Synthesis G. Stach et al. Paper

Synthesis of 2-(Arylselanyl)benzo[*b*]chalcogenophenes via Intramolecular Cyclization of Vinyl Selenides

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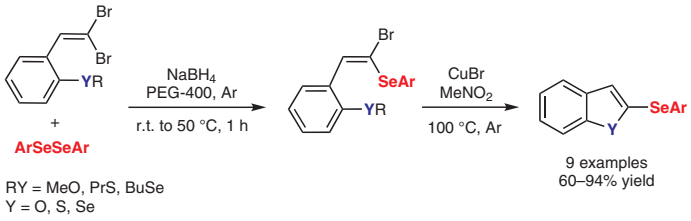


Received: 04.07.2018
Accepted after revision: 23.08.2018
Published online: 19.09.2018
DOI: 10.1055/s-0037-1610656; Art ID: ss-2018-z0454-op

Abstract An efficient protocol to access 2-arylselanylbenzo[*b*]chalcogenophene derivatives through the Cu(I)-catalyzed annulation of vinyl selenides is described. The key vinyl selenides were easily prepared from properly functionalized 1,1-dibromostyrenes and the method allowed the synthesis of 2-arylselanylfurans, -thiophenes, and -selenophenes in moderate to excellent yields.

Key words 2-arylselanylbenzo[*b*]chalcogenophenes, copper catalysis, annulation

Heterocycles are among the most important classes of compounds found in nature, occurring mainly in the form of alkaloids.[1] Their reputation is closely linked to their use in the pharmaceutical industry; once in 2010, over 80% of the top small-molecule drugs marketed in the USA contained at least one heterocyclic unit in the structure.[1d]

In this context, the benzo[*b*]chalcogenophenes have attracted attention due to their wide range of biological activities. For instance, benzo[*b*]furans are widely present in nature,[2] and their derivatives exhibit a broad range of medically important activities,[3] such as antioxidant,[3c] antihistaminic,[3d] PTP-1B inhibitor,[3f] and against pancreatic cancer.[3g] Benzo[*b*]thiophenes, in turn, are present in the structure of worldwide marketed drugs, such as, Raloxifene (**A**), used in the treatment and prevention of osteoporosis in menopausal women,[4] and Zileuton (**B**), which is used by asthmatic patients in the prevention of acute asthma attacks.[5] In addition, between 1999 and 2002, Pinney[6] and Flynn[7] disclosed that benzo[*b*]thiophene **C** and benzo[*b*]furan **D** derivatives are able to inhibit the tubulin polymerization, showing the promising capacity to be applied as anticancer agents, acting mimetically to combretastatin A-4, a powerful naturally occurring inhibitor of tubulin polymerization (Figure 1).

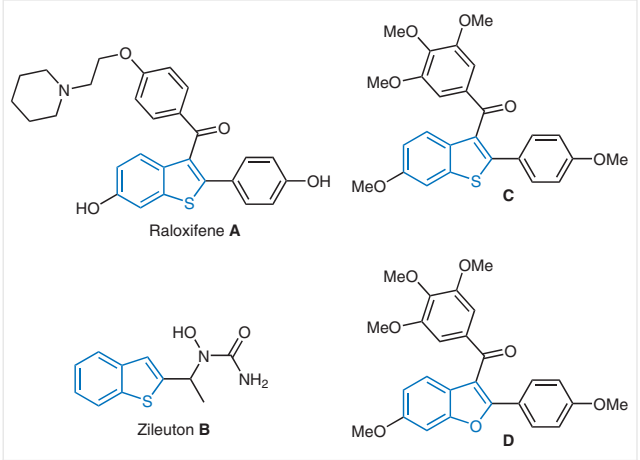


Figure 1 Benzo[*b*]chalcogenophene derivatives of interest in medicinal chemistry

Sartans are a new class of antihypertensive drugs acting as Ang II receptor antagonists. Examples of thiophene-containing sartan derivatives are milfasartan (**E**), which has reached the phase I of clinical trials,[8] and eprosartan (**F**), marketed in some countries under the tradename Teveten®, used in the treatment of arterial hypertension (Figure 2).[9]

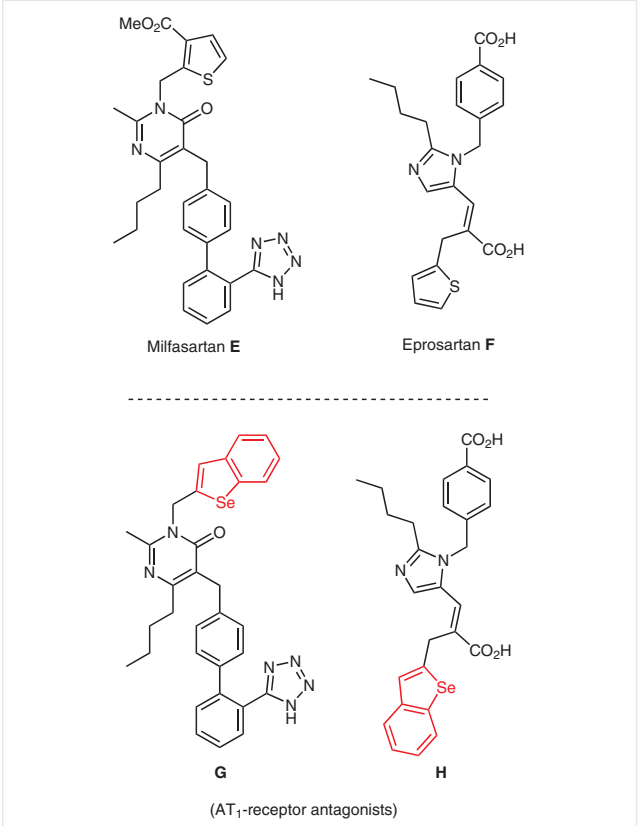
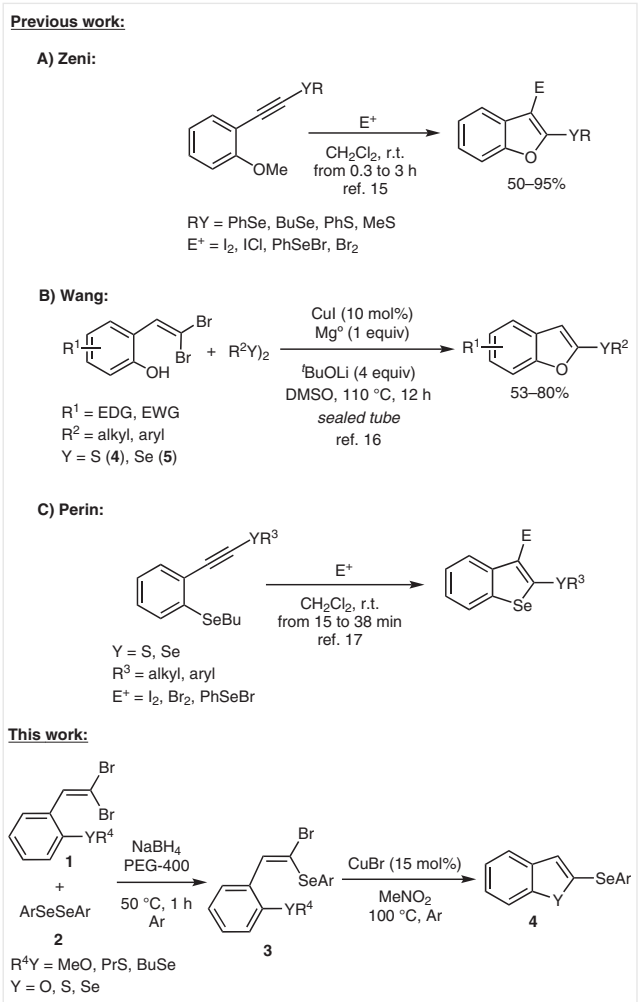


Figure 2 Biologically active sartan derivatives

In view of this, between 2007 and 2012, Schiesser and co-workers[10] developed a deep study on the synthesis of selenium-containing sartan derivatives, in order to discover AT_1-receptor antagonists, candidates to new antihypertensive drugs. Among the designed compounds, benzoselenophene derivatives **G** and **H** of milfasartan and eprosartan, respectively, (Figure 2) showed to be excellent AT_1-receptor antagonists compared to the thio-analogues, presenting good binding ability and therefore quoted as drug candidates for the treatment of hypertension.[3d]

With regard to the importance of organoselenium compounds, heterocycles bearing a selenium atom on their structure, in the form of selenides, have been displaying remarkable performance in biological assays, presenting important activities, such as antioxidant,[11] anticancer,[12] antiviral,[13] and antihelminthic.[14]

Based on what was described above, 2-selanylbenzo[*b*]chalcogenophenes can be considered as a promisor class of compounds, combining two units of biologically important scaffolds. However, synthetic methodologies to access such molecular hybrids are still very scarce. In 2009, Zeni and co-workers[15] reported the electrophilic cyclization of 2-chalcogenealkynyl anisole, promoted by different electrophiles, such as I_2, ICl, Br_2, and PhSeBr, under mild reaction conditions, affording 3-substituted 2-organochalcogenylbenzo[*b*]furan derivatives in moderate to excellent yields (Scheme 1 A). In 2013, Wang and co-workers[16] reported the synthesis of 2-chalcogenylbenzo[*b*]furans via a Cu(I)-catalyzed tandem annulation of 2-(1,1-dibromovinyl)phenols with diorganyl dichalcogenides. The reaction was conducted in the presence of *t*-BuOLi as a base, Mg as an additive, and DMSO as the solvent. The functionalized benzofurans were obtained in moderate to very good yields after 12 hours of reaction at 110 °C (Scheme 1 B).



Scheme 1 Preview of reported methods for the synthesis of 2-selanylbenzo[*b*]chalcogenophenes and our general reaction scheme

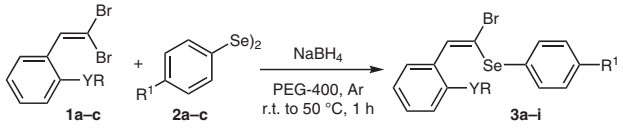
Recently, we have described the synthesis of 3-substituted 2-organochalcogenylbenzo[*b*]selenophenes, via an electrophilic cyclization of 1-(2-chalcogenylethynyl)-2-butylselenanybenzenes promoted by I_2, Br_2, and PhSeBr in dichloromethane as the solvent.[17] The desired selenophenes were obtained in moderate to excellent yields in short reaction time at room temperature (Scheme 1 C).

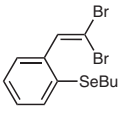
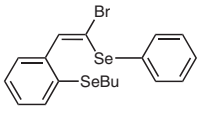
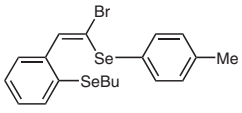
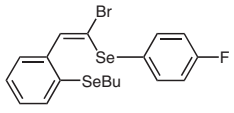
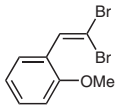
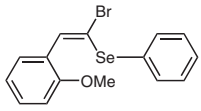
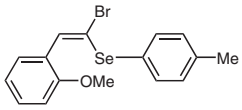
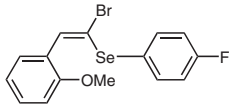
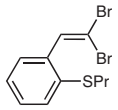
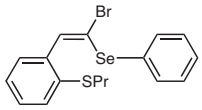
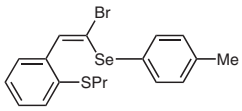
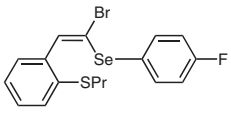
On the other hand, 1,1-dibromoalkenes are versatile building blocks in organic synthesis, widely applied in several transformations.[18] In this context, we have recently described a robust protocol for easily accessing (*E*)-1-bromo-1-selenanylalkenes and ketene selenoacetals starting from 1,1-dibromoalkenes.[19]

Thus, aiming to expand the use of (*E*)-1-bromo-1-arylselenoalkenes **3** as a versatile intermediate in organic synthesis, herein we describe our results on the Cu(I)-catalyzed annulation of properly functionalized alkenes **3**, affording the respective 2-arylselanylbenzo [*b*]chalcogenophenes **4** (Scheme 1, bottom panel). The key intermediates **3** were prepared by the reaction of 1,1-dibromoalkenes **1** with diorganyl diselenides.[19]

Our initial studies were focused in the synthesis of the substrates **3**, the synthetic precursors of the title chalcogenophenes **4**. Based on the methodology developed by us in 2016,[19] the 1-(2,2-dibromovinyl)-2-chalcogenylbenzenes **1a–c** were subjected to the reaction with diaryl diselenides **2** in the presence of $NaBH_4$ as a reducing agent and PEG-400 as the solvent. After 1 hour at 50 °C under argon atmosphere, the respective (*E*)-1-bromo-1-arylselenoalkenes **3a–i** were selectively formed (see Supporting Information for NMR spectra) in good to very good yields (Table 1). The high selectivity in the formation of the (*E*)-1-bromo-1-arylselenoalkenes **3a–i** (>99% of *E*-isomer) is similar to that observed starting from unsubstituted 1,1-dibromoalkenes.[19] This outcome indicates that the presence of the *o*-chalcogen substituent in **1** did not influence the selectivity of the reaction, with the *E*-isomers of **3a–i** being the only observed products by GC.

Table 1 Synthesis of the Synthetic Precursors (*E*)-**3a–i**[a]



Entry	Alkene **1**	R^1 **2**	Product **3**	Yield (%)[b]
1	 **1a**	H, **2a**	 **3a**	88
2	**1a**	Me, **2b**	 **3b**	74
3	**1a**	F, **2c**	 **3c**	80
4	 **1b**	H, **2a**	 **3d**	78
5	**1b**	Me, **2b**	 **3e**	76
6	**1b**	F, **2c**	 **3f**	84
7	 **1c**	H, **2a**	 **3g**	85
8	**1c**	Me, **2b**	 **3h**	76
9	**1c**	F, **2c**	 **3i**	78

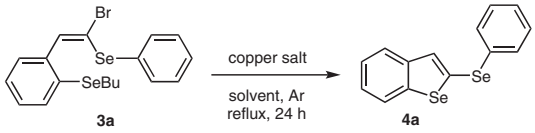
[a] The reaction was performed using 1,1-dibromoalkene **1** (0.5 mmol), diorganyl diselenide **2** (0.25 mmol), and $NaBH_4$ (0.75 mmol) as reducing agent in PEG-400 (3 mL) as solvent at 50 °C, under argon atmosphere.
[b] Yields are given for isolated products after column chromatography.

There was no substantial influence of electronic effects in the aromatic ring of the diaryl diselenides **2a–c** and equally good yields were obtained starting from electron-rich and electron-deficient diselenides. Correspondingly, similar outcomes were observed regardless of the organochalcogen appending group in the vinyl dibromide (SeBu **1a**, OMe **1b**, or SPr **1c**), showing the robustness of the methodology in the synthesis of **3** (Table 1).

With a well-established general method to access the starting materials **3a–i** in hand, the *o*-seleno-substituted (*E*)-1-bromo-1-phenylselenoalkene **3a** was selected as a

standard substrate and a careful optimization study to access the desired compound **4a** via a copper-catalyzed annulation was performed. Initially, CuBr (30 mol%) was used as the catalyst in $MeNO_2$ as the solvent and, after 24 hours under argon atmosphere at refluxing temperature, the title benzoselenophene **4a** was obtained in 95% yield (Table 2, entry 1).

Table 2 Optimization Study to the Cu-Catalyzed Annulation of **3a**[a]



Entry	Solvent	Cu salt (mol%)	Yield (%)[b]
1	$MeNO_2$	CuBr (30)	95
2	DMSO	CuBr (30)	–
3	DMF	CuBr (30)	50
4	MeCN	CuBr (30)	10
5[c]	PEG-400	CuBr (30)	7
6	$MeNO_2$	CuI (30)	76
7	$MeNO_2$	$Cu(OAc)_2$ (30)	44
8	$MeNO_2$	$CuBr_2$ (30)	95
9	$MeNO_2$	CuBr (20)	92
10	$MeNO_2$	CuBr (15)	90
11	$MeNO_2$	CuBr (10)	85
12	$MeNO_2$	CuBr (5)	56
13	$MeNO_2$	CuBr (1)	30
14[d]	$MeNO_2$	CuBr (15)	35
15[e]	$MeNO_2$	CuBr (15)	–
16[f]	$MeNO_2$	CuBr (15)	92

[a] Reaction was performed using a mixture of **3a** (0.15 mmol), the copper salt, and solvent (3 mL), under argon at reflux for 24 h.
[b] Yields of isolated product, after column chromatography.
[c] Reaction at 90 °C.
[d] Reaction at 75 °C.
[e] Reaction at r.t.
[f] After 40 h of reaction.

Based on this result, CuBr (30 mol%) was set as the catalyst and other organic solvents were tested, at their respective reflux temperatures, such as DMSO, DMF, and MeCN (Table 2, entries 2–4). As shown in Table 2, none of them was more effective than $MeNO_2$ in this annulation reaction, affording poor to moderate yields of product **4a**. Additionally, PEG-400 was used as a non-conventional solvent at 90 °C, affording **4a** in only 7% yield (entry 5), thus confirming $MeNO_2$ as the better solvent for this transformation.

Next, different copper catalysts, both Cu(I) and Cu(II) salts, were tested. Initially, CuI was used as an alternative Cu(I) specie, but the reaction yield decreased from 95 to 76%, showing that bromide is a better counterion than iodine in this reaction (Table 2, entry 1 vs entry 6). In addition, Cu(II) species were also employed as catalysts, with $Cu(OAc)_2$ affording the respective product **4a** in 44% yield, while $CuBr_2$ efficiently catalyzed the reaction, affording **4a** in 95% yield, confirming the best performance of bromide salts (entries 7 and 8). Considering that CuBr is cheaper than $CuBr_2$, it was chosen as the catalyst for the reaction. Hence, the catalyst loading was reduced to 20, 15, 10, 5, and 1 mol%, and it was observed that no substantial decrease in the reaction yield was observed using 20 or 15 mol% (90% yield of **4a**, entries 9 and 10).

The effect of the reaction temperature was also significant. When the reaction was performed at 75 °C, a considerable decrease in the reaction yield was observed, with **4a** being obtained in only 35% (Table 2, entry 14). At room temperature, no product was detected after 24 hours, and the starting material **3a** was recovered (entry 15). Finally, the reaction was prolonged up to 40 hours under reflux (100 °C) and **4a** was obtained in 92% yield, similar to that obtained in 24 hours (entry 16 vs entry 10).

Thus, the best reaction conditions for the copper-catalyzed annulation of the substrate **3a** to give **4a**, was defined as using CuBr (15 mol%) as the catalyst, $MeNO_2$ as the solvent, under argon atmosphere and refluxing conditions, for 24 hours (Table 2, entry 10). With the best reaction conditions in hand, our efforts were concentrated in the study of the reaction scope, aiming to prepare a variety of 2-selanylbenzo[*b*]chalcogenophenes **4a–i** (Table 3).

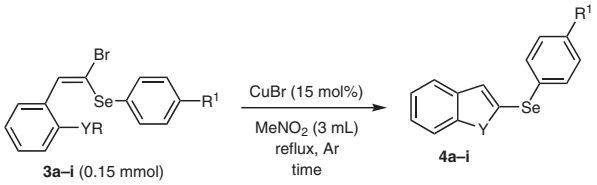
Initially, the *ortho*-seleno-substituted (*E*)-1-bromo-1-arylselenoalkenes **3b**,**c**, bearing electron-releasing (Me) and electron-withdrawing group (F), were subjected to the annulation under the optimized conditions. As shown in Table 3, the presence of the methyl group positively influences the reaction, and 2-(4-tolylselanyl)benzo[*b*]selenophene (**4b**) was obtained in 94% yield after 16 hours (Table 3, entry 2). In contrast, the electron-withdrawing fluorine caused an increase in the reaction time, and 38 hours were necessary to obtain the expected benzoselenophene **4c** (R^1 = F) in 60% yield (entry 3).

Very similar results were obtained when the method was expanded to the annulation of the *o*-methoxy- and *o*-propylthio-substituted (*E*)-1-bromo-1-arylselenoalkenes **3d–f** and **3g–i**. Good to very good yields of the respective 2-arylselanylbenzo[*b*]furans **4d–f** and 2-arylselanylbenzo[*b*]thiophenes **4g–i** were obtained under the optimized reaction conditions (Table 3, entries 4 to 9).

The same electronic effect was observed, with the electron-poor fluoro-containing substrates **3f** and **3i** being less reactive. The unsubstituted starting materials **3d** and **3g** (R^1 = H) were cyclized to 2-(phenylselanyl)benzofuran **4d** and 2-(phenylselanyl)benzo[*b*]thiophene **4g** in 80% and 81% yield, respectively, after 24 hours (Table 3, entries 4 and 7). In the presence of an EDG (R^1 = Me), the expected products **4e** and **4h** were obtained in 85% and 84% yield, respectively, after 16 hours (entries 5 and 8). The presence of an EWG

(R^1 = F) negatively affects the reaction, as observed for the seleno-substituted analogue **3c**, affording the respective products **4f** and **4i** in 63% and 72% yields after 38 hours of reaction (entries 6 and 9).

Table 3 Synthesis of 2-Selanylbenzo[*b*]chalcogenophenes **4a–i**[a]



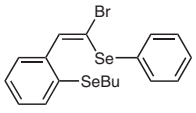
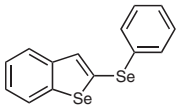
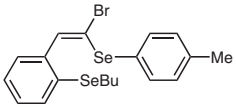
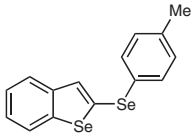
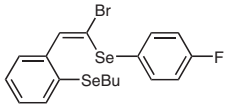
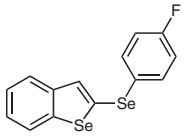
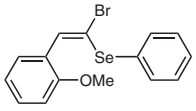
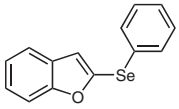
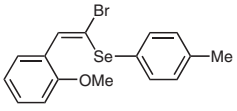
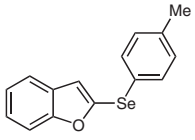
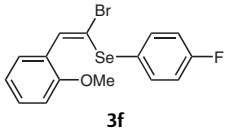
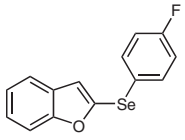
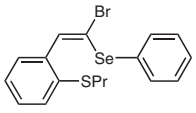
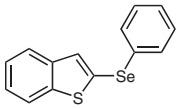
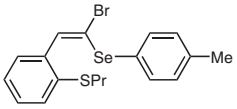
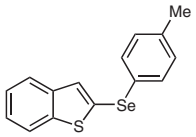
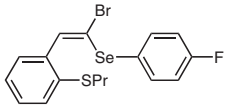
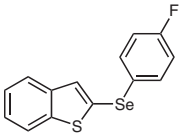
Entry	Vinyl selenide **3**	Time (h)	Product **4**	Yield (%)[b]
1	 **3a**	24	 **4a**	90
2	 **3b**	16	 **4b**	94
3	 **3c**	38	 **4c**	60
4	 **3d**	24	 **4d**	80
5	 **3e**	16	 **4e**	85
6	 **3f**	38	 **4f**	63
7	 **3g**	24	 **4g**	81

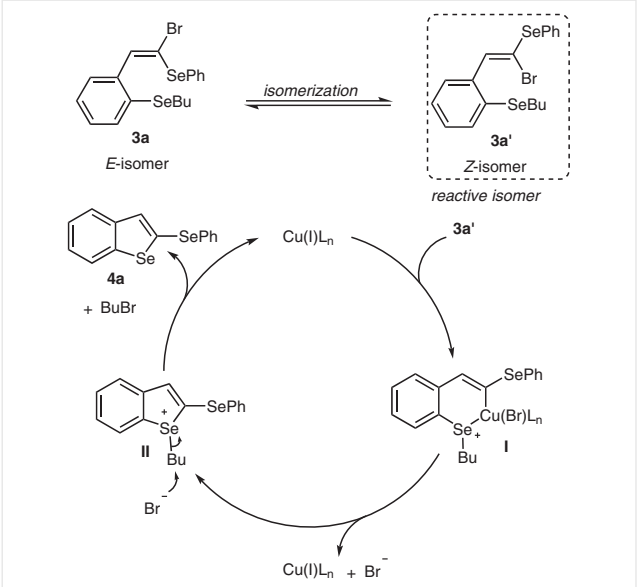
Table 3 (continued)

Entry	Vinyl selenide **3**	Time (h)	Product **4**	Yield (%)[b]
8	 **3h**	16	 **4h**	84
9	 **3i**	38	 **4i**	72

[a] The reaction was performed using **3a–i** (0.15 mmol) and CuBr (15 mol%) as the catalyst in $MeNO_2$ (3 mL) as the solvent at 100 °C under argon atmosphere.
[b] Yields are given for isolated products after column chromatography.

Based on previous works[17,20] and in our own observations, a proposed mechanism for the Cu(I)-catalyzed annulation of **3a** is depicted in Scheme 2. Initially, an isomerization step is needed to the conversion of the *E*-isomer **3a** to the *Z*-isomer **3a′**, which presents a more suitable configuration to undergo an oxidative addition to the coordination sphere of Cu(I) specie, leading to the selenonium intermediate **I**. To confirm this hypothesis [the pre-isomerization (*E*)-**3a** → (*Z*)-**3a**], a control experiment using pure (*E*)-1-bromo-1-(phenylselanyl)-2-phenylethene (**6**) was conducted under the optimized reaction conditions (CuBr/$MeNO_2$ under reflux) and, after 24 hours, 45% of the *E*-isomer was isomerized to the *Z*-isomer (determined by GC/MS analysis), confirming that the reactive specie is formed in situ (see Supporting Information for experimental details and GC chromatograms). Then, an Ullmann-type coupling affords the intermediate **II**, releasing the copper catalyst and bromide. Finally, bromide acts as a nucleophile, attacking the butyl group via an S_N2 mechanism, releasing the desired product **4a** as a leaving group and affording 1-bromobutane as a by-product (Scheme 2).

In conclusion, we have developed an efficient methodology to access 2-arylselanylbenzo[*b*]chalcogenophene derivatives through a Cu(I)-catalyzed annulation of properly substituted (*E*)-1-aryl-1-bromoselenoalkenes. This is the first general protocol to access seleno-functionalized benzo[*b*]chalcogenophenes in moderate to excellent yields using easily available starting materials.



Scheme 2 A plausible mechanism for the formation of **4a**

Pre-coated TLC sheets ALUGRAM® Xtra SIL G/UV_{254} using UV light and acidic ethanolic vanillin solution (5% in 10% H_2SO_4) were used to follow the reaction progress. Aldrich technical grade silica gel (pore size 60 Å, 230–400 mesh) was used for flash chromatography. ^1H NMR spectra were recorded in $CDCl_3$ on a Bruker Ascend 400 spectrometer at 400 MHz. Chemical shifts are reported in ppm, referenced against TMS as internal standard. Standard abbreviations are used to describe ^1H coupling patterns. Coupling constants (*J*) are reported in Hz. ^{13}C NMR spectra were recorded on a Bruker Ascend 400 spectrometer at 100 MHz. The chemical shifts (δ) are reported in ppm, referenced to the solvent peak ($CDCl_3$). The high-resolution atmospheric pressure chemical ionization (APCI-QToF) analyses were performed on a Bruker Daltonics micrOTOF-Q II instrument operating in the positive ion detection mode. For data acquisition and processing, Compass 1.3 for micrOTOF-Q II software (Bruker Daltonics, USA) was used. Melting point (mp) values were measured in a Marte PFD III instrument with a 0.1 °C precision.

(*E*)-1-Aryl-1-bromoselenoalkenes 3a–i;[19] General Procedure

To a solution of the appropriate diaryl diselenide **2a–c** (0.25 mmol) in PEG-400 (1 mL) under argon atmosphere was added $NaBH_4$ (0.75

mmol) at r.t. and the mixture was stirred for 30 min. Then, the respective 1,1-dibromoalkene **1a–c**[21] (0.5 mmol) was added and the temperature was slowly raised to 50 °C. The reaction progress was monitored by TLC. After 1 h, the reaction mixture was quenched with H_2O (10 mL) and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The required product was isolated by column chromatography using hexane as the eluent.

(*E*)-{1-Bromo-2-[2-(butylselanyl)phenyl]vinyl}phenylselane (3a)

Yield: 0.209 g (88%); yellowish oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.65 (s, 1 H), 7.45–7.39 (m, 3 H), 7.30–7.19 (m, 4 H), 7.17–7.13 (m, 2 H), 2.82 (t, *J* = 7.3 Hz, 2 H), 1.61 (quint, *J* = 7.3 Hz, 2 H), 1.36 (sext, *J* = 7.3 Hz, 2 H), 0.84 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 141.2, 138.9, 133.7, 131.8, 131.3, 130.1, 129.7, 129.1, 128.7, 128.2, 126.3, 111.3, 31.9, 27.5, 23.0, 13.6.

MS: *m*/*z* (%) = 395 (M^+ – ^{79}Br, 14.0), 338 (8.3), 317 (25.2), 261 (25.8), 258 (37.7), 182 (50.8), 180 (27.4), 89 (23.9), 77 (16.2), 57 (100.0).

HRMS (APCI-QTOF): *m*/*z* calcd $C_{18}H_{19}BrSe_2$ $[M + H]^+$: 474.9079; found: 474.9072.

(*E*)-{1-Bromo-2-[2-(butylselanyl)phenyl]vinyl}-4-tolylselane (3b)

Yield: 0.181 g (74%); yellowish oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.61 (s, 1 H), 7.44–7.40 (m, 1 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.30–7.28 (m, 1 H), 7.19–7.13 (m, 2 H), 7.05 (d, *J* = 8.0 Hz, 2 H), 2.83 (t, *J* = 7.3 Hz, 2 H), 2.27 (s, 3 H), 1.61 (quint, *J* = 7.3 Hz, 2 H), 1.37 (sext, *J* = 7.3 Hz, 2 H), 0.85 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 140.3, 139.0, 138.5, 134.3, 131.9, 131.3, 129.9, 129.7, 128.6, 126.4, 126.3, 112.1, 32.0, 27.5, 23.0, 21.3, 13.6.

MS: *m*/*z* (%) = 409 (M^+ – ^{79}Br, 13.6), 352 (14.1), 317 (28.3), 272 (50.1), 261 (32.4), 182 (42.0), 180 (23.1), 89 (30.8), 77 (3.6), 57 (100.0).

HRMS (APCI-QTOF): *m*/*z* calcd for $C_{19}H_{21}BrSe_2$ $[M + H]^+$: 488.9235; found: 488.9237.

(*E*)-{2-[2-Bromo-2-(4-fluorophenyl)selanyl]vinylphenyl}butylselane (3c)

Yield: 0.197 g (80%); yellowish oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.66 (s, 1 H), 7.50–7.46 (m, 3 H), 7.33–7.30 (m, 1 H), 7.26–7.22 (m, 2 H), 6.99 (t, *J* = 8.7 Hz, 2 H), 2.90 (t, *J* = 7.3 Hz, 2 H), 1.69 (quint, *J* = 7.3 Hz, 2 H), 1.44 (sext, *J* = 7.3 Hz, 2 H), 0.92 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 163.0 (d, *J* = 247.3 Hz), 140.4, 138.8, 136.5 (d, *J* = 8.1 Hz), 131.7, 131.4, 129.7, 128.7, 126.2, 124.6 (d, *J* = 3.2 Hz), 116.3 (d, *J* = 21.8 Hz), 111.8, 31.9, 27.4, 23.0, 13.5.

MS: *m*/*z* (%) = 413 (M^+ – ^{79}Br, 7.9), 355 (3.9), 317 (23.6), 276 (15.0), 261 (21.8), 182 (56.3), 180 (31.6), 89 (26.0), 77 (1.1), 57 (100.0).

HRMS (APCI -QTOF): *m*/*z* calcd for $C_{18}H_{18}BrFSe_2$ $[M + H]^+$: 492.8985; found: 492.8981.

(*E*)-1-Bromo-2-(2-methoxyphenyl)vinylphenylselane (3d)

Yield: 0.143 g (78%); yellowish oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.65 (s, 1 H), 7.47–7.42 (m, 2 H), 7.35 (d, *J* = 7.5 Hz, 1 H), 7.26–7.20 (m, 4 H), 6.87 (t, *J* = 7.5 Hz, 1 H), 6.79 (d, *J* = 8.3 Hz, 1 H), 3.77 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.6, 137.7, 133.4, 130.6, 129.8, 129.79, 129.1, 128.0, 125.7, 120.1, 110.5, 109.3, 55.4.

MS: *m*/*z* (%) = 370 (20.9), 368 (28.4), 289 (19.3), 274 (31.9), 194 (100.0), 131 (63.7), 89 (51.6), 77 (38.3).

HRMS (APCI-QTOF): *m*/*z* calcd for $C_{15}H_{13}BrOSe$ $[M + H]^+$: 368.9393; found: 368.9396.

(*E*)-1-Bromo-2-(2-methoxyphenyl)vinyl-4-tolylselane (3e)

Yield: 0.145 g (76%); yellowish oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.68 (s, 1 H), 7.45–7.39 (m, 3 H), 7.32–7.28 (m, 1 H), 7.11 (d, *J* = 7.9 Hz, 2 H), 6.95 (t, *J* = 7.4 Hz, 1 H), 6.88–6.85 (m, 1 H), 3.83 (s, 3 H), 2.33 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.6, 138.3, 136.7, 133.9, 129.9, 129.8, 129.7, 126.8, 125.7, 120.0, 110.4, 110.1, 55.4, 21.2.

MS: *m*/*z* (%) = 384 (65.6), 382 (81.9), 303 (70.4), 288 (57.3), 208 (99.0), 131 (100.0), 89 (66.2), 77 (22.4).

HRMS (APCI-QTOF): *m*/*z* calcd for $C_{16}H_{15}BrOSe$ $[M + H]^+$: 382.9550; found: 382.9540.

(*E*)-1-Bromo-2-(2-methoxyphenyl)vinyl-4-fluorophenylselane (3f)

Yield: 0.162 g (84%); yellowish oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.67 (s, 1 H), 7.51–7.46 (m, 2 H), 7.38–7.36 (m, 1 H), 7.30 (td, *J* = 8.0, 1.6 Hz, 1 H), 7.01–6.93 (m, 3 H), 6.86 (d, *J* = 8.2 Hz, 1 H), 3.82 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.9 (d, *J* = 247.1 Hz), 156.5, 136.9, 136.2 (d, *J* = 8.1 Hz), 129.82, 129.75, 125.5, 125.1 (d, *J* = 3.5 Hz), 120.0, 116.2 (d, *J* = 21.7 Hz), 110.4, 109.8, 55.3.

MS: *m*/*z* (%) = 388 (45.3), 386 (58.7), 307 (42.4), 292 (42.4), 212 (61.6), 131 (100.0), 89 (51.7), 77 (14.8).

HRMS (APCI-QTOF): *m*/*z* calcd for $C_{15}H_{12}BrFOSe$ $[M]^+$: 385.9221; found: 385.9230.

(*E*)-{2-[2-Bromo-2-(phenylselanyl)vinyl]phenyl}propylsulfane (3g)

Yield: 0.175 g (85%); yellowish oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.84 (s, 1 H), 7.63–7.57 (m, 2 H), 7.45–7.35 (m, 6 H), 7.27 (td, *J* = 7.4, 1.2 Hz, 1 H), 2.97 (t, *J* = 7.3 Hz, 2 H), 1.77 (sext, *J* = 7.3 Hz, 2 H), 1.13 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 140.0, 137.1, 136.1, 133.6, 130.1, 129.7, 129.1, 128.7, 128.5, 128.1, 125.3, 111.1, 35.6, 22.4, 13.5.

MS: *m*/*z* (%) = 333 (M^+ – ^{79}Br, 17.4), 290 (8.0), 257 (28.2), 213 (32.9), 210 (45.3), 176 (32.0), 134 (100.0), 89 (19.5), 77 (11.7), 43 (55.5).

HRMS (APCI-QTOF): *m*/*z* calcd for $C_{17}H_{17}BrSSe$ $[M + H]^+$: 412.9478; found: 412.9473.

(*E*)-{2-[2-Bromo-2-(4-tolylselanyl)vinyl]phenyl}propylsulfane (3h)

Yield: 0.162 g (76%); yellowish oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.70 (s, 1 H), 7.40 (d, *J* = 8.0 Hz, 2 H), 7.36–7.32 (m, 2 H), 7.27 (dt, *J* = 7.4, 0.9 Hz, 1 H), 7.18 (dt, *J* = 7.4, 0.9 Hz, 1 H), 7.11 (d, *J* = 8.0 Hz, 2 H), 2.87 (t, *J* = 7.3 Hz, 2 H), 2.33 (s, 3 H), 1.67 (sext, *J* = 7.3 Hz, 2 H), 1.03 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 139.1, 138.4, 137.2, 136.0, 134.2, 129.9, 129.7, 128.6, 126.4, 125.3, 111.9, 35.6, 22.4, 21.2, 13.5.

MS: *m*/*z* (%) = 347 (M^+ – ^{79}Br, 17.9), 304 (17.6), 257 (32.6), 224 (100.0), 213 (41.0), 176 (33.6), 134 (86.9), 89 (29.4), 77 (4.9), 43 (75.5).

HRMS (APCI-QTOF): *m*/*z* calcd for $C_{18}H_{19}BrSSe$ [M + H]$^+$: 426.9634; found: 426.9633.

(*E*)-{2-[2-Bromo-2-(4-fluorophenylselanyl)vinyl]phenyl}propylsulfane (3i)

Yield: 0.168 g (78%); yellowish oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.61 (s, 1 H), 7.43–7.39 (m, 2 H), 7.26–7.19 (m, 3 H), 7.11 (td, *J* = 7.4, 1.2 Hz, 1 H), 6.94–6.89 (m, 2 H), 2.80 (t, *J* = 7.3 Hz, 2 H), 1.60 (sext, *J* = 7.3 Hz, 2 H), 0.96 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 163.0 (d, *J* = 247.3 Hz), 139.2, 136.9, 136.4 (d, *J* = 8.1 Hz), 136.2, 129.7, 128.7, 128.3, 125.3, 124.7 (d, *J* = 3.4 Hz), 116.3 (d, *J* = 21.6 Hz), 111.6, 35.5, 22.4, 13.5.

MS: *m*/*z* (%) = 351 (M^+ – ^{79}Br, 13.8), 308 (7.6), 257 (27.2), 228 (47.1), 213 (28.7), 176 (30.1), 134 (100.0), 89 (22.9), 77 (2.2), 43 (64.4).

HRMS (APCI-QTOF): *m*/*z* calcd for $C_{17}H_{16}BrFSSe$ [M + H]$^+$: 430.9384; found: 430.9389.

2-Arylselanylbenzo[*b*]chalcogenophenes 4a–i; General Procedure

To a two-necked round-bottomed flask, equipped with magnetic stirring and a reflux condenser under argon atmosphere was added a solution of the respective (*E*)-1-bromo-1-arylselenoalkene **3a–i** (0.15 mmol) in $MeNO_2$ (3 mL). Then, CuBr (15 mol%) was added and the temperature was raised to the reflux temperature. After the time indicated in Table 3, the reaction mixture was poured into H_2O (30 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo, and the required product was isolated by column chromatography using hexane as the eluent.

2-(Phenylselanyl)benzo[*b*]selenophene (4a)

Yield: 0.046 g (90%); yellowish solid; mp 73–74 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.72 (d, *J* = 7.9 Hz, 1 H), 7.66 (d, *J* = 7.9 Hz, 1 H), 7.63 (s, 1 H), 7.47–7.45 (m, 2 H), 7.28–7.24 (m, 1 H), 7.22–7.15 (m, 4 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 145.4, 142.6, 135.3, 132.2, 131.8, 129.5, 129.4, 127.6, 125.2, 125.0, 124.8, 124.7.

MS: *m*/*z* (%) = 338 (37.2), 258 (100.0), 178 (53.3), 89 (22.4), 77 (12.9).

HRMS (APCI-QTOF): *m*/*z* calcd for $C_{14}H_{10}Se_2$ [M]$^+$: 337.9113; found: 337.9132.

2-(4-Tolylselanyl)benzo[*b*]selenophene (4b)

Yield: 0.050 g (94%); yellowish solid; mp 75–77 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.67 (d, *J* = 7.9 Hz, 1 H), 7.60 (d, *J* = 7.9 Hz, 1 H), 7.55 (s, 1 H), 7.40–7.36 (m, 2 H), 7.24–7.20 (m, 1 H), 7.14–7.10 (m, 1 H), 7.01 (d, *J* = 7.9 Hz, 2 H), 2.23 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 145.0, 142.7, 137.9, 134.0, 132.6, 130.8, 130.2, 128.1, 125.1, 124.8, 124.6, 124.5, 21.1.

MS: *m*/*z* (%) = 352 (35.9), 272 (100.0), 192 (18.5), 89 (20.2), 77 (2.6).

HRMS (APCI-QTOF): *m*/*z* calcd for $C_{15}H_{12}Se_2$ [M + H]$^+$: 352.9348; found: 352.9135.

2-[(4-Fluorophenyl)selanyl]benzo[*b*]selenophene (4c)

Yield: 0.032 g (60%); yellowish solid; mp 75–76 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.77 (d, *J* = 7.9 Hz, 1 H), 7.71 (d, *J* = 7.9 Hz, 1 H), 7.65 (s, 1 H), 7.55–7.52 (m, 2 H), 7.34–7.30 (m, 1 H), 7.25–7.20 (m, 1 H), 6.98 (t, *J* = 8.7 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.7 (d, *J* = 246.5 Hz), 145.2, 142.5, 134.6, 134.5 (d, *J* = 7.9 Hz), 130.1, 126.4 (d, *J* = 3.4 Hz), 125.1, 125.0, 124.78, 124.76, 116.6 (d, *J* = 21.7 Hz).

MS: *m*/*z* (%) = 356 (34.1), 276 (100.0), 196 (62.0), 89 (27.4), 77 (0.9).

HRMS (APCI-QTOF): *m*/*z* calcd for $C_{14}H_9FSe_2$ [M]$^+$: 355.9019; found: 355.9031.

2-(Phenylselanyl)benzofuran (4d)

Yield: 0.033 g (80%); yellowish oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.55–7.53 (m, 1 H), 7.49–7.45 (m, 3 H), 7.29–7.19 (m, 5 H), 7.02 (d, *J* = 0.8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 157.5, 143.6, 131.6, 129.8, 129.4, 128.5, 127.5, 124.8, 122.9, 120.7, 115.8, 111.3.

MS: *m*/*z* (%) = 274 (22.9), 194 (100.0), 165 (25.1), 89 (10.0), 77 (9.1).

HRMS (APCI-QTOF): *m*/*z* calcd for $C_{14}H_{10}OSe$ [M]$^+$: 273.9897; found: 273.9904.

2-(4-Tolylselanyl)benzofuran (4e)

Yield: 0.037 g (85%); yellowish oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.53–7.50 (m, 1 H), 7.45–7.40 (m, 3 H), 7.25 (td, *J* = 7.3, 1.2 Hz, 1 H), 7.20 (td, *J* = 7.3, 1.2 Hz, 1 H), 7.07 (d, *J* = 7.9 Hz, 2 H), 6.96 (d, *J* = 0.6 Hz, 1 H), 2.30 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 157.4, 144.4, 137.8, 132.3, 130.2, 128.6, 125.7, 124.6, 122.9, 120.5, 115.0, 111.2, 21.1.

MS: *m*/*z* (%) = 288 (20.3), 208 (100.0), 179 (5.6), 89 (11.7), 77 (2.4).

HRMS (APCI-QTOF): *m*/*z* calcd for $C_{15}H_{12}OSe$ [M]$^+$: 288.0053; found: 288.0068.

2-[(4-Fluorophenyl)selanyl]benzofuran (4f)

Yield: 0.028 g (63%); reddish oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.54–7.44 (m, 4 H), 7.27 (td, *J* = 7.3, 1.2 Hz, 1 H), 7.22 (td, *J* = 7.3, 1.2 Hz, 1 H), 7.00–6.94 (m, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.6 (d, *J* = 246.4 Hz), 157.4, 143.8, 134.3 (d, *J* = 8.0 Hz), 128.5, 124.9, 123.9 (d, *J* = 3.5 Hz), 123.0, 120.7, 116.6 (d, *J* = 21.9 Hz), 115.3, 111.2.

MS: *m*/*z* (%) = 292 (18.3), 212 (100.0), 183 (25.4), 89 (9.4), 77 (1.9).

HRMS (APCI-QTOF): *m*/*z* calcd for $C_{14}H_9FOSe$ [M]$^+$: 291.9803; found: 291.9806.

2-(Phenylselanyl)benzo[*b*]thiophene (4g)

Yield: 0.035 g (81%); yellowish solid; mp 57–58 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.68–7.62 (m, 2 H), 7.43 (s, 1 H), 7.40–7.37 (m, 2 H), 7.26–7.19 (m, 2 H), 7.17–7.13 (m, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 143.8, 140.2, 132.2, 131.7, 131.4, 129.3, 127.3, 126.9, 124.6, 124.4, 123.3, 121.8.

MS: *m*/*z* (%) = 290 (26.8), 210 (100.0), 89 (8.2), 77 (6.9).

HRMS (APCI-QTOF): *m*/*z* calcd for $C_{14}H_{10}SSe$ [M]$^+$: 289.9668; found: 289.9683.

2-(4-Tolylselanyl)benzo[*b*]thiophene (4h)

Yield: 0.038 g (84%); yellowish solid; mp 85–86 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.62 (t, *J* = 7.2 Hz, 2 H), 7.37 (s, 1 H), 7.32 (d, *J* = 7.9 Hz, 2 H), 7.23–7.15 (m, 2 H), 6.97 (d, *J* = 7.9 Hz, 2 H), 2.20 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 143.5, 140.2, 137.7, 132.2, 131.1, 130.1, 128.0, 127.6, 124.4, 124.3, 123.1, 121.7, 21.1.

MS: *m*/*z* (%) = 304 (23.4), 224 (100.0), 89 (8.1), 77 (1.5).

HRMS (APCI-QTOF): *m*/*z* calcd for $C_{15}H_{12}SSe$ $[M]^+$: 303.9825; found: 303.9842.

2-[(4-Fluorophenyl)selanyl]benzo[*b*]thiophene (4i)

Yield: 0.033 g (72%); yellowish solid; mp 54–55 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.72 (t, *J* = 6.9 Hz, 2 H), 7.50–7.47 (m, 3 H), 7.34–7.27 (m, 2 H), 6.95 (t, *J* = 8.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.5 (d, *J* = 246.4 Hz), 143.6, 140.1, 134.1 (d, *J* = 7.9 Hz), 131.5, 127.4, 125.9 (d, *J* = 3.4 Hz), 124.7, 124.5, 123.3, 121.8, 116.5 (d, *J* = 21.3 Hz).

MS: *m*/*z* (%) = 308 (26.9), 228 (100.0), 89 (9.9), 77 (1.5).

HRMS (APCI-QTOF): *m*/*z* calcd for $C_{14}H_9FSSe$ $[M]^+$: 307.9574; found: 307.9579.

Funding Information

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001. CNPq, FAPERGS and FINEP are thanked for financial support.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610656.

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