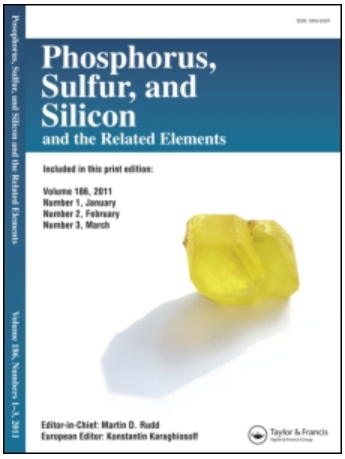

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis of a Selenium-Substituted Diselenide

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To cite this Article Cox, Matthew and Wirth, Thomas(2005) 'Synthesis of a Selenium-Substituted Diselenide', Phosphorus, Sulfur, and Silicon and the Related Elements, 180: 3, 659 — 666
To link to this Article: DOI: 10.1080/10426500590907282
URL: http://dx.doi.org/10.1080/10426500590907282

Phosphorus, Sulfur, and Silicon, 180:659–666, 2005

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500590907282

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Synthesis of a Selenium-Substituted Diselenide

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A wide range of diselenides as precursors for selenium electrophiles is already known, but the development of reagents with higher selectivity is still ongoing. Herein we report the first synthesis of selenium-stabilized diselenides together with some preliminary reactions of these reagents in stereoselective selenenylation reactions.

Keywords Diselenides; selenium electrophiles; stereoselective synthesis

INTRODUCTION

For several decades now, selenium reagents have attracted growing interest for their application in organic synthesis.[1,2] In particular, the oxidative functionalization of nonactivated or only slightly activated carbon carbon double bonds with selenium-based reagents and the cyclization of unsaturated alcohols, amines and carbonyl derivates offer a wide range of applications. Selenium electrophiles are highly potent for such transformations because of their high anti-Markovnikov selectivity, their mild reaction conditions as well as their ability to undergo a wide range of further reactions leading to even higher functionalized compounds.[3–5]

The introduction of a large number of chiral, non-racemic selenium electrophiles for stereoselective variants of the aforementioned transformation has led to much interest in organoselenium chemistry. We have developed a series of differentially substituted chiral diselenides **1** as versatile precursors for selenium electrophiles **2** (Scheme 1). A nonbonded interaction between the lone pair of the heteroatom X and

Received January 6, 2004; in final form September 29, 2004.
We are thankful for the high-resolution mass spectrometric data obtained from the EPSRC National Mass Spectrometry Service Centre, Swansea, UK. We like to thank EPSRC for support (M.C.).
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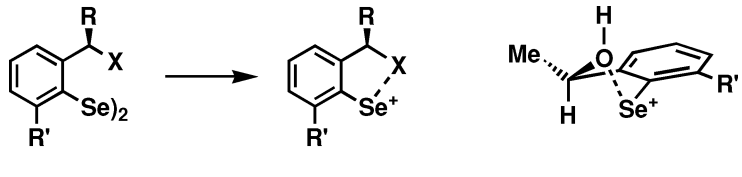


1 2 3

SCHEME 1 Heteroatom-interaction with selenium electrophiles.

the σ^*-orbital of the selenium cation stabilizes the electrophilic species. Furthermore, this interaction brings the chiral benzylic carbon atom close to the electrophilic selenium atom. The coordination of the lone pair of an oxygen-heteroatom (X = O) to the electrophile was already subject of calculations showing that a rotation of the oxygen-atom out of the aromatic plane by approximately 30° as shown in **3** is resulting in conformations having lowest energies.[6]

Strong evidence for such an oxygen–selenium interaction has been also found by NMR spectroscopy.[7] Other heteroatoms like nitrogen in similar position have been investigated previously, recently other research groups have reported on fluorine heteroatoms[8] and on sulfur heteroatoms.[9]

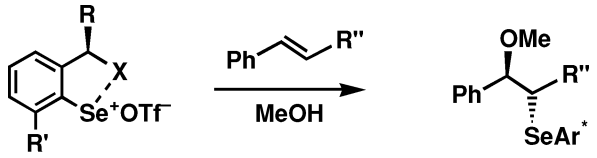
The strength of the heteroatom–selenium coordination is reflected in different properties of these reagents. One indication is the ^{77}Se NMR shift of the corresponding diselenides **1**. Some of those values are summarized in Table I.[5,7–11] A better coordination of the heteroatom is indicated by higher ^{77}Se NMR shift values of **1**.

The interaction of the heteroatom X with the selenium electrophile has obviously also an influence on the selectivities in addition reactions. Some of the highest selectivities of a range of selenenylations of alkenes observed to date have been achieved using *ortho*-methoxy substituted

TABLE I ^{77}Se NMR Values of Diselenides 1

Diselenide	X	R	R′	^{77}Se [ppm]	Reference
1a	OH	Me	H	445.9	[7]
1b	OMe	Me	H	427.5	[7]
1c	OEt	Me	H	424.8	[7]
1d	SEt	Me	H	430.2	[8]
1e	NMe_2	Me	H	454.1	[9]
1f	NEt_2	Me	H	439.1	[9]
1g	F	H	H	437.3	[5]
1h	OH	Me	OMe	365.6	[10]
1i	SMe	Me	OMe	365.7	[11]

TABLE II Methoxyselenenylation of Styrene-Derivatives (R = Me)

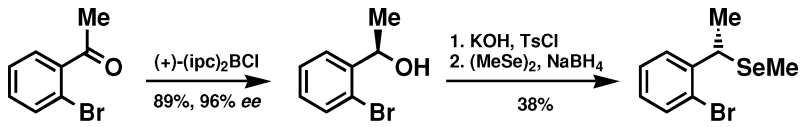


2 4

Diselenide	X	R′	R″	**4** yield	**4** (*de*)	Reference
1b	OMe	H	H	67%	83%	[10]
1j	SMe	H	H	80%	92%	[6a]
1h	OMe	OMe	H	55%	96%	[7]
1i	SMe	OMe	H	72%	96%	[11]
1h	OMe	OMe	Me	50%	85%	[7]
1i	SMe	OMe	Me	75%	96%	[11]

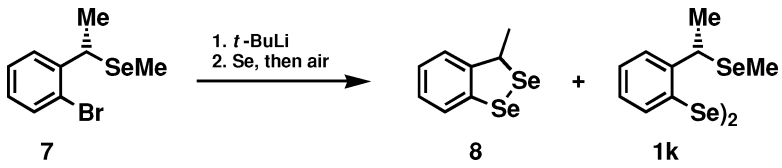
electrophiles (R′ = OMe) derived from diselenides **1g** and **1h**. Although having similar ^{77}Se NMR shifts, the selectivities obtained with selenium electrophiles stabilized by a sulfur-atom in the chiral side chain are in some cases higher than with the corresponding oxygen analogues as shown in Table II.

We are interested in extending this concept to selenium-stabilized selenium electrophiles.[12–14] To access the corresponding diselenides, we followed the procedure published by Tiecco for the synthesis of the sulfur-containing diselenides.[15] The selenium containing aryl bromide **7** were prepared (Scheme 2) by reduction of 2-bromoacetophenone **5** with (+)-chloro diisopinocampheyl borane [(+)-(ipc)$_2$BCl] to give the alcohol **6** in 89% yield and 96% *ee*. The alcohol **6** was then converted into the corresponding tosylate by treatment with potassium hydroxide and tosyl chloride. The selenium nucleophile required to displace the tosylate was generated *in situ* from dimethyl diselenide and sodium borohydride in ethanol. The tosylate was not isolated but immediately treated with the methylselenolate complex to give the selenide **7** in 38% yield.



5 6 7

SCHEME 2 Synthesis of selenium-containing precursor molecules.

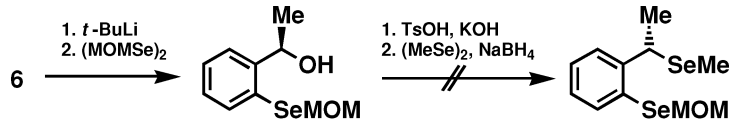


7 8 1k

SCHEME 3 Synthesis of diselenide **1k**.

Attempts to introduce the selenium via a bromine–lithium exchange followed by treatment with elemental selenium caused a range of side reaction to occur. Foremost among these side reactions was the formation of the novel diselenide **8** (Scheme 3). This cyclic diselenide formed in yields up to 57% though optically inactive. The formation of this diselenide appears to involve the exchange of both the bromine on the aromatic ring and the selenium on the side chain with lithium. The dilithiated species can react with elemental selenium followed by an oxidative workup to give **8**. By varying the reaction conditions, a small amount of the diselenide **1k** was finally obtained. The preparation of a Grignard-reagent from the precursor **7** failed as well under various reaction conditions.

In an alternative approach towards the synthesis of **1k**, the initial introduction of the aromatic selenium atom was successful using bis(methoxymethyl)diselenide.[16] The subsequent introduction of the side-chain selenium moiety, however, was again unsuccessful as shown in Scheme 4. Also the selenolate derived from diphenyl diselenide did show no reaction.



10 11

SCHEME 4 Attempted synthesis of compound **11**.

Using diselenide **1k** for the generation of the corresponding selenium electrophile **2k**, we perfomed the methoxyselenenylation of styrene. The addition product **4k** was obtained in reasonable yield of 73%, although the diastereomeric excess as determined by NMR was found to be only 81% and lower as the diastereoselectivities observed for the corresponding addition products **4** using oxygen-containing electrophile **2b** (**4b**: 83% *de*) and the sulfur-containing electrophile **2j** (**4j**: 92% *de*) as shown in Table II.

In conclusion, we were able to synthesize a selenium-stabilized diselenide. The selenium electrophile generated did, however, not show higher selectivities in the methoxyselenenylation of styrene.

EXPERIMENTAL

General: ^{1}H and ^{13}C NMR experiments were carried out on a Bruker 400-DPX spectrometer. IR measurements were taken using a Perkin-Elmer 1600FTIR spectrometer as a liquid film. Low resolution mass spectrometry was carried out using a Varian Saturn 2 GC-MS. Flash chromatography was carried out using Fisher Silica Gel (35–70 mesh). Preparative thin layer chromatography was carried out using Merck silica gel 60 F254 on glass plates. All solvents used were dried and purified by standard methods. Reactions requiring the exclusion of air were carried out under an atmosphere of argon in oven dried glassware.

(1*R*)-1-(2-Bromophenyl)ethanol) 6

Prepared according to ref. 13.

(*S*)-1-Bromo-2-(1-methylselanyl-ethyl)-benzene 7

Enantiomerically pure (1*R*)-1-(2-bromophenyl)ethanol) **6** (1.005 g, 5 mmol) was dissolved in ethanol (15 mL) and cooled to −20°C. The solution was treated with potassium hydroxide (560 mg, 10 mmol) and tosyl chloride (980 mg, 5 mmol) and stirred for 24 h. In a separate flask, dimethyl diselenide (470 mg, 2.5 mmol) was dissolved in ethanol (10 mL), cooled to 0°C and treated with sodium borohydride (190 mg, 5 mmol). This solution was added to the tosylate and slowly warmed to room temperature. After stirring for 18 h, water and diethyl ether were added and organic layer dried over magnesium sulfate. The solvent was removed and the product was purified by flash chromatography (eluent 9:1 petroleum ether:diethyl ether) to give **7** as a red oil. (526 mg, 38% yield, 94% *ee*).

$[\alpha]_D = +118.4$ (c 0.5 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.64$ (3 H, d, $J = 7.1$, CH_3), 1.83 (3 H, s, SeCH_3), 4.57 (1 H, q, $J = 7.1$, C*H*), 6.99 (1 H, dt, $J = 8.0$, $J = 1.5$, Ar-*H*), 7.24 (1 H, t, $J = 7.7$, Ar-*H*), 7.41 (1 H, dd, $J = 7.8$, $J = 1.5$, Ar-*H*), 7.46 (1 H, d, $J = 8.0$, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 4.2$ (Se*C*H$_3$), 22.0 (CH*C*H$_3$), 36.1 (*C*H), 124.3 (Ar), 128.2 (Ar), 128.4 (Ar), 128.6 (Ar), 133.7 (Ar), 143.6 (Ar); IR (NaCl): $\nu = 2963$, 2922, 2863, 1588, 1563, 1468, 1437, 1374, 1272, 1175, 1052, 1021, 899, 755, 723, 661 cm^{-1}; *m/z* (int.): 279 (7%) [M^{+}], 185 (84%), 183

(85%), 104 (100%), 77 (32%), 51 (18%); HRMS for $C_9H_{11}BrSe$: calcd. 277.9204, found 277.9202.

Bis-[2-(1-Methylselanyl-ethyl]diselenide 1k

Rac-7 (277 mg, 1 mmol) was dissolved in hexane (5 mL), cooled to –78°C and treated with *t*-BuLi (1.5 mmol, 1.6 M in hexane). The solution was allowed to warm to room temperature and stirred for 30 min then recooled to −78°C and treated with THF (5 mL). The solution was allowed to warm to room temperature and stirred for a further 30 min before cooling to −78°C. Elemental selenium (86 mg, 1.1 mmol) was added and the solution warmed slowly to room temperature. After stirring for 4 h, HCl (1 M, 10 mL) was added, followed by diethyl ether and water. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. The solvent was removed and the product purified by flash chromatography (eluent 9:1 petroleum ether:diethyl ether) to give diselenide **1k** as a red oil. (40 mg, 16% yield). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.62$ (3 H, d, $J = 6.8$, CHCH_3), 1.69 (3 H, d, $J = 7.1$, CHCH_3), 1.81 (3 H, s, SeCH_3) 1.83 (3 H, s, SeCH_3), 4.48 (1 H, q, $J = 7.1$, C*H*), 4.52 (1 H, q, $J = 6.8$, C*H*Se), 6.95 (2 H, m, Ar-*H*), 7.14 (2 H, m, Ar-*H*), 7.23 (2 H, m, Ar-*H*), 7.65 (1 H, d, $J = 7.7$, Ar-*H*), 7.73 (1 H, d, $J = 7.9$, Ar-*H*).

3-Methyl-3*H*-benzo[1,2]-diselenacyclopentane 8

Synthesized and purified as above but using enantiomerically pure selenide. (147 mg, 56% yield); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.78$ (3 H, d, $J = 6.8$, CH_3), 4.87 (1 H, q, $J = 6.8$, C*H*), 6.96–7.08 (3 H, m, Ar-*H*), 7.24 (1 H, dd, $J = 6.9$, $J = 1.7$, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 23.3$ (*C*H$_3$), 49.7 (*C*H), 125.9 (Ar), 126.2 (Ar), 127.1 (Ar), 127.7 (Ar), 137.1 (Ar), 148.2 (Ar); ^{77}Se NMR (95 MHz $CDCl_3$): $\delta = 366.7$, 509.8; IR (NaCl): $\nu = 2955$, 2363, 2338, 1548, 1463, 1433, 1363, 1252, 1157, 1056, 1021, 750 cm^{-1}; *m/z* (int.): 266 (28%), 264 (100%) [M$^+$], 262 (88%), 261 (36%), 260 (55%), 249 (65%), 247 (57%), 245 (31%), 183 (94%), 181 (46%), 103 (40%), 102 (57%), 78 (28%), 77 (36%), 63 (25%), 51 (39%); HRMS for $C_8H_8Se_2$: calcd 263.8951, found 263.8952.

1-(2-{[(2-Methoxy-2-phenyl)ethyl]seleno}phenyl) ethylmethylselenide 4k

The diselenide **1k** (40 mg, 0.07 mmol) was dissolved in diethyl ether (2 mL), cooled to 0°C, and treated with bromine (0.07 mmol, 1M solution in CCl_4). After stirring for 5 min the solution was cooled to −78°C

and treated with silver triflate (50 mg, 0.19 mmol as a solution in 2 mL of methanol). The solution was stirred for a further 5 min, then treated with styrene (15 mg, 0.14 mmol). The reaction mixture was stirred at −78°C for 4 h and then allowed to warm slowly to room temperature before quenching with *sym*-collidine (0.1 mL). Water and diethyl ether were then added and the organic layer separated and dried over magnesium sulfate. Purification by preparative TLC (eluent 20:1 petroleum ether:diethyl ether) gave **4k** as a clear oil (41 mg, 72% yield, 82% *de*). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.67$ (3 H, d, $J = 7.0$, $CHCH_3$), 1.81 (3 H, s, $SeCH_3$), 3.03 (1 H, dd, $J = 12.2$, $J = 4.9$, $SeCHH$), 3.17 (3 H, s, OCH_3), 3.21 (1 H, dd, $J = 12.3$, $J = 8.7$, $SeCHH$), 4.26 (1 H, dd, $J = 8.8$, $J = 4.7$, $CHOCH_3$), 4.69 (1 H, q, $J = 7.0$, $CHCH_3$), 7.01 (1 H, dt, $J = 7.7$, $J = 1.0$, Ar-*H*), 7.14–7.33 (7 H, m, Ar-*H*), 7.42 (1 H, d, $J = 7.7$, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 4.2$ ($SeCH_3$), 22.3, ($CHCH_3$), 36.2 ($SeCH_2$), 36.7 (OCH_3) 57.4 (OCH_3), 83.4 ($PhCHOCH_3$); *m/z* (int.) 414 (38%) [M^+], 399 (49%), 319 (4%), 287 (55%), 279 (95%), 206 (3%), 183 (79%), 135 (53%), 121 (52%), 103 (100%), 91 (85%), 77 (42%), 59 (15%), 51 (33%), 43 (39%).

(*R*)-1-(2-Methoxymethylselanylbenzene)ethanol 10

Enantiomerically pure (1*R*)-1-(2-bromophenyl)ethanol **6** (201 mg, 1 mmol) was dissolved in THF (10 mL), cooled to −78°C and treated with *t*-butyllithium (1.5 mmol of a 1.5M solution in hexane). After warming up to room temperature and stirring for 30 min, bis(methoxymethyl)diselenide (271 mg, 1.1 mmol) was added at 0°C. The reaction was stirred for a further 6 h, treated with aq. HCl (1M, 10 mL) and extracted with diethyl ether (3 × 20 mL). The organic layer was washed with water, dried over magnesium sulfate, then treated with powdered potassium hydroxide (50 mg). The solvent was removed and the crude mixture purified by flash chromatography (eluent 4:1 petroleum ether:diethyl ether) gave **10** as a yellow oil (164 mg, 67% yield). $[\alpha]_D = -29.2$ (c = 1.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.41$ (3 H, d, $J = 6.8$, $CHCH_3$), 2.60 (1 H, br, OH), 3.33 (3 H, s, OCH_3), 5.08 (2 H, s, CH_2), 5.23 (1 H, q, $J = 6.8$, CH), 7.12 (1 H, dt, $J = 6.4$, $J = 1.2$, Ar-*H*), 7.25 (1 H, dt, $J = 8.0$, $J = 1.2$, Ar-*H*), 7.46 (1 H, dd, $J = 7.6$, $J = 1.2$, Ar-*H*), 7.61 (1 H, dd, $J = 7.6$, $J = 1.2$, Ar-*H*);^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 23.6$ (CH_3), 57.6 (OCH_3), 69.3 (CH), 75.4 (CH_2), 126.0 (1 C), 128.6 (1 C), 128.7 (1 C), 129.8 (1 C), 135.0 (1 C), 147.7 (1 C); ^{77}Se NMR (95 MHz $CDCl_3$) $\delta = 285.6$; IR (NaCl): $\nu = 2920$, 1448, 1273, 1180, 1085, 926, 877, 757 cm^{-1}; *m/z* (intensity) 246 (100%) [M^+], 229 (63%), 214 (10), 199 (7%), 184 (14%), 122 (12%), 104 (5%); HRMS for $C_{10}H_{14}O_2Se$ calcd: 246.0154, found 246.0156.

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