Reaction of Difluoromethyl Phenyl Selenoxide with Acetic Anhydride. A Route to Difluoro(phenylseleno)methylation of Ethers

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Received April 5, 1994®

Difluoromethyl phenyl selenoxide (**2**) has been prepared and allowed to react with acetic anhydride in the presence of cyclic ethers and sulfides. Difluorophenylselenomethylation occurred smoothly on reacting **2** with Ac_2O in refluxing dichloromethane to give ω-[difluoro(phenylseleno)methoxy]-alkyl acetates **4** in 34–87% yields. A sequential reaction of Pummerer type rearrangement, difluorocarbene formation, electrophilic addition of the carbene to oxygen of ethers leading to oxonium ylide, and trapping with phenylselenenyl acetate is proposed.

Introduction

Introduction of the fluorine atom into organic molecules sometimes brings about a dramatic change of the physical and chemical properties of the parent molecules and often results in enhancement of biological activities or alternation of the unique physical responses in material science.[1] In recent years, bioactive compounds bearing the difluoromethylene group have attracted great interest[2] and several new methods for the preparation of the functionalized difluoromethylene compounds have been developed.[3] These preparations involve the nucleophilic reactions of the substituted difluoromethyl carbanions (XCF_2^-) which are derived by the metal-induced reactions of halodifluoroacetates,[4] halodifluoromethyl ketones,[5] difluoroallyl halides,[6] halodifluoromethylphosphonates,[7] 2,2-difluoroketene silyl acetals,[8] and dibromodifluoromethane (CF_2Br_2).[9] Meanwhile, the electrophilic reactions of the substituted difluoromethyl radicals ($XCF_2^•$) derived by the metal-initiated reactions of iododifluoroacetates[10] and CF_2Br_2,[11] and difluorocarbene ($:CF_2$) generated from CF_2Br_2 and other halodifluoromethanes[12] have been also employed for the purpose. But there has been no report on the electrophilic reactions of the substituted difluoromethyl carbocations (XCF_2^+)[13] in spite of their potentiality for the synthesis of difluoromethylene compounds. We have communicated a formal generation of the difluoro(phenylseleno)-methyl carbocation equivalent via the Pummerer rearrangement of difluoromethyl phenyl selenoxide (**2**) and its electrophilic reaction with ethers.[14] In this paper, we describe the scope and limitation of the reaction along with the reaction mechanism.

Results and Discussion

The synthesis of **2** is shown in Scheme 1. Aryl difluoromethyl selenides have been already prepared by the reaction of areneselenolates and chlorodifluoromethane (Freon 22) in an alkaline medium.[15] On the other hand, we found that the reaction of benzeneselenolate prepared from diphenyl diselenide and sodium borohydride in EtOH–DMF (2:1) with CF_2Br_2 gave difluoromethyl phenyl selenide (**1**) as a major product in 55% yield. In contrast, difluoromethyl phenyl sulfide became a minor product in the reaction of benzenethiolate with CF_2Br_2.[16] The selenoxide **2** was quantitatively prepared by the oxidation of **1** with hydrogen peroxide in CH_2Cl_2.

The reaction of **2** with acetic anhydride in the presence of cyclic ethers and sulfides **3** proceeds smoothly in refluxing CH_2Cl_2 to give the difluoro(phenylseleno)methyl compounds **4** (Scheme 2). The structure of 4-[difluoro-(phenylseleno)methoxy]butyl acetate (**4c**) was spectroscopically determined. The IR absorption of 1740 cm^{-1} and a singlet of $\delta = 2.04$ (s, 3H) in ^{1}H-NMR reveal the acetoxy group. A series of a multiplet ($\delta = 1.54–1.76$, 4H) and two triplets [$\delta = 3.94$ (2H, $J = 5.9$ Hz) and $\delta = 4.02$ (2H, $J = 6.0$ Hz)] suggests a carbon chain of -O $(CH_2)_4O$-. A triplet at $\delta = 123.2$ ($J = 312.2$ Hz) in ^{13}C

® Abstract published in *Advance ACS Abstracts,* December 15, 1994.

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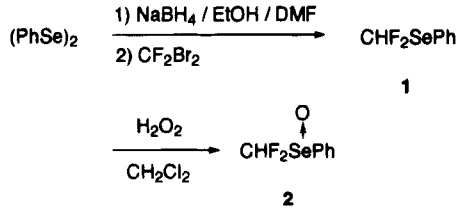
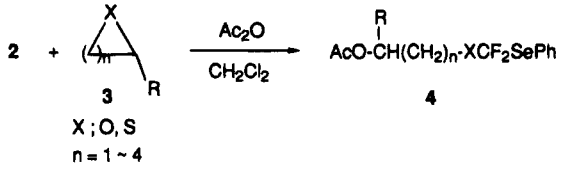
Scheme 1



Scheme 2



Scheme 3

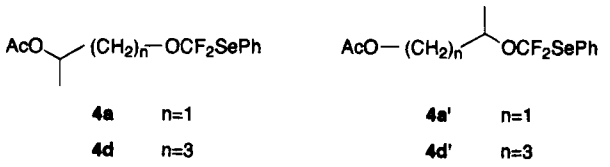


Table 1. Difluoro(phenylseleno)methylation of Ethers and Sulfide[a]

entry	3	n	X	R		yield of 4 (%)[b]
1	**3a**	1	O	Me	(5.0 eq)	34[c,d]
2	**3b**	2	O	H	(5.0 eq)	60
3	**3c**	3	O	H	(2.0 eq)	45
4					(5.0 eq)	68
5					(10.0 eq)	73
6					(2.0 mL)	87
7	**3d**	3	O	Me	(2.0 mL)	56[c,d]
8	**3e**	4	O	H	(1.0 mL)	74
9	**3f**[e]	4	O	H	(1.0 mL)	63
10	**3g**	3	S	H	(5.0 eq)	53[f]

[a] The reaction was carried out with 5 mol equiv of Ac_2O in CH_2Cl_2 (**3c** and **3d** as the solvent, entries 6 and 7) at refluxing temperature for 1 h (entries 6 and 7) or 4 h (others). [b] Isolated yield. [c] Yield of regioisomers. Isomer ratios are 3.5:1 (**4a**:**4a'**) and 1.3:1 (**4d**:**4d'**). [d] Structure of products **4a**, **4a'**, **4d**, and **4d'** are shown in Scheme 3. [e] 1,4-Dioxane. [f] NMR yield was obtained with ^{19}F NMR using *N*-(*p*-anisyl)-2,2,2-trifluoroacetamide as an internal standard.

NMR and a singlet at $\delta = 121.1$ in ^{19}F NMR of **4c** clearly indicate a partial structure of -OCF_2SePh.

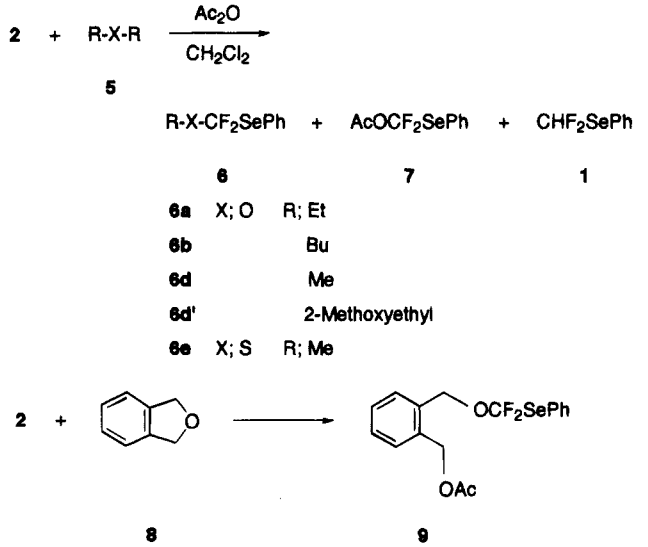
The results of the reaction with a variety of cyclic ethers and a sulfide are summarized in Table 1. The concentration of cyclic ethers affected the yields of **4**. The yield of **4c** increased gradually (45, 68, 73, and 87%) by increasing the concentration of **3c** (2.0, 5.0, 10.0 equiv, and as the solvent; entries 3–6 in Table 1). Similarly, the desired products **4** were provided in moderate yields by using 2-methyltetrahydrofuran (**3d**), tetrahydropyran (**3e**), and 1,4-dioxane (**3f**) as the solvent (entries 7, 8, and 9 in Table 1). In contrast, solutions of propylene oxide (**3a**) and oxetane (**3b**) favored the formation of **4a** and **4b** (entries 1 and 2 in Table 1), whereas using **3a** and **3b** as the solvent decreased the yields of **4a** and **4b** and those of oligomers increased. Steric hindrance disfavored the reaction. The reactivities of the methyl-substituted tetrahydrofurans were in the order of tetrahydrofuran > 2-methyltetrahydrofuran ≫ 2,2-dimethyltetrahydrofuran. In particular, the reaction with 2,2-dimethyltetrahydrofuran provided only a trace amount of the desired product. The regiochemistry of the ring opening of **3a** and **3d** were controlled by Markovnikov's rule. The secondary alkyl acetates **4a** and **4d** became major regioisomers (**4a**:**4a'** = 3.5:1 and **4d**:**4d'** = 1.3:1) (Scheme 3).

Table 2. Difluoro(phenylseleno)methylation of Acyclic Ethers and Sulfide[a]

	yields[b]		
ethers (sulfide) **5**	**6**[c] (%)	**7**[d] (%)	**1** (%)
5a EtOEt	**6a** (36)	31	2
5b BuOBu	**6b** (12)	41	4
5c CF_3CH_2OBu	–	66	5
5d DME	**6d** (24), **6d'** (29)	11	5
5e MeSMe	**6e** (29)	3	6

[a] The reaction was carried out with 5 mol equiv of Ac_2O in CH_2Cl_2 at refluxing temperature for 4 h. [b] Yields were obtained by ^{19}F NMR using *N*-(*p*-anisyl)-2,2,2-trifluoroacetamide as an internal standard. [c] Structure of products **6** are shown in Scheme 4. [d] See ref 20.

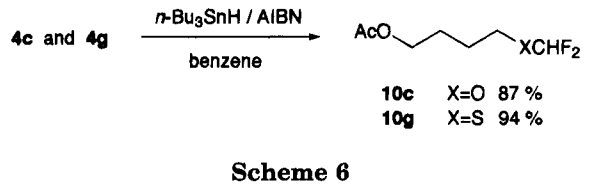
Scheme 4



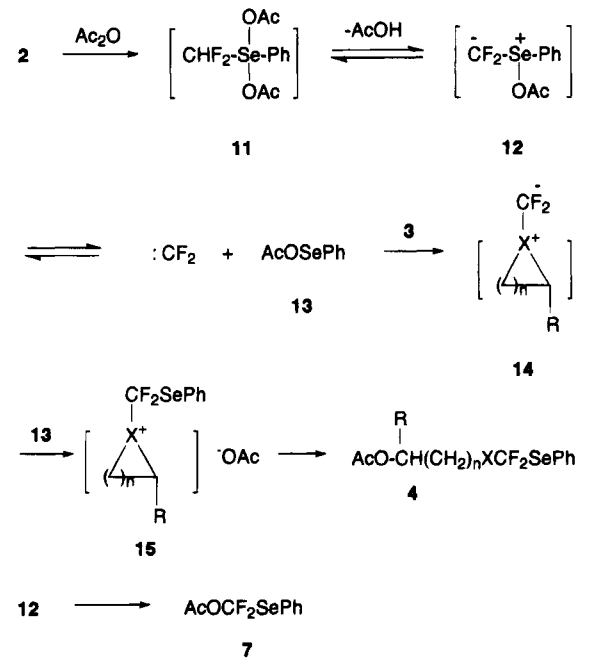
The results of the reaction with acyclic ethers and a sulfide are summarized in Table 2. It is noteworthy that even the carbon–oxygen bond of diethyl ether **5a** is cleaved at about 40 °C to give the desired product **6a** in 36% yield (Scheme 4). However, the reactions with acyclic ethers resulted generally in low yields. In particular, dibutyl ether provided only 12% of **6b**. The competitive reaction of THF and Et_2O with **2** revealed that THF was more reactive than ethyl ether since the compound **4c** and the compound **6a** were obtained in 65 and 4% yields, respectively, on reacting **2** in a mixture of equimolar amounts of THF and Et_2O. These results suggest that steric hindrance plays an important role in the reaction of acyclic ethers as observed in the reaction of the methyl-substituted tetrahydrofurans.

Aromatic ethers are unreactive under these reaction conditions. The reaction of **2** with anisole, 1,4-hydroquinone dimethyl ether, and 2,3-dihydrobenzofuran did not provide the desired products but gave the Pummerer product **7** as a major product (50–60%). It is noteworthy that 1,3-dihydroisobenzofuran **8** gave difluoro(phenylseleno)methyl compound **9** in 58% yield, but 2,3-dihydrobenzofuran did not. The poor reactivity of these aromatic ethers would be due to less nucleophilicity of the oxygen atom attached to an aromatic ring and the steric hindrance of the aromatic group. The electronic nature of alkyl group in ethers also strongly affected the reaction course. Butyl 2,2,2-trifluoroethyl ether **5c** pro-

Scheme 5



Scheme 6



vided neither **6b** nor difluoro(phenylseleneno)methyl 2,2,2-trifluoroethyl ether.

The reactions of **2** with sulfides such as tetrahydrothiophene **3g** and dimethyl sulfide (**5e**) provided the desired products **4g** and **6e** in low yields. Meanwhile, pyrrolidine, *N*-methylpyrrolidine, and *N*-acetylpyrrolidine provided none of the desired products.

Deselenation of **4c** and **4g** by an *n*-Bu_3SnH–AIBN–benzene system afforded the desired difluoromethyl ether **10c** and the sulfide **10g** in 87 and 94% yields, respectively (Scheme 5).

A plausible reaction mechanism is shown in Scheme 6. The selenoxide **2** reacts with acetic anhydride to form the tetravalent selenium intermediate **11** which could be observed by ^{19}F NMR. On adding Ac_2O to **2** in THF–$CDCl_3$ at 20 °C in an NMR tube, two doublets of doublets of **2** with coupling constants of J_1 = 249.9 Hz and J_2 = 53.4 Hz at 49.0 and 50.9 ppm disappeared within 1 h and one doublet (J = 54.0 Hz) of **11** at 61.6 ppm appeared in ^{19}F NMR spectrum. The signal change from the doublet of doublet of **2** to a single doublet clearly suggests a loss of an asymmetric center of the substrate. The tetravalent bisacetates like **11** are known.[17] The intermediate **11** releases acetic acid to produce the ylide intermediate **12** which decomposes into difluorocarbene and benzeneselenenyl acetate **13**. The intermediate **12** would also partially rearrange to the Pummerer product **7**. Judging from the steric and electronic effects of ethers shown in Tables 1 and 2, the two pathways of **12** (**12** → **13** → **14** and **12** → **7**) are competitive and strongly dependent on the reactivity of ethers. Difluorocarbene

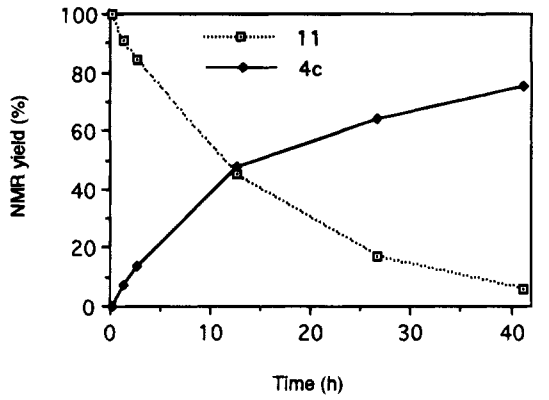
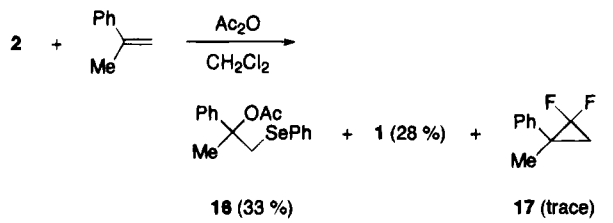
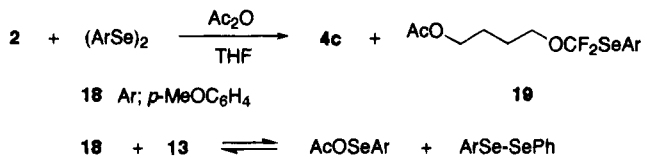


Figure 1. Reaction of **2** with Ac_2O in $CDCl_3$–THF.

Scheme 7



Scheme 8



attacks the oxygen atom of the ethers **3**,[18] producing the oxonium ylide **14** which subsequently would react with **13** to give the final product **4**. The time-dependent yield of **4c** and consumption of the intermediate **11** were measured in $CDCl_3$ by ^{19}F NMR (Figure 1). In the meantime, the reaction of **2** with Ac_2O in the presence of α-methylstyrene produced the compound **16** and the selenide **1** in 33 and 28% yields, respectively, along with difluorocyclopropane **17**, the structure of which was spectroscopically consistent with the authentic sample[19] (Scheme 7). Although the yield of **17** was small, difluorocyclopropanation clearly demonstrates the carbene formation. The formation of **16** also supports the existence of **13**. Meanwhile, the reaction of **2** with Ac_2O in the presence of $(p\text{-}MeOC_6H_4Se)_2$ **18** in THF provided **4c** and the aryl selenide **19** (Scheme 8). The amount of **18** affected the yield of **19**. The yield of **19** increased gradually and the yield of **4c** decreased as increasing amounts of **18** were added as shown in Figure 2.

The Pummerer product **7** was too unstable to be isolated in a pure form. So, the acetate **7** in situ-generated by the reaction of **2** with Ac_2O in CH_2Cl_2[20] was subjected to the reaction with THF under the Pummerer reaction conditions, but none of **4c** was detected. This experimental result suggests that deacetoxylation of **7** leading to difluoro(phenylseleno)methyl carbocation does not occur.

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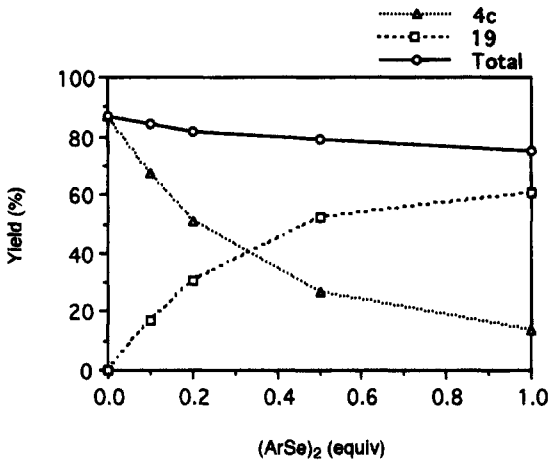
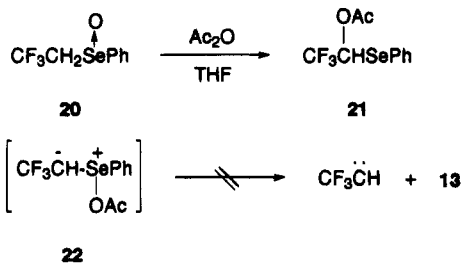


Figure 2. Reactionof **2** with Ac_2O in the presence of $(ArSe)_2$ in THF.

Scheme 9



The competitive reaction of THF and the sulfide **3g** with **2** revealed that **3g** was more reactive than THF since the compound **4g** and the compound **4c** were obtained in 34 and 20% yields, respectively, on reacting **2** in a mixture of equimolar amounts of **3g** and THF. But the reaction of **2** with the sulfide **3g** provided the desired product **4g** in the lower yield (53%) as compared with that (68%) of THF. This result is due to the fact that oxygen transfer from the selenoxide **2** to tetrahydrothiophene occurred.[21] So, the reaction of **2** with Ac_2O competes with the oxygen transfer reaction to **3g** from **2**, resulting in the lower yield of **4g**.

In contrast to the fast leaving of difluorocarbene from the Pummerer intermediate **12**, the reaction of phenyl 2,2,2-trifluoroethyl selenoxide **20** with Ac_2O in THF gave exclusively the Pummerer rearrangement product **21** in 94% yield (Scheme 9). The intermediate **22** could undergo the normal Pummerer rearrangement since the leaving of 2,2,2-trifluoroethyl carbene from **22** is unfavorable. It is well-known that the carbenes bearing halogens and heteroatoms are in general stable; meanwhile, those bearing the strongly electron-withdrawing groups are unstable. Difluorocarbene is such a good leaving group that the process from **12** to **13** would be fast.

In conclusion, difluoromethyl phenyl selenoxide (**2**) reacts smoothly with acetic anhydride in methylene chloride to generate the difluoromethylene selenonium ylide **12**, which undergoes competitively carbon–selenium bond cleavage leading to the formation of difluoro carbene and phenylselenenyl acetate (**13**) and the normal Pummerer rearrangement. Aliphatic ethers, in particular, cyclic ethers, are transformed to ω-acetoxyalkyl difluoro(phenylseleno)methyl ethers **4** under those reaction conditions.

Experimental Section

IR spectra were taken on a Hitachi 270-30 spectrometer. The ^1H, ^{13}C, and ^{19}F NMR spectra were measured on a Varian VXR-500 and -200 instruments using TMS and C_6F_6 as internal standards. Some yields were obtained by ^{19}F NMR using *N*-(*p*-anisyl)-2,2,2-trifluoroacetamide as an internal standard. Melting points and boiling points are uncorrected. Boiling points are indicated as a temperature of a glass tube oven.

Difluoromethyl Phenyl Selenide (1).[15] Benzeneselenolate was prepared by reduction of $(PhSe)_2$ (23.4 g, 75 mmol) with $NaBH_4$ (8.5 g, 225 mmol) dissolved in dry DMF (112.5 mL) and dry EtOH (225 mL) at 0 °C for 15 min under Ar atmosphere. The reaction mixture was cooled to −80 °C, CF_2Br_2 (20.1 mL, 225 mmol) was added and then the temperature of the mixture was allowed to rise at room temperature for 1 h. The reaction mixture was poured into water, neutralized with aqueous NH_4Cl, and extracted with hexane several times. The extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane) to give a mixture of **1** and $(PhSe)_2$, which was distilled at reduced pressure to give **1** (17.2 g, 55% based on benzeneselenolate) as a colorless oil: bp 89–90 °C (35 Torr); IR (neat) 1478, 1442, 1272, 1062 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18 (t, 1H, J = 55.5 Hz), 7.34–7.75 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 117.1 (t, J = 287.3 Hz), 123.5 (t, J = 2.7 Hz), 129.4, 129.5 (2C), 136.3 (2C); ^{19}F NMR ($CDCl_3$) δ 71.5 (d, J = 55.5 Hz).

Difluoromethyl Phenyl Selenoxide (2). To a solution of **1** (3.11 g, 15 mmol) in CH_2Cl_2 (20 mL) was added aqueous H_2O_2 (7.4 mL, 75 mmol), and then the resulting mixture was refluxed under vigorous stirring for 4 h. The reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with AcOEt several times. The extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was recrystallized from hexane and CH_2Cl_2 to provide **3** (3.35 g, quant) as white crystals: mp 97–98 °C; IR (Nujol) 1478, 1444, 1262, 1072 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.29 (dd, 1H, J_1 = 53.1 Hz, J_2 = 52.9 Hz), 7.61–7.78 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 121.5 (t, J = 305.1 Hz), 126.4 (2C), 129.7 (2C), 132.2, 135.3 (t, J = 2.3 Hz); ^{19}F NMR ($CDCl_3$) δ 49.0 (dd, 1F, J_1 = 249.9 Hz, J_2 = 53.4 Hz), and 50.9 (dd, 1F, J_1 = 249.9 Hz, J_2 = 53.4 Hz). Anal. Calcd for $C_7H_6F_2OSe$: C, 37.69; H, 2.71. Found: C, 37.79; H, 2.86.

General Experimental Procedure. To a solution of **2** (111.6 mg, 0.5 mmol) and ethers or sulfides in dry CH_2Cl_2 (2.0 mL) was added acetic anhydride (0.24 mL, 2.5 mmol) at 0 °C under Ar atmosphere, and then the resulting mixture was refluxed under stirring for 4 h. The reaction mixture was washed with aqueous Na_2CO_3, neutralized with aqueous NH_4Cl, and extracted with AcOEt several times. The extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. An internal standard (*N*-(*p*-anisyl)-2,2,2-trifluoroacetamide) was added to the residue, and yields of products were obtained by ^{19}F NMR.

2-[3-[Difluoro(phenylseleno)methoxy]propyl] Acetate (4a) and 2-[Difluoro(phenylseleno)methoxy]propyl Acetate (4a'). To a solution of **2** (111.6 mg, 0.5 mmol) and propylene oxide (**3a**) (0.35 mL, 2.5 mmol) in dry CH_2Cl_2 (2.0 mL) was added acetic anhydride (0.24 mL, 2.5 mmol) at 0 °C under Ar atmosphere, and then the resulting mixture was refluxed under stirring for 4 h. The reaction mixture was washed with aqueous Na_2CO_3, neutralized with aqueous NH_4Cl, and extracted with AcOEt several times. The extracts were washed with brine, dried over $MgSO_4$, and concentrated in

(20) To a solution of the selenoxide **2** in CH_2Cl_2 was added Ac_2O at 0 °C under Ar atmosphere, and then the resulting mixture was refluxed under stirring for 4 h. After the selenoxide **2** was completely consumed, THF was added, and then the resulting mixture was refluxed under stirring for 1 day. None of the desired product **4c** was detected. The compound **7** was too unstable to be purified for elemental analysis: ^1H NMR ($CDCl_3$) δ 2.12 (s, 3H), 7.32–7.77 (m, 5H); ^{19}F NMR ($CDCl_3$) δ 119.6 (s).

(21) For a review of selenoxides as oxidizing agents, see: Reich, H. J. *Oxidations in Organic Reactions, Part C*; Trahanovsky, W. S., Ed.; Academic Press: New York, 1978; Chapter 1.

vacuo. The residue was chromatographed on silica gel (elution with hexane–AcOEt 20:1) to give a mixture of two regioisomers **4a** and **4a'** (55.4 mg, 34%) as a colorless oil (the ratio of **4a** and **4a'** = 3.5:1): IR (neat) 1744 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) (**4a**) δ 1.19 (d, 3H, J = 6.5 Hz), 2.00 (s, 3H), 3.92 (d, 2H, J = 4.9 Hz), 4.96–5.11 (m, 1H), 7.30–7.73 (m, 5H); (**4a'**) δ 1.26 (d, 3H, J = 6.4 Hz), 2.03 (s, 3H), 4.04 (d, 2H, J = 5.5 Hz), 4.55–4.70 (m, 1H), 7.30–7.73 (m, 5H); ^{13}C NMR ($CDCl_3$) (**4a**) δ 16.2, 21.1, 67.9, 68.1 (t, J = 4.6 Hz), 123.2 (t, J = 315.6 Hz), 124.6, 129.2 (2C), 129.4, 136.5 (2C), 170.3; (**4a'**) δ 17.7, 20.6, 66.1, 72.3 (t, J = 3.8 Hz), 123.1 (t, J = 314.4 Hz), 124.9, 129.1 (2C), 129.3, 136.3 (2C), 170.6; ^{19}F NMR ($CDCl_3$) (**4a**) δ 120.3 (s); (**4a'**) δ 123.1 (s). Anal. Calcd for $C_{12}H_{14}F_2O_3Se$: C, 44.90; H, 4.37. Found: C, 44.60; H, 4.44.

3-[Difluoro(phenylseleno)methoxy]propyl acetate (4b): yield 60%; a colorless oil; IR (neat) 1746 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.91 (quint, 2H, J = 6.2 Hz), 2.04 (s, 3H), 4.00 (t, 2H, J = 6.2 Hz), 4.06 (t, 2H, J = 6.2 Hz), 7.28–7.74 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.8, 28.1, 60.5, 63.2 (t, J = 4.6 Hz), 123.2 (t, J = 312.6 Hz), 124.7, 129.2 (2C), 129.4, 136.3 (2C), 170.8; ^{19}F NMR ($CDCl_3$) δ 120.6 (s). Anal. Calcd for $C_{12}H_{14}F_2O_3Se$: C, 44.60; H, 4.37. Found: C, 44.97; H, 4.65.

4-[Difluoro(phenylseleno)methoxy]butyl acetate (4c): yield 87%; a colorless oil; IR (neat) 1740 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54–1.76 (m, 4H), 2.04 (s, 3H), 3.94 (t, 2H, J = 5.9 Hz), 4.02 (t, 2H, J = 6.0 Hz), 7.28–7.76 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.7, 24.8, 25.4, 63.6, 66.2 (t, J = 4.6 Hz), 123.2 (t, J = 312.2 Hz), 124.8, 129.1 (2C), 129.2, 136.2 (2C), 170.8; ^{19}F NMR ($CDCl_3$) δ 121.1 (s). Anal. Calcd for $C_{13}H_{16}F_2O_3Se$: C, 46.30; H, 4.78. Found: C, 46.57; H, 4.95.

4-[Difluoro(phenylseleno)methoxy]-1-methylbutyl acetate (4d) and 4-[Difluoro(phenylseleno)methoxy]-4-methylbutyl acetate (4d'): yield 56%; a colorless oil (a mixture of two regioisomers **4d** and **4d'**; the ratio = 1.3:1); IR (neat) 1738 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) (**4d**) δ 1.18 (d, 3H, J = 6.3 Hz), 1.45–1.70 (m, 4H), 2.03 (s, 3H), 3.92 (t, 2H, J = 5.9 Hz), 4.78–4.94 (m, 1H), 7.30–7.75 (m, 5H); (**4d'**) δ 1.26 (d, 3H, J = 6.2 Hz), 1.45–1.70 (m, 4H), 2.04 (s, 3H), 3.99 (t, 2H, J = 6.2 Hz), 4.37–4.51 (m, 1H), 7.30–7.75 (m, 5H); ^{13}C NMR ($CDCl_3$) (**4d**) δ 19.9, 21.3, 24.9, 32.0, 66.5 (t, J = 4.7 Hz), 70.3, 123.3 (t, J = 314.9 Hz), 124.9, 129.2 (2C), 129.3, 136.4 (2C), 170.7; (**4d'**) δ 20.9, 24.2, 33.1, 53.4, 63.9, 70.9 (t, J = 3.9 Hz), 123.1, (t, J = 313.3 Hz), 124.8, 129.0 (2C), 129.3, 136.3 (2C), 171.0; ^{19}F NMR ($CDCl_3$) (**4d**) δ 121.2 (s); (**4d'**) δ 124.0 (s). Anal. Calcd for $C_{14}H_{18}F_2O_3Se$: C, 47.87; H, 5.17. Found: C, 47.99; H, 5.30.

5-[Difluoro(phenylseleno)methoxy]pentyl acetate (4e): yield 74%; a colorless oil; IR (neat) 1738 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24–1.43 (m, 2H), 1.50–1.72 (m, 4H), 2.04 (s, 3H), 3.91 (t, 2H, J = 6.3 Hz), 4.01 (t, 2H, J = 6.5 Hz), 7.28–7.74 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.9, 22.1, 28.0, 28.4, 64.1, 66.6 (t, J = 4.6 Hz), 123.3 (t, J = 312.0 Hz), 125.0, 129.1 (2C), 129.3, 136.3 (2C), 171.0; ^{19}F NMR ($CDCl_3$) δ 121.8 (s). Anal. Calcd for $C_{14}H_{18}F_2O_3Se$: C, 47.87; H, 5.17. Found: C, 48.09; H, 5.28.

2-[2-[Difluoro(phenylseleno)methoxy]ethoxy]ethyl acetate (4f): yield 63%; a colorless oil; IR (neat) 1740 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.08 (s, 3H), 3.59–3.69 (m, 4H), 4.07 (t, 2H, J = 4.8 Hz), 4.17 (t, 2H, J = 4.7 Hz), 7.29–7.76 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.9, 63.4, 66.1 (t, J = 4.6 Hz), 68.9, 69.2, 123.4 (t, J = 312.8 Hz), 124.8, 129.2 (2C), 129.4, 136.4 (2C), 170.9; ^{19}F NMR ($CDCl_3$) δ 120.9 (s). Anal. Calcd for $C_{13}H_{16}F_2O_4Se$: C, 44.21; H, 4.57. Found: C, 44.61; H, 4.69.

4-[[Difluoro(phenylseleno)methyl]thio]butyl acetate (4g): yield 53%; a colorless oil: IR (neat) 1738 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65–1.78 (m, 4H), 2.04 (s, 3H), 2.78–2.92 (m, 2H), 3.99–4.12 (m, 2H), 7.30–7.77 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.9, 26.2, 27.5, 31.2, 63.6, 125.7, 127.0 (t, J = 326.6 Hz), 129.2 (2C), 129.8, 136.9 (2C), 171.1; ^{19}F NMR ($CDCl_3$) δ 115.2 (s). Anal. Calcd for $C_{13}H_{16}F_2O_2SSe$: C, 44.20; H, 4.56. Found: C, 44.59; H, 4.70.

Difluoro(phenylseleno)methyl Ethyl Ether (6a). Column chromatography on silica gel (elution with hexane) gave a mixture of **6a** and $(PhSe)_2$, which was distilled under reduced pressure to give **6a** (32.5 mg, 26%) as a colorless oil: bp 100 °C (10 Torr); IR (neat) 1480, 1442, 1262, 1190, 1046 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H, J = 7.1 Hz), 3.99 (q, 2H, J = 7.1 Hz), 7.30–7.75 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.6, 63.0 (t, J = 5.0 Hz), 123.4 (t, J = 312.2 Hz), 124.9, 129.2 (2C), 129.3, 136.4 (2C); ^{19}F NMR ($CDCl_3$) δ 121.6 (s). Anal. Calcd for $C_9H_{10}F_2OSe$: C, 43.05; H, 4.01. Found: C, 43.45; H, 4.37.

Butyl difluoro(phenylseleno)methyl ether (6b): yield 12%; a colorless oil; bp 100 °C (11 Torr); IR (neat) 1478, 1440, 1184, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 7.3 Hz), 1.22–1.40 (m, 2H), 1.50–1.64 (m, 2H), 3.92 (t, 2H, J = 6.5 Hz), 7.28–7.72 (m, 5H); ^{19}F NMR ($CDCl_3$) δ 121.5 (s). Anal. Calcd for $C_{11}H_{14}F_2OSe$: C, 47.32; H, 5.05. Found: C, 47.20 ; H, 5.29.

Difluoro(phenylseleno)methyl methyl ether (6d): yield 24%; a colorless oil; bp 80 °C (13 Torr); IR (neat) 1478, 1442, 1210, 1166, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.62 (s, 3H), 7.30–7.74 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 53.4 (t, J = 5.8 Hz), 123.8 (t, J = 312.3 Hz), 124.7, 129.2 (2C), 129.4, 136.3 (2C); ^{19}F NMR ($CDCl_3$) δ 118.5 (s). Anal. Calcd for $C_8H_8F_2OSe$: C, 40.53; H, 3.40. Found: C, 40.88; H, 3.48.

Difluoro(phenylseleno)methyl 2-Methoxyethyl Ether (6d'). Column chromatography on silica gel (elution with hexane–AcOEt 40:1): yield 29%; a colorless oil; IR (neat) 1478, 1442, 1246, 1178, 1022 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.34 (s, 3H), 3.51–3.58 (m, 2H), 4.02–4.09 (m, 2H), 7.28–7.75 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 59.0, 65.9 (t, J = 4.6 Hz), 70.2, 123.4 (t, J = 313.2 Hz), 124.7, 129.1 (2C), 129.3, 136.4 (2C); ^{19}F NMR ($CDCl_3$) δ 120.9 (s). Anal. Calcd for $C_{10}H_{12}F_2O_2Se$: C, 42.72; H, 4.30. Found: C, 42.88; H, 4.25.

Difluoro(phenylseleno)methyl Methyl Sulfide (6f). Column chromatography on silica gel (elution with hexane) gave a mixture of **6f** and $(PhSe)_2$, which was distilled under reduced pressure to give **6f** as a yellow oil: yield 29%; bp 50 °C (1 Torr); IR (neat) 1478, 1440, 1034 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.31 (s, 3H), 7.30–7.80 (m, 5H); ^{19}F NMR ($CDCl_3$) δ 111.8 (s). Anal. Calcd for $C_8H_8F_2SSe$: C, 37.95; H, 3.18. Found: C, 38.17; H, 3.19.

2-[[Difluoro(phenylseleno)methoxy]methyl]benzyl acetate (9): yield 58%; a brown oil; IR (neat) 1744 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.08 (s, 3H), 5.04 (s, 2H), 5.08 (s, 2H), 7.26–7.72 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 20.7, 63.4, 65.9 (t, J = 5.4 Hz), 123.2 (t, J = 313.8 Hz), 124.5, 128.6, 128.8, 129.1, 129.3 (2C), 129.5, 129.6, 133.3, 134.4, 136.4 (2C), 170.4; ^{19}F NMR ($CDCl_3$) δ 120.7 (s). Anal. Calcd for $C_{17}H_{16}F_2O_3Se$: C, 52.99; H, 4.19. Found: C, 52.93; H, 4.25.

4-(Difluoromethoxy)butyl Acetate (10c). To a suspension of **4c** (199.1 mg, 0.59 mmol) and 2,2'-azobisisobutyronitrile (19.4 mg, 0.12 mmol) in dry benzene (2.0 mL) was added tri-*n*-butyltin hydride (0.25 mL, 0.89 mmol), and then the resulting mixture was refluxed under stirring for 15 min.. The mixture was washed with aqueous HCl, neutralized with aqueous $NaHCO_3$, and extracted with ether several times. The extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane–AcOEt (20:1)) to give **10** (92.9 mg, 87%) as a colorless oil: IR (neat) 1738 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68–1.82 (m, 4H), 2.06 (s, 3H), 3.84–3.92 (m, 2H), 4.07–4.15 (m, 2H), 6.20 (t, 1H, J = 74.9 Hz); ^{13}C NMR ($CDCl_3$) δ 20.9, 25.0, 25.8, 62.9 (t, J = 5.5 Hz), 63.8, 116.0 (t, J = 258.4 Hz), 171.1; ^{19}F NMR ($CDCl_3$) δ 77.6 (d, J = 74.9 Hz). Anal. Calcd for $C_7H_{12}F_2O_3$: C, 46.15; H, 6.64. Found: C, 46.19; H, 6.90.

4-[(Difluoromethyl)thio]butyl acetate (10g): yield 94%; a colorless oil; IR (neat) 1738 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68–1.83 (m, 4H), 2.05 (s, 3H), 2.78–2.90 (m, 2H), 4.04–4.12 (m, 2H), 6.81 (t, 1H, J = 56.2 Hz); ^{13}C NMR ($CDCl_3$) δ 20.7, 26.6 (t, J = 3.2 Hz), 26.7, 27.5, 63.5, 120.5 (t, J = 270.8 Hz), 170.9; ^{19}F NMR ($CDCl_3$) δ 69.0 (d, J = 56.2 Hz). Anal. Calcd for $C_7H_{12}F_2O_2SSe$: C, 42.41; H, 6.10. Found: C, 42.32; H, 6.37.

Reaction of 2 with Ac_2O in the Presence of (p-$MeOC_6H_4Se)_2$ (18) in THF. To a solution of **2** (111.6 mg, 0.5 mmol) and **18** in dry THF (2.0 mL) was added acetic anhydride (0.24 mL, 2.5 mmol) at 0 °C under Ar atmosphere, and then the resulting mixture was refluxed under stirring for 1 h. The reaction mixture was washed with aqueous Na_2CO_3, neutralized with aqueous NH_4Cl, and extracted with AcOEt several times. The extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chro-

matographed on silica gel (hexane–AcOEt (20:1)) to give **4c** and **19**, respectively.

4-[Difluoro(*p*-anisylseleno)methoxy]butyl acetate (19): a yellow oil; IR (neat) 1738 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55–1.75 (m, 4H), 2.05 (s, 3H), 3.82 (s, 3H), 3.93 (t, 2H, J = 6.0 Hz), 4.03 (t, 2H, J = 6.2 Hz), 6.87 (dd, 2H, J_1 = 8.9 Hz, J_2 = 2.6 Hz), 7.62 (dd, 2H, J_1 = 8.9 Hz, J_2 = 2.6 Hz); ^{13}C NMR ($CDCl_3$) δ 20.9, 24.9, 25.5, 55.2, 63.7, 66.0 (t, J = 4.9 Hz), 114.7 (2C), 115.1, 123.2 (t, J = 313.0 Hz), 138.4 (2C), 160.7, 171.0; ^{19}F NMR ($CDCl_3$) δ 119.8 (s). Anal. Calcd for $C_{14}H_{18}O_4F_2Se$: C, 45.79; H, 4.94. Found: C, 45.47; H, 4.82.

Oxygen Transfer Reaction from 2 to the Sulfide 3g. To a solution of **2** (111.6 mg, 0.5 mmol) in CH_2Cl_2 was added the sulfide **3g** (52.9 mg, 0.6 mmol) at 0 °C under Ar atmosphere, and then the resulting mixture was refluxed under vigorously stirring overnight. The reaction mixture was concentrated in vacuo, and then the residue was chromatographed on silica gel (hexane–MeOH) to give the selenide **1** (85.0 mg, 82%), and crude tetramethylene sulfoxide was distilled under reduced pressure to give the sulfoxide (44.6 mg, 86%).

Phenyl 2,2,2-Trifluoroethyl Selenoxide (20). To a solution of $(PhSe)_2$ (6.24 g, 20 mmol) in dry THF (10 mL) was added sodium metal (0.93 g, 40 mmol) and the resulting mixture was allowed to reflux for 4 h under Ar atmosphere. After the mixture was cooled to rt, HMPA (4.0 mL) and then 2,2,2-trifluoroethyl tosylate (10.16 g, 40 mmol) in dry THF (10 mL) were added. The mixture was stirred under refluxing for 4 h. The reaction mixture was neutralized and extracted with hexane several times. The extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was distilled under reduced pressure to give phenyl 2,2,2-trifluoroethyl selenide (8.24 g, 86%) as a colorless oil. Then, to a solution of AcOH (16 mL) and aqueous H_2O_2 (37.3 g, 340 mmol) in CH_2Cl_2 (24 mL) was added the selenide (8.24 g, 34 mmol) at 0 °C, and the resulting mixture was stirred vigorously for 4 h at rt. The reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with AcOEt several times. The extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was recrystallized from hexane and CH_2Cl_2 to provide the selenoxide **20** (4.70 g, 54%) as white crystals: mp 94–95 °C; IR (Nujol) 1466, 1252, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.46 (dq, 1H, J_1 = 13.4 Hz, J_2 = 11.1 Hz), 3.56 (dq, 1H, J_1 = 13.4 Hz, J_2 = 11.1 Hz), 7.50–7.87 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 55.9 (q, J = 29.1 Hz), 123.6 (q, J = 274.7 Hz), 125.6 (2C), 130.1 (2C), 132.3, 139.8; ^{19}F NMR ($CDCl_3$) δ 102.5 (t, J = 11.1 Hz). Anal. Calcd for $C_8H_7F_3OSe$: C, 37.67; H, 2.77. Found: C, 37.90; H, 2.80.

1-(Phenylseleno)-2,2,2-trifluoroethyl Acetate (21). To a solution of **20** (127.6 mg, 0.5 mmol) in dry THF (2.0 mL) was added acetic anhydride (0.24 mL, 2.5 mmol) at 0 °C under Ar atmosphere, and then the resulting mixture was stirred at rt for 0.5 h. The reaction mixture was washed with aqueous Na_2CO_3, neutralized with aqueous NH_4Cl, and extracted with AcOEt several times. The extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane–AcOEt (20:1)) to give **21** (139.8 mg, 94%) as a colorless oil: IR (neat) 1776 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13 (s, 3H), 6.37 (q, 1H, J = 7.5 Hz), 7.28–7.74 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.5, 70.8 (q, J = 35.5 Hz), 123.3 (q, J = 276.6 Hz), 126.1, 129.4 (2C), 129.5, 136.4 (2C), 167.9; ^{19}F NMR ($CDCl_3$) δ 87.6 (d, J = 7.5 Hz). Anal. Calcd for $C_{10}H_9F_3O_2Se$: C, 40.42; H, 3.05. Found: C, 40.82; H, 3.19.

Acknowledgment. Authors are grateful to the Ministry of Education, Culture, and Science of Japan for the financial support (No. 06227248) and the SC-NMR Laboratory of Okayama University for ^{19}F NMR.

JO940539D