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Copper Iodide and Diorganyl Diselenides-Promoted Cyclization of 2-Alkynyl-phenols: Alternative Approach to 3-Organoselanyl-benzo[*b*]furans

Jean C. Kazmierczak,[a] Ana M. S. Recchi,[b] Fabiane Gritzenco,[a] Everton B. Balbom,[a] Thiago Barcellos,[c] Adriane Sperança,[d] and Benhur Godoi*, [a]

Abstract: This manuscript describes an alternative method for the synthesis of 3-organoselanyl-benzo[*b*]furans through intramolecular cyclization of 2-alkynyl-phenols promoted by copper iodide and diorganyl diselenides. The cyclization reactions were carried out at room temperature in the absence of base and under ambient atmosphere (open flask). This synthetic methodology proved to be efficient to both diorganyl diselenides and 2-alkynyl-phenols bearing neutral, electron-donating and electron-withdrawing substituents. The 2-phenyl-3-phenylselanyl-benzo[*b*]furan was applied as a synthetic precursor in organochalcogen-lithium exchange and bromination reactions, allowing the synthesis of functionalized benzo[*b*]furans in good yields.

Introduction

Organic compounds bearing benzo[*b*]furan nucleus are known to have a range of biological properties.[1] Diverse benzo[*b*]furan scaffold containing substances have demonstrated pharmacological activities, such as anticancer and antiangiogenic,[2] antidepressant,[3] anticonvulsant and anti-inflammatory.[4] Potentially, small molecules derived from benzo[*b*]furans were active as inhibitors of human protein kinases, which are able to modify other proteins via phosphorylation processes, being directly related with viral infections and cancer disease.[5] For example, the benzo[*b*]furan-2-carboxamide **A**[6] and benzo[*b*]furan-2-carbaldehyde **B**[7] (Figure 1) have been reported to have potential as antiproliferative agents against tumor cells through the inhibition of cyclin-dependent kinases.

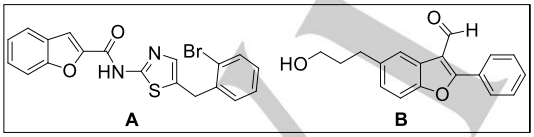
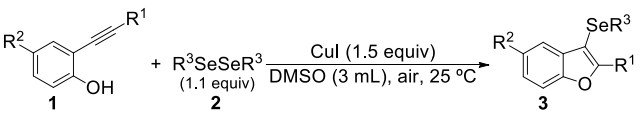


Figure 1. Inhibitors of cyclin-dependent kinases.

Furthermore, benzo[*b*]furan derivatives have also found application on the materials chemistry being useful to organic field effect transistors[8] and for electro-optical materials.[9] Such applicability become benzo[*b*]furan rings important synthetic targets and a range of strategies for the construction of these heterocyclic derivatives have been developed from distinct precursors by using different conditions.[10] Among them, synthetic approaches based on electrophilic cyclization and transition-metals mediated cyclization reactions of acyclic substrates consist in a very useful tool to this aim.[11] In this way, 2-alkynyl-phenols and 2-alkynyl-anisoles are the most employed precursors.[12]

In the last years, reaction systems combining stoichiometric or catalytic amounts of transition-metal salts and diorganyl dichalcogenides have emerged as an alternative tool to promote intramolecular cyclization of acyclic alkynes. Palladium, copper and iron salts have being successfully used in these transformations affording the synthesis of various heterocycle scaffolds.[13] For a long period, organochalcogen derivatives, in special organoselenium compounds, had a bad reputation wrongfully receipt relating to their toxicity, instability and odor. However, recent advances in the studies regarding their pharmacological and toxicological properties highlight these substances as promising therapeutic agents due to their singular features.[14] In addition, the presence of an organochalcogen moiety in the structure of different substances have drawn attention of the scientific community because of their influence in pharmacological activities[15] and large applicability as reactive sites in different organic compound classes.[16] Considering that there is no protocol describing the use of copper iodide and dichalcogenide as the cyclization promoters of 2-alkynyl-phenols for the preparation of benzo[*b*]furan nucleus in the scientific literature, in this study we reported the synthesis of 3-organoselanyl-benzo[*b*]furans **3** by intramolecular cyclization of 2-alkynyl-phenols **1** combining copper iodide and diorganyl diselenides **2** to promote these transformations (Scheme 1).



R^1, R^3 = alkyl, aryl; R^2 = H, F, Me;

Scheme 1. CuI/R^3SeSeR^3-promoted cyclization of 2-alkynyl-phenols.

Results and Discussion

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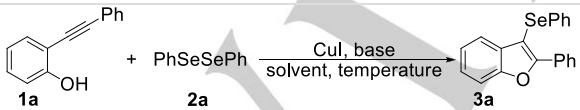
In order to determine the ideal reaction conditions, 2-phenyl(ethynyl)phenol **1a**, copper iodide and diphenyl diselenide were chosen as standard substrates to screen the cyclization reaction parameters such as temperature, base, solvent, reaction stoichiometry, amount of copper iodide and reaction atmosphere. The results of these experiments are summarized in table 1. Firstly, 2-alkynyl-phenol **1a** (0.25 mmol) was added to a mixture of copper iodide (1 equiv) and PhSeSePh **2a** (1.1 equiv) in DMF, at room temperature under ambient atmosphere (open flask). By using these conditions, the 2-phenyl-3-phenylselanyl-benzo[*b*]furan **3a** was isolated in 48% yield (Table 1, entry 1). The evaluation of different solvents showed that both DMF and DMSO afforded the desired product while MeCN and DCM were quite inefficient (Table 1, entries 1-4). In order to verify the influence of bases in the cyclization process, the reactions were carried out using 1.5 equivalents of $NaHCO_3$, K_2CO_3 and NaOH. These tests showed that the presence of bases did not significantly improve the cyclization yields (Table 1, entries 5-7). Increasing the diphenyl diselenide amount from 0.5 to 1.5 equivalents did not improve the reaction yields (Table 1, entries 8-10). However, when the amount of PhSeSePh **2a** was kept constant and increasing the amount of copper iodide from 1.0 to 1.5 equivalents a significant increment in the cyclization efficiency was observed, giving the 3-organoselanyl-benzo[*b*]furan **3a** in 72% yield (Table 1, entry 13). Using more than 1.5 equivalents of copper iodide, a slight decrease in the reaction yield was observed even if higher temperature was used (Table 1, entries 14-16). When copper iodide was employed in catalytic quantities, the cyclization yields dramatically decreased (Table 1, entries 11-12). Regarding the influence of temperature into cyclization, it was clear that high temperature had no positive effect, affording the product **3a** in lower yields (Table, entries 16-18). The cyclization proved to be no sensitive to the oxygen present in the air because when the reactions were carried out under argon atmosphere no difference in the reaction behavior was observed (Table, entries 19-20). The fact that, this cyclization protocol was carried out at room temperature, in the absence of bases and under an open flask, represents economical and practical advantages compared with other methodologies.

Table 1. Effects of Different Reaction Parameters on the CuI/PhSeSePh-Promoted Cyclization of **1a**.[a]



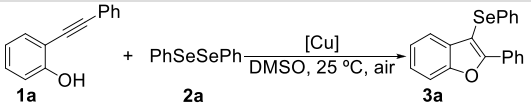
1a **2a** **3a**

Entry	CuI (equiv)	$(PhSe)_2$ (equiv)	Base (equiv)	Solvent (3 mL)	Yield (%)
1	1.0	1.1	-	DMF	48
2	1.0	1.1	-	MeCN	2
3	1.0	1.1	-	DCM	-
4	1.0	1.1	-	DMSO	48
5	1.0	1.1	$NaHCO_3$ (1.5)	DMSO	22
6	1.0	1.1	K_2CO_3 (1.5)	DMSO	25
7	1.0	1.1	NaOH (1.5)	DMSO	52
8	1.0	0.5	-	DMSO	44
9	1.0	0.75	-	DMSO	40
10	1.0	1.5	-	DMSO	44
11	0.2	1.1	-	DMSO	4
12	0.5	1.1	-	DMSO	6
13	1.5	1.1	-	DMSO	72
14	2.0	1.1	-	DMSO	65
15	2.0	0.75	-	DMSO	58
16	2.0	0.75	-	DMSO	58[b]
17	1.5	1.1	-	DMSO	52[c]
18	1.5	1.1	-	DMSO	68[d]
19	1.5	1.1	-	DMSO	70[e]
20	2.0	1.1	-	DMSO	72[e]

[a] The reaction was performed in the presence of **1a** (0.25 mmol), solvent (3 mL), in an open flask for 20 h. [b] Reaction was performed at 100 ºC. [c] The Reaction was performed at 80 ºC. [d] Reaction was performed at 50 ºC. [e] The Reaction carried out under argon.

In addition, we carried out some experiments to evaluate the reaction behavior by employing different copper salts and these results are shown in table 2. When Cu(I) species such as CuCl and CuBr were used, the expected benzo[*b*]furan **3a** was obtained in lower yield compared with that of copper iodide (Table 2, entries 1-2). On the other hand, Cu(II) salts, such as $CuBr_2$, CuO and CuO_{nano}, showed low or no activity to promote the cyclization of **1a** (Table 2, entries 3-5). These results could suggest that the halogen atom present in the copper salt plays an important role in the cyclization process. We also observed that in the absence of copper salt the cyclization did not proceed (Table 2, entry 6). Thus, the best reaction condition to provide the cyclization of the 2-alkynyl-phenol **1a** (0.25 mmol) consisted in the use of copper iodide (1.5 equiv), diphenyl diselenide **2a** (1.1 equiv), employing DMSO (3 mL) as solvent in the absence of bases, at room temperature and in an open flask.

Table 2. Effects of Different Copper Salts on the Cyclization of **1a**.[a]



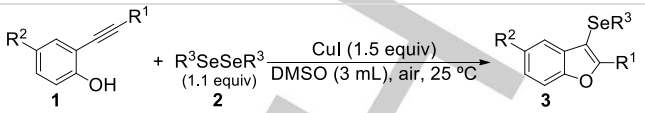
1a **2a** **3a**

Entry	[Cu] (1.5 equiv)	Yield (%)
1	CuCl	30
2	CuBr	53
3	$CuBr_2$	9
4	CuO	-
5	CuO_{nano}	-
6	-	-

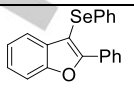
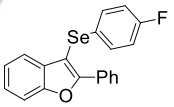
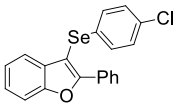
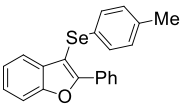
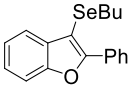
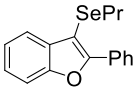
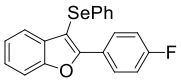
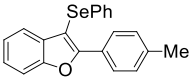
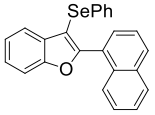
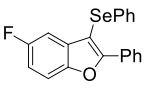
[a] Reaction was performed using **1a** (0.25 mmol), **2a** (1.1 equiv) in DMSO (3 mL) at 25 ºC, in an open flask for 20h.

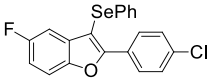
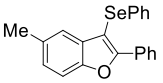
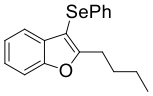
Once determined the best cyclization parameters, we focused on the study of scope and limitations of the methodology (Table 3). The cyclization approach proved to be tolerant to electron-donating and electron-withdrawing groups into the aromatic rings bonded to the selenium atom of the diaryl diselenides **2** given the corresponding 3-organoselanyl-benzo[*b*]furans **3** in good yields (Table 3, entries 2-4). These results suggest that the cyclization was not sensitive to electronic effects of the groups bonded to the diaryl diselenides. When dialkyl diselenides were used, a decrease in the cyclization yield was observed and the 3-alkylselanyl-benzo[*b*]furans **3e** and **3f** were isolated in 30 and 32% yields, respectively (Table 3, entries 5-6). In order to evaluate the influence of electronic effects of the aromatic rings directly bonded to the triple bond in the 2-alkynyl-phenols **1**, the substrates **1b-d** were submitted to the cyclization conditions and the results indicate that the expected product was obtained in a moderate yield, suggesting a negative influence of the electron-withdrawing fluorine atom (Table 3, entry 7). The methyl group did not significantly affect the reaction behavior leading to the benzo[*b*]furan **3h** in good yield (Table 3, entry 8). The cyclization approach showed toleration to the presence of the bulky 1-naphthyl group bonded to the C*sp* on the substrate **1e** furnishing the benzo[*b*]furan derivative **3j** in 57% yield (Table 3, entry 9). The reaction showed to be sensitive to electronic effects from substituents bonded into the phenol ring (Table 3, entries 10-12). In fact, the electron-withdrawing fluorine atom in the substrates **1e** and **1f** did not negatively affect the reaction efficiency and the corresponding benzo[*b*]furans **3j** and **3k** were obtained in good yields (Table 3, entries 10 and 11). However, the presence of an electron-donating methyl group led to a decrease in the cyclization yield (Table 3, entry 12). In addition, the reaction proved to be tolerant to the presence of an alkyl group directly bonded to the carbon-carbon triple bond and the reaction of the 2-alkynyl-phenol **1h** and dyphenyl diselenide **2a** under the optimized conditions furnished the desired 2-butyl-3-(phenylselanyl)benzo[*b*]furan **3m** in 55% yield (Table 1, entry 13).

Table 3. Scope and Limitations of the CuI/R^3SeSeR^3-Promoted Cyclization of 2-Alkynyl-phenols **1**.[a]



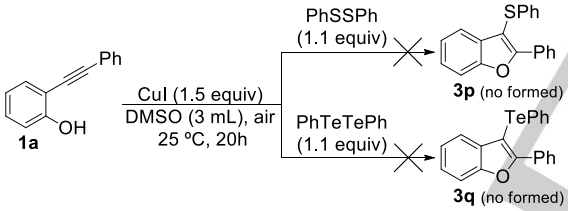
1 2 3

Entry	2-alkynyl-phenols **1**	$(R^3Se)_2$ **2**	Product **3**	Yield (%)/(h)
1	$R^1 = C_6H_5$; R^2 = H; **1a**	$(PhSe)_2$ **2a**	 **3a**	72/(20)
2	**1a**	**2b** $(p\text{-}FC_6H_4Se)_2$	 **3b**	57/(2
3	**1a**	**2c** $(p\text{-}ClC_6H_4Se)_2$	 **3c**	61/(2
4	**1a**	**2d** $(p\text{-}MeC_6H_4Se)_2$	 **3d**	63/(2
5	**1a**	$(BuSe)_2$ **2e**	 **3e**	30/(2
6	**1a**	$(PrSe)_2$ **2f**	 **3f**	32/(2
7	$R^1 = p\text{-}FC_6H_4$; R^2 = H: **1b**	**2a**	 **3g**	47/(2
8	$R^1 = p\text{-}MeC_6H_4$; R^2 = H; **1c**	**2a**	 **3h**	57/(2
9	R^1 = 1-naphthyl; R^2 = H; **1d**	**2a**	 **3i**	57/(2
10	$R^1 = C_6H_5$; R^2 = F; **1e**	**2a**	 **3j**	63/(22)

11	R^1 = *p*-ClC$_6$H$_4$; R^2 = F; **1f**	**2a**	 **3k**	61/(22)
12	R^1 = C$_6$H$_5$; R^2 = Me; **1g**	**2a**	 **3l**	24/(24)
13	R^1 = Bu; R^2 = H; **1h**	**2a**	 **3m**	55/(23)

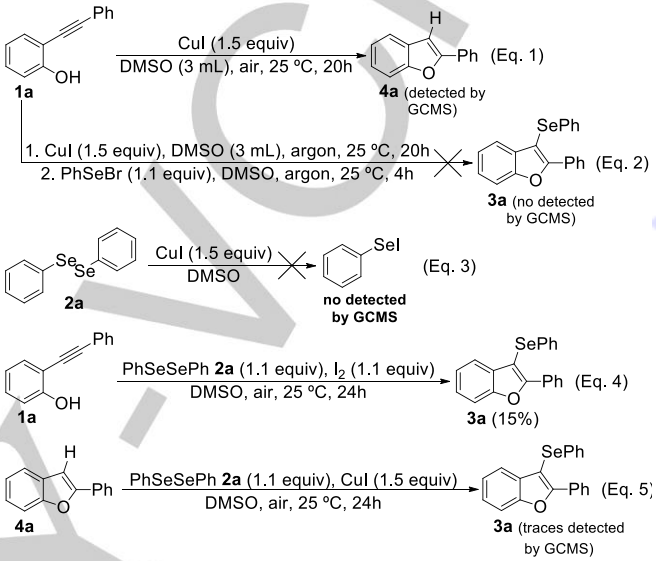
[a] The reaction was performed using 2-alkynyl-phenols **1** (0.25 mmol), R^3SeSeR^3 **2** (1.1 equiv), CuI (1.5 equiv) in DMSO (3 mL) at 25 ºC, in an open flask.

With the aim of studying the generality of the cyclization method for the synthesis of organosulfur and organotellurium benzo[*b*]furan derivatives, the substrate **1a** was submitted to the cyclization reaction in the presence of diphenyl disulfide and diphenyl ditelluride (Scheme 2). Unfortunately, these experiments demonstrated a limitation of the synthetic protocol because the expected products **3p** and **3q** were not formed, under the optimized conditions.



Scheme 2. Cyclization of 2-alkynyl-phenols using disulfide and ditelluride.

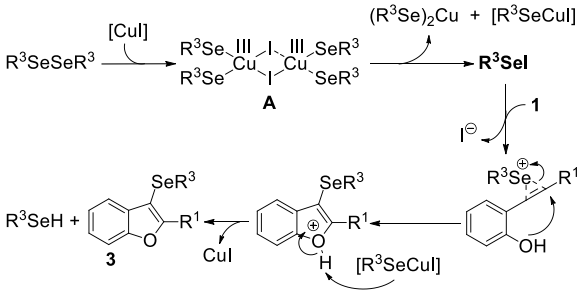
Regarding the mechanisms involved in the cyclization process, we are not able to infer an undoubted proposal. Herein, based on previous reports[17] and considering that the cyclization system seems to be catalytically inactive (Table 1, entries 11-12) we carried out some experiments in order to become the cyclization pathway as clear as possible aiming to obtain relevant data that could support a plausible mechanism (Scheme 3). First, the substrate **1a** was submitted to the cyclization conditions in the absence of diorganyl dichalcogenides **2** (Scheme 3, Eq. 1). Analysis by GC-MS showed the formation of the benzo[*b*]furan **4a**, which contains a hydrogen atom at C-3 position. As expected, when the reaction was performed in the absence of any cooper salt no cyclized product was detected and both substrates **1a** and **2a** were recovered (Table 2, entry 6). These results confirm that copper iodide plays an important role in the cyclization reaction by activating the C-C triple bond. In order to investigate if dichalcogenides could be acting as electrophilic sources by replacing a Csp^2-Cu bond for the organochalcogenyl moiety, the 2-alkynyl-phenol **1a** was stirred in the presence of copper iodide under inert atmosphere, until its complete consumption and then the selenium electrophile PhSeBr was added to the reaction mixture (Scheme 3, Eq. 2). Using this protocol, the benzo[*b*]furan **3a** was not detected by GC-MS analysis. In fact, this experiment became clear the importance of the simultaneous presence of copper iodide and dichalcogenide to the effectiveness of the cyclization system, becoming plausible the formation of the Cu(III)-complex **A** shown in Scheme 4.



Scheme 3. Experiments regarding the mechanistic studies.

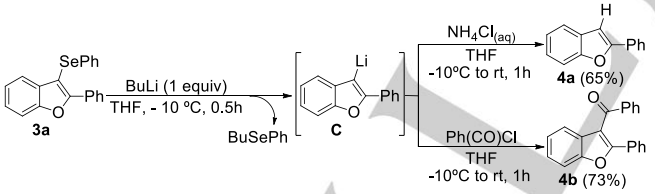
According to the scientific literature, electrophilic agents, such as PhSeI, could be formed from the corresponding diorganyl dichalcogenide in the presence of molecular iodine and palladium salts.[13f] Through this system it is possible to promote the cyclization of 2-alkynyl-anisoles and a plausible route for this transformation involves the formation of an organochalcogenonium intermediate, which is responsible to activate the alkyne for the electrophilic cyclization. In this context we performed some experiments to examine if an organochalcogenyl electrophilic species could be *in situ* formed, becoming plausible an electrophilic cyclization pathway for this transformation (Scheme 3, Eq. 3-4). Herein, when PhSeSePh **2a** and copper iodide reacted under the cyclization conditions, without any substrate **1**, the formation of the electrophilic PhSeI was not observed by GCMS analysis of the crude reaction mixture (Scheme 3, Eq. 3). To further support this idea, we submitted the substrate **1a** to the electrophilic cyclization reaction, in which the electrophilic source was PhSeI, prepared by reaction of PhSeSePh **2a** and molecular iodine. Under the standard reaction parameters, this cyclization system proved to be active to promote the cyclization of **1a** affording the cyclized product **3a** in 15% yield (Scheme 3, Eq. 4). By analyzing these results, an electrophilic cyclization pathway involving the R^3SeI as cyclizing agent cannot be discarded. This mechanistic hypothesis could involve the *in situ* formation of R^3SeI from decomposition of the Cu(III)-tetracoordinated complex **A** by the displacement of $(R^3Se)_2Cu$ and $[(R^3Se)CuI]$. The mechanistic sequence should follow a typical electrophilic cyclization route via activation of the alkyne by the electrophile (R^3SeI) and

subsequent attack of oxygen to the activated C*sp*; a further deprotonation step could provide the expected product **3** (Scheme 4). The supposed generation of the $(R^3Se)_2Cu(II)$ species could justify the necessity of stoichiometric amounts of copper iodide and diorganyl diselenide, because Cu(II) salts proved to be inefficient to promote cyclization process (Table 2, entries 3-5). Furthermore, the benzo[*b*]furan **4a** was submitted to the standard cyclization conditions using CuI and diphenyl diselenide **2a** (Scheme 3, Eq. 5). Herein, traces of the 3-(phenylselanyl)benzo[*b*]furan **3a** were observed by analysis of the crude reaction mixture by GC-MS. This result suggest that a C-H activation pathway cannot be totally discarded.[18]



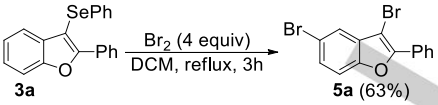
Scheme 4. Electrophilic cyclization hypothesis.

Aiming to explore the synthetic applicability of the organoselanyl groups as potentially reactive molecular sites for the preparation of different functionalized substances, the 2-phenyl-3-phenylselanyl-benzo[*b*]furan **3a** was employed as precursor to organochalcogen-lithium exchange reactions (Scheme 5). Butyllithium was used to promote the formation of the organometallic intermediate **C**, which was subsequently trapped with different electrophiles, such as aqueous ammonium chloride and benzoyl chloride. Through these reactions, the benzo[*b*]furans **4a** and **4b** were obtained in 65 and 73% yield, respectively.



Scheme 5. Organochalcogen-lithium exchange reaction.

The introduction of halogen atoms in the structure of organic compounds consist in a versatile synthetic tool, because the C-halogen bond can be easily replaced under several protocols, being especially useful on transition-metal catalyzed cross-coupling reactions.[19] Thus, we tested the behavior of the benzo[*b*]furan **3a** as substrate under bromination reaction conditions (Scheme 6). By this protocol, the benzo[*b*]furan **5a** bearing two bromine atoms into the benzofuran ring was obtained in 63% yield. This result must be highlighted because it becomes possible the high functionalization of the heterocycles by a range of methodologies.



Scheme 6. Bromination reaction of **3a**.

Conclusions

In this study, we described an alternative method to access 3-organoselanyl-benzo[*b*]furans by using 2-alkynyl-phenols **1** as substrates to undergo intramolecular cyclization reactions promoted by copper iodide and diorganyl diselenides, using DMSO as solvent, at room temperature, under ambient atmosphere (air) and in the absence of bases. Through this protocol, the benzo[*b*]furan derivatives **3** could be obtained in moderate to good yields, under mild reaction conditions. In fact, this is the first report of copper iodide/R^3SeSeR^3-promoted cyclization of 2-alkynyl-phenols. Furthermore, the 2-phenyl-3-(phenylselanyl)benzo[*b*]furan **3a** proved to be a versatile substrate to different synthetic transformations such as organochalcogen-lithium exchange and bromination reactions, being useful to the preparation of multi-functionalized benzo[*b*]furan units.

Experimental Section

General Procedure for the CuI/R^3SeSeR^3-Promoted Cyclization of 2-Alkynyl-phenols 1 for Preparation of Benzo[*b*]furans 3: In a reaction tube, under ambient atmosphere (air), containing the appropriated diorganyl diselenide **2** (1.1 equiv) and CuI (1.5 equiv) at 25 ºC was added DCM (3 mL). To the stirring reaction mixture was added the proper 2-alkynyl-phenol **1** (0.25 mmol) diluted in 2 mL of DCM, in one portion. The reaction mixture was stirred for the required time at 25 ºC. After that, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (5 mL) and the aqueous layer was extracted with AcOEt (3 x 5 mL) and dried over $MgSO_4$. After filtering, the organic solution was concentrated using a rotary evaporator under reduced pressure. The product was purified by flash chromatography in silica gel using hexane/ethyl acetate as eluent.

2-phenyl-3-(phenylselanyl)benzo[*b*]furan (3a):[13e] Yield: 0.063g (72%) NMR ^{1}H: $CDCl_3$, 400 MHz, δ(ppm): 8.24-8.16 (m, 2H), 7.58-7.49 (m, 2H), 7.48-7.41 (m, 2H), 7.40-7.32 (m, 1H), 7.31-7.26 (m, 2H), 7.25-7.19 (m, 1H), 7.18-7.06 (m, 4H). NMR ^{13}C: $CDCl_3$, 100 MHz, δ(ppm): 157.2, 154.1 131.9, 131.4, 130.1, 129.3, 129.2, 129.1, 128.4, 127.8, 126.2, 125.2, 123.4, 121.2, 111.1, 99.7. MS (EI, 70 eV) *m/z* (relative intensity): 350 (27), 348 (14), 270 (100), 255 (10), 241 (21), 165 (62), 139 (14), 77 (9).

3-((4-fluorophenyl)selanyl)-2-phenylbenzo[*b*]furan (3b): Yield: 0.052g (57%). NMR ^{1}H: $CDCl_3$, 400 MHz, δ(ppm): 8.20 (d, *J* = 7.7 Hz, 2H), 7.54-7.20 (m, 9H), 6.85 (t, *J* = 8.8 Hz, 2H). NMR ^{13}C: $CDCl_3$, 100 MHz, δ(ppm): 161.9 (d, $^1J_{CF}$ = 246.0 Hz), 157.0, 154.0, 131.7, 131.5 (d, $^3J_{CF}$ = 7.7 Hz), 130.1, 129.3, 128.5, 127.8, 125.6 (d, $^4J_{CF}$ = 3.3 Hz), 125.2, 123.4 121.0, 116.4 (d, $^2J_{CF}$ = 21.8 Hz), 111.2, 100.2. MS (EI, 70 eV) *m/z* (relative intensity): 368 (26), 367 (3), 288 (100), 259 (14), 165 (33), 139 (7), 115 (4), 77 (2). HRMS calcd for $C_{20}H_{13}FOSe$: $[M]^+$ 368.0116. Found $[M]^+$ 368.0112.

3-((4-chlorophenyl)selanyl)-2-phenylbenzo[*b*]furan (3c):[13e] Yield: 0.058g (61%). NMR ^{1}H: $CDCl_3$, 400 MHz, δ(ppm): 8.17 (d, *J* = 7.0 Hz, 2H), 7.55 (d, J = 8.2 Hz, 1H), 7.49-7.37 (m, 4H), 7.36-7.31 (m, 1H), 7.26-7.18 (m, 3H), 7.11 (d, *J* = 8.7 Hz, 2H). NMR ^{13}C: $CDCl_3$, 100 MHz, δ(ppm): 157.4, 154.1, 132.4, 131.6, 130.5, 130.0, 129.6, 129.5, 129.4, 128.5, 127.8, 125.3, 123.5, 121.0, 111.2, 99.4. MS (EI, 70 eV) *m/z* (relative intensity): 386 (14), 384 (29), 383 (4), 306 (34), 304 (100), 268 (22), 241 (19), 165 (56), 115 (8), 105 (2), 77 (4).

3-((4-methylphenyl)selanyl)-2-phenylbenzo[*b*]furan (3d):[13e] Yield: 0.057g (63%). NMR ^{1}H: $CDCl_3$, 400 MHz, δ(ppm): 8.22-8.19 (m, 2H), 7.55-7.50 (m, 2H), 7.47-7.42 (m, 2H), 7.41-7.36 (m, 1H), 7.34-7.29 (m, 1H), 7.24-7.19 (m, 3H), 6.97 (d, *J* = 7.9 Hz, 2H), 2.24 (s, 3H). NMR ^{13}C: $CDCl_3$, 100 MHz, δ(ppm): 156.9, 154.1, 136.2, 132.0, 130.2, 130.1, 129.6, 129.2, 128.4, 127.8, 127.4, 125.1, 123.3, 121.2, 111.1, 100.1, 20.9. MS (EI, 70 eV) *m/z* (relative intensity): 364 (24), 363 (3), 284 (100), 269 (13), 255 (10), 241 (14), 165 (27), 115 (4), 77 (2).

3-(butylselanyl)-2-phenylbenzo[*b*]furan (3e):[13e] Yield: 0.025g (30%). NMR ^{1}H: $CDCl_3$, 400 MHz, δ(ppm): 8.32-8.28 (m, 2H), 7.69-7.67 (m, 1H), 7.53-7.45 (m, 3H), 7.41-7.37 (m, 1H), 7.35-7.28 (m, 2H), 2.79 (t, *J* = 7.3 Hz, 2H), 1.56 (quint, J = 7.3 Hz, 2H), 1.33 (sex, *J* = 7.3 Hz, 2H), 0.79 (t, *J* = 7.3 Hz, 3H). NMR ^{13}C: $CDCl_3$, 100 MHz, δ(ppm): 155.8, 153.8, 132.7, 130.6, 128.8, 128.3, 127.6, 124.9, 123.1, 121.0, 111.0, 100.3, 32.3, 28.2, 22.7, 13.4. MS (EI, 70 eV) *m/z* (relative intensity): 330 (24), 329 (3), 274 (9), 245 (12), 194 (100), 165 (43), 115 (3), 77 (3), 57 (3).

2-phenyl-3-(propylselanyl)benzo[*b*]furan (3f): Yield: 0.025g (32%). NMR ^{1}H: $CDCl_3$, 400 MHz, δ(ppm): 8.30 (d, *J* = 7.4 Hz, 2H), 7.69-7.67 (m, 1H), 7.51-7.44 (m, 3H), 7.40-7.36 (m, 1H), 7.34-7.26 (m, 2H), 2.77 (t, *J* = 7.3 Hz, 2H), 1.60 (sex, J = 7.3 Hz, 2H), 0.90 (t, J = 7.3 Hz, 3H). NMR ^{13}C: $CDCl_3$, 100 MHz, δ(ppm): 155.9, 153.9, 132.8, 130.7, 128.8, 128.3, 127.7, 124.9, 123.1, 121.0, 111.1, 100.4, 30.6, 23.7, 14.2. MS (EI, 70 eV) *m/z* (relative intensity): 316 (30), 315 (3), 273 (10), 245 (18), 194 (100), 165 (58), 115 (4), 77 (4). HRMS calcd for $C_{17}H_{16}OSe$: $[M]^+$ 316.0366. Found $[M]^+$ 316.0362.

2-(4-fluorophenyl)-3-(phenylselanyl)benzo[*b*]furan (3g): Yield: 0.043g (47%). NMR ^{1}H: $CDCl_3$, 400 MHz, δ(ppm): 8.21-8.17 (m, 2H), 7.54-7.50 (m, 2H), 7.34-7.21 (m, 5H), 7.18-7.10 (m, 4H). NMR ^{13}C: $CDCl_3$, 100 MHz, δ(ppm): 163.9 (d, $^1J_{CF}$ = 249.0 Hz), 156.4, 154.0, 131.9, 131.6, 131.2, 129.8 (d, $^3J_{CF}$ = 8.2 Hz), 129.3, 129.1, 126.4 (d, $^4J_{CF}$ = 3.3 Hz), 126.3, 125.3, 123.5, 121.2, 115.5 (d, $^2J_{CF}$ = 21.7 Hz), 111.1. MS (EI, 70 eV) *m/z* (relative intensity): 368 (26), 367 (3), 288 (100), 259 (16), 183 (43), 165 (3), 157 (11), 77 (9). HRMS calcd for $C_{20}H_{13}FOSe$: $[M]^+$ 368.0116. Found $[M]^+$ 368.0111.

2-(4-methylphenyl)-3-(phenylselanyl)benzo[*b*]furan (3h):[13e] Yield: 0.052g (57%). NMR ^{1}H: $CDCl_3$, 400 MHz, δ(ppm): 8.10 (d, *J* = 8.2 Hz, 2H), 7.54-7.48 (m, 2H), 7.32-7.19 (m, 6H), 7.16-7.09 (m, 3H), 2.38 (s, 3H). NMR ^{13}C: $CDCl_3$, 100 MHz, δ(ppm): 157.6, 154.1, 139.5, 132.1, 131.6, 129.3, 129.2, 129.1, 127.7, 127.4, 126.2, 125.0, 123.3, 121.1, 111.1, 99.1, 21.4. MS (EI, 70 eV) *m/z* (relative intensity): 364 (31), 363 (4), 284 (100), 269 (11), 255 (9), 241 (13), 178 (33), 165 (4), 115 (1), 77 (22).

2-(1-naphthyl)-3-(phenylselanyl)benzo[*b*]furan (3i): Yield: 0.057g (57%). NMR ^{1}H: $CDCl_3$, 400 MHz, δ(ppm): 7.97-7.88 (m, 3H), 7.67 (dd, *J* = 7.1 Hz; *J* = 1.1 Hz, 1H), 7.60-7.44 (m, 5H), 7.39-7.35 (m, 1H), 7.30-7.23 (m, 3H), 7.13-7.08 (m, 3H). NMR ^{13}C: $CDCl_3$, 100 MHz, δ(ppm): 158.9, 154.9, 133.7, 132.2, 131.3, 130.9, 130.4, 129.9, 129.8, 129.1, 128.4, 127.3, 126.7, 126.3, 126.1, 125.9, 125.1, 124.8, 123.5, 121.3, 111.5, 103.8. MS (EI, 70 eV) *m/z* (relative intensity): 400 (63), 399 (8), 320 (100), 291 (23), 243 (27), 215 (41), 189 (13), 159 (9), 77 (8). HRMS calcd for $C_{24}H_{16}OSe$: $[M]^+$ 400.0366. Found $[M]^+$ 400.0364.

5-fluoro-2-phenyl-3-(phenylselanyl)benzo[*b*]furan (3j): Yield: 0.058g (63%). NMR ^{1}H: $CDCl_3$, 400 MHz, δ(ppm): 8.20-8.17 (m, 2H), 7.48-7.37 (m, 4H), 7.29-7.23 (m, 2H), 7.20-7.12 (m, 4H), 7.02 (td, *J* = 2.6 Hz; *J* = 9.0 Hz, 1H). NMR ^{13}C: $CDCl_3$, 100 MHz, δ(ppm): 159.6 (d, $^1J_{CF}$ = 239.6 Hz), 158.9, 150.2, 133.1 (d, $^3J_{CF}$ = 10.6 Hz), 130.9, 129.7, 129.5, 129.3, 129.1, 128.5, 127.7, 126.4, 112.9 (d, $^2J_{CF}$ = 26.5 Hz), 111.9 (d, $^3J_{CF}$ = 9.5 Hz), 106.7 (d, $^2J_{CF}$ = 25.6 Hz), 99.6 (d, $^4J_{CF}$ = 4.1 Hz) . MS (EI, 70 eV) *m/z* (relative intensity): 368 (35), 288 (100), 273 (8), 259 (17), 183 (42), 163 (7), 143 (6), 105 (2), 77 (6). HRMS calcd for $C_{20}H_{13}FOSe$: $[M]^+$ 368.0116. Found $[M]^+$ 368.0122.

2-(4-chlorophenyl)-5-fluoro-3-(phenylselanyl)benzo[*b*]furan (3k): Yield: 0.061g (61%). NMR ^{1}H: $CDCl_3$, 400 MHz, δ(ppm): 8.16-8.12 (m, 2H), 7.47-7.43 (m, 1H), 7.42-7.38 (m, 2H), 7.27-7.23 (m, 2H), 7.20-7.13 (m, 4H), 7.03 (td, *J* = 2.6 Hz; *J* = 9.0 Hz, 1H). NMR ^{13}C: $CDCl_3$, 100 MHz, δ(ppm): 159.6 (d, $^1J_{CF}$ = 239.9 Hz), 157.7, 150.1, 135.5, 133.0 (d, $^3J_{CF}$ = 10.6 Hz), 130.6, 129.4, 129.2, 129.9, 128.7, 128.2, 126.6, 113.2 (d, $^2J_{CF}$ = 26.6 Hz), 111.9 (d, $^3J_{CF}$ = 9.5 Hz), 106.8 (d, $^2J_{CF}$ = 25.6 Hz), 100.2 (d, $^4J_{CF}$ = 4.1 Hz) . MS (EI, 70 eV) *m/z* (relative intensity): 404 (M+2; 16), 402 (M^+; 40), 324 (34), 322 (100), 286 (19), 259 (15), 217 (24), 181 (26), 143 (12), 105 (1), 77 (7). HRMS calcd for $C_{20}H_{12}ClFOSe$: $[M]^+$ 401.9726. Found $[M]^+$ 401.9727.

5-methyl-2-phenyl-3-(phenylselanyl)benzo[*b*]furan (3l): Yield: 0.022g (24%). NMR ^{1}H: $CDCl_3$, 400 MHz, δ(ppm): 8.20-8.17 (m, 2H), 7.45-7.40 (m, 3H), 7.39-7.34 (m, 1H), 7.32-7.30 (m, 1H), 7.29-7.25 (m, 2H), 7.18-7.10 (m, 4H), 2.40 (s, 3H). NMR ^{13}C: $CDCl_3$, 100 MHz, δ(ppm): 157.4, 152.5, 133.0, 131.9, 131.6, 130.2, 129.3, 129.2, 128.8, 128.4, 127.7, 126.5, 126.0, 120.8, 110.7, 99.1, 21.4. MS (EI, 70 eV) *m/z* (relative intensity): 364 (31), 362 (16), 284 (100), 255 (7), 178 (35), 152 (8), 105 (1), 77 (8). HRMS calcd for $C_{21}H_{16}OSe$: $[M]^+$ 364.0366. Found $[M]^+$ 364.0372.

2-butyl-3-(phenylselanyl)benzo[*b*]furan (3m): Yield: 0.045g (55%). NMR ^{1}H: $CDCl_3$, 400 MHz, δ(ppm): 7.46-7.41 (m, 2H), 7.27-7.08 (m, 7H), 2.97 (t, *J* = 7.4 Hz, 2H), 1.71 (quint, *J* = 7.4 Hz, 2H), 1.35 (sext, *J* = 7.4 Hz, 2H), 0.89 (t, *J* = 7.4 Hz, 3H). NMR ^{13}C: $CDCl_3$, 100 MHz, δ(ppm): 163.7, 154.4, 131.8, 130.6, 129.1, 129.0, 126.0, 124.0, 123.0, 120.3, 110.9, 100.0, 30.3, 27.0, 22.2, 13.7. MS (EI, 70 eV) *m/z* (relative intensity): 330 (57), 328 (30), 287 (34), 250 (46), 207 (100), 178 (36), 131 (48), 115 (13), 105 (1), 77 (14). HRMS calcd for $C_{18}H_{18}OSe$: $[M]^+$ 330.0523. Found $[M]^+$ 330.0525.

General Procedure for the Organochalcogen-lithium Exchange Reaction of 3a for the Preparation of the Benzo[*b*]furan 4a: To a two-necked round-bottomed flask, containing a solution of **3a** (0.5 mmol) in THF (5 mL) at -10 °C, under argon, was added dropwise BuLi (0.6 mmol, of a 2.5 M solution in hexane). The reaction mixture has stirred for 30 minutes at -10 ºC and then saturated aqueous NH_4Cl solution (2 mL) was gradually added. The reaction mixture was warmed to 25 °C and stirred for 1h. After this time, the mixture was diluted in ethyl acetate (10 mL) and washed with a saturated aqueous NaCl solution (3 × 10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure using a rotary evaporator. The product was purified by flash chromatography in silica gel using hexane as eluent.

2-phenyl-benzo[*b*]furan (4a): Yield: 0.032g (65%). NMR ^{1}H: $CDCl_3$, 400 MHz, δ(ppm): 7.55-7.51 (m, 2H), 7.42-7.44 (m, 4H), 7.29-7.22 (m, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.89 (td, *J* = 7.6 Hz; *J* = 1.1 Hz, 1H), 5.86 (s, 1H) NMR ^{13}C: $CDCl_3$, 100 MHz, δ(ppm): 156.5, 131.6, 131.5, 130.4, 128.8, 128.4, 122.3, 120.4, 114.7, 109.5, 96.3, 83.0. MS (EI, 70 eV) *m/z* (relative intensity): 195 (16), 194 (100, 165 (83), 139 (9), 115 (4), 82 (10), 63 (5).

General Procedure for the Organochalcogen-lithium Exchange Reaction of 3a for the Preparation of the Benzo[*b*]furan 4b: To a two-necked round-bottomed flask, containing a solution of **3a** (0.5 mmol) in THF (5 mL) at -10 °C, under argon, was added dropwise BuLi (0.6 mmol, of a 2.5 M solution in hexane). The reaction mixture has stirred for 30 minutes at -10 ºC and then benzoyl chloride (1.1 equiv) diluted in THF (2 mL) was gradually added. The reaction mixture was warmed to 25 °C and stirred for 1h at this temperature. After that, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl (10 mL) and extracted with AcOEt (3 × 10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure using a rotary evaporator. The product was purified by flash chromatography in silica gel using hexane/AcOEt (99:1) as eluent.

2-phenyl-benzo[*b*]furan (4b): Yield: 0.054g (73%). NMR ^{1}H: $CDCl_3$, 400 MHz, δ(ppm): 8.31-8.28 (m, 2H), 7.65-7.59 (m, 2H), 7.52-7.48 (m, 2H), 7.42-7.37 (m, 1H), 7.31-7.15 (m, 7H). NMR ^{13}C: $CDCl_3$, 100 MHz, δ(ppm): 164.7, 151.9, 133.6, 132.8, 131.4, 130.3, 129.5, 129.4, 128.5, 128.3, 128.1, 125.9, 122.8, 122.4, 117.5, 94.5, 84.4. MS (EI, 70 eV) *m/z* (relative intensity): 299 (7), 298 (29), 221 (2), 165 (7), 139 (3), 115 (2), 105 (100), 77 (34).

General Procedure for the Bromination Reaction of 3a for the Preparation of the Benzo[*b*]furan 5a: To a solution of the 3-phenylselanyl-benzo[*b*]furan **3a** (0.25 mmol) in dried DCM (5 mL) under argon, was slowly added the bromine (4 equiv) diluted in dried DCM (1 mL). Then, the reaction was warmed to reflux and stirred for 3h. After this time, the mixture was diluted in DCM (10 mL) and washed with a saturated aqueous NaCl solution (3 × 10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure using a rotary evaporator. The product was purified by flash chromatography in silica gel using hexane as eluent.

3,5-dibromo-2-phenylbenzo[*b*]furan (5a): Yield: 0.055g (63%). NMR ^{1}H: $CDCl_3$, 400 MHz, δ(ppm): 8.11 (d, *J* = 7.3 Hz, 2H), 7.65 (s, 1H), 7.49-7.36 (m, 5H). NMR ^{13}C: $CDCl_3$, 100 MHz, δ(ppm): 153.3, 151.0, 131.9, 129.3, 128.8, 128.0, 126.9, 126.7, 120.8, 118.9, 114.7, 93.5. MS (EI, 70 eV) *m/z* (relative intensity): 354 (49), 352 (100), 350 (52), 245 (19), 243 (19), 192 (9), 163 (48), 138 (5), 122 (6), 82 (19), 63 (5). HRMS calcd for $C_{14}H_8Br_2O$: $[M]^+$ 349.8942. Found $[M]^+$ 349.8976.

Supporting Information (see footnote on the first page of this manuscript): experimental procedures and characterization data, including ^{1}H and ^{13}C NMR spectra.

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Keywords: Benzo[*b*]furans • Organoselanyl • Cyclization • Copper • Heterocycles

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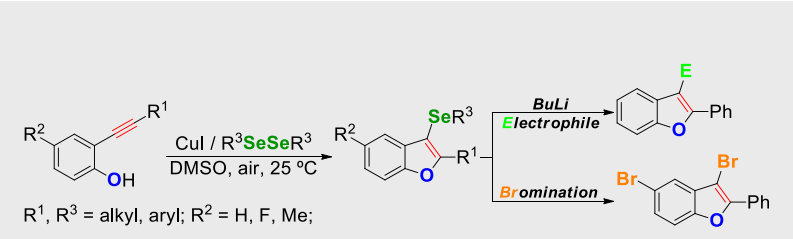

Synthesis of benzo[*b*]furans*

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Copper Iodide and Diorganyl Diselenides-Promoted Cyclization of 2-Alkynyl-phenols: Alternative Approach to 3-Organoselanyl-benzo[*b*]furans

*Heterocycles, Cyclization