, s), 2.46 (3H, d, *J* = 11.3 Hz), 2.51 (3H, d, *J* = 11.3 Hz), 7.69 (1H, dd, *J* = 7.30, 7.48 Hz), 7.74 (1H, dd, *J* = 7.65, 7.48 Hz), 7.80 (1H, d, *J* = 7.65 Hz), 7.89 (1H, d, *J* = 7.30 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 29.8, 36.0, 41.1, 60.2, 124.2, 125.6, 129.7, 132.7, 133.6, 144.7, 165.9; MS (EI, 30 eV) *m/z* 301 (M$^+$), 285 (M$^+$ − O), 152, 135; IR (KBr) 2894, 1693 (C=O), 1457, 1296, 1059 (S=O), 754 cm^{-1}; UV (2-propanol) λ_{max} 277 (ε 2.97 × 10^3), 234 (sh, ε 5.93 × 10^3), 200 (ε 3.75 × 10^4) nm; Anal. Calcd for C$_{17}$H$_{19}$NO$_2$S: N, 4.65; C, 67.74; H, 6.35. Found: N, 4.61; C, 67.59; H, 6.35.

Optical Resolution of Sulfinamides 2a and 2b. A racemic sample of **2a** and **2b** (10 mg) in eluent (0.5 mL) was charged to a chiral column packed with cellulose carbamate derivative silica gel (Daicel Chiralcel OD; 10 × 250 mm) and a chiral column packed with amylase carbamate derivative silica gel (Daicel Chiralpak AS; 10 × 250 mm), respectively, and eluted with hexane containing 25 vol % of 2-propanol at a flow rate of 1.5 mL min^{-1}. In the case of **2a**, about 5 mg of optically active sulfinamides was collected from the first eluted portion and the next portion, and optically pure (+)-**2a** was obtained by repeated chromatography. In the case of **2b**, 54% ee of (+)-**2b** was obtained from the first half of the first peak.

Compound (*R*)-(+)-2a. 100% ee; mp 170 °C (colorless prisms from acetone; dec); [α]$_D^{27}$ +72.8 (*c* 0.138, 2-propanol);

(15) Kamigata, N.; Hashimoto, S.; Kobayashi, M. *Org. Prep. Proced. Int.* **1983**, *15*, 315.

$[\alpha]_{435}^{26}$ +133 (*c* 0.0500, 2-propanol); CD (2-propanol) 284 ($[\theta]$ 2.31 × 10⁴), 251 ($[\theta]$ −3.90 × 10⁴) nm. ¹H, ¹³C NMR, and IR spectra were almost the same as those of the racemic sample.

Compound (S)-(+)-2b. 54% ee; mp 143−144 °C (colorless powder); $[\alpha]_{D}^{29}$ +2.2 (*c* 0.037, 2-propanol); $[\alpha]_{435}^{29}$ +9.3 (*c* 0.037, 2-propanol); CD (2-propanol) 277 ($[\theta]$ −1.76 × 10⁴), 232 ($[\theta]$ 3.58 × 10⁴) nm. ¹H, ¹³C NMR, and IR spectra were almost the same as those of the racemic sample.

General Procedure for Reaction of Sulfinamides with Methylmagnesium Chloride. To a THF (2 mL) solution of sulfinamides (3−30 mg) was slowly added an excess amount of methylmagnesium chloride at −78 °C. After the mixture was stirred for 1 h, brine and 1 M HCl were added and the solution was extracted with dichloromethane, then the organic layer was dried over anhydrous sodium sulfate. The solution was concentrated under reduced pressure and purification of the residue by silica gel column chromatography afforded the products.

Methyl 2-*N*-(1-Adamantyl)aminocarbonylphenyl Sulfoxide (3a, racemic). 63%; mp 198 °C (colorless prisms from dichloromethane/hexane; dec); ¹H NMR (500 MHz, CDCl₃) δ 1.73 (6H, s), 2.11 (6H, s), 2.14 (3H, s), 2.87 (3H, s), 5.97 (1H, s), 7.47−7.54 (2H, m), 7.69 (1H, dd, *J* = 6.45, 7.95 Hz), 8.22 (1H, d, *J* = 7.95 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 29.4, 36.2, 41.5, 44.9, 52.9, 124.4, 126.2, 130.2, 131.8, 133.5, 147.7, 165.5; MS (EI, 70 eV) *m/z* 317 (M⁺), 302 (M⁺ − Me), 301 (M⁺ − O), 286, 167, 151, 135; IR (KBr) 3268 (br, NH), 2908, 1649 (C= O), 1542, 1306, 1018 (S=O) cm⁻¹; HRMS (70 eV) *m/z* 317.1455 (C₁₈H₂₃NO₂S requires 317.1449).

Compound (*R*)-(+)-3a. 70%; 99% ee; mp 199 °C (colorless powder; dec); $[\alpha]_{D}^{26}$ +70 (*c* 0.236, ethanol). ¹H NMR, MS, and IR spectra were almost the same as those of the racemic sample.

Theoretical Study. Geometries were optimized by using the MP2¹³ method with the LANL2DZ¹⁴ basis set. All calculations were performed by using the Gaussian98¹⁶ program on an IBM p690−681 (RegattaH) computer. Vibrational frequency analysis of each geometry of transition states of vertex inversion of seleninamide **4** showed one imaginary frequency that corresponds to the vertex inversion mode, clearly indicating the real saddle point in the reaction pathway. The difference in the zero-point energies between the saddle point of inversion and the ground state is 1.0 kcal mol⁻¹, and thus the energy is uncorrected. The values for energy changes of the addition of water to sulfinamide **5** and seleninamide **4** are corrected for zero-point vibrational energies by using a scaling factor of 0.9434 at the standard state (298.15 K, 1 atm).

Supporting Information Available: Compound characterization data for selenenamides, **1b**, **1d**, **2b**, **3b**, and (*S*)- (−)-**3b**, and Cartesian coordinates and computed total energies for **4** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048302X

(16) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millan, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malich, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzales, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andreas, J. L.; Head-Gordon, M.; Reploge, E. S.; Pople, J. A. *Gaussian 98*; Gaussian Inc.; Pittsburgh, PA, 1998.