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Acid-promoted selective synthesis of trifluoromethylselenolated benzofurans with *Se*-(trifluoromethyl) 4-methylbenzenesulfonoselenoate

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ABSTRACT

A Brönsted acid-promoted trifluoromethylselenolation of benzofurans was disclosed by using *Se*-(trifluoromethyl) 4-methylbenzenesulfonoselenoate as a stable and easily prepared electrophilic trifluoromethylselenolating reagent. A wide range of $SeCF_3$-substituted benzofuran derivatives were obtained in moderate to good yields with excellent regioselectivity. The tandem cyclization/trifluoromethylselenolation procedure of 1-methoxy-2-(arylethynyl)benzenes were also realized by engaging $FeCl_3$ as the catalyst.

Introduction

The benzofuran scaffold constitutes prevalent in biologically active natural products or pharmaceutically active molecules [1]. Benzofuran derivatives, especially for 2-arylbenzofurans, exhibit a broad range of biological activities, such as anti-HIV, anticancer, antifungal, immunosuppressive, and anti-cardiovascular aging activity [2]. The pharmaceutical and biochemical significance of benzofuran scaffold has made it great demanding to develop new routes for assembling this privileged structure [3]. Great progress has been made to develop efficient synthetic methods for accessing poly-substituted benzofurans

On the other hand, owing to the enhancement of lipophilicity, good cell membrane permeability and better resistance during metabolism process, the trifluoromethyl chalcogenation protocol has attracted great attentions [4]. Compared with the well-developed trifluoromethoxylation (OCF_3) [5] and trifluoromethylthiolation (SCF_3) [6] process, the introduction of trifluoromethylselanyl group ($SeCF_3$) into organic molecules has still less development. Due to the specific electronic effect and superior lipophilicity (π_R = 1.29) [7], incorporation the $SeCF_3$ group into the benzofuran derivatives will significantly enhance their biological and medical properties.

Aiming to achieve the synthesis of fluoroalkylselenolated benzofurans, Billard and co-workers disclosed a metal-free process of 1-methoxy-2-(2-phenylethynyl)benzene using *in situ* formed CF_3-SeCl as the selenium source (Scheme 1, a) [8a]. However, the instability of CF_3SeCl limited its application in organic synthesis. In addition, a series of nucleophilic trifluoromethylthiolating reagents has also been developed [9]. In 2017, *Se*-(trifluoromethyl) 4-methylbenzenesulfonoselenoate ($TsSeCF_3$), which was synthesized and characterized by Tlili and Billard for the first time, has been engaged as a stable and efficient trifluoromethylselenolating reagent to successfully realize the trifluoromethylselenolation of various substrates [10]. In 2019, we have achieved the $FeCl_3$-catalyzed trifluoromethylselenolation of a wide range of *N*-containing heterocycles with $TsSeCF_3$ (Scheme 1, b) [11]. Considering about the importance of functionalized benzofuran motif, we have designed an acid-promoted direct trifluoromethylselenolation of benzofurans, as well as a one-pot electrophilic ring-closure trifluoromethylselenolation of 1-methoxy-2-(arylethynyl)benzenes by using bench-stable $TsSeCF_3$ under mild conditions (Scheme 1, c).

Results and discussion

At the outset, we started the investigation by using $FeCl_3$ as the catalyst to promote the trifluoromethylselenolation of 2-phenylbenzofuran **1a** with *Se*-(trifluoromethyl) 4-methylbenzenesulfonoselenoate **2a** in DCE at 70 °C. To our delight, the selective

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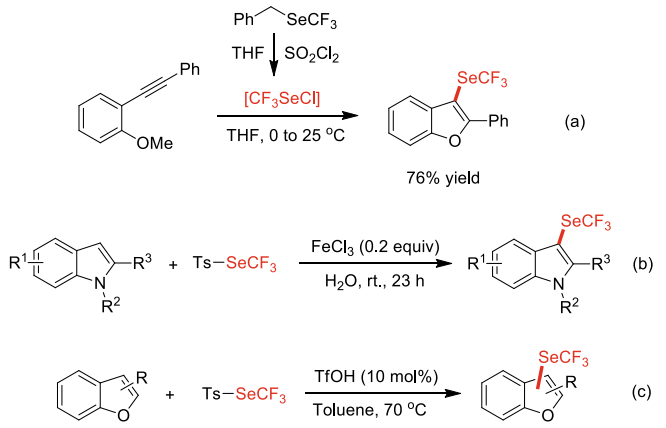
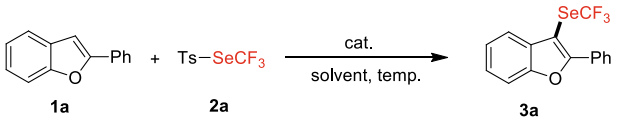


Scheme 1. Electrophilic trifluoromethylselenolation.

Table 1
Optimization of the trifluoromethylselenolation of 2-phenylbenzofuran.[a]



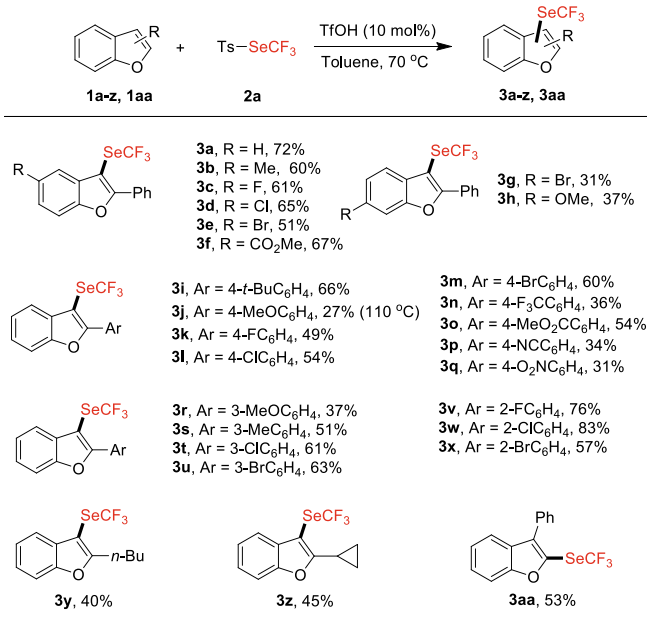
Entry	Loading of **2** (equiv.)	Solvent	T (°C)	Cat. (mol %)	Yield (%)[b]
1	1.2	DCE	70	$FeCl_3$ (10)	37
2	1.2	MeCN	70	$FeCl_3$ (10)	trace
3	1.2	Toluene	70	$FeCl_3$ (10)	60
4	1.2	Toluene	70	$FeBr_3$ (10)	53
5	1.2	Toluene	70	$AlCl_3$ (10)	0
6	1.2	Toluene	70	$TsOH·H_2O$ (10)	47
7	1.2	Toluene	70	TfOH (10)	63
8	1.2	Toluene	70	TfOH (15)	49
9	1.0	Toluene	70	TfOH (10)	56
10	**1.5**	**Toluene**	**70**	**TfOH (10)**	**72**
11	2.0	Toluene	70	TfOH (10)	51
12[c]	1.5	Toluene	70	TfOH (10)	56
13[d]	1.5	Toluene	70	TfOH (10)	46
14	1.5	Toluene	60	TfOH (10)	51
15[e]	1.5	Toluene	70	TfOH (10)	56
16[f]	1.5	Toluene	70	TfOH (10)	53

[a] Reaction conditions: 2-phenylbenzofuran **1a** (0.25 mmol, 1.0 equiv), **2a** (0.25–0.5 mmol, 1–2 equiv), solvent (0.6 mL), 6 h.
[b] Isolated yields.
[c] Toluene (0.3 mL).
[d] Toluene (1.0 mL).
[e] Using *Se*-(trifluoromethyl) 4-fluorobenzenesulfonoselenoate **2b** instead of **2a**.
[f] Using *Se*-(trifluoromethyl) 4-methoxybenzenesulfonoselenoate **2c** instead of **2a**. DCE = 1,2-dichloroethane.

trifluoromethylselenolated product **3a** was obtained with 37% yield (Table 1, entry 1). In order to improve the yield, we screened other solvents, including acetonitrile, toluene, among which toluene gave the highest yield (entry 2, 3). After testing various acids, the results indicated that the yield of **3a** was highest when using trifluoromethanesulfonic acid as the catalyst (entry 4–7). Then the loadings of **2a** and TfOH were tested (entry 8–11), and found that increasing the loading of TfOH to 1.5 equiv diminished the yield, while increasing the loading of **2a** to 1.5 equiv increased the yield to 72% (entry 10). However, further increasing the loading of **2a** to 2 equiv did not afford superior result (entry 11). Variation of the concentration or temperature could not give better yields (entry 12–14). We also tested other trifluoromethylselenolating reagents, such as *Se*-(trifluoromethyl) 4-fluorobenzenesulfonoselenoate **2b** or 4-methoxybenzenesulfonoselenoate **2c** to replace **2a**. However, diminished yields were obtained (entry 15, 16). Therefore, the optimized reaction conditions for the trifluoromethylselenolation of benzofuran **1a** were as follows: **1a** (0.25 mmol), **2a** (0.375 mmol), TfOH (1 mol/L in toluene) (0.025 mmol, 25 μL), toluene (0.6 mL), stirred 6 h at 70 °C.

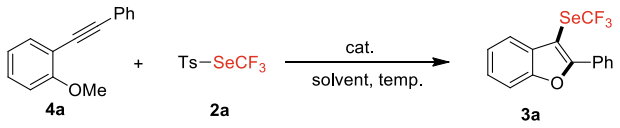
After obtaining the optimal reaction conditions, we then examined the generality of this trifluoromethylselenolation reaction with a wide range of benzofurans as the substrates (Scheme 2). In most cases, the reaction proceeded smoothly, and the desired 3-trifluoromethylselenolated benzofurans were obtained in moderate to good yields (31–83%). For example, the substrates containing electron-donating or electron-withdrawing groups attaching on 4-position of benzofuran scaffold are compatible during this transformation (**1b**-**1f**). However, when there are substituents attached to the 5-position (**1g**, **1h**) of benzofuran, the yields are diminished. Then we investigated the effect of the reaction with substituents attached to the aromatic ring of 2-arylbenzofuran derivatives. The results indicate that when an electron-withdrawing substituent is attached to the *para*-position of the aryl group, such as halogen (**1k**-**1m**), ester group (**1o**), the desired products can be obtained in moderate yields. However, when a strong electron-withdrawing group, such as cyano (**1p**) and nitro group (**1q**) or an electron-donating group (**1j**) is attached to the *para*-position of the aryl group, a relative low yields were observed. When the *meta*- (**1r**-**1u**) and *ortho*-position (**1v**-**1x**) of the aryl group are substituted, the corresponding 3-trifluoromethylselenolated benzofurans can be obtained in good yields. In addition, the 2-alkyl substituted benzofurans are also suitable in this protocol, affording the corresponding products with moderate yields (**3y**, **3z**). Moreover, when the 3-position is blocked, this reaction can also occur, 2- trifluoromethylselenolated product **3aa** can be obtained with 53% yield (Scheme 2).

Furthermore, we have optimized the electrophilic ring-closure trifluoromethylselenolation reaction of 1-methoxy-2-(phenylethynyl)benzene **4a** with **2a**. Unfortunately, when using TfOH as the acid, only trace product of **3a** was observed (Table 2, entry 1). After evaluating different acid promoters, this reaction afforded **3a** with 37% yield catalyzing by 10 mol % $FeCl_3$ (entry 2). The variation of



Scheme 2. Scope of substrates. [a]Reaction conditions: **1a-z**, 1aa (0.25 mmol), **2a** (0.375 mmol), TfOH (1 mol/L in toluene) (0.025 mmol, 25 μL), toluene (0.6 mL), 70 °C, 6–10 h. Isolated yields.

Table 2
Optimization of the trifluoromethylselenolation of 1-methoxy-2-(phenylethynyl)benzene.[a]

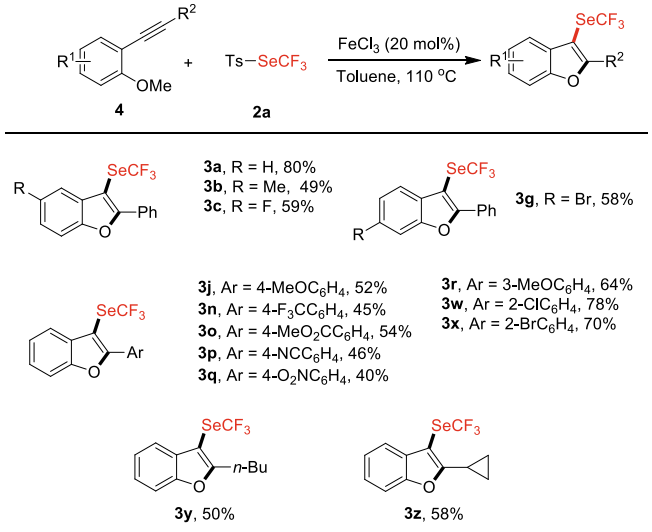


Entry	Loading of **2a** (equiv.)	Solvent	T (°C)	Cat. (mol %)	Yield (%)[b]
1	1.2	Toluene	110	TfOH (10)	trace
2	1.2	Toluene	110	$FeCl_3$ (10)	37
3	1.2	Toluene	110	$FeCl_3$ (20)	50
4	1.2	Toluene	110	$FeCl_3$ (30)	47
5	1.2	Toluene	110	$FeCl_3$ (50)	trace
6	1.2	C_6H_5Cl	110	$FeCl_3$ (20)	37
7	1.2	DCE	110	$FeCl_3$ (20)	21
8	1.2	MeCN	110	$FeCl_3$ (20)	47
9	1.2	Toluene	80	$FeCl_3$ (20)	41
10[c]	1.2	Toluene	110	$FeCl_3$ (20)	25
11	**1.5**	**Toluene**	**110**	**$FeCl_3$ (20)**	**80**
12	2.0	Toluene	110	$FeCl_3$ (20)	70

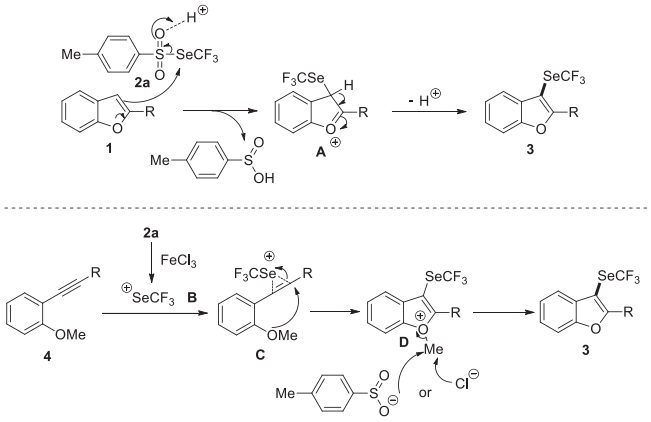
[a] Reaction conditions: 1-methoxy-2-(phenylethynyl)benzene **4a** (0.25 mmol, 1.0 equiv), **2a** (0.3–0.5 mmol, 1.2–2 equiv), solvent (0.6 mL), 5 h.
[b] Isolated yields.
[c] Toluene (0.3 mL).

equivalent of catalyst showed that 20 mol % of $FeCl_3$ gave the best yields (entry 3–5). Then we tested different solvents including chlorobenzene, DCE, MeCN (entry 6–8). Neither of these solvents gave superior results than toluene. We also found that decreasing the reaction temperature or increasing the concentration diminished the yields (entry 9, 10). Finally, after tuning the loading of **2a** (entry 11, 12), we have got the optimized reaction condition as follows: **4a** (0.25 mmol), **2a** (1.5 equiv), $FeCl_3$ (20 mol %), toluene (0.6 mL), stirred 5 h at 110 °C.

Continuously, the substrate scope of this $FeCl_3$-catalyzed electrophilic ring-closure trifluoromethylselenolation reaction was examined (Scheme 3). Overall, these 1-methoxy-2-(arylethynyl) benzene substrates containing various substituents either on the benzene ring or on the triple bond can proceed smoothly, affording 3-trifluoromethylselenolated benzofurans with moderate yields. Compared with the previous protocol, when the aryl moiety attaching to triple bond has an electron-donating group, the reaction can also obtain the product with 52% yield (**3j**). The alkyl substituents attaching to the triple bond are also compatible, affording corresponding products (**3y**, **3z**) in slightly higher yields than previous protocol.



Scheme 3. Scope of substrates. [a]Reaction conditions: **4** (0.25 mmol), **2a** (0.375 mmol), $FeCl_3$ (0.05 mmol), toluene (0.6 mL), 110 °C, 5–10 h. Isolated yields.



Scheme 4. Possible reaction mechanism.

Based on our previous investigation and literature precedents [8], an electrophilic pathway was proposed to account for the Brönsted acid-promoted trifluoromethylselenolation of benzofurans. As shown in Scheme 4, $TsSeCF_3$ **2a** is activated by TfOH, which facilitates the nucleophilic attack by benzofuran to afford intermediate A along with the extrusion of 4-methylbenzenesulfinic acid. Finally, deprotonative aromatization of **A** affords desired product **3**. As for the electrophilic cyclotrifluoromethylselenylation, $FeCl_3$-catalyzed decomposition of $TsSeCF_3$ **2a** initially occurs to generate $SeCF_3$ cation **B**. Then, triple bond moiety of alkyne **4** attacks **B** to form intermediate **C**, followed by sequential intramolecular cyclization to generate intermediate **D**. Upon the attack of 4-methylbenzenesulfinate or chloride anion, the methyl group of **D** leaves to obtain product **3**.

Conclusion

In conclusion, we utilized $TsSeCF_3$ as the electrophilic trifluoromethylselenolating reagent to realize the TfOH-catalyzed selective trifluoromethylselenolation reaction of benzofurans, as well as the $FeCl_3$-catalyzed intramolecular electrophilic ring-closure trifluoromethylselenolation of 1-methoxy-2-(arylethynyl)benzene derivatives. These methods feature a mild reaction conditions, stable and easily prepared trifluoromethylselenolating reagent which makes it an alternative and practical strategy for the

trifluoromethylselenolation of the electron-rich heterocyclic compounds. Considering about the importance of benzofuran scaffold, this synthetic route demonstrate potential applications in pharmaceutical and biochemical research.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152809.

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