Direct Conversion of a Benzylic Hydroxy Group into a Selenenyl Group Using the Phenyl Trimethylsilyl Selenide–Aluminum Bromide Combination

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Received February 27, 1998; accepted May 12, 1998

A new reagent system, phenyl trimethylsilyl selenide–aluminum bromide, was developed for the direct conversion of various benzylic hydroxy groups into a selenenyl group. Treatment of cinnamyl alcohol with this reagent system yielded 3,4-dihydro-4-phenyl-2*H*-1-benzoselenin *via* a [3,3]-sigmatropic rearrangement of the intermediate cinnamyl phenyl selenide.

Key words phenyl trimethylsilyl selenide; benzyl alcohol; aluminum bromide; [3,3]-sigmatropic rearrangement

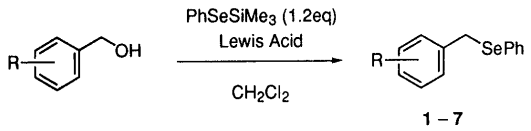
Organoselenium compounds have played an important role in synthetic chemistry.[1] Well known useful transformations using organoselenium compounds, such as β-elimination of a selenoxide[2] and radical fission reaction of a carbon–selenium bond,[3] are frequently employed in the syntheses of various natural products.[4] Although many reagents have been developed to introduce a selenium group into organic molecules,[5] few methods to transform hydroxy group into selenenyl group directly are known; an exception is Grieco's reagent system.[6] Recently, we reported that a benzylic hydroxy group could be substituted by a selenenyl group when the alcohol was treated with methyl selenolate, prepared by reductive cleavage of dimethyl diselenide in the presence of aluminum chloride.[7] However, the utility of this method is quite limited because the reaction conditions are somewhat vigorous, *i.e.* both high temperature and highly reductive conditions are necessary. Thus, in order to carry out this transformation under mild conditions, we selected a silyl selenide[8] as a nucleophilic selenium species, instead of selenolate. We describe here that a novel reagent system, a combination of silyl selenide and Lewis acid, is effective for direct conversion of a benzylic hydroxy group into a selenenyl group under mild conditions.

Initial studies were focused on the reaction of benzyl alcohol with phenyl trimethylsilyl selenide and various Lewis acids (Table 1, entries 1—7). When ZnI_2, $TiCl_4$ or $AlCl_3$ was employed, benzyl phenyl selenide (**1**) was obtained in poor to moderate yields (entries 1, 3, 6). On the other hand, $BF_3 \cdot Et_2O$, $Al(O\text{-iso-}Pr)_3$ or AlF_3 gave no selenide product (entries 2, 4, 5), however, phenyl trimethylsilyl ether was obtained in the reactions using $Al(O\text{-iso-}Pr)_3$ and AlF_3 (entries 4, 5). Optimum yield was observed when $AlBr_3$ was employed as an additive (entry 7). While performing this reaction at room temperature did not affect the yield of **1**, it was possible to shorten the reaction time (entries 7, 8). The yield of **1** was affected dramatically by the amount of $AlBr_3$. Use of excess $AlBr_3$ led to decomposition of the generated selenide **1** (entry 9) and the reaction rate was notably reduced when 0.5 eq of $AlBr_3$ was used (entry 10).

We examined the reaction of several benzyl alcohols possessing a substituent on the phenyl ring using $AlBr_3$ (1.0 eq) at 0 °C or room temperature. Reactions of methoxy-, methyl-, and chloro- substituted benzyl alcohols with the phenyl trimethylsilyl selenide–$AlBr_3$ system proceeded smoothly, and the yields of the products **2**—**6** varied from modest to good (entries 11—15). However, reaction of 4-carbomethoxy benzyl alcohol gave no selenide **7**, and only resulted in recovery of the starting alcohol (entry 16).

As shown in Table 2, several types of alcohols were subjected to this reaction using phenyl trimethylsilyl selenide (1.2 eq) and $AlBr_3$ (1.0 eq). Although a benzylic hydroxy group could be easily converted into a selenenyl group (entries 1—3), non-benzylic hydroxy groups were inert under these reaction conditions (entry 4). Surprisingly, the reaction of cinnamyl alcohol produced the benzoselenane derivative **11**, and not the corresponding selenide **12** (entry 5). The reaction pathway to produce **11** presumably involves a [3,3]-sigmatropic rearrangement of the initially generated selenide **12** (Chart 1).[9] In order to clarify this reaction pathway, we treated **12** with $AlBr_3$ in dichloromethane. As expected, the rearranged product **11**

Table 1. Reaction of Primary Benzyl Alcohols



1 – 7

Entry	R	Lewis acid (mol eq)	Temp.	Time (h)	Product	Yield (%)[a]
1	H	ZnI_2 (1.0)	r.t.	17	**1**	29 (23)
2	H	$BF_3 \cdot Et_2O$ (1.0)	r.t.	22	**1**	0 (88)
3	H	$TiCl_4$ (1.0)	r.t.	0.3	**1**	52 (0)
4	H	$Al(O\text{-iso-}Pr)_3$ (1.0)	0 °C	3.5	**1**	0 (49)[b]
5	H	AlF_3 (1.0)	0 °C	3.5	**1**	0 (30)[b]
6	H	$AlCl_3$ (1.0)	0 °C	2	**1**	46 (32)
7	H	$AlBr_3$ (1.0)	0 °C	4	**1**	70 (8)
8	H	$AlBr_3$ (1.0)	r.t.	1	**1**	69 (4)
9	H	$AlBr_3$ (2.0)	r.t.	0.8	**1**	34 (0)
10	H	$AlBr_3$ (0.5)	r.t.	3	**1**	2 (85)
11	4-OMe	$AlBr_3$ (1.0)	0 °C	0.5	**2**	75 (trace)
12	3-OMe	$AlBr_3$ (1.0)	0 °C—r.t.	3—2	**3**	50 (0)
13	2-OMe	$AlBr_3$ (1.0)	0 °C—r.t.	3—2	**4**	53 (15)
14	4-Me	$AlBr_3$ (1.0)	r.t.	0.8	**5**	60 (trace)
15	4-Cl	$AlBr_3$ (1.0)	0 °C	4.5	**6**	64 (10)
16	4-CO_2Me	$AlBr_3$ (1.0)	r.t.	29	**7**	0 (94)

a) Values in parentheses are % yields of the starting alcohol recovered. *b*) [(Trimethylsiloxy)methyl]benzene was obtained. (Entry 4: 38%; entry 5: 56%)

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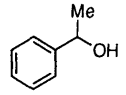
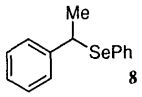
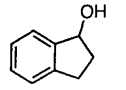
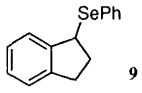
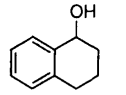
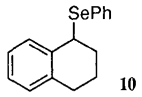
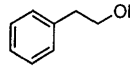
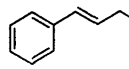
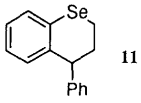
Table 2. Reaction of Various Alcohols

Alcohol —($PhSeSiMe_3$ (1.2eq), $AlBr_3$ (1.0eq), CH_2Cl_2)→ Selenide

Entry	Alcohol	Temp.	Time	Selenide	Yield (%)[a]
1		r.t.	10 min	 **8**	69 (9)
2		0 °C	1 h	 **9**	85 (trace)
3		0 °C	2 h	 **10**	71 (trace)
4		r.t.	2.5 h	—	0 (85)
5		r.t.	2 h	 **11**	69 (0)

a) Values in parentheses are % yields of the starting alcohols recovered.

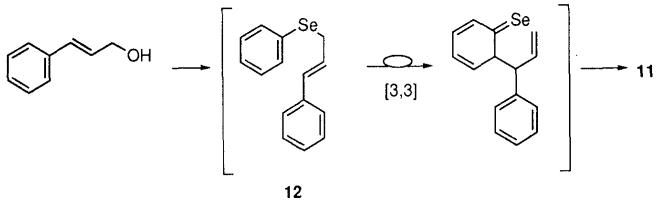


Chart 1

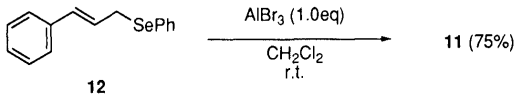


Chart 2

was obtained in good yield (Chart 2).

In sharp contrast to the results in Tables 1 and 2, when methyl trimethylsilyl selenide was employed, only low yields of substituted products **13**—**17** were observed (Table 3). At present we cannot explain the difference of reactivities between phenyl and methyl silyl selenide.

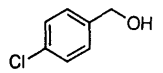
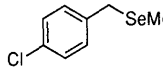
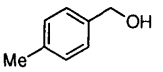
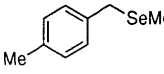
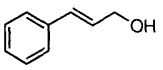
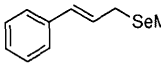
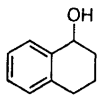
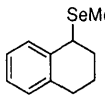
Mechanistic aspects on this substitution reaction, and application and generalization regarding benzoselenane formation are now being studied in our laboratory.

Experimental

Melting points were measured with a Yanagimoto micro melting point hot-plate apparatus and are uncorrected. IR spectra were recorded on a JASCO A-102 spectrometer. NMR spectra were taken with a Varian VXR-500, VXR-200 or Hitachi R-1500 instrument with chemical shifts reported as δ ppm and couplings expressed in Hertz. Internal standards for NMR were tetramethylsilane for ^{1}H-NMR and dimethyl selenide for ^{77}Se-NMR. Silica gel column chromatography was carried out with Wako-gel C-200. Merck Silica-gel 60 F254 plates (No. 5744) were used for preparative TLC. All reactions were carried out under argon atmosphere.

Table 3. Reaction with Methyl Trimethylsilyl Selenide

Alcohol —($MeSeSiMe_3$ (1.2eq), $AlBr_3$ (1.0 eq), CH_2Cl_2)→ Selenide

Entry	Alcohol	Temp.	Time	Selenide	Yield (%)[a]
1		0 °C	8 h	 **13**	13 (15)
2		r.t.	1 h	 **14**	23 (trace)
3		r.t.	2 h	 **15**	20 (trace)
4		0 °C	0.25 h	 **16**	59 (6)
5	Ph_3COH	0 °C	2 h	Ph_3CSeMe **17**	20 (22)

a) Values in parentheses are % yields of the starting alcohols recovered.

Phenyl Trimethylsilyl Selenide[8a] This compound was prepared by a modification of the reported method. To a solution of diphenyl diselenide (10.2 g, 31.9 mmol) in dry dioxane (50 ml) was added Na (1.76 g, 76.6 mmol) at room temperature. After refluxing for 2 h, the mixture was cooled to room temperature. Trimethylsilyl chloride (9.7 ml, 76.6 mmol) was then added dropwise to the reaction mixture over a period of 20 min. The mixture was stirred for 1 h at room temperature and then for 30 min at 60 °C. After volatile materials were removed *in vacuo*, the residue was distilled under reduced pressure (77—81 °C at 6—7 mmHg) to give the title compound (8.93 g, 61%) as a pale yellow oil. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.38 (9H, s), 7.10—7.61 (5H, m). ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 1.5, 125.2, 126.9, 128.8, 136.6. ^{77}Se-NMR (38 MHz, $CDCl_3$) δ: 90.0.

Methyl Trimethylsilyl Selenide[8b] To a suspension of $LiAlH_4$ (0.71 g, 0.019 mol) in dry Et_2O (10 ml) was added a solution of dimethyl diselenide (7.0 g, 0.037 mol) in dry Et_2O (10 ml) at 0 °C. The reaction mixture was then stirred for 20 min at 0 °C. Trimethylsilyl chloride (9.5 ml, 0.074 mol) was added dropwise to the mixture, which was then stirred for 1 h at 0 °C and for 40 min at refluxing temperature. The materials whose boiling points were below 65 °C were removed by heating under atmospheric pressure. After cooling to room temperature, the residual oil was distilled under reduced pressure (18—33 °C at 15 mmHg) to give an yellow oil (4.96 g), which was distilled again under atmospheric pressure (128—131 °C). On the basis of ^{1}H-NMR, the obtained yellow oil (2.7 g) contained dimethyl diselenide (7%) as an impurity. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.41 (9H, s), 1.79 (3H, s).

Typical Procedure for Substitution Reaction Using Silyl Selenide (Table 1, Entry 7) A solution of benzyl alcohol (79.5 mg, 0.73 mmol) in dry CH_2Cl_2 (1.0 ml) was added to a solution of trimethylsilyl phenyl selenide (202.1 mg, 0.88 mmol) in dry CH_2Cl_2 (2.0 ml) at 0 °C. After $AlBr_3$ (196.2 mg, 0.73 mmol) was added at 0 °C, the mixture was stirred for 4 h and poured into water. The mixture was then extracted with CH_2Cl_2 and the organic layer washed with brine and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave a residue which was subjected to silica gel column chromatography (5% to 33% AcOEt in hexane). Pure **1** (109.1 mg, 60.1%) was obtained from the 5% AcOEt/hexane fraction, and starting benzyl alcohol (6.6 mg, 8.3%) from the 33% fraction. A mixture (71.8 mg) of **1** and diphenyl diselenide was also obtained from the other fractions. This mixture was further purified by preparative TLC with 17% CH_2Cl_2 in hexane to give pure **1** (18.1 mg, 10.0%). Spectroscopic data for **1** were identical with those of an authentic sample.[7]

Spectroscopic data for **2**, **3**, **5**, **6**, **13**, **14**, **16** and **17** were identical with

those of authentic samples.[7]

1-Methoxy-2-[(phenylseleno)methyl]benzene (**4**)[10]: Yellow oil. IR ($CHCl_3$) cm^{-1}; 1610, 1585, 1500, 1485, 1470, 1445, 1250, 1025, 690. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.80 (s, 3H), 4.13 (s, 2H), 6.79 (dd, 1H, J=7.4, 1.2), 6.83 (d, 1H, J=7.6), 7.03 (dd, 1H, J=1.8, 7.6), 7.16—7.30 (m, 4H), 7.44—7.52 (m, 2H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 26.9, 55.3, 110.5, 120.2, 127.0, 127.3, 128.2, 128.7, 130.1, 131.0, 133.7, 157.1. ^{77}Se-NMR (38 MHz, $CDCl_3$) δ: 373.6. *Anal.* Calcd for $C_{14}H_{14}OSe$: C, 60.66; H, 5.09. Found: C, 60.85; H, 5.03.

[1-(Phenylseleno)ethyl]benzene (**8**)[3a]: Colorless oil. IR (neat) cm^{-1}; 3100, 1590, 1485, 1470, 1300, 765, 740, 695. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.74 (d, 3H, J=7.0), 4.45 (q, 1H, J=7.0), 7.16—7.28 (m, 8H), 7.41—7.44 (m, 2H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 22.1, 42.5, 126.9, 127.2, 127.8, 128.3, 128.8, 129.8, 135.4, 143.6. ^{77}Se-NMR (38 MHz, $CDCl_3$) δ: 494.3. *Anal.* Calcd for $C_{14}H_{14}Se$: C, 64.37; H, 5.40. Found: C, 64.45; H, 5.48.

1-(Phenylseleno)indan (**9**): Yellow oil. IR ($CHCl_3$) cm^{-1}; 2900, 1590, 1490, 1030, 690. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.29 (dddd, 1H, J=2.5, 2.5, 7.5, 13.5), 2.55 (ddd, 1H, J=7.5, 7.5, 13.5), 2.82 (ddd, 1H, J=2.5, 7.5, 16.5), 2.99 (td, 1H, J=7.5, 16.5), 4.90 (dd, 1H, J=2.5, 7.5), 7.13—7.31 (m, 7H), 7.50—7.54 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 30.9, 34.0, 47.2, 124.6, 124.8, 126.4, 127.5, 128.9, 130.4, 134.5, 143.6, 143.7. ^{77}Se-NMR (38 MHz, $CDCl_3$) δ: 433.1. *Anal.* Calcd for $C_{15}H_{14}Se$: C, 65.94; H, 5.16. Found: C, 66.24; H, 5.24.

1-(Phenylseleno)-1,2,3,4-tetrahydronaphthalene (**10**): Yellow oil. IR ($CHCl_3$) cm^{-1}; 2975, 1590, 1485, 1460, 1445, 1275, 1180, 1025, 690. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.74—1.81 (m, 1H), 1.98—2.08 (m, 2H), 2.20—2.30 (m, 1H), 2.77 (ddd, 1H, J=6.0, 11.0, 17.0), 2.83 (ddd, 1H, J=3.5, 8.5, 17.0), 4.78 (t, 1H, J=3.5), 7.04—7.13 (m, 3H), 7.27—7.36 (m, 4H), 7.58—7.61 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 19.1, 29.0, 29.1, 44.5, 125.6, 126.8, 127.5, 129.0, 129.2, 130.4, 131.0, 134.7, 136.3, 137.1. ^{77}Se-NMR (38 MHz, $CDCl_3$) δ: 454.5. *Anal.* Calcd for $C_{16}H_{16}Se$: C, 66.90; H, 5.61. Found: C, 67.12; H, 5.76.

3,4-Dihydro-4-phenyl-2*H*-1-benzoselenin (**11**): Colorless prisms; mp 33.5—35.0 °C (ether–hexane). IR ($CHCl_3$) cm^{-1}; 3050, 1610, 1600, 1505, 1485, 1440, 700. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.29—2.44 (m, 2H), 2.82—2.90 (m, 2H), 4.20 (dd, 1H, J=4.0, 5.0), 6.89 (d, 1H, J=8.0), 6.98 (td, 1H, J=1.0, 7.5), 7.03—7.10 (m, 3H), 7.16—7.33 (m, 4H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 16.6, 30.5, 45.7, 124.8, 126.3, 127.1, 128.36, 128.39, 128.9, 131.3, 138.2, 143.7. ^{77}Se-NMR (38 MHz, $CDCl_3$) δ: 215.9. *Anal.* Calcd for $C_{15}H_{14}Se$: C, 65.94; H, 5.16. Found: C, 65.91; H, 5.12.

(*E*)-3-Methylseleno-1-phenyl-1-propene (**15**): Colorless oil. IR ($CHCl_3$) cm^{-1}; 3000, 2925, 1495, 1420, 960, 690. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.95 (s, 3H), 3.32 (d, 2H, J=8.0), 6.27 (dt, 1H, J=8.0, 15.5), 6.35 (d, 1H, J=15.5), 7.22 (tt, 1H, J=1.5, 7.5), 7.31 (t, 2H, J=7.5), 7.37 (dd, 2H, J=7.5). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 3.7, 26.8, 126.2, 126.3, 127.4, 128.6, 131.4, 136.8. ^{77}Se-NMR (38 MHz, $CDCl_3$) δ: 123.9. *Anal.* Calcd for $C_{10}H_{12}Se$: C, 56.88; H, 5.73. Found: C, 56.80; H, 5.58.

(*E*)-Cinnamyl phenyl selenide (**12**) was prepared by a previously reported method.[11]

[3,3]-Sigmatropic Rearrangement of 12 (Chart 2) A solution of **12** (33.9 mg, 0.12 mmol) in CH_2Cl_2 (0.9 ml) was added to a solution of $AlBr_3$ (33.1 mg, 0.12 mmol) in CH_2Cl_2 (0.5 ml) at room temperature. The reaction mixture was stirred for 2 h at room temperature, and poured into 1 N NaOH aqueous solution. After extraction with CH_2Cl_2, the organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (10% CH_2Cl_2 in hexane) to give **11** (25.4 mg, 74.9%).

Acknowledgements The authors are grateful to the SC-NMR Laboratory of Okayama University for ^{1}H-, ^{13}C- and ^{77}Se-NMR experiments.

References and Notes

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