OL Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Selenium Radical Mediated Cascade Cyclization: Concise Synthesis of Selenated Benzofurans (Benzothiophenes)

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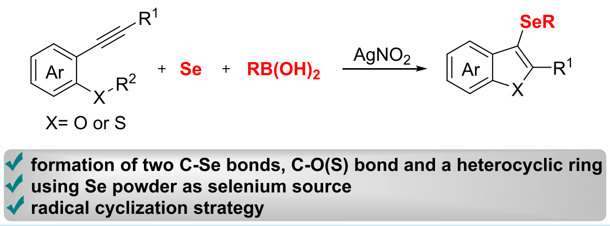
Supporting Information

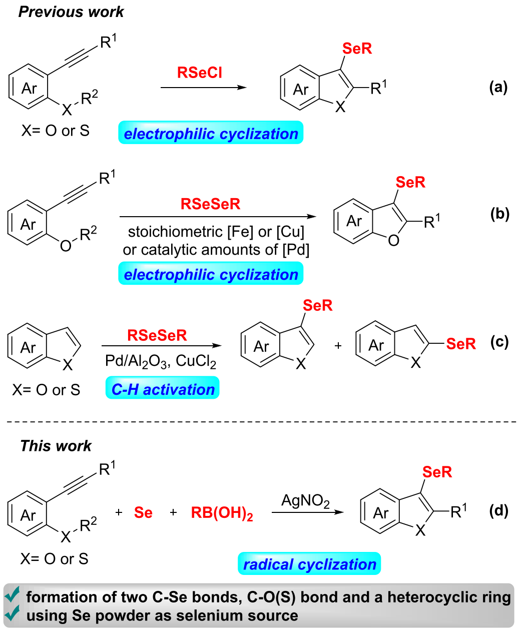
ABSTRACT: Presented in this work is a novel methodology for the synthesis of selenated benzofurans (or benzothiophenes) via $AgNO_2$-catalyzed radical cyclization of 2-alkynylanisoles (or 2-alkynylthioanisoles), Se powder, and arylboronic acids. This method enables the construction of a benzofuran (benzothiophene) ring, two C−Se bonds, and a C−O(S) bond as well as the cleavage of a C−O(S) bond in a single step. Preliminary mechanistic studies imply that the $AgNO_2$-catalyzed cyclization proceeds via an aryl selenium radical intermediate.



Organoselenium compounds represent an important class of molecules with numerous applications in drug, agricultural chemicals, and catalysis as well as functional organic materials.[1] In this regard, the installation of the selenium moiety onto organic molecules is of significant importance in organic synthesis. Much effort has been devoted to the construction of C−Se bonds, which serves as an important strategy for the synthesis of organoselenium compounds.[2] In particular, the selenation of heteroarenes including benzofurans and benzothiophenes has attracted considerable attention, allowing for diversification of these privileged scaffolds to further open up promising avenues for drug discovery. Pioneering work toward the synthesis of selenated benzofurans or benzothiophenes relied on an electrophilic cyclization strategy using commercially unavailable, toxic, and instable RSeCl as the selenium source (Scheme 1a).[3,4] Another method to access selenenylbenzofurans via electrophilic annulation reactions of 2-alkynylphenol derivatives with diselenides has been developed, yet with the requirement of precious Pd catalyst or stoichiometric Fe (Cu) catalysts (Scheme 1b).[5] In addition, direct C−H thiolation of heteroarenes catalyzed by a heterogeneous catalyst Pd/Al_2O_3 has proven to be a successful strategy to provide selenenylbenzofurans and selenenylbenzothiophenes, but it suffered from low yields and moderate selectivities, particularly for the formation of selenenylbenzofurans (Scheme 1c).[6] From an economic point of view, the use of Se powder[7] as the selenium source is more attractive, yet it is indeed beyond the scope of current methodologies for the synthesis of selenenylbenzofurans or selenenylbenzothiophenes. Therefore, the development of general methods for the preparation of selenated benzofurans or benzothiophenes from simple and readily accessible building blocks is still desirable.

Over the last decades, radical transformations have emerged as a powerful tool for construction of C−heteroatom bonds due to their high efficiency and powerful functions in the organic synthesis. Inspired by our previous work,[8] we were interested in the reactivity of aryl selenium radical intermediates derived from arylboronic acids and Se powder in the synthesis of organoselenium compounds. On this basis, we questioned whether in situ generated aryl selenium radicals could undergo the radical tandem cyclization with 2-

Scheme 1. Diverse Synthetic Routes to Selenenylbenzofurans or Selenenylbenzothiophenes



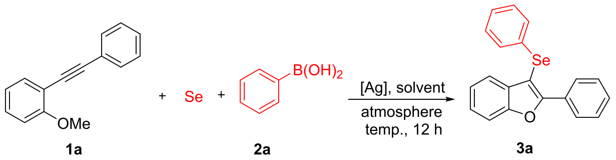
Received: July 4, 2019

DOI: 10.1021/acs.orglett.9b02315
Org. Lett. XXXX, XXX, XXX−XXX

alkynylanisoles (or 2-alkynylthioanisoles) as other radicals do,[9−11] thus providing a direct and facile access to selenated benzofurans or benzothiophenes.

Our initial effort focused on identifying the optimal reaction conditions by selecting 2-alkynylanisole **1a** and phenylboronic **2a** as model substrates. A set of optimal reaction conditions including catalyst, solvent, atmosphere, and temperature were identified as shown in Table 1. We were pleased to find that $AgNO_3$ successfully enabled this transformation in DMSO at 120 °C under O_2, furnishing the desired product **3a** in 77% yield (entry 1). Excessive amounts of alkynylanisole **1a** are essential for complete conversion owing to the unavoidable oxidation of **1a** to afford dicarbonyl compound. Screening several Ag salts revealed that the use of $AgNO_2$ was the best choice and delivered **3a** in 99% yield (entry 2). Further screening of solvents demonstrated that the solvents such as DMF, CH_3CN, and dioxane were inferior to DMSO (entries 8−10). Other solvents including toluene and ^{i}PrOH shut down this transformation completely (entries 11 and 12). Based on the examination of reaction temperature (entries 14−16), we chose 100 °C as the optimal reaction temperature. Reducing the amount of either $AgNO_2$ or Se powder decreased the yield of **3a** (entries 17 and 18). It was found that air atmosphere resulted in a low yield (entry 19), while N_2 atmosphere led to trace amount of **3a** (entry 20). Therefore, the reaction conditions of entry 14 proved to be optimal.

Table 1. Optimization of Reaction Conditions[a]

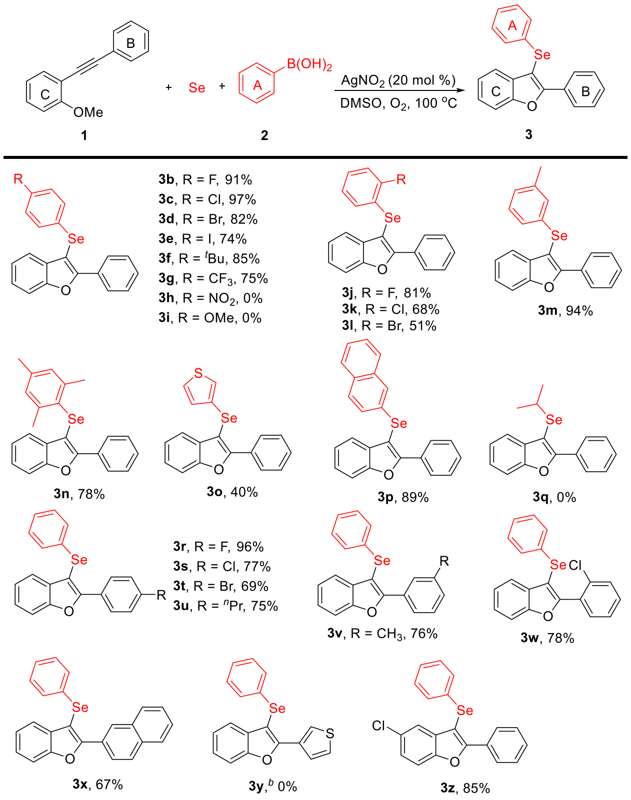


entry	catalyst	solvent	temp (°C)	yield (%)
1	$AgNO_3$	DMSO	120	77
2	$AgNO_2$	DMSO	120	99
3	AgOAc	DMSO	120	45
4	$AgSbF_6$	DMSO	120	trace
5	Ag_2SO_4	DMSO	120	trace
6	Ag_2CO_3	DMSO	120	trace
7	Ag_2O	DMSO	120	trace
8	$AgNO_2$	DMF	120	20
9	$AgNO_2$	CH_3CN	120	28
10	$AgNO_2$	dioxane	120	15
11	$AgNO_2$	toluene	120	0
12	$AgNO_2$	^{i}PrOH	120	0
13	$AgNO_2$	DMSO	130	82
14	$AgNO_2$	DMSO	100	99
15	$AgNO_2$	DMSO	90	97
16	$AgNO_2$	DMSO	80	58
17[b]	$AgNO_2$	DMSO	100	67
18[c]	$AgNO_2$	DMSO	100	83
19[d]	$AgNO_2$	DMSO	100	66
20[e]	$AgNO_2$	DMSO	100	trace

[a] Reaction conditions: **1a** (0.4 mmol), Se powder (0.4 mmol), **2a** (0.2 mmol), catalyst (0.04 mmol), solvent (2.0 mL), under O_2, 12 h, isolated yield. [b] 15 mmol % of $AgNO_2$ was used. [c] 1.6 equiv of Se powder was used. [d] Under air. [e] Under N_2.

With the optimal reaction conditions in hand, we sought to assess the scope of the three-component reactions of 2-alkynylanisoles, Se powder, and arylboronic acids (Table 2). A range of arylboronic acids bearing various substituents were found to be suitable substrates. For example, halogen-substituted arylboronic acids underwent radical cyclization with 2-phenylethynylanisole in the presence of Se powder, delivering the corresponding products in moderate to good yields (**3b**−**3e**, **3j**−**3l**). We noticed that the yields were generally distinctly lower in the case of *ortho*-substituted arylboronic acids. In addition to halogen, substituents including ^{t}Bu (**1f**), CF_3 (**1g**), and methyl groups (**1m** and **1n**) all worked well. For the substrates bearing the substituents with strong electron effects such as nitro and methoxy, the reactions led to no formation of the desired products (**3h** and **3i**), while most of the starting materials were converted into dicarbonyl compounds (**3h** and **3i**). It is worth noting that this transformation was not sensitive to steric hindrance as demonstrated by using mesitylboronic acid as a substrate (**1n**). Boronic acid bearing an aromatic heterocycle or a fused ring proved to be a suitable substrate (**1o** and **1p**), whereas alkylboronic acid (**1q**) was ineffective under the standard conditions, probably due to the poorer stability of in situ generated alkyl selenium radical than aryl selenium radical. Subsequently, the scope with respect to 2-alkynylanisoles was also investigated. It was found that halogen and alkyl groups on the ring B were amenable to the standard reaction conditions and afforded the desired products in 69−96% yields (**3r**−**3w**). The terminal alkynyl position (ring B) could be functionalized with a fused ring (**1x**). When the ring B was installed with a thiophene ring (**1y**), no reaction occurred. On the other hand, ring C could be a halogen-substituted phenyl moiety (**1z**).

Table 2. Substrate Scope for the Reactions of 2-Alkynylanisoles, Se powder, and Arylboronic Acids[a]

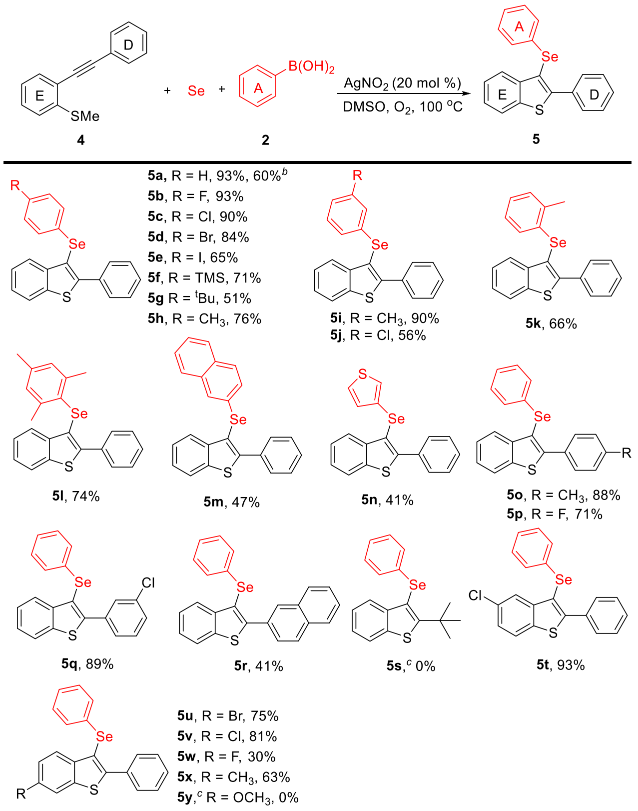


[a] Reaction conditions: **1** (0.4 mmol), Se powder (0.4 mmol), **2** (0.2 mmol), $AgNO_2$ (0.04 mmol), DMSO (2.0 mL), under O_2, 100 °C, 12 h, isolated yield. [b] Most of starting materials were recovered.

Next, the strategy was expanded toward the synthesis of selenated benzothiophenes (Table 3). To our delight, the three-component reaction of 2-alkynylanisoles, Se powder, and arylboronic acids could be successfully achieved under the same reaction conditions, and no conversion of 2-alkynylthioanisoles to dicarbonyl compounds was observed.

As a result, a mixture containing alkynylthioanisoles, Se powder, and boronic acids with a ratio of 1:2:2 was submitted to standard reaction conditions. Arylboronic acids with substitutions such as halogen, TMS, and alkyl reacted well with 2-phenylethynylanisole to provide the desired products (**5b**−**5k**) under the standard conditions. The reaction of **4a**, Se powder, and phenylboronic acid was run on a 10 mmol scale, affording 60% yield of **5a** with 35% of **4a** being recovered. Hindered arylboronic acid also underwent radical cyclization with 2-phenylethynylanisole as well as Se powder, yielding the desired product (**5l**) in good yield. Boronic acid bearing a naphthalene or thiophene ring was effective as well under the standard reaction conditions, giving the desired products in 47% and 41% yields, respectively (**5m** and **5n**). On the other hand, the scope with respect to 2-alkynylanisoles was also tested. This radical cyclization strategy displayed high efficiency toward 2-alkynylanisoles bearing methyl and halogen on the ring D or E (**4o**−**4q** and **4t**−**4x**). Furthermore, ring D could be a fused ring, with 41% yield of **5r** being obtained.

Table 3. Substrate Scope for the Reactions of 2-Alkynylthioanisoles, Se Powder, and Arylboronic Acids[a]

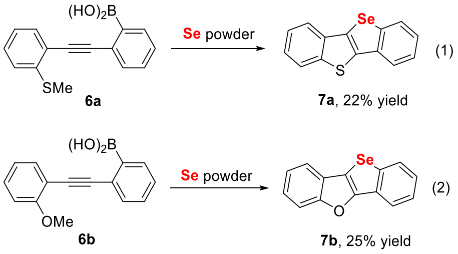


[a]Reaction conditions: **4** (0.2 mmol), Se powder (0.4 mmol), **2** (0.4 mmol), AgNO$_2$ (0.04 mmol), DMSO (2.0 mL), under O$_2$, 100 °C, 12 h, isolated yield. [b]The reaction was conducted on a 10 mmol scale. [c]Most of the starting material was recovered.

When ring D was replaced by ^{t}Bu group the reaction failed to deliver the desired product **5s** but with most of starting material being recovered, and same result was observed by using substrate **4y** in which ring E carried a strong electron-donor substituent.

Finally, we investigated whether this methodology could be used to intramolecular radical cyclization (Scheme 2). Gladly, the arylboronic acids bearing methylthio group successfully underwent intramolecular radical cyclization with Se powder, enabling one-pot synthesis of benzo[*b*]benzo[4,5]-selenopheno[2,3-*d*]thiophene (**7a**) albeit in 22% yield (eq 1). In a similar manner, the arylboronic acids bearing methoxy group delivered the corresponding product (**7b**) in 25% yield (eq 2).

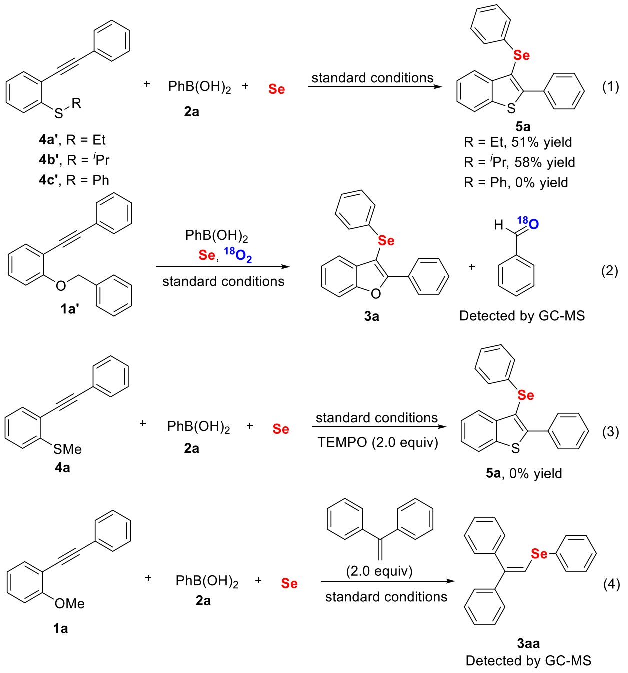
Scheme 2. Ag-Catalyzed Intramolecular Cyclization[a]



[a]Standard conditions: **6** (0.2 mmol), Se powder (0.4 mmol), AgNO$_2$ (0.04 mmol), DMSO (2.0 mL), under O$_2$, 100 °C, 12 h, isolated yields.

Further control experiments were designed to gain a deeper understanding of the catalytic process (Scheme 3). Preliminary investigation on the substituents on the S atom showed that in addition to the methyl group, the reaction was shown to

Scheme 3. Some Control Experiments[a]



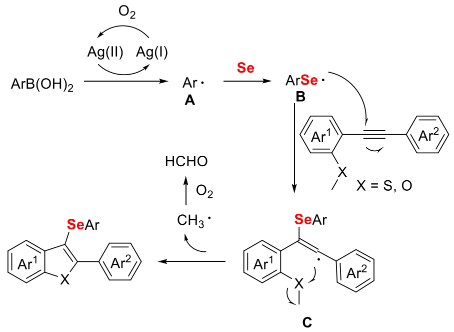
[a]Standard conditions: **1** or **4** (0.2 mmol), Se powder (0.4 mmol), **2a** (0.4 mmol), AgNO$_2$ (0.04 mmol), DMSO (2.0 mL), under O$_2$, 100 °C, 12 h, isolated yields.

DOI: 10.1021/acs.orglett.9b02315
Org. Lett. XXXX, XXX, XXX−XXX

tolerate the sterically bulkier substituents such as ethyl and isopropyl groups, whereas a phenyl group resulted in no product (eq 1). When the reaction of **1a′**, Se powder, and $PhB(OH)_2$ was performed in the $^{18}O_2$ atmosphere, we detected ^{18}O-labeled benzaldehyde (eq 2). The reaction was completely inhibited upon the addition of TEMPO under the standard conditions, supporting a radical process (eq 3). When a mixture of ethene-1,1-diyldibenzene, $PhB(OH)_2$, and Se powder was subjected to the standard conditions, product **3aa** was detected by GC−MS (eq 4), providing experimental evidence for the formation of aryl selenium radical.

According to these results and relevant literature,[9−11] a possible pathway for the radical cascade cyclization is described in Scheme 4. At the beginning, $ArB(OH)_2$ is oxidized into an aryl radical species in the presence of an catalytic system of $AgNO_2/O_2$. The resulting aryl radical is then trapped by Se powder to generate an aryl selenium radical **B** which undergoes radical addition with 2-alkynylanisole (or 2-alkynylthioanisole) to afford intermediate **C**. Finally, intermediate **C** undergoes cyclization to give the desired product, along with methyl radical being converted into formaldehyde. It could be inferred from the propose mechanism that the butyl group is difficult to stabilize alkenyl radical intermediate in contrast to aryl group, which could be responsible for the failure in the synthesis of **5s**.

Scheme 4. Possible Pathway for the Cascade Cyclization



In conclusion, we disclosed a novel methodology for the preparation of selenated benzofurans (or benzothiophenes) via $AgNO_2$-catalyzed radical cyclization of 2-alkynylanisoles (or 2-alkynylthioanisoles), Se powder, and arylboronic acids. It is worth noting that the method enables the formation of a benzofuran (benzothiophene) ring, two C−Se bonds, and C−O(S) bond as well as the cleavage of C−O(S) bond in one step. It also proved to be available for intramolecular radical cyclization to provide polycyclic selenium-containing heteroaromatics. Preliminary mechanistic studies imply that the three-component cyclization involved an aryl selenium radical intermediate in situ generated from arylboronic acids and Se powder, thus in turn demonstrating a novel strategy of activating Se powder by in situ generated aryl radical. Selenium radical mediated cyclization has heavy development potentiality to construct complex Se-containing compounds, and more efforts are underway to expand the selenium radical intermediates for the preparation of other selenated heteroarenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02315.

Experimental procedures, GC−MS data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the National Natural Science Foundation of China (21472140 and 21372177), the Wenzhou Science & Technology Bureau Program (No. G20170021), and Xinmiao Talent Planning Foundation of Zhejiang Province (No. 2018R429058).

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