JOC Article

Highly Enantioselective Reaction of α-Selenoorganolithium Compounds with Chiral Bis(oxazoline)s and Preparation of Enantioenriched Benzylidencyclohexanes

Shuichi Nakamura, Takayuki Aoki, Takahiro Ogura, Libo Wang, and Takeshi Toru*

Department of Applied Chemistry, Graduate School of Engineering, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan

toru@nitech.ac.jp

Received August 26, 2004

The enantioselective reaction of α-seleno carbanions derived from bis(phenylseleno)acetal and bis-(2-pyridylseleno)acetal in the presence of bis(oxazoline)s with various electrophiles gave products with high enantioselectivity. The enantioselective reaction of α-lithio benzyl 2-pyridyl selenide gave the products with stereochemistry reverse to that obtained in the reaction of α-lithio benzyl phenyl selenide. Mechanistic investigation suggests the enantiodetermination of these reactions at −78 °C depends on dynamic thermodynamic resolution. The enantioselective reaction was applied to the preparation of enantioenriched olefins and epoxide.

Introduction

Asymmetric reactions of prochiral compounds having a sufficiently acidic C−H bond are of great importance in the access to enantiomerically pure compounds. Enantioselective reactions of dipole-stabilized α-alkoxy-[1] and α-aminoorganolithium[2] compounds have been thoroughly studied and it has been confirmed that these carbanions are configurationally stable enough to proceed through an asymmetric deprotonation pathway. However, the configurational stability of α-seleno carbanion is lower than that of α-oxy carbanion.[3] Configurationally labile α-thio carbanion[4,5] shows lower enantioselectivity than dipole-stabilized α-oxyorganolithium having a similar structural arrangement. We have previously reported highly enantioselective reactions of α-thio carbanions derived from benzyl phenyl and pyridyl sulfides, which were proven to proceed through different resolution pathways, i.e., dynamic kinetic resolution for the former carbanion and dynamic thermodynamic resolution for the latter.[6,7] These results showed that pivotal resolution pathways can be chosen by changing the substituent on

* Address correspondence to this author. Phone and Fax: +81-52-735-5217.

(1) (a) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem.*, *Int. Ed. Engl.* **1990**, *29*, 1422−1424. (b) Hoppe, D.; Hense, T. *Angew. Chem.*, *Int. Ed. Engl.* **1997**, *36*, 2282−2316 and references therein. (c) Férézou, J. P.; Julia, M.; Khourzom, R.; Pancrazi, A.; Robert, P. *Synlett* **1991**, 611−614. (d) Woltering, M. J.; Fröhlich, R.; Hoppe, D. *Angew. Chem.*, *Int. Ed. Engl.* **1997**, *36*, 1764−1766. (e) Oestreich, M.; Fröhlich, R.; Hoppe, D. *Tetrahedron Lett.* **1998**, *39*, 1745−1748. (f) Tomooka, K.; Komine, N.; Sasaki, T.; Shimizu, H.; Nakai, T. *Tetrahedron Lett.* **1998**, *39*, 9715−9718. (g) Woltering, M. J.; Fröhlich, R.; Wibbeling, B.; Hoppe, D. *Synlett* **1998**, 797−800. (h) Deiters, A.; Hoppe, D. *Angew. Chem.*, *Int. Ed.* **1999**, *38*, 546−548. (i) Oestreich, M.; Hoppe, D. *Tetrahedron Lett.* **1999**, *40*, 1881−1884. (j) van Bebber, J.; Ahrens, H.; Fröhlich, R.; Hoppe, D. *Chem. Eur. J.* **1999**, *5*, 1905−1916. (k) Oestreich, M.; Fröhlich, R.; Hoppe, D. *J. Org. Chem.* **1999**, *64*, 8616−8626. (l) Hoppe, D.; Woltering, M. J.; Oestreich, M.; Fröhlich, R. *Helv. Chim. Acta* **1999**, *82*, 1860−1877. (m) Kleinfeld, S. H.; Wegelius, E.; Hoppe, D. *Helv. Chim. Acta* **1999**, *82*, 2413−2424.

(2) (a) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231−3239. (b) Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715−721. (c) Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 12218−12219. (d) Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561−11570. (e) Park, Y. S.; Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 10537−10538. (f) Gross, K. M. B.; Jun, Y. M.; Beak, P. *J. Org. Chem.* **1997**, *62*, 7679−7689.

(3) Hoffmann and co-workers have developed a protocol for surveying the configurational stability of organolithium compounds, showing that the α-lithio benzyl phenyl selenide is configurationally labile in THF, see: (a) Hoffmann, R. W.; Rühl, T.; Harbach, J. *Liebigs Ann. Chem.* **1992**, 725−730. (b) Ruhland, T.; Dress, R.; Hoffmann, R. W. *Angew. Chem.*, *Int. Ed. Engl.* **1993**, *32*, 1467−1468. However, α-lithio pentyl phenyl selenide is configurationally stable in THF. (c) Hoffmann, R. W. In *Organic Synthesis via Organometallics*; Enders, D., Gais, H.-J., Keim, W., Eds.; Vieweg: Braunschweig, 1993; p 79. (d) Hoffmann, R. W.; Julius, M.; Chemla, F.; Ruhland, T.; Frenzen, G. *Tetrahedron* **1994**, *50*, 6049−6060.

(4) Kaiser, B.; Hoppe, D. *Angew. Chem.*, *Int. Ed. Engl.* **1995**, *34*, 323−325.

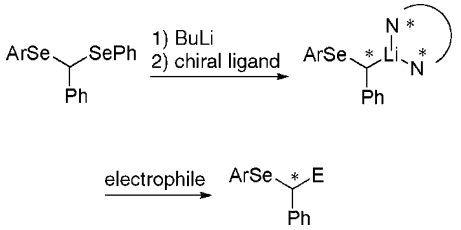
(5) For configurational stability of the α-thio carbanion, see: (a) McDougal, P. G.; Condon, B. D.; Laffosse, M. D., Jr.; Lauro, A. M.; VanDerveer, D. *Tetrahedron Lett.* **1988**, *29*, 2547−2550. (b) McDougal, P. G.; Condon, B. D. *Tetrahedron Lett.* **1989**, *30*, 789−790. (c) Krief, A.; Evrard, G.; Badaoui, E.; De Beys, V.; Dieden, R. *Tetrahedron Lett.* **1989**, *30*, 5635−5638. (d) Reich, H. J.; Bowe, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 8994−8995. (e) Hoffmann, R. W.; Bewersdorf, M. *Liebigs Ann. Chem.* **1992**, 643−653. (f) Brickmann, K.; Brückner, R. *Chem. Ber.* **1993**, *126*, 1227−1239. (g) Wang, F.; Tang, J.; Labaudiniére, L.; Marek, I.; Normant, J.-F. *Synlett* **1995**, 723−725. For the reaction of configurationally stable dipole-stabilized α-thiobenzyllithium in THF, see: (h) Hoppe, D.; Kaiser, B.; Stratmann, O.; Fröhlich, R. *Angew. Chem.*, *Int. Ed. Engl.* **1997**, *36*, 2784−2786. (i) Marr, F.; Fröhlich, R.; Hoppe, D. *Org. Lett.* **1999**, *1*, 2081−2083.

(6) (a) Nakamura, S.; Nakagawa, R.; Watanabe, Y.; Toru, T. *Angew. Chem.*, *Int. Ed.* **2000**, *39*, 353−355. (b) Nakamura, S.; Nakagawa, R.; Watanabe, Y.; Toru, T. *J. Am. Chem. Soc.* **2000**, *122*, 11340−11347. (c) Nakamura, S.; Furutani, A.; Toru, T. *Eur. J. Org. Chem.* **2002**, 1690−1695. (d) Nakamura, S.; Kato, T.; Nishimura, H.; Toru, T. *Chirality* **2004**, *16*, 86−89.

(7) For the enantioselective reaction of the α-carbanion derived from dithioacetals, see: Nakamura, S.; Ito, Y.; Wang, L.; Toru, T. *J. Org. Chem.* **2004**, *69*, 1581−1589. For enantioselective reaction of the α-carbanion derived from *N*,*S*-acetals with (−)-sparteine, see: Wang, L.; Nakamura, S.; Toru, T. *Org. Biomol. Chem.* **2004**, *2*, 2168−2169. Wang, L.; Nakamura, S.; Ito, Y.; Toru, T. *Tetrahedron*: *Asymmetry* **2004**, *15*, 3059−3072.

10.1021/jo048505l CCC: $27.50
Published on Web 11/10/2004

SCHEME 1

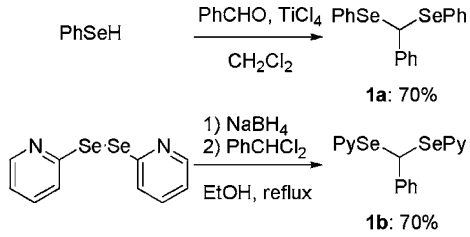


the sulfur. Hoffmann and co-workers have reported that α-seleno carbanions are more configurationally stable than α-thio carbanions but less stable than α-oxy carbanions.[3,5] Since chiral selenides have the potential to be asymmetric catalysts[8,9] and synthetic intermediates,[10,11] it is important to develop the highly enantioselective reaction of α-seleno carbanions and to clarify the reaction pathways in more detail.[12,13] We now report enantioselective reactions of α-lithio benzyl phenyl selenide and α-lithio benzyl 2-pyridyl selenide with electrophiles in the presence of an external chiral ligand (Scheme 1), including the reaction mechanism, on the basis of Beak's test using a deficient amount of the electrophile[14] and the warm-cool procedure[14a−c] together with the analysis of the data obtained by the MO calculation. We also report a highly enantioselective olefination involving the enantioselective reaction of the α-seleno carbanion with 4-substituted cyclohexanones and the subsequent stereospecific elimination reaction.[15]

Results

Lithiation−Substitution. We chose bis(arylseleno)-phenylmethanes **1a**,**b** as the substrates for the formation of α-seleno carbanions due to the ease of their preparation and lithiation. Diselenoacetals **1** were prepared on treatment of selenophenol with benzaldehyde in the presence of $TiCl_4$[16] or dipyridyl diselenide with sodium borohydride and subsequently with 1,1-dichlorotoluene (Scheme 2).

SCHEME 2



Treatment of a cumene solution of the diselenoacetal **1a** or **1b** with 1.05 equiv of *n*-BuLi and 1.1 equiv of a chiral ligand for 10 min at −78 °C formed the lithiated species Li-**1**, which was allowed to react with an electrophile to give the products **2**.[17,18] The yields and enantioselectivities obtained in the reaction of lithiated **1a** and **1b** with various electrophiles are summarized in Table 1.[19]

The reaction of Li-**1a** with benzophenone and (*S*)-bis-(oxazoline)s **3a**−**d** gave the product **2a** in moderate yields with moderate to high enantioselectivities (entries 1−5). Among the bis(oxazoline)s, (*S*)-bis(oxazoline)-^{i}Pr **3a** showed the highest enantioselectivity. Low enantioselectivity was obtained in the reaction with use of (−)-sparteine **4** (entry 6), which often has been used as a chiral ligand in the asymmetric reactions of dipole-stabilized α-oxy and α-amino carbanions. The reaction carried out at −50 and −90 °C showed slightly lowered enantioselectivity in comparison with that at −78 °C (entries 7, 8, and 9). The reaction of Li-**1a** with acetone or cyclohexanone gave the products **2b** and **2c** in high yields with high enantioselectivities (entries 10−12). It was rather surprising that acetone and cyclohexanone having acidic protons showed yields and enantioselectivities as good as those obtained in the reaction with benzophenone. Methylation and silylation with $(CH_3)_2SO_4$ and $(CH_3)_3SiOTf$ showed moderate enantioselectivity, whereas the reaction with CH_3I and $(CH_3)_3SiCl$ did not show good enantioselectivity (entries 13−16). We next studied the enantioselective reaction of α-lithio benzyl 2-pyridyl selenide Li-**1b**. When the reaction was carried out under the same reaction conditions as in the reaction of Li-**1a**, the product **2f** was obtained with moderate enantioselectivity (entries 17 and 18). The yield was markedly improved when 2.1 equiv of *n*-BuLi and 2.2 equiv of (*S*)-bis(oxazoline)-^{t}Bu **3b** were used, where the seleno alcohol **2f** was formed in high yield but with moderate enantioselectivity (entries 19 and 20). The enantioselectivity in the reaction of Li-**1b** with benzophenone varied depending on the temperature of deprotonation: High enantioselectivity was obtained at

(8) For a review, see: Nishibayashi, Y.; Uemura, S. Organoselenium Chemistry. In *Topics in Current Chemistry*; Wirth, T., Ed.; Springer: New York, 2000; Vol. 208, pp 235−255.

(9) (a) Hiroi, K.; Suzuki, Y.; Abe, I. *Tetrahedron*: *Asymmetry* **1999**, *10*, 1173−1188. (b) Miyake, Y.; Oda, M.; Oyamada, A.; Takada, H.; Ohe, K.; Uemura, S. *J. Organomet. Chem.* **2000**, *611*, 475−487. (c) Braga, A. L.; Rodrigues, O. E. D.; Paixão, M. W.; Appelt, H. R.; Silveira, C. C.; Bottega, D. P. *Synthesis* **2002**, 2338−2340.

(10) For a review, see: Wirth, T. *Angew. Chem.*, *Int. Ed.* **2000**, *39*, 3740−3749.

(11) (a) Krief, A.; Castillo-Colaux, C. *Synlett* **2001**, 501−504. (b) Huang, X.; Xu, W. *Tetrahedron Lett*. **2002**, *43*, 5495−5497. (c) Tiecco, M.; Testaferri, L.; Santi, C.; Tomassini, C.; Marini, F.; Bagnoli, L.; Temperini, A. *Angew. Chem.*, *Int. Ed.* **2003**, *42*, 3131−3133.

(12) For a review, see: Toru, T.; Nakamura, S. Organolithiums in Enantioselective Synthesis. In *Topics in Organometallic Chemistry*; Hodgson, G., Ed.; Springer, New York, 2003; Vol. 5, pp 177−216.

(13) The reaction of nondipole-stabilized α-seleno carbanions proceeds through a dynamic thermodynamic resolution pathway with good enantioselectivity, see: (a) Klute, W.; Dress, R.; Hoffmann, R. W. *J. Chem. Soc.*, *Perkin Trans. 2* **1993**, 1409−1411. (b) Hoffmann, R. W.; Klute, W.; Dress, R. K.; Wenzel, A. *J. Chem. Soc.*, *Perkin Trans. 2* **1995**, 1721−1726. (c) Hoffmann, R. W.; Klute, W. *Chem. Eur. J.* **1996**, *2*, 694−700.

(14) (a) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552−560. (b) Thayumanavan, S.; Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 8209−8216. (c) Weisenburger, G. A.; Faibish, N. C.; Pippel, D. J.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 9522−9530. (d) Gallagher, D. J.; Du, H.; Long, S. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 11391−11398.

(15) We preliminarily communicated the preparation of optically pure axially chiral compounds using α-thio and α-seleno carbanions, see: Nakamura, S.; Ogura, T.; Wang, L.; Toru, T. *Tetrahedron Lett.* **2004**, *45*, 2399−2402.

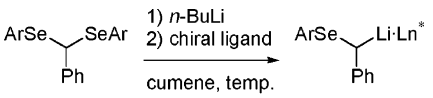
(16) Clarembeau, M.; Cravador, A.; Dumont, W.; Hevesi, L.; Krief, A.; Lucchetti, J.; Van Ende, D. *Tetrahedron* **1985**, *41*, 4793−4812.

(17) Cumene was found to be a solvent suitable for maximizing the difference in the reaction rate between the catalyzed and noncatalyzed reactions: see ref 6. When the reaction was carried out in a coordinative solvent such as THF or Et_2O, the selenoacetal **1a** was spontaneously lithiated on treatment with *n*-BuLi without addition of a chiral ligand to give the product **2** in high yield but with low enantioselectivity.

(18) When the aging time for lithiation in the presence of a chiral ligand was longer, the yield was lower.

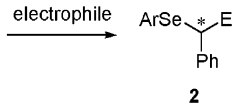
(19) These results were replicated at least 2 times and they were reproducible to <3%.

TABLE 1. Enantioselective Reaction of Li-1a and Li-1b with Electrophiles in the Presence of Various Chiral Ligands

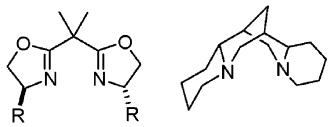


1a: Ar = Ph
1b: Ar = 2-Py

Li-**1**



2



3a: R = ^{i}Pr
b: R = ^{t}Bu
c: R = Ph
d: R = CH_2Ph

4

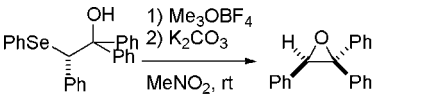
entry	seleno-acetal	chiral ligand	electro-phile	temp (°C)	product	yield (%)	ee[a] (%)
1	**1a**	**3a**	Ph_2CO	−78	**2a**	60	85
2	**1a**	**3b**	Ph_2CO	−78	**2a**	63	70
3[b]	**1a**	**3b**	Ph_2CO	−78	**2a**	78	78
4	**1a**	**3c**	Ph_2CO	−78	**2a**	62	81
5	**1a**	**3d**	Ph_2CO	−78	**2a**	51	67
6	**1a**	**4**	Ph_2CO	−78	**2a**	79	5
7	**1a**	**3a**	Ph_2CO	−90	**2a**	62	80
8	**1a**	**3a**	Ph_2CO	−50	**2a**	56	62
9	**1a**	**3b**	Ph_2CO	−90	**2a**	63	72
10	**1a**	**3a**	$(CH_3)_2CO$	−78	**2b**	73	95
11	**1a**	**3a**	cyclohexanone	−78	**2c**	71	88
12	**1a**	**3b**	cyclohexanone	−78	**2c**	83	95
13	**1a**	**3a**	CH_3I	−78	**2d**	63	17
14	**1a**	**3a**	$(CH_3)_2SO_4$	−78	**2d**	62	41
15	**1a**	**3a**	$(CH_3)_3SiCl$	−78	**2e**	80	3
16	**1a**	**3a**	$(CH_3)_3SiOTf$	−78	**2e**	59	65
17	**1b**	**3a**	Ph_2CO	−78	**2f**	50	56
18	**1b**	**3b**	Ph_2CO	−78	**2f**	51	41
19[c]	**1b**	**3a**	Ph_2CO	−78	**2f**	99	39
20[c]	**1b**	**3b**	Ph_2CO	−78	**2f**	85	46
21[c]	**1b**	**3b**	Ph_2CO	−50	**2f**	73	77
22[c]	**1b**	**3b**	Ph_2CO	−30	**2f**	64	47
23[c]	**1b**	**3a**	Ph_2CO	−50	**2f**	49	73
24[c]	**1b**	**3c**	Ph_2CO	−50	**2f**	77	64

[a] Determined by the HPLC analysis with a Chiralcel OD-H. [b] *n*-BuLi (1.3 equiv), 1.4 equiv of **3**, and 2.0 equiv of Ph_2CO were used. [c] *n*-BuLi (2.10 equiv), 2.2 equiv of **3**, and 2.3 equiv of Ph_2CO were used.

−50 °C with (*S*)-bis(oxazoline)-^{t}Bu **3b** which gave higher enantioselectivity than other bis(oxazoline)s (entries 21−24).[20]

The absolute configuration of **2a** was determined to be *S* by stereospecific conversion to the epoxide **5** (Scheme 3).[21] Thus, treatment of the product **2a** with trimethyloxonium tetrafluoroborate gave the selenonium ion, which was then allowed to react with K_2CO_3 to give the epoxide **5**. The epoxide **5** was confirmed to have an *R*-configuration by comparison of the value of the specific rotation with that reported.[22] Since a reaction of the pyridylseleno alcohol **2f** similar to the above failed to give the epoxide, **2f** was converted to the selenoxide with *m*-CPBA, which was then treated with aqueous NaOH solution to give the known epoxide (*S*)-**5**. Thus, the absolute configuration of **2f** obtained in the reaction of α-lithio benzyl 2-pyridyl selenide Li-**1b** with benzophenone was determined to be *R* (Scheme 4).[23]

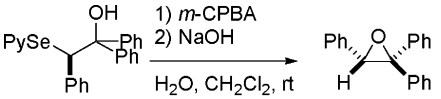
SCHEME 3



(*S*)-**2a**: 85% ee

(*R*)-**5**
47%, 83% ee
$[\alpha]_D^{25}$ -36.0 (*c* 0.76, EtOH)

SCHEME 4



(*R*)-**2f**: 66% ee

(*S*)-**5**
10%, 58% ee

Preparation of Axially Chiral Compounds. The Horner−Wadsworth−Emmons reaction is one of the most useful methods for making a double bond from carbonyl compounds. Recently, the asymmetric Horner−Wadsworth−Emmons reactions using external chiral ligands have been reported.[24] We have reported stereospecific transformation of α-seleno alcohols into (*Z*)-olefins α to a carbonyl group.[25] The above stereospecific *β*-elimination of *β*-seleno alcohols allowed us to examine application of the present reaction to the synthesis of axially chiral olefins.[15] First, Li-**1a** was allowed to react with 4-*tert*-butylcyclohexanone in the presence of chiral ligands **3a**−**c** affording *cis*- and *trans*-seleno alcohols **6**−**8** (Table 2, entries 1−3). The highest enantioselectivity was obtained when bis(oxazoline)-^{t}Bu **3b** was used.[26] The reaction with other 4-substituted cyclohexanones and **3b** also afforded the seleno alcohols **7** and **8** with high enantioselectivity (entries 4 and 5). Each diastereomer was easily separated by column chromatography.[27]

(20) Determination of the optical purity of the products obtained in the reaction of Li-**1b** with other electrophiles such as acetone, cyclohexanone, CH_3I, and $(CH_3)_3SiCl$ could not be determined because of their insufficient separation by the HPLC analyses with use of various chiral columns.

(21) Shanklin, J. R.; Johnson, C. R.; Ollinger, J.; Coates, R. M. *J. Am. Chem. Soc.* **1973**, *95*, 3429−3431.

(22) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224−11235.

(23) Ceccherelli, P.; Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *J. Org. Chem.* **1995**, *60*, 8412−8413.

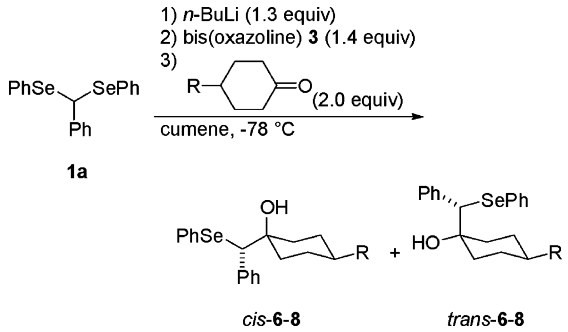
(24) For enantioselective Wittig−Horner and Horner−Wadsworth−Emmons reactions with external chiral ligands, see: (a) Toda, F.; Akai, H. *J. Org. Chem.* **1990**, *55*, 3446−3447. (b) Kumamoto, T.; Koga, K. *Chem. Pharm. Bull.* **1997**, *45*, 753−755. (c) Mizuno, M.; Fujii, K.; Tomioka, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 515−517. (d) Arai, S.; Hamaguchi, S.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 2997−3000. (e) Sano, S.; Yokoyama, K.; Teranishi, R.; Shiro, M.; Nagao, Y. *Tetrahedron Lett.* **2002**, *43*, 281−284. For the enantioselective Peterson olefination, see: Iguchi, M.; Tomioka, K. *Org. Lett.* **2002**, *4*, 4329−4331.

(25) (a) Toru, T.; Hayakawa, T.; Nishi, T.; Watanabe, Y.; Ueno, Y. *Phosphorus Sulphur Silicon* **1998**, 653−658. (b) Nakamura, S.; Hayakawa, T.; Nishi, T.; Watanabe, Y.; Toru, T. *Tetrahedron* **2001**, *57*, 6703−6711. See also reviews: (c) Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049−1132. (d) Krief, A. *Tetrahedron* **1980**, *36*, 2531−2640.

(26) The reaction of α-thio carbanions with 4-alkylcyclohexanones showed high enantioselectivity; see ref 15.

(27) We also examined the enantioselective reaction of Li-**1b** with 4-substituted cyclohexanones, but the attempts to separate the obtained diastereomeric isomers by column chromatography failed.

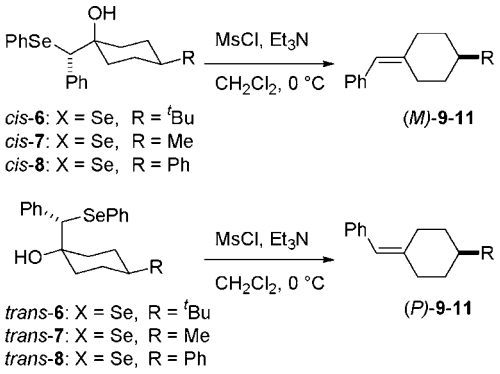
TABLE 2. Enantioselective Reaction of Li-1a with 4-Substituted Cyclohexanones



entry	ligand	electrophile R	product	yield (%)	ratio[a] cis:trans	ee (%) cis	ee (%) trans[b]
1	**3a**	^{t}Bu	**6**	79	60:40	74[b]	67
2	**3b**	^{t}Bu	**6**	68	65:35	86[b]	90
3	**3c**	^{t}Bu	**6**	58	71:29	73[b]	39
4	**3b**	Me	**7**	74	69:31	91[c]	90
5	**3b**	Ph	**8**	65	51:49	90[d]	89

[a] Determined by ^{1}H NMR analysis. [b] Enantiomeric excess was determined after conversion to olefins. [c] Determined by HPLC analysis with Chiralpak AD-H. [d] Determined by HPLC analysis with Chiralcel OJ-H. [e] Determined by HPLC analysis with Chiralcel OD-H.

TABLE 3. Preparation of Axially Chiral Olefins 9−11 from Seleno Alcohols 6−8



entry	substrate	ee (%)	product	yield (%)	ee (%)[a]	config.
1	*cis*-**6**	86	**9**	89	86	(*M*)
2	*cis*-**7**	91	**10**	91	91	(*M*)
3	*cis*-**8**	90	**11**	92	90	(*M*)
4	*trans*-**6**		**9**	91	90	(*P*)
5	*trans*-**7**		**10**	90	90	(*P*)
6	*trans*-**8**		**11**	88	89	(*P*)

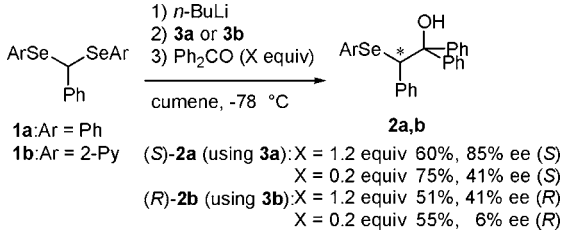
[a] Determined by HPLC analysis with Chiralcel OD-H.

The separated diastereomeric seleno alcohols **6**−**8** were treated with methanesulfonyl chloride and Et_3N in CH_2Cl_2 to give axially chiral olefins **9**−**11** with high optical purity (Table 3). The optical purity of the chiral olefins was determined by the HPLC analysis with Chiralcel OD-H and the olefination was found to proceed without loss of optical purity. The absolute stereochemistry of the chiral olefins **9**−**11** was assigned by comparison of the values of the specific rotation with those reported.[28]

Discussion

Diselenoacetals **1a**,**b** were lithiated by the Se−Li exchange reaction with *n*-BuLi to afford the organolithium species Li-**1**, which was treated with an electrophile to give the products **2a**−**f**. It is not likely that the reaction proceeds through an enantioselective replacement of the prochiral seleno group with lithium, i.e., through an enantioselective deselenenylation pathway, because configurational stability of the α-seleno carbanion is assumed to be insufficient. Thus, asymmetric induction occurs in a postdeselenenylation step through an asymmetric substitution pathway controlled either by the stability of lithium carbanion−chiral ligand complexes, i.e., through dynamic thermodynamic resolution,[29] or by the complex−electrophile interaction in the transition state, i.e., dynamic kinetic resolution.[30] The reaction with a different amount of an electrophile enables us to differentiate these resolution pathways. In the case of dynamic kinetic resolution, the enantiomer ratio depends solely upon the difference between the activation energies in the formation of enantiomers ($\Delta\Delta G^{\ddagger}$) and is independent of the amount of electrophile. In the case of dynamic thermodynamic resolution, the amount of electrophile affects the enantioenrichment of the product, because the two diastereomeric complexes would have different activation energies for the reaction with the electrophile. In fact, the reaction of **1a** or **1b** afforded the products (*S*)-**2a** and (*R*)-**2b** in different enantiomer ratios depending on the reactions with a different amount of benzophenone (Scheme 5).

SCHEME 5



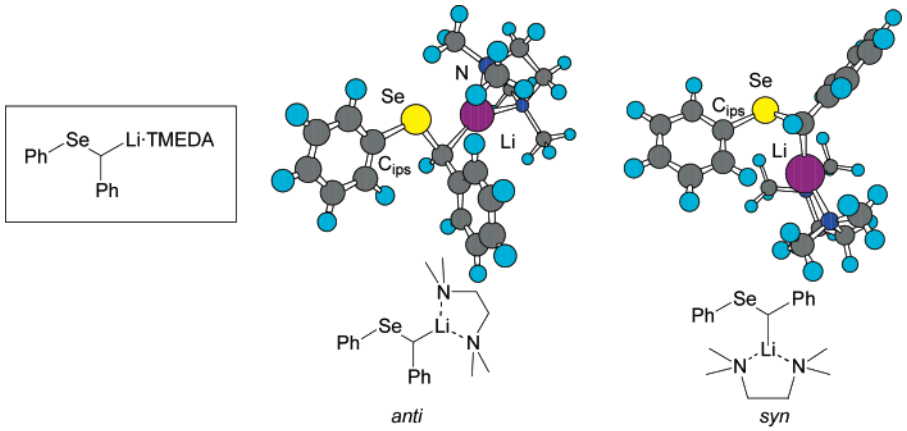
These results suggest that the enantioselective reaction of **1a** or **1b** proceeds through a dynamic thermodynamic resolution pathway, i.e., the reaction with a benzophenone occurs before the inversion between diastereomeric complexes of lithiated **1a** or **1b** with the bis(oxazoline).[31] In this case, the enantiomeric excess of the product formed from the reaction of Li-**1** with benzophenone depends on the difference in the stability between the two diastereomeric Li-**1**−bis(oxazoline) complexes ($\Delta\Delta G$ in Figure 4). The decrease in the enantiomer ratios of **2a** and **2b** in the reaction with a limited amount of

(28) (a) Denmark, S. E.; Chen, C.-T. *J. Am. Chem. Soc.* **1992**, *114*, 10674−10676. (b) Henessian, S.; Beaudoin, S. *Tetrahedron Lett.* **1992**, *33*, 7655−7658.

(29) Beak, P.; Anderson, D. R.; Curtis, M. D.; Laumer, J. M.; Pippel, D. J.; Weisenburger, G. A. *Acc. Chem. Res.* **2000**, *33*, 715−727.

(30) (a) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36−56. (b) Ward, R. S. *Tetrahedron*: *Asymmetry* **1995**, *6*, 1475−1490. (c) Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, 447−456. (d) Pellissier, H. *Tetrahedron* **2003**, *59*, 8291−8327.

(31) The same range of enantioselectivity should be obtained irrespective of the electrophile through a dynamic thermodynamic resolution process. The reactions with CH_3I, $(CH_3)_2SO_4$, $(CH_3)_3SiCl$, and $(CH_3)_3SiOTf$ gave the products with lower enantioselectivity than that obtained in the reaction with benzophenone. The decreased enantioselectivity in the reaction with alkylating reagents is ascribed to the activation energy. The alkylation of Li-**1a**, in which the alkylating reagent approaches without coordination to lithium, would have higher activation energy than the reaction with carbonyl compounds and proceed not only through a dynamic thermodynamic resolution but also through a dynamic kinetic resolution.



MOPAC93/PM3	0 kcal / mol	3.15 kcal / mol
HF/3-21G	0 kcal / mol	2.54 kcal / mol
HF/6-31+G*	0 kcal / mol	2.13 kcal / mol

FIGURE 1. Geometry optimization of *anti*- and *syn*-Li-**1a**−TMEDA Complexes.

benzophenone also implies that a more stable diastereomeric complex has higher activation energy to react with benzophenone ($\Delta G_R^{\ddagger} > \Delta G_S^{\ddagger}$ in Figure 4). Interestingly, the enantioselective reaction of α-lithiated benzyl phenyl sulfide proceeds through a dynamic kinetic resolution pathway with high enantioselectivity,[6] indicating that the α-seleno carbanion (Li-**1a**) has a higher inversion barrier than that of the α-thio carbanion of benzyl phenyl sulfide. The inversion barrier of α-thio- and α-seleno carbanions can be ascribed to the stabilization energy of the n−σ_{X-C} negative hyperconjugation.[32] Thus, we performed the MO calculation for the Li-**1a**-TMEDA. The calculations for these complexes by Gaussian 98 HF/3-21G, HF/6-31+G*,[33] and MOPAC 93/PM3[34] methods showed a significant level of difference in energy between *anti*- and *syn*-Li-**1a**−TMEDA complexes as shown in Figure 2.[35]

The anti arrangement of the C−Li bond to the Se−C_{ips} bond of Li-**1a** was clearly shown to be a preferable conformation by these calculations. This would be due to an n−σ^*_{Se-C} negative hyperconjugation, where the unshared electron pair of carbanions can overlap with the antibonding Se−C bond (σ^*_{Se-C}) in the present model

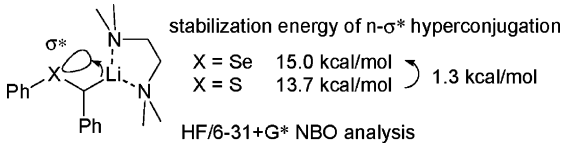


FIGURE 2. Stabilization energy of n−σ^* negative hyperconjugation.

compounds. We also calculated the n−σ^*_{X-C} negative hyperconjugation energies of α-lithiated benzyl phenyl selenide and α-lithiated benzyl phenyl sulfide by the natural bond orbital (NBO) analysis at the HF/6-31+G* level[36,37] (Figure 2). Both compounds were found to have a significant level of stabilization energy by the n−σ^* negative hyperconjugation. The α-seleno carbanion was found to be more stabilized by the negative hyperconjugation than the α-thio carbanion by 1.3 kcal/mol, showing the former has a higher inversion barrier than the latter.[38]

The stability of diastereomeric complexes of Li-**1a** with **3a** was estimated by the MO calculation with use of HF/3-21G and the (*R*)-Li-**1a**−**3a** complex was found to be slightly more stable than the (*S*)-Li-**1a**−**3a** complex as shown in Figure 3. Thus, it was reasonably inferred that the reaction of Li-**1a** with electrophiles such as aldehydes and ketones proceeded with retention of configuration through coordination of a carbonyl oxygen to lithium to afford the (*S*)-isomer (S_E2_{ret} reaction[39]).[40] This reaction pathway is well-illustrated by the energy diagram of the enantioselective reaction of Li-**1a** as shown in Figure 4.

(32) (a) Lehn, J.-M.; Wipff, G.; Demuynck, J. *Helv. Chim. Acta* **1977**, *60*, 1239−1246. (b) Ruhland, T.; Dress, R.; Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1467−1468. (c) Dress, R. K.; Rölle, T.; Hoffmann, R. W. *Chem. Ber.* **1995**, *128*, 673−677. (d) Hoffmann, R. W.; Dress, R. K.; Ruhland, T.; Wenzel, A. *Chem. Ber.* **1995**, *128*, 861−870.

(33) (a) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, 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.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; 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.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.6; Gaussian, Inc.: Pittsburgh, PA, 1998. For the Becke3LYP hybrid method, see: (b) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623−11627.

(34) (a) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209−220. (b) For the lithium parameter for PM3, see: Anders, E.; Koch, R.; Freunscht, P. *J. Comput. Chem.* **1993**, *14*, 1301−1312.

(35) No negative frequency of these optimized structures was confirmed by the frequency calculation.

(36) *NBO* Version 3.1; Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. See also: (a) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735−746. (b) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899−926.

(37) (a) Salzner, U.; Schleyer, P. R. *J. Org. Chem.* **1994**, *59*, 2138−2155. (b) Cortes, F.; Tenorio, J.; Collera, O.; Cuevas, G. *J. Org. Chem.* **2001**, *66*, 2918−2924. (c) Hetényi, A.; Martinek, T. A.; Lázár, L.; Zalán, Z.; Fülöp, F. *J. Org. Chem.* **2003**, *68*, 5707−5705.

(38) By the ^{1}H NMR spectral analysis, Hoffmann and co-workers have estimated a higher inversion barrier of the α-seleno carbanion than that of the α-thio carbanion by 1.1 kcal/mol, which accords with our calculation results, see refs 12 and 31d.

(39) Gawley, R. E. *Tetrahedron Lett.* **1999**, *40*, 4297−4300.

(40) The inversion/inversion pathway is unlikely, because carbonyl compounds usually react with organometallic compounds in a retentive manner through coordination with the metal center.

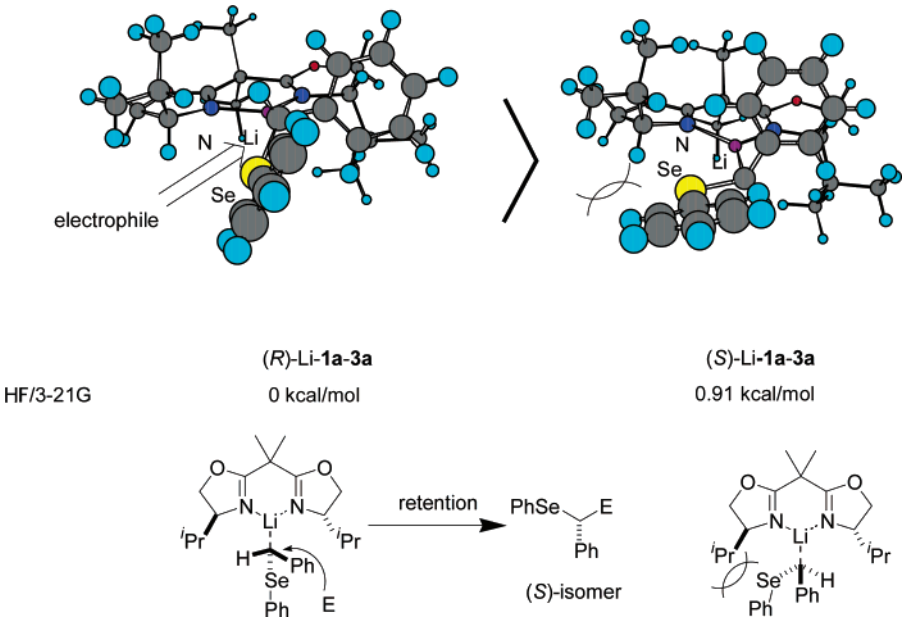


FIGURE 3. Geometry optimization of α-lithio benzyl phenyl selenide Li-**1a** with bis(oxazoline)-^{i}Pr **3a**.

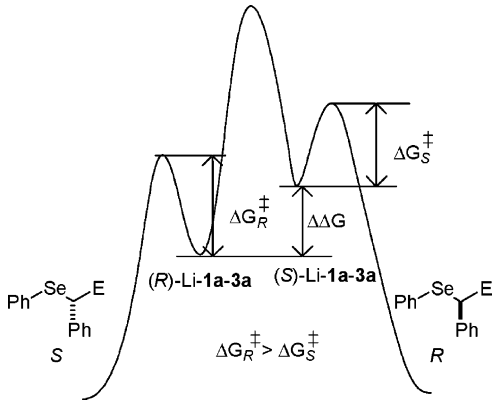
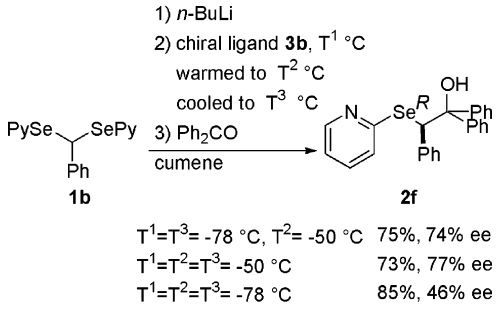


FIGURE 4. The assumed energy diagram of the enantioselective reaction for the Li-**1a** under dynamic thermodynamic resolution.

The enantioselectivity in the reaction of Li-**1b** with benzophenone depends on the temperature of the deprotonation (Table 1, entries 18, 21, and 22). These results indicate that the enantioselective reaction of Li-**1b** proceeds through a dynamic thermodynamic resolution pathway. Beak's "warm-cool procedure"[14a−c] also confirmed this assumption. A cumene solution of **1b** was treated with 2.1 equiv of *n*-BuLi at −78 °C for 10 min, and then 2.2 equiv of bis(oxazoline)-^{t}Bu **3b** was added. After being stirred for 30 min at −50 °C, the reaction mixture was cooled to −78 °C, and then 2.3 equiv of benzophenone was added (Scheme 6). The enantioselectivity in this reaction was substantially the same as that obtained in the reaction performed at −50 °C (77% ee, Table 1, entry 21), and was lowered when the reaction was performed at −78 °C (46% ee, Table 1, entry 20) as shown in Scheme 6.

These results indicate that the diastereomeric complexes derived from Li-**1b** and bis(oxazoline)-^{t}Bu **3b** are configurationally stable at temperatures lower than −50 °C at least on the time scale of the reaction with electrophiles, i.e., the diastereomeric complexes of Li-**1b**

SCHEME 6



with **3b** equilibrate at −50 °C, and the enantiomeric excess of **2f** reflects the ratio of these two diastereomeric complexes. To gain more quantitative insight into the reaction mechanism of Li-**1b**, the diastereomeric complexes with **3b** were estimated by the MO calculation by using the HF/3-21G and MOPAC 93/PM3 methods. The relative energies of the optimized structures obtained by these calculations are depicted in Figure 5.

In each optimized structure, a nitrogen of pyridine is coordinated to the lithium ion together with the two nitrogens of the bis(oxazoline), giving the fully coordinated lithium complex. Calculations by both methods showed that the (*R*)-Li-**1b**−**3b** complex is more stable than the (*S*)-Li-**1b**−**3b** complex. Since the lithium ion is fully coordinated, the substitution reaction may occur with inversion of configuration (S_E2_{inv}).[39,41]

Conclusion

In summary, we have demonstrated a highly enantioselective reaction of the configurationally labile α-carbanions derived from benzyl phenyl selenide and benzyl 2-pyridyl selenide in the presence of bis(oxazoline)s as a chiral ligand. We established the enantiodetermining step to be a dynamic thermodynamic resolution. Conve-

(41) This stereochemical pathway is in accord with that in the reaction of lithiated benzyl 2-pyridyl sulfide, see ref 6.

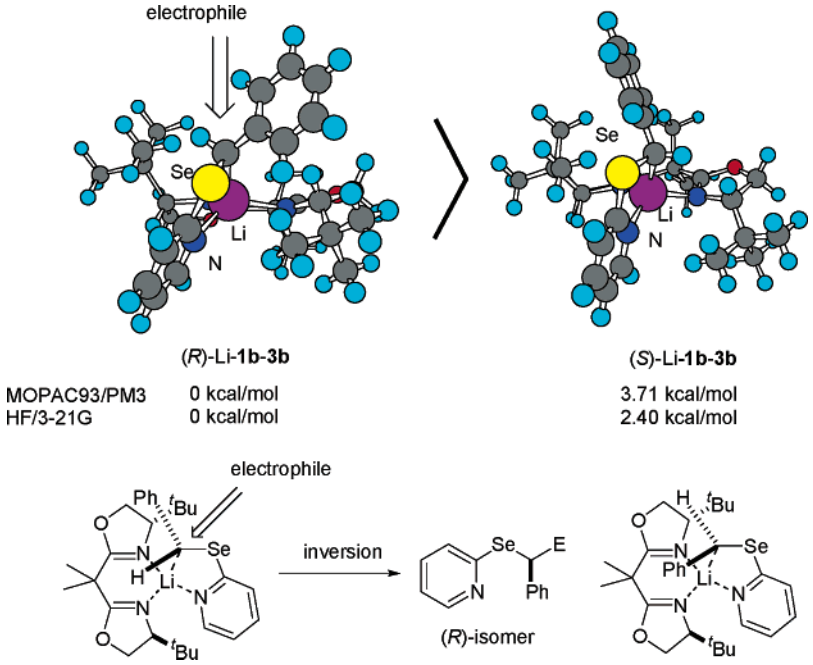


FIGURE 5. Geometry optimization of (*R*)- and (*S*)-Li-**1b**−**3b** complexes.

nient removal of the seleno group from the products provides an efficient method for the preparation of axially chiral olefins or a chiral epoxide.

Experimental Section

Preparation of Diselenoacetals: Bis(2-pyridylseleno)-phenylmethane (1b). To a solution of di(2-pyridyl) diselenide (1.0 g, 3.18 mmol) in ethanol (10 mL) was added $NaBH_4$ (263 mg, 6.94 mmol) at room temperature, and the solution was stirred for 30 min. Benzal chloride (0.37 mL, 2.88 mmol) was then added and the solution was heated to reflux for an additional 24 h. The reaction was quenched with a 1 mol/L HCl solution and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude oil that was purified by column chromatography (silica gel 20 g, hexane/CH_2Cl_2 80/20) to afford **1b** (818 mg, 70%). R_f 0.20 (hexane/ethyl acetate 80/20); ^{1}H NMR($CDCl_3$) δ 6.74 (s, 1H), 6.98−7.66 (m, 10H), 7.76−7.84 (m, 2H), 8.40−8.48 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 39.2, 120.7, 125.5, 127.4, 128.0, 128.2, 136.0, 141.1, 149.7, 156.1; IR (KBr) 1570, 1442, 1411, 1273, 1108, 1052 cm^{-1}; MS (EI) *m/z* 403 (M^+). Anal. Calcd for $C_{17}H_{14}N_2Se_2$: C, 50.51; H, 3.49; N, 6.93. Found: C, 50.49; H, 3.52; N, 6.91.

Enantioselective Reaction of Lithiated Benzyl Phenyl Selenide (Li-1a) with an Electrophile in the Presence of a Chiral Ligand: 1,1,2-Triphenyl-2-(phenylseleno)-ethanol (2a). To a solution of bis(phenylseleno)phenyl-methane (**1a**) (27 mg, 0.068 mmol) in cumene (0.45 mL) was added *n*-BuLi (0.050 mL, 1.43 mol/L solution in hexane, 0.072 mmol) at −78 °C, and the solution was stirred for 10 min. Bis-(oxazoline)-*i*Pr (20 mg, 0.075 mmol) was then added and the solution was stirred for an additional 10 min. A solution of benzophenone (15 mg, 0.082 mmol) in cumene (0.20 mL) was then added. After the mixture was stirred for 5 min, the reaction was quenched with saturated aqueous NH_4Cl and the aqueous solution was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude oil that was purified by column chromatography (silica gel 10 g, hexane/ethyl acetate 95/5) affording **2a** (18 mg, 62%) as a colorless solid. R_f 0.36 (hexane/ethyl acetate 90/10); mp 127−128 °C; $[\alpha]^{20}_D$ +38.8 (*c* 0.40, $CHCl_3$); ^{1}H NMR δ 3.55 (s, 1H), 5.46 (s, 1H), 6.95−7.30 (m, 18H), 7.59−7.65 (m, 2H); ^{13}C NMR δ 60.6, 80.6, 125.8, 126.0, 126.3, 126.6, 127.1, 127.6, 128.1, 128.6, 130.2, 135.6, 138.9, 144.2, 146.2; IR (KBr) 3450, 3020, 1492, 1448, 1332, 1171 cm^{-1}; MS (EI) *m/z* 255 (M^+ − PhSeOH). Anal. Calcd for $C_{26}H_{22}OSe$: C, 72.71; H, 5.16. Found: C, 72.63; H, 5.06. HPLC (Daicel Chiralcel OD-H, hexane/*i*PrOH 97/3, 0.5 mL/min) t_R 13.8 (*R*) and 40.2 (*S*) min (82% ee).

2-Methyl-1-phenyl-1-(phenylseleno)-2-propanol (2b): R_f 0.21 (hexane/ethyl acetate 90/10); $[\alpha]^{20}_D$ +307.9 (*c* 0.42, $CHCl_3$); ^{1}H NMR δ 1.30 (s, 3H), 1.32 (s, 3H), 4.27 (s, 1H), 5.29 (s, 1H), 7.13−7.45 (m, 10H); ^{13}C NMR δ 27.8, 65.0, 73.5, 126.9, 127.2, 127.8, 128.7, 129.2, 130.2, 133.8, 140.5; IR (neat) 3450, 3057, 2971, 1578, 1476, 1369, 1332 cm^{-1}; MS (EI) *m/z* 289 (M^+ − H_2O). Anal. Calcd for $C_{16}H_{18}OSe$: C, 62.95; H, 5.94. Found: C, 62.95; H, 6.28. HPLC (Daicel Chiralcel OD-H, hexane/*i*PrOH 95/5, 0.5 mL/min) t_R 12.3 (*R*) and 15.5 (*S*) min (95% ee).

1-[1-Phenyl-1-(phenylseleno)methyl]-1-cyclohexanol (2c): R_f 0.30 (hexane/ethyl acetate 90/10); $[\alpha]^{25}_D$ +242.2 (*c* 0.72, $CHCl_3$); ^{1}H NMR δ 1.40−1.65 (m, 8H), 1.84−2.00 (m, 2H), 2.10 (s, 1H), 4.25 (s, 1H), 7.09−7.43 (m, 10H); ^{13}C NMR δ 22.1, 22.3, 25.6, 35.5, 37.3, 64.6, 74.0, 126.8, 127.2, 127.8, 128.7, 128.9, 129.4, 134.0, 140.3; IR (KBr) 3483, 2936, 2852, 1578, 1477 cm^{-1}; MS *m/z* 329 (M^+ − H_2O). Anal. Calcd for $C_{19}H_{22}OSe$: C, 66.08; H, 6.42. Found: C, 66.13; H, 6.72. HPLC (Daicel Chiralcel OD-H, hexane/2-propanol 98/2, 0.5 mL/min) t_R 14.0 (*R*) and 18.0 (*S*) min (95% ee).

1-Phenyl-1-(phenylseleno)ethane (2d):[42] R_f 0.22 (hexane); ^{1}H NMR δ 1.74 (d, J = 7.2 Hz, 3H), 4.44 (q, J = 7.2 Hz, 1H), 7.12−7.48 (m, 10H). HPLC (Daicel Chiralcel OD-H, hexane, 0.5 mL/min) t_R 20.9 and 22.9 min (41% ee).

1-Phenyl-1-(phenylseleno)-1-trimethylsilylmethane (2e):[42b,43] R_f 0.29 (hexane); $[\alpha]^{21}_D$ +202.9 (*c* 0.44, CH_2Cl_2); ^{1}H NMR δ 0.14 (s, 9H), 3.74 (s, 1H), 7.10−7.36 (m, 10H); ^{13}C NMR δ −1.8, 38.0, 125.1, 126.4, 127.9, 128.1, 128.5, 131.7, 131.9, 142.0; IR (neat) 3057, 3020, 2955, 2895, 1578, 1476, 1248 cm^{-1}; MS

(42) (a) Lapkin, I. I.; Bogoslovskii, N. I. *Zh. Obsh. Khim.* **1972**, *49*, 1972−1974. (b) Reich, H.-J.; Shah, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 3250−3252. (c) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697−1705.

(43) Reich, H. J.; Shah, S. K. *J. Org. Chem.* **1977**, *42*, 1773−1776.

m/z 320 (M^+, 40), 163 (80), 135 (100). Anal. Calcd for $C_{16}H_{20}SiSe$: C, 60.17; H, 6.31. Found: C, 60.32; H, 6.38. HPLC (Daicel Chiralpak AD-H, hexane, 0.5 mL/min) t_R 8.1 (*S*) and 8.9 (*R*) min (66% ee).

1,1,2-Triphenyl-2-(2-pyridylseleno)ethanol (2f): R_f 0.34 (hexane/ethyl acetate 80/20); mp 141 °C; $[\alpha]^{23}_D$ +32.8 (*c* 0.67, CH_2Cl_2); ^{1}H NMR δ 5.93 (s, 1H), 5.97 (s, 1H), 6.95−7.45 (m, 16H), 7.65−7.75 (m, 2H), 8.45−8.50 (m, 1H); ^{13}C NMR δ 58.6, 81.0, 121.1, 125.7, 126.0, 126.4, 125.4, 127.3, 127.5, 127.8, 129.9, 136.7, 139.6, 144.7, 147.8, 148.3, 152.8; IR (KBr) 3200, 1577, 1451, 1413, 1109, 1049 cm^{-1}; MS (EI) *m/z* 255 ($PhCH{=}CPh_2^+$). Anal. Calcd for $C_{25}H_{21}NOSe$: C, 69.76; H, 4.92; N, 3.25. Found: C, 69.73; H, 4.70; N, 3.32. HPLC (Daicel Chiralcel OD-H, hexane/2-propanol 80/20, 0.5 mL/min) t_R 14.8 (*R*) and 19.5 (*S*) min (77% ee).

Conversion of 2a to (*R*)-5. To a solution of the seleno alcohol **2a** (128 mg, 0.298 mmol) in nitromethane (2 mL) was added trimethyloxonium tetrafluoroborate (88 mg, 0.596 mmol) at room temperature and the mixture was stirred for 45 min. Then the mixture was added to a methanol (1 mL) solution of potassium carbonate (82 mg, 0.596 mmol). After 1 h, a saturated aqueous NaCl solution was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude oil that was purified by column chromatography (silica gel 10 g, hexane/ethyl acetate 95/5) affording (*R*)-**5** (38 mg, 47%). R_f 0.39 (hexane/ethyl acetate 90/10); $[\alpha]_D^{25}$ −36.0 (83% ee, *c* 0.76, EtOH) [lit.[21] $[\alpha]_D^{25}$ −43.2 (*c* 0.82, EtOH)]; ^{1}H NMR δ 4.33 (s, 1H), 7.00−7.40 (m, 15H).

Conversion 2f to (*S*)-5. To a solution of the seleno alcohol **2f** (66% ee, 60 mg, 0.139 mg) in CH_2Cl_2 (1 mL) was added *m*-chloroperbenzoic acid (172 mg, 70% purity, 0.697 mmol) and the solution was stirred for 5 min at room temperature. A 1 mol/L aqueous NaOH solution (3 mL) was added and the mixture was stirred for 12 h. Workup and purification as above gave (*S*)-**5** (4 mg, 10%). HPLC (Daicel Chiralcel OD-H, hexane/2-propanol 95/5, 1.0 mL/min) t_R 5.1 (*S*) and 10.2 (*R*) min (58% ee).

(*S*)-1-[1-Phenyl-1-(phenylseleno)methyl]-4-*tert*-butylcyclohexan-1-ol (*cis*- and *trans*-6): *cis*-**6**: R_f 0.34 (hexane/ethyl acetate 90/10); mp 94−95 °C; $[\alpha]^{25}_D$ +208.3 (*c* 1.62, $CHCl_3$); ^{1}H NMR δ 0.82 (s, 9H), 1.25−1.58 (m, 8H), 1.99−2.10 (m, 1H), 2.11 (s, 1H), 4.19 (s, 1H), 7.15−7.40 (m, 10H, Ar); ^{13}C NMR δ 22.7, 22.9, 27.7, 32.4, 35.6, 37.4, 47.5, 65.7, 73.5, 126.8, 127.2, 127.7, 128.7, 129.4, 130.4, 133.8, 140.3; IR (KBr) 3449, 3056, 2956, 2865, 1578, 1479, 1435, 1364, 1262, 1245, 1074, 963, 729, 700, 688 cm^{-1}; MS (FAB) *m/z* 385 (M^+ − OH). Anal. Calcd for $C_{23}H_{30}OSe$: C, 68.81; H, 7.53. Found: C, 68.59; H, 7.75. HPLC (Daicel Chiralpak AD-H, hexane/^{i}PrOH 96/4, 0.5 mL/min) t_R 15.2 (*R*) and 19.9 (*S*) min (86% ee). *trans*-**6**: R_f 0.23 (hexane/ethyl acetate 90/10); $[\alpha]^{25}_D$ +183.4 (*c* 0.97, $CHCl_3$); ^{1}H NMR δ 0.75 (s, 9H), 0.96−1.52 (m, 8H), 2.01 (s, 1H), 2.45−2.54 (m, 1H), 4.45 (s, 1H), 7.06−7.33 (m, 10H); ^{13}C NMR δ 23.9, 24.4, 27.7, 32.4, 36.7, 39.4, 47.1, 57.1, 74.7, 126.7, 127.3, 127.9, 128.6, 129.1, 130.1, 134.8, 140.3; IR (neat) 3446, 3058, 3024, 2945, 2867, 1475, 1453, 1437, 1365, 1074, 1053, 736, 692 cm^{-1}; MS (FAB) *m/z* 385 (M^+ − OH). Anal. Calcd for $C_{23}H_{30}OSe$: C, 68.81; H, 7.53. Found: C, 68.53; H, 7.81.

(*S*)-1-[1-Phenyl-1-(phenylseleno)methyl]-4-methylcyclohexan-1-ol (*cis*- and *trans*-7): *cis*-**7**: R_f 0.35 (hexane/ethyl acetate 85/15); mp 73.5−74.5 °C; $[\alpha]^{25}_D$ +272.4 (*c* 1.65, $CHCl_3$); ^{1}H NMR δ 0.87 (d, 3H, *J* = 5.6 Hz), 1.20−1.60 (m, 8H), 1.97−2.05 (m, 1H), 2.08 (s, 1H), 4.19 (s, 1H), 7.12−7.38 (m, 10H); ^{13}C NMR δ 22.3, 30.4, 30.5, 32.0, 35.2, 36.9, 65.6, 73.5, 126.8, 127.2, 127.7, 128.7, 129.4, 130.3, 133.9, 140.3; IR (KBr) 3481, 3057, 3025, 2921, 2852, 1578, 1491, 1476, 1438, 1371, 1158, 1022, 987, 737, 700, 662 cm^{-1}; MS (FAB) *m/z* 343 (M^+ − OH). Anal. Calcd for $C_{20}H_{24}OSe$: C, 66.84; H, 6.73. Found: C, 66.65; H, 6.95. HPLC (Daicel Chiralcel OD-H, hexane/^{i}PrOH 99/1, 0.5 mL/min) t_R 16.8 (*R*) and 24.6 (*S*) min (91% ee). *trans*-**7**: R_f 0.24 (hexane/ethyl acetate 85/15); $[\alpha]^{25}_D$ +267.0 (*c* 1.25, $CHCl_3$); ^{1}H NMR δ 0.87 (d, 3H, *J* = 6.4 Hz), 1.00−1.75 (m, 8H), 2.13 (s, 1H), 2.23−2.30 (m, 1H), 4.45 (s, 1H), 7.13−7.40 (m, 10H); ^{13}C NMR δ 20.8, 30.7, 31.1, 34.9, 37.2, 59.2, 74.5, 126.7, 127.3, 127.8, 128.6, 129.2, 130.1, 134.7, 140.4; IR (neat) 3446, 3059, 2925, 2855, 1455, 1375; 1156, 1045, 989, 737, 700 cm^{-1}; MS (FAB) *m/z* 385 (M^+ − OH). Anal. Calcd for $C_{20}H_{24}OSe$: C, 66.84; H, 6.73. Found: C, 66.71; H, 6.93.

(*S*)-1-[1-Phenyl-1-(phenylseleno)methyl]-4-phenylcyclohexan-1-ol (*cis*- and *trans*-8): *cis*-**8**: R_f 0.25 (hexane/ethyl acetate 90/10); mp 132−133 °C; $[\alpha]^{25}_D$ +199.1 (*c* 0.53, $CHCl_3$); ^{1}H NMR δ 1.12−2.42 (m, 8H), 2.01−2.10 (m, 2H), 4.26 (s, 1H), 7.10−7.40 (m, 15H); ^{13}C NMR δ 29.4, 29.6, 35.4, 37.0, 43.7, 65.8, 73.2, 125.8, 126.6, 126.9, 127.3, 127.9, 128.1, 128.7, 129.5, 130.3, 133.9, 140.1, 146.6; IR (KBr) 3577, 3066, 3023, 2928, 1492, 1474, 1438, 1136, 977, 756, 737, 701, 669 cm^{-1}; MS (FAB) *m/z* 405 (M^+ − OH). Anal. Calcd for $C_{25}H_{26}OSe$: C, 71.25; H, 6.22. Found: C, 70.96; H, 6.51. HPLC (Daicel Chiralpak AD-H, hexane/^{i}PrOH 95/5, 0.75 mL/min) t_R 19.5 (*R*) and 25.6 (*S*) min (90% ee). *trans*-**8**: R_f 0.16 (hexane/ethyl acetate 90/10); $[\alpha]^{25}_D$ +154.3 (*c* 0.37, $CHCl_3$); ^{1}H NMR δ 1.45−1.90 (m, 7H), 2.26 (s, 1H), 2.56−2.63 (m, 2H), 4.63 (s, 1H), 7.14−7.40 (m, 15H); ^{13}C NMR δ 30.3, 30.8, 36.3, 38.8, 42.8, 57.7, 74.4, 125.9, 126.5, 126.8, 127.5, 128.0, 128.2, 128.7, 128.9, 129.1, 134.9, 140.2, 145.6; IR (neat) 3446, 3058, 3025, 2928, 2858, 1578, 1493, 1475, 1451, 1437, 1074, 1046, 738, 698 cm^{-1}; MS (FAB) *m/z* 405 (M^+ − OH). Anal. Calcd for $C_{25}H_{26}OSe$: C, 71.25; H, 6.22. Found: C, 71.05; H, 6.42.

Typical Procedure for the Preparation of Chiral Benzylidenecyclohexanes: (*M*)-1-Benzylidene-4-*tert*-butylcyclohexane [(*M*)-9].[28] To a solution of *cis*-**6** (77 mg, 0.19 mmol) in CH_2Cl_2 (1.9 mL) was added methanesulfonyl chloride (0.31 mL, 3.9 mmol) at 0 °C and the solution was stirred for 30 min. Triethylamine (1.3 mL, 9.3 mmol) was then added and the reaction mixture was stirred for 1 h. The cooling bath was removed and the mixture was stirred for an additional 1 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude oil that was purified by column chromatography (silica gel 25 g, hexane) to afford (*M*)-**9** (39 mg, 89%). $[\alpha]^{25}_D$ −37.4 (*c* 0.59, CH_3OH) [lit. (*P*-isomer): $[\alpha]^{rt}_D$ +43.3 (*c* 1.23, CH_3OH)]; ^{1}H NMR δ 0.86 (s, 9H), 0.95−1.27 (m, 3H), 1.80−1.97 (m, 3H), 2.12−2.27 (m, 1H), 2.35−2.43 (m, 1H), 2.93−3.02 (m, 1H), 6.21 (s, 1H), 7.16−7.33 (m, 5H). HPLC (Daicel Chiralcel OD-H, hexane, 0.2 mL/min) t_R 27.8 (*R*) and 33.5 (*S*) min (86% ee).

(*M*)-1-Benzylidene-4-methylcyclohexane [(*M*)-10]:[28] $[\alpha]^{25}_D$ −36.5 (*c* 0.84, CH_3OH) [lit. (*P*-isomer): $[\alpha]^{rt}_D$ +40.2 (*c* 0.33, CH_3OH)]; ^{1}H NMR δ 0.92 (d, 3H, *J* = 6.4 Hz), 0.88−1.19 (m, 2H), 1.54−1.70 (m, 1H), 1.73−2.00 (m, 3H), 2.15−2.40 (m, 2H), 2.82−2.90 (m, 1H), 6.22 (s, 1H), 7.16−7.29 (m, 5H). HPLC (Daicel Chiralcel OD-H, hexane, 0.2 mL/min) t_R 29.0 (*R*) and 40.1 (*S*) min (91% ee).

(*M*)-1-Benzylidene-4-phenylcyclohexane [(*M*)-11]:[28] $[\alpha]^{25}_D$ −36.5 (*c* 0.84, CH_3OH) [lit. (*P*-isomer): $[\alpha]^{rt}_D$ +110.2 (*c* 0.67, CH_3OH)]; ^{1}H NMR δ 1.49−1.76 (m, 2H), 1.94−2.12 (m, 3H), 2.31−2.53 (m, 2H), 2.68−2.83 (m, 1H), 3.00−3.07 (m, 1H), 6.30 (s, 1H), 7.17−7.32 (m, 10H). HPLC (Daicel Chiralcel OD-H, hexane, 0.5 mL/min) t_R 31.0 (*R*) and 41.1 (*S*) min (90% ee).

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (no. 11650890) from the Ministry of Education, Science, Sports and Culture of Japan and NIT research promotion program. We thank Dr. Shinya Kusuda, Ono Pharmaceutical Co., Ltd., for the mass spectra measurements.

Supporting Information Available: Calculation results of *anti*-Li-**1a**−TMEDA, *syn*-Li-**1a**−TMEDA, (*R*)-Li-**1a**−**3a**, (*S*)-Li-**1a**−**3a**, (*R*)-Li-**1b**−**3b**, and (*S*)-Li-**1b**−**3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048505L