Asymmetric Oxidation of Alkyl Aryl Selenides under Sharpless Oxidation Conditions

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Synopsis. Optically active alkyl aryl selenoxides were synthesized by the asymmetric oxidation of corresponding selenides under Sharpless oxidation conditions. The absolute configurations of the optically active alkyl aryl selenoxides prepared were estimated by comparisons of their circular dichroism spectra with those of the optically active sulfoxides.

Although optically active sulfoxides were resolved in the early twenties century,[1] there had been no example of an optically active selenoxide for a long time. Recently, though, optically active alkyl aryl and dialkyl selenoxides were obtained by kinetic resolution (5—11% e.e.)[2] or by complexation with optically active diol.[3] We also obtained optically active selenoxides by the optical resolution of racemic selenoxides[4] and the asymmetric oxidation of selenide.[5] Furthermore, we found that chromatographic resolution of racemic selenoxides using an optically active column was effective for preparing optically active diaryl selenoxides.[6] However, alkyl aryl selenoxides could not be separated by this method, and there has been no report on an effective synthetic method for such optically active compounds. Very recently, the asymmetric oxidation of 2-methoxy-2,2-diphenylethyl aryl selenides to corresponding selenoxides (18—40% e.e.) under Sharpless oxidation conditions was reported by Tiecco et al.[7] We have also investigated the asymmetric synthesis of optically active alkyl aryl selenoxides by the asymmetric oxidation of the corresponding selenides under Sharpless oxidation conditions. We report here the results and an estimation of the absolute configurations of the optically active alkyl aryl selenoxides obtained by a comparison of their circular dichroism spectra with those of optically active alkyl aryl sulfoxides.

Results and Discussion

Asymmetric oxidations of methyl 2,4,6-triisopropylphenyl selenide (**1a**) were examined in dichloromethane using titanium tetraisopropoxide and (+)-diethyl tartrate ((+)-DET) under several reaction temperatures. The highest enantiomeric excess (e.e.) of methyl 2,4,6-triisopropylphenyl selenoxide (+)-**2a** was obtained at −15 °C. The results are summarized in Table 1 (Entries 1—4). When (−)-DET was used in place of (+)-DET, (−)-selenoxide (−)-**2a** was obtained (Entry 5). The reaction conditions of the asymmetric oxidations of **1a** were examined by using some tartrates and Lewis acids (Entries 6—9). However, only a decrease of e.e. was observed. It was observed that the most effective combination of tartrate and Lewis acid was that of diethyl tartrate and titanium tetraisopropoxide. It was reported that the addition of equimolar amounts of water increased the e.e. of optically active sulfoxides in the asymmetric

$$\underset{\mathbf{1}}{\text{R-Se-Ar}} + \underset{\text{acid}}{\text{Lewis}} + \text{Tartrate} \xrightarrow{\text{t-BuOOH}} \underset{\mathbf{2}}{\text{R-}\overset{\overset{\text{O}}{\|}}{\text{Se}}^{*}\text{-Ar}}$$

a: R = Methyl, Ar = 2,4,6-Triisopropylphenyl
b: R = Methyl, Ar = 2,4,6-Tri-t-butylphenyl
c: R = Neopentyl, Ar = 2,4,6-Tri-t-butylphenyl
d: R = Benzyl, Ar = 2,4,6-Tri-t-butylphenyl
e: R = o-Methoxybenzyl, Ar = 2,4,6-Tri-t-butylphenyl

Table 1. Asymmetric Oxidation of Methyl 2,4,6-Triisopropylphenyl Selenide (**1a**)

Entry	Lewis acid	Tartrate[a]	Solvent	Condition	Selenoxide (2a) Chem. yield /%	$[\alpha]_D^{b)}$ /°	E.e.[c] /%
1	$Ti(OPr^i)_4$	(+)-DET	CH_2Cl_2	0 °C, 5 h	70	+7.42	11.0
2	$Ti(OPr^i)_4$	(+)-DET	CH_2Cl_2	−10 °C, 14 h	61	+7.48	11.1
3	$Ti(OPr^i)_4$	(+)-DET	CH_2Cl_2	−15 °C, 18 h	58	+19.0	28.2
4	$Ti(OPr^i)_4$	(+)-DET	CH_2Cl_2	−25 °C, 26 h	56	+16.6	24.6
5	$Ti(OPr^i)_4$	(−)-DET	CH_2Cl_2	−15 °C, 18 h	57	−14.2	21.1
6	$Ti(OPr^i)_4$	(+)-DMT	CH_2Cl_2	−15 °C, 18 h	57	+13.7	20.3
7	$Ti(OPr^i)_4$	(+)-DIPT	CH_2Cl_2	−15 °C, 18 h	74	+7.28	10.8
8	$Ti(OBu^n)_4$	(+)-DET	CH_2Cl_2	−15 °C, 18 h	53	+8.14	12.1
9	$Al(OPr^i)_3$	(+)-DET	CH_2Cl_2	−15 °C, 70 h	3.8	−0.96	1.4
10[d]	$Ti(OPr^i)_4$	(+)-DET	CH_2Cl_2	−28 °C, 40 h	27	−0.35	0.5
11	$Ti(OPr^i)_4$	(+)-DET	Et_2O	−15 °C, 20 h	51	−2.50	3.7
12	$Ti(OPr^i)_4$	(−)-DET	Et_2O	−15 °C, 20 h	47	+1.65	2.4
13	$Ti(OPr^i)_4$	(+)-DET	CH_3CN	−15 °C, 18 h	54	+5.58	8.3

a) DMT: dimethyl tartrate, DET: diethyl tartrate, DIPT: diisopropyl tartrate. b) Optical rotations were taken in chloroform. c) Determined by ^1H NMR by using optically active shift reagent, $Eu(hfc)_3$. d) Equimolar water (1 mmol) was added to the mixture of Lewis acid and tartrate.

Table 2. Asymmetric Oxidation of Alkyl 2,4,6-Tri-*t*-butylphenyl Selenide (**1b**—**1e**)a)

Entry	Selenide	DETb)	Solvent	Condition	Selenoxide			
						Chem. yield /%	$[\alpha]_D^{c)}$ /°	E.e.d) /%
1	**1b**	(+)-DET	CH_2Cl_2	−15 °C, 63 h	**2b**	12	−9.60	7.9
2	**1b**	(−)-DET	CH_2Cl_2	−15 °C, 63 h	**2b**	15	+9.17	7.5
3	**1b**	(+)-DET	Et_2O	−15 °C, 63 h	**2b**	12	−39.9	32.7
4	**1b**	(−)-DET	Et_2O	−15 °C, 63 h	**2b**	9.0	+32.1	26.3
5	**1c**	(+)-DET	CH_2Cl_2	25 °C, 160 h	**2c**	18	+2.65	2.8
6	**1c**	(+)-DET	Et_2O	25 °C, 160 h	**2c**	30	+10.8	11.4
7	**1d**	(+)-DET	CH_2Cl_2	25 °C, 72 h	**2d**	22	+5.97	6.6
8	**1e**	(+)-DET	CH_2Cl_2	25 °C, 72 h	**2e**	19	+27.8	16.7

a) Titanium tetraisopropoxide was used as the Lewis acid. b) DET: diethyl tartrate. c) Optical rotations were taken in chloroform. d) Determined by ^1H NMR by using optically active shift reagent, $Eu(hfc)_3$

oxidation of sulfides.8) We studied the oxidation of **1a** by adding equimolar amounts of water to our reaction systems. However, the addition of water only decreased the ratio of the enantiomers (Entry 10). The oxidation of **1a** was also carried out in ether or acetonitrile (Entries 11—13). Though the e.e. decreased in both solvents, (+)-selenoxide (+)-**2a** and (−)-selenoxide (−)-**2a** were obtained by the use of (−)-DET and (+)-DET, respectively, in ether (Entries 11 and 12). The absolute configurations of **2a** obtained in ether were opposite to the results found in dichloromethane or acetonitrile. These results suggest that there is an interaction between the Lewis acid and the lone pair of oxygen atoms of solvent ether, which reverses the selectivity of the enantio-face in the oxidation of the selenide.

The asymmetric oxidations of several alkyl 2,4,6-tri-*t*-butylphenyl selenides (**1b**—**1e**) were carried out using diethyl tartrate and titanium tetraisopropoxide. Methyl, neopentyl, and benzyl groups were chosen as alkyl groups since the existence of *β*-hydrogen of selenoxide easily caused *β*-elimination.9) The results are shown in Table 2. In the oxidation of **1b**, (−)-**2b** was obtained in 33% optical yield in ether using (+)-DET, although the reaction was slow and the chemical yield was 12% after 63 h (Entry 3). Similarly, (+)-**2b** were obtained in 26% optical yield by the oxidation of **1b** using (−)-DET in ether (Entry 4). Asymmetric oxidations of **1c** were also carried out in dichloromethane or ether using (+)-DET (Entries 5 and 6). A higher e.e. of **2c** was obtained in ether than in dichloromethane. However in this case, optically active (+)-selenoxide (+)-**2c** was formed in both solvents.

The solvent effects in the oxidations of **1a**—**1c** prompted us to study the oxidations of benzyl 2,4,6-tri-*t*-butylphenyl selenide (**1d**) and *o*-methoxybenzyl 2,4,6-tri-*t*-butylphenyl selenide (**1e**) in order to clarify the effect of the oxygen atom of the methoxyl group in **1e**. The oxidations of **1d** and **1e** gave optically active selenoxides (**2d** and **2e**) in 7 and 17% optical yields, respectively (Entries 7 and 8). The ortho methoxyl group in **1e** pretty much increased the e.e. in the oxidation of the selenides. The solvent effect and substrate dependence are very interesting, though the mechanism of the asymmetric oxidation of selenides under these conditions is not clear at the present time.

Davis et al. proposed that the absolute configurations of selenoxides (+)-**2a** and (−)-**2a** are *S* and *R* forms, respectively.2) However, the optically active selenoxides, **2b**—**2e**, are new compounds and the absolute configurations are not known. We tried to estimate the optically active alkyl aryl selenoxides **2a**—**2e** by comparisons of the circular dichroism spectra with those of alkyl aryl sulfoxides. All (+)-selenoxides (+)-**2a**—**2b** showed positive first Cotton effects in the 258—301 nm region on circular dichroism spectra, as shown in Table 3. On the other hand, alkyl aryl sulfoxides, such as (+)-methyl *p*-tolyl sulfoxide, showed a positive first Cotton effect at 241 nm10) and (+)-ethyl phenyl sulfoxide also had a positive Cotton effect at 245 nm.11) Since both (+)-sulfoxides had been determined to be *R*-configuration, the (+)-selenoxides (+)-**2a**—**2e** were estimated to be of *R* form. These estimations are opposite to those absolute configurations proposed by Davis et al.2)

Experimental

Materials. **Methyl 2,4,6-triisopropylphenyl selenide (1a)** was prepared by the reaction of 2,4,6-triisopropylphenylmagnesium bromide with dimethyl diselenide,12) and alkyl 2,4,6-tri-*t*-butylphenyl selenides (**1b**—**1e**) were prepared by the reaction of 2,4,6-tri-*t*-butylphenyllithium with the corresponding dialkyl diselenides. The physical and spectral data are as follows.

1a: Mp 43—44 °C; IR (KBr) 3000—2800, 1460, 1360, and 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.23 (18H, d, *J*=7.2 Hz), 2.07 (3H, s), 2.86 (1H, hep., *J*=7.2 Hz), 3.84 (2H, hep., *J*=7.2 Hz), and 6.93 (2H, s); MS (70 eV) *m*/*z* 298 (M^+)(^{80}Se); Found: *m*/*z* 298.1230, Calcd for $C_{16}H_{26}{}^{80}Se$: M, 298.1200.

1b: Mp 86.5—87.0 °C; IR(KBr) 3000—2800, 1580, 1465, 1380, 1350, and 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.28 (9H, s),

Table 3. Circular Dichroism of Optically Active Selenoxides (+)-**2a**—**2e**

Selenoxide	First Cotton effect /sign (nm)
(+)-**2a**	+(258)
(+)-**2b**	+(262)
(+)-**2c**	+(263)
(+)-**2d**	+(301)
(+)-**2e**	+(290)

1.59 (18H, s), 1.93 (3H, s), and 7.31 (2H, s,); MS (70 eV) *m/z* 340 (M$^+$) (^{80}Se); Found: *m/z* 340.1650, Calcd for $C_{19}H_{32}{}^{80}Se$: M, 340.1669.

1c: Mp 118—119 °C; IR (KBr) 3000—2800, 1585, 1460, 1380, 1355, 1240, 1210, and 875 cm^{-1}; ^{1}H NMR(CDCl$_3$) δ=1.02 (9H, s), 1.28 (9H, s), 1.59 (18H, s), 2.43 (2H, s), and 7.27 (2H, s); MS (70 eV) *m/z* 396 (M$^+$) (^{80}Se); Found: *m/z* 396.2299, Calcd for $C_{23}H_{40}{}^{80}Se$: M, 396.2295.

1d: Mp 82—83 °C; IR (KBr) 3000—2800, 1500, 1450, 1390, and 1360 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=1.31 (9H, s), 1.59 (18H, s), 3.65 (2H, s), 7.0—7.3 (5H, m), and 7.36 (2H, s); MS (70 eV) *m/z* 416 (M$^+$) (^{80}Se); Found: *m/z* 416.1989, Calcd for $C_{25}H_{36}{}^{80}Se$: M, 416.1982.

1e: Mp 132.5—133.0 °C; IR (KBr) 3000—2800, 1590, 1490, 1465, 1390, 1360, and 1250 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=1.31 (9H, s), 1.57 (18H, s), 3.64 (2H, s), 3.74 (3H, s), 6.6—7.2 (4H, m), and 7.27 (2H, s); MS (70 eV) *m/z* 446 (M$^+$) (^{80}Se); Found: *m/z* 446.2079, Calcd for $C_{26}H_{38}O{}^{80}Se$: M, 446.2088.

General Procedure for the Asymmetric Oxidation of Selenides. A typical manner for the oxidation of **1a** is described below. (+)-Diethyl tartrate (0.34 cm^3, 2.0 mmol) and titanium tetraisopropoxide (0.30 cm^3, 1.0 mmol) were dissolved in 8.0 cm^3 of dichloromethane under nitrogen, and the mixture was stirred for 30 min. Methyl 2,4,6-triisopropylphenyl selenide (**1a**) (297 mg, 1.0 mmol) was added to the mixture and cooled to −15 °C. A solution of *t*-butyl hydroperoxide (1.3 mmol), dried over magnesium sulfate prior to use, in dichloromethane (2.0 cm^3) was added to the cooled solution. Stirring was continued for 18 h at −15 °C. The reaction mixture was subjected to alumina column chromatography without evaporation of the solvent using hexane–ethyl acetate as an eluent to give 182 mg (58%) of methyl 2,4,6-triisopropylphenyl selenoxide (**2a**). $[\alpha]_D^{22}$ + 19.0° (*c* 1.17, chloroform). Enantiomeric excess (e.e.) was determined to be 28.2% by ^{1}H NMR using optically active shift reagent (Eu(hfc)$_3$).

(*R*)-(+)-2a: Mp 154.0—154.5 °C; $[\alpha]_D^{22}$ +19.0° (*c* 1.17, chloroform); e.e.=28.2%; IR (KBr) 820 (Se=O) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=1.20, 1.23, and 1.27 (18H, d, *J*=7.2 Hz, methyl of isopropyl), 2.74 (3H, s), 2.5—3.1 (1H, m), 3.92 (2H, hep.), and 7.03 (2H, s); UV (methanol) 261 (ε 5.03×10^3), 233 (ε 1.09×10^4), and 208 (ε 3.80×10^4) nm; CD (methanol) 258 ([θ] +5.13×10^3) and 228 ([θ] −2.21×10^3) nm; MS (30 eV) *m/z* 314 (M$^+$) (^{80}Se); Found *m/z* 314.1154, Calcd for $C_{16}H_{26}O{}^{80}Se$: M, 314.1149.

(*S*)-(−)-2a: 154.5—155.0 °C; $[\alpha]_D^{27}$ −14.2° (*c* 1.35, chloroform); e.e.=21.1%; IR (KBr) 820 (Se=O) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=1.20, 1.23, and 1.27 (18H, d, *J*=7.2 Hz, methyl of isopropyl), 2.74 (3H, s), 2.5—3.1 (1H, m), 3.92 (2H, hep.), and 7.03 (2H, s); UV (methanol) 261 (ε 4.70×10^3), 233 (ε 1.04×10^4), and 208 (ε 3.75×10^4) nm; CD (methanol) 258 ([θ] −3.24×10^3) and 227 ([θ] +1.50×10^3) nm; MS (30 eV) *m/z* 314 (M$^+$) (^{80}Se); Found *m/z* 314.1159, Calcd for $C_{16}H_{26}O{}^{80}Se$: M, 314.1149.

(*R*)-(+)-2b: Mp 123.5—124.0 °C; $[\alpha]_D^{26}$ +32.1° (*c* 0.64, chloroform); e.e.=26.3%; IR (KBr) 830 (Se=O) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=1.29 (9H, s), 1.55 (18H, s), 2.55 (3H, s), and 7.37 (2H, s); UV (methanol) 261 (ε 3.40×10^3), 235 (ε 1.02×10^4), and 208 (ε 3.00×10^4) nm; CD (methanol) 262 ([θ] +7.42×10^3), 237 ([θ] −1.13×10^3), and 223 ([θ] +7.41×10^3) nm; MS (30 eV) *m/z* 356 (M$^+$)(^{80}Se); Found: *m/z* 356.1615, Calcd for $C_{19}H_{32}O{}^{80}Se$: M, 356.1618.

(*S*)-(−)-2b: Mp 124.0—124.5 °C; $[\alpha]_D^{28}$ −39.9° (*c* 0.88, chloroform); e.e.=32.7%; IR (KBr) 830 (Se=O) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=1.29 (9H, s), 1.55 (18H, s), 2.55 (3H, s), and 7.37 (2H, s); UV (methanol) 262 (ε 3.61×10^3), 236 (ε 1.07×10^4), and 207 (ε 3.14×10^4) nm; CD (methanol) 262 ([θ] −9.32×10^3), 237 ([θ] +1.24×10^3), and 221 ([θ] −1.02×10^4) nm; MS (30 eV) *m/z* 356 (M$^+$)(^{80}Se); Found: *m/z* 356.1548, Calcd for $C_{19}H_{32}O{}^{80}Se$: M, 356.1618.

(*R*)-(+)-2c: Mp 114.5—115.0 °C; $[\alpha]_D^{22}$ +10.8° (*c* 1.24, chloroform); e.e.=11.4%; IR (KBr) 830 (Se=O) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=1.09 (9H, s), 1.30 (9H, s), 1.58 (18H, s), 2.08 and 3.17 (2H, ABq, *J*=12.0 Hz), and 7.35 (2H, s); UV (methanol) 270 (ε 3.77×10^3), 243 (ε 9.26×10^3), and 208 (ε 3.02×10^4) nm; CD (methanol) 263 ([θ] +2.78×10^3) and 232 ([θ] −3.30×10^3) nm; MS (30 eV) *m/z* 412 (M$^+$) (^{80}Se); Found: *m/z* 412.2208, Calcd for $C_{23}H_{40}O{}^{80}Se$: M, 412.2244.

(*R*)-(+)-2d: Mp 138 °C (decomp); $[\alpha]_D^{22}$ +5.97° (*c* 0.71, chloroform); e.e.=6.6%; IR (KBr) 840 (Se=O) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=1.32 (9H, s), 1.41 (18H, s), 4.0—4.2 (2H, m), 6.4—7.2 (5H, m), and 7.29 (2H, s); UV (methanol) 281 (ε 2.39×10^3), 237 (ε 1.18×10^4), and 203 (ε 4.02×10^4) nm; CD (methanol) 301 ([θ]+2.94×10^3) and 244 ([θ]+3.23×10^3) nm; MS (30 eV) *m/z* 432 (M$^+$) (^{80}Se); Found: *m/z* 432.1915, Calcd for $C_{25}H_{36}O{}^{80}Se$: M, 432.1931.

(*R*)-(+)-2e: Viscous oil; $[\alpha]_D^{22}$ +27.8° (*c* 0.96, chloroform); e.e.=16.7%; IR (liq. film) 840 (Se=O) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=1.37 (9H, s), 1.48 (18H, s), 3.81 (3H, s), 4.1—4.2 (2H, m), 6.4—7.5 (4H, m), and 7.32 (2H, s); UV (methanol) 280 (ε 3.39×10^3), 230 (ε 1.31×10^4), and 202 (ε 3.71×10^4) nm; CD (methanol) 290 ([θ]+6.99×10^3) and 238 ([θ]+1.45×10^4) nm; MS (30 eV) *m/z* 462 (M$^+$) (^{80}Se); Found: *m/z* 462.1992, Calcd for $C_{26}H_{38}O_2{}^{80}Se$: M, 462.2037.

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