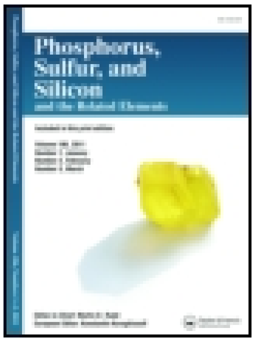

Phosphorus, Sulfur, and Silicon and the Related Elements

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SHORT COMMUNICATION

Copper-catalyzed three-component *ortho*-selective selenation of phenols

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ABSTRACT
An efficient and convenient copper-catalyzed three-component reaction has been developed for the arylselenation of phenols with Se powder and aryl iodides. This one-pot procedure provides a straightforward approach to the synthesis of *ortho*-arylselenylphenols with high regioselectivity. This practical process shows good functional group tolerance, providing the corresponding products in moderate to good yields.

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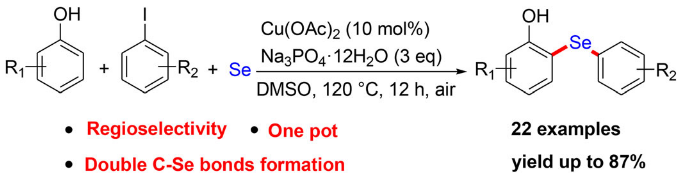
KEYWORDS
Selenation; phenols; Se powder; copper; regioselectivity

GRAPHICAL ABSTRACT



Introduction

The construction of selenium-containing architectures has already attracted increasing attention, due to the fact that selenium-containing compounds are found in natural products, drugs, and active molecules.[1] In particular, organoselenium compounds exhibit a diverse of biological activities such as lipoxygenase inhibitor, anti-Alzheimer, antimicrobial, antioxidant, antiproliferative functions, and antitumor agent (Figure 1).[2] In recent decades, many selenium reagents including selenol,[3] $ArSeSnR_3$,[4] diselenide,[5] SeO_2,[6] KSeCN,[7] and NaO_2SeR[8] have been successfully used for building diaryl selenides. However, these selenium reagents suffer from longer synthetic steps, relatively high cost or environmental problems. Currently, the application of selenium powder for C–Se bonds construction has aroused the interest of organic chemists, which is stable, cheap, and easy to handle.[7,9]

Phenols are often used as important intermediates and exhibit higher reactivities in various chemical transformations.[10] Among them, selenium-containing phenol derivatives have several pharmacological applications. But the regioselective selenation of phenols is still challenging and few practical methods have been reported. Recently, Takaki and coworkers[11] reported the direct selenylation of phenols using a stoichiometric amount of $FeCl_3$ under an oxygen atmosphere (Scheme 1, Eq. a). In other study, Yeung and coworkers developed highly practical *ortho*-selective phenylselenation of phenols catalyzed by ammonium salts (Scheme 1, Eq. b).[12] More recently, Yang and coworkers described a metal-free synthesis of phenol-aryl selenides via coupling reaction of aryl selenoxides with phenols (Scheme 1, Eq. c).[13] Inspired by the above successful research on the selenylation of phenols, we herein report the first example of copper-catalyzed *ortho* arylselenation of phenols via three-component coupling reaction of aryl iodides, Se powder and phenols.

Here we began this study by choosing 4-methoxyphenol **1a** and iodobenzene **2a** as model substrates in the presence of elemental selenium (Table 1). The desired *ortho*-selective arylselenation product **3a** was obtained in 58% yield by using 10 mol% of CuO as catalyst, 3 equiv of K_3PO_4 as base in DMSO at 120 °C for 12 h (Table 1, entry 1). Among other copper salts tested, $Cu(OAc)_2$ displayed the best choice and afforded the desired product **3a** in 81% yield (Table 1, entries 2–5). Next, we investigated the influence of bases. The replacement of K_3PO_4 by K_2CO_3, KOH, and *t*-BuOK was ineffective (Table 1, entries 6–8). The yield of corresponding product **3a** increased to 85% when $Na_3PO_4 \cdot 12H_2O$ was used as base (Table 1, entry 9). The effect of solvents on this transformation was also screened. The use of other solvents (DMF, 1,4-Dioxane, CH_3CN, DCE, and Toluene) led to poor yields (Table 1, entries 10–14). An attempt to reduce or increase the reaction temperature resulted in a lower yield of the desired product **3a** (Table 1, entries 15 and

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Supplemental data for this article is available online at https://doi.org/10.1080/10426507.2021.1945600.

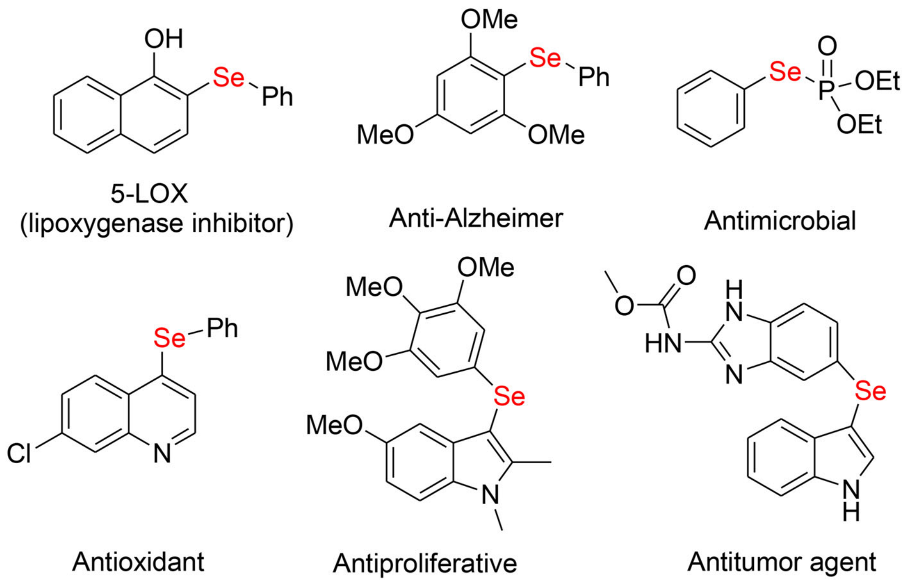
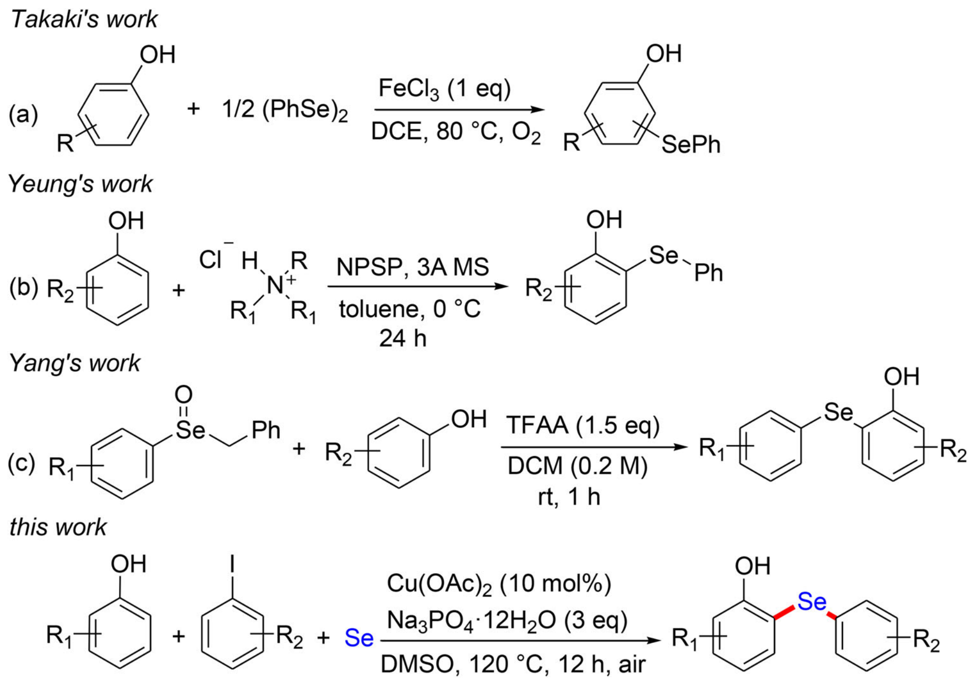


Figure 1. Organoselenium compounds with biological activity.

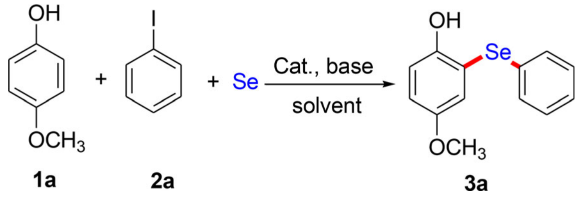


Scheme 1. Examples of direct arylselenation of phenols.

16). The reaction could not occur in the absence of copper catalyst (Table 1, entry 17). Using bromobenzene instead of iodobenzene afforded only a trace of **3a** (Table 1, entry 18).

With the optimized conditions in hand, we next turned our attention to the scope of aryl iodides and phenols. As shown in Table 2, a variety of aryl iodides with either electron-withdrawing or electron-donating groups in the *ortho*, *meta*, or *para* position of benzene rings, were reacted smoothly with 4-methoxyphenol **1a** and generated the desired products **3a–3l** in moderate to good yields. As expected, methyl group and halogen atoms (F, Cl, Br) were well-tolerated. Notably, this arylselenation was slighted affected by the steric hindrance on the *ortho*-position of aryl iodides (**3b**, **3e**, **3g**). The strong electron-withdrawing group (–CF_3) on the phenyl ring of aryl iodides was compatible under this condition, and the desired product **3k** was isolated in 67% yield. Pleasing, this

Table 1. Optimization of the reaction conditions.



Entry	Catalyst	Base	Solvent	Yield (%)[a]
1	CuO	K_3PO_4	DMSO	58
2	CuI	K_3PO_4	DMSO	60
3	$CuCl_2$	K_3PO_4	DMSO	72
4	$CuBr_2$	K_3PO_4	DMSO	70
5	$Cu(OAc)_2$	K_3PO_4	DMSO	81
6	$Cu(OAc)_2$	K_2CO_3	DMSO	65
7	$Cu(OAc)_2$	KOH	DMSO	47
8	$Cu(OAc)_2$	*t*-BuOK	DMSO	73
9	$Cu(OAc)_2$	$Na_3PO_4{\cdot}12H_2O$	DMSO	85
10	$Cu(OAc)_2$	$Na_3PO_4{\cdot}12H_2O$	DMF	72
11	$Cu(OAc)_2$	$Na_3PO_4{\cdot}12H_2O$	1,4-dioxane	40
12	$Cu(OAc)_2$	$Na_3PO_4{\cdot}12H_2O$	CH_3CN	56
13	$Cu(OAc)_2$	$Na_3PO_4{\cdot}12H_2O$	DCE	Trace
14	$Cu(OAc)_2$	$Na_3PO_4{\cdot}12H_2O$	Toluene	–
15[b]	$Cu(OAc)_2$	$Na_3PO_4{\cdot}12H_2O$	DMSO	41
16[c]	$Cu(OAc)_2$	$Na_3PO_4{\cdot}12H_2O$	DMSO	69
17	–	$Na_3PO_4{\cdot}12H_2O$	DMSO	–
18[d]	$Cu(OAc)_2$	$Na_3PO_4{\cdot}12H_2O$	DMSO	Trace

Reaction conditions: 4-methoxyphenol **1a** (0.5 mmol), iodobenzene **2a** (0.2 mmol), Se (0.6 mmol), catalyst (10 mol%), base (3 equiv) in 2 mL of solvent at 120 °C for 12 h, under air.

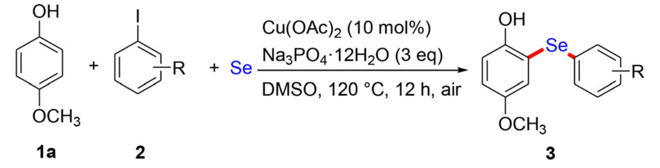
[a] Isolated yield.

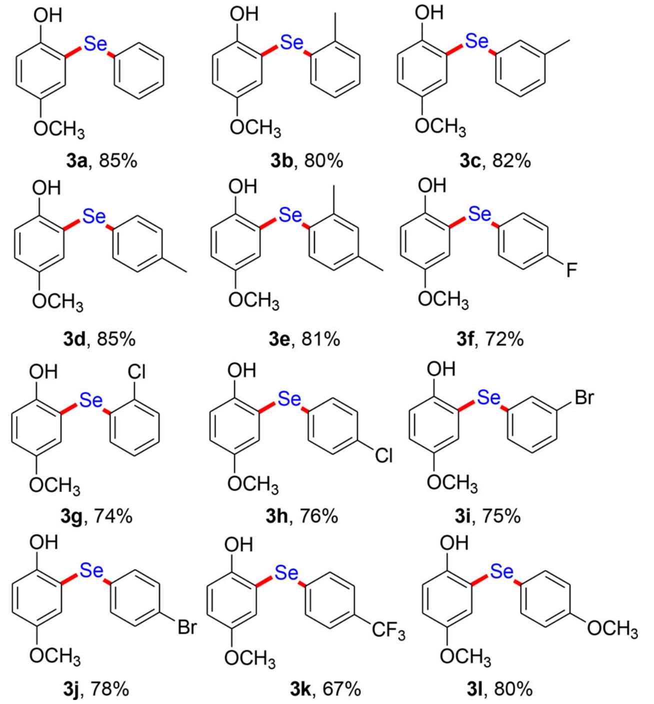
[b] 80 °C.

[c] 140 °C.

[d] Bromobenzene was used instead of iodobenzene.

Table 2. Scope of the aryl iodides.





All reaction were performed with **1a** (0.5 mmol), **2** (0.2 mmol), Se (0.6 mmol), $Cu(OAc)_2$ (10 mol%) and $Na_3PO_4{\cdot}12H_2O$ (0.6 mmol) in 2 mL of DMSO at 120 °C for 12 h, under air. Isolated yields.

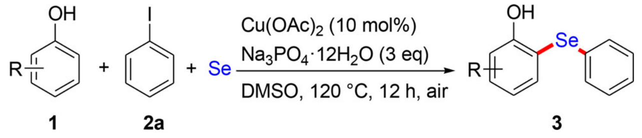
arylselenation reaction was highly regioselective at *ortho*-position on the phenol ring under our standard experimental conditions.

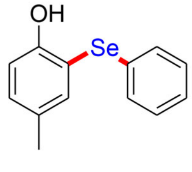
Furthermore, a variety of substituted phenols were studied under optimized reaction conditions to explore the scope and generality of this transformation (Table 3). Phenols with different functional groups such as methyl, ethyl, isopropyl, chloro, and phenyl groups at *para*-position successfully afforded the desired products **3m–3q** in good yields. When carbomethoxy group was introduced at *para*-position of phenol, the corresponding product **3r** was obtained in 78% yield. To investigate the regioselectivity of this arylselenation reaction, *meta* and *ortho*-substituted phenols bearing methyl, *tert*-butyl and methoxy groups were tested and gave the arylselenation products **3s–3v** with complete *ortho*-selectivity. The above results highlight the generality of this new system. Complete experimental details, characterization and sample ^{1}H, ^{13}C, and ^{19}F NMR spectra are presented in the Supplemental Materials (Figures S1–S46).

In an effort to gain more preliminary insight into the reaction mechanism, several control experiments were carried out as shown in Scheme 2. Diphenyl diselenide **4** was obtained in 90% yield by treating iodobenzene **2a** with Se powder under the standard reaction conditions (Scheme 2, Eq. 1). Next, the coupling reaction of diphenyl diselenide **4** with 4-methoxyphenol **1a** generated the desired product **3a** in 80% yield, indicating that diselenide may be a key reaction intermediate (Scheme 2, Eq. 2). Finally, by the addition of radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under the optimized reaction conditions, the desired product was smoothly produced; this results indicated that radical pathway was not occurred in the arylselenation reaction (Scheme 2, Eq. 3).

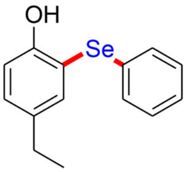
Based on the above results and previous reports,[5k, 7, 9a–c] a plausible mechanism for the regioselective copper-catalyzed selenation reaction is illustrated in Scheme 3. Initially, the copper selenide intermediate **A** is formed by the reaction of iodobenzene **2a** with Se powder in the presence of copper catalyst and base. The intermediate **A** may oxidize to the key species diphenyl diselenide **4** under air atmosphere. The interaction of diphenyl diselenide **4** with CuI leads to a Cu^{III} tetracoordinated square planar sulfate **B**. Phenol **1a** would attack the intermediate

Table 3. Scope of the phenols.

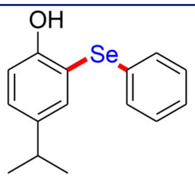




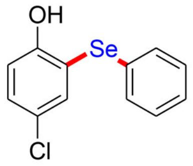
3m, 84%



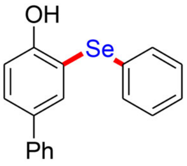
3n, 87%



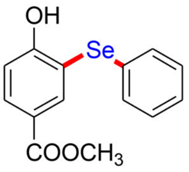
3o, 86%



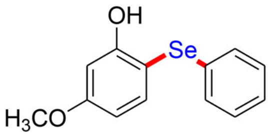
3p, 81%



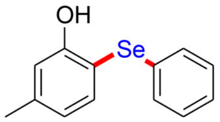
3q, 83%



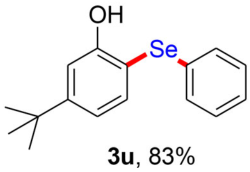
3r, 78%



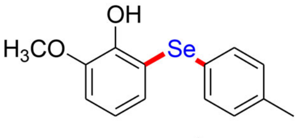
3s, 82%



3t, 76%



3u, 83%



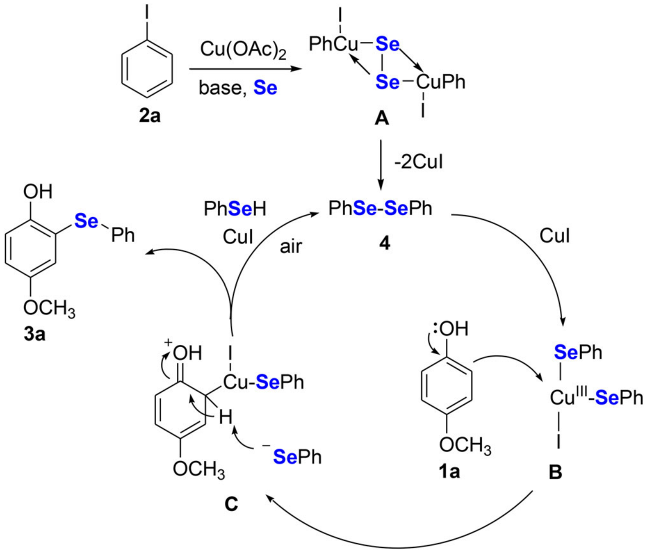
3v, 73%[b]

All reaction were performed with **1** (0.5 mmol), **2a** (0.2 mmol), Se (0.6 mmol), Cu(OAc)$_2$ (10 mol%) and Na$_3$PO$_4$·12H$_2$O (0.6 mmol) in 2 mL of DMSO at 120 °C for 12 h, under air. Isolated yields.
p-Iodotoluene was used instead of iodobenzene.

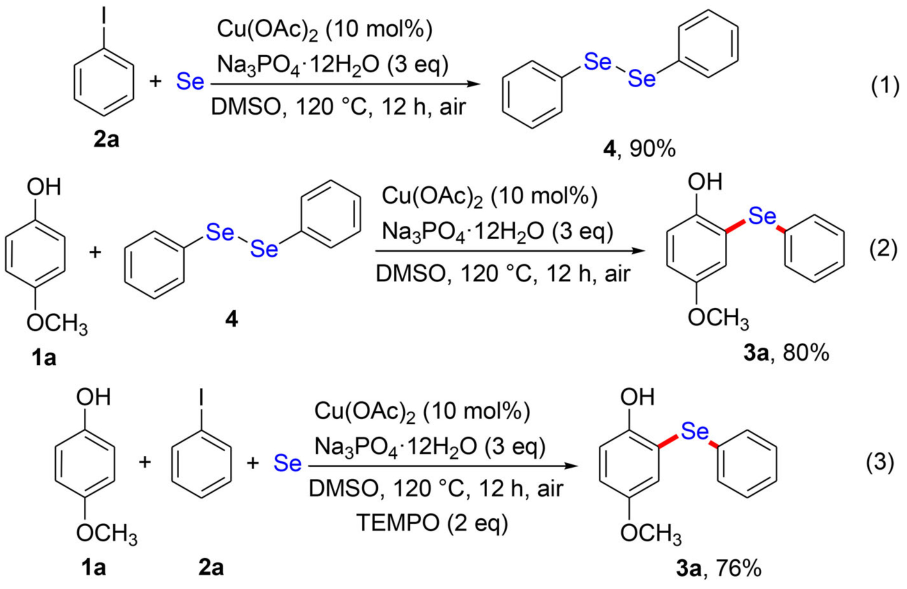
B at the *ortho*-position to generate intermediate **C**. A proton elimination from intermediate **C** gives target product **3a**, releasing arylselenol species and copper catalyst for next recycle.

Conclusion

In conclusion, a novel and facial method for synthesis of arylselenylphenols via copper-catalyzed three-component coupling reaction of phenols, Se powder, and aryl iodides has been developed. This approach employs commercially available elemental selenium as a selenating reagent. Importantly, the reaction proceeds with high *ortho*-selectivity and broad functional group tolerance. Due to the importance of C–Se bonds formation, further studies to



Scheme 3. Proposed reaction mechanism.



Scheme 2. Control reactions.

expand the substrate scope and detail reaction mechanism are currently underway.

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