OL | Organic Letters

Letter

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

pubs.acs.org/OrgLett

Oxidative Aminoarylselenation of Maleimides via Copper-Catalyzed Four-Component Cross-Coupling

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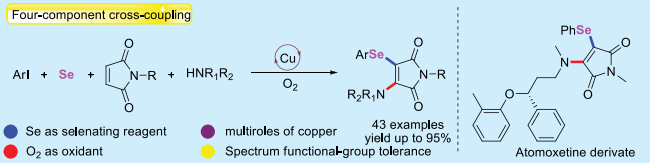
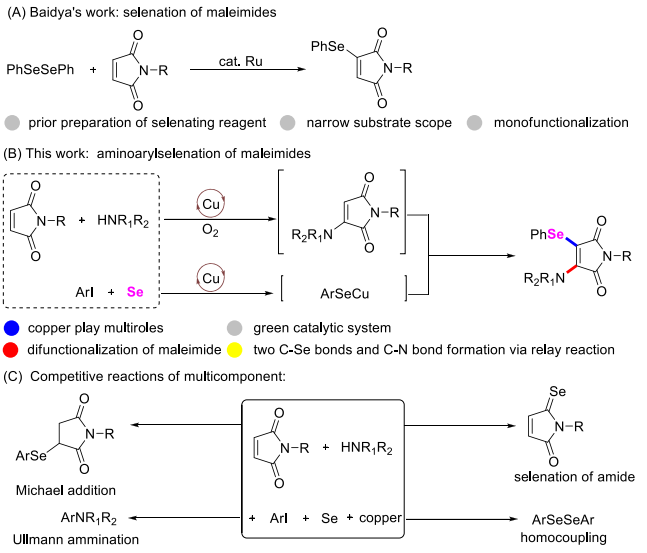
Supporting Information

ABSTRACT: The first example of copper-catalyzed four-component coupling reaction of aryl iodides, Se powder, secondary amines, and maleimides is developed. This reaction provides an efficient and concise route to access amino-arylselenated maleimides via double C−Se bonds and C−N bond formation. The appealing features of this transformation are the use of Se powder as a selenating reagent, a green catalytic system, a wide range of substrate scope, and late-stage selenation of bioactive compounds.



Vinyl selenides are of particular importance, due to their reactive handles in further manipulation of complex compounds and since they are useful building blocks for drug candidates and agrochemicals.[1] To date, transition-metal-catalyzed alkyne hydroselenation is a practical and efficient method for vinyl selenide synthesis.[2] Palladium-catalyzed carboselenation of alkynes with sulfenamides and diselenides to prepare β-selenyl acrylamides has also been reported.[3] Most recently, Baidya developed an efficient Ru-catalyzed C−H selenylation of maleimides with diselenides via an umpolung protocol (Scheme 1A).[4] However, the use of readily available starting material for preparation of structurally diverse selenated enamides remains to be elusive. Only one intermolecular, three-component aminoselenation of alkynes has been developed by Zheng.[5] Issues associated with prior preparation of selenating reagent and narrow substrate scope would dramatically restrict their application on late-stage transformation of bioactive compounds. Undoubtedly, the use of elemental selenium as a selenating reagent involved in transition-metal-catalyzed oxidative selenoamination of alkenes would be an attractive and promising strategy. To the best of our knowledge, there is no such report to construct the 2-amino vinyl selenides.

Scheme 1. Copper-Catalyzed Four-Component Cross-Coupling



In continuing our study toward diverse utility of Se powder,[6] we envisaged developing copper-catalyzed four-component cross-coupling of aryl iodides, Se powder, maleimides, and amines (Scheme 1B). As part of our design, we speculated that enamides and arylselenocopper species could be generated on the basis of distinct mechanisms of copper-catalyzed reactions in a one-pot manner and then two competent intermediates undergo selective cross-coupling to afford the corresponding product. However, a formidable challenge in this approach is to overcome a number of competitive reactions, including copper-catalyzed Ullmann amination,[7] seleno-Michael addition,[8] selenation of maleimides,[9] and homocoupling[10] (Scheme 1C). As a result, this transformation establishes a useful approach to access arylselenoamination of maleimides via one C−N bond and double C−Se bond formation processes. Furthermore, this protocol provides a complementary scope for the existing three-component aminoarylselenation of alkynes.[11]

We initially chose iodobenzene **1a**, Se powder, *N*-methylmaleimide **2a**, and morpholine **3a** as model substrates to examine the feasibility of copper-catalyzed four-component

Received: December 13, 2018

DOI: 10.1021/acs.orglett.8b03980
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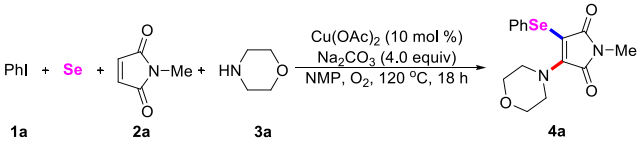
cross-coupling reactions. To our delight, it was found that the desired product **4a** was isolated in 85% yield along with a small amount of diphenyl diselenide when the reaction was performed using $Cu(OAc)_2$ as a catalyst and Na_2CO_3 as a base in NMP under an O_2 atmosphere at 120 °C (Table 1, entry 1). Remarkably, the Ullmann amination, selenation of maleimides, and seleno-Michael addition with elemental selenium were not observed at all under the optimized reaction conditions. Following encouraging results, a variety of copper catalysts were examined. Other Cu(II) salts, such as $Cu(TFA)_2$, $CuCl_2$, and $CuBr_2$, were ineffective; only CuI could afford a comparable yield (entries 2−5). The influence of base was next assayed; the desired reactions could be completely inhibited by switching Na_2CO_3 to a stronger base, such as K_2CO_3 and Cs_2CO_3 (entries 7 and 8). It is worth noting that the choice of solvent is critical for the success of transformation. Only polar solvents are beneficial for the reaction efficiency; other apolar and weak coordination solvents were unsuitable (entries 9−11). The addition of Phen as a ligand did not enhance the reaction outcome (entry 12). What is more, this reaction is very sensitive to N_2 atmosphere (entry 13). Furthermore, no product was detected in the absence of base (entries 14); perhaps base was serving as an activator of elemental selenium and assisting Michael addition of secondary amine with maleimide. No desired product was formed without copper catalyst, thus demonstrating that copper played an indispensable role in promoting the reaction (entry 15).

Table 1. Reaction Optimization[a]

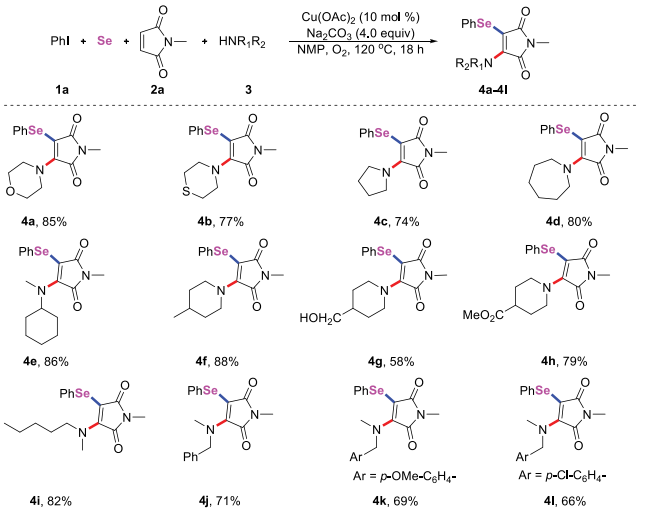


entry	alteration	yield[b] (%)
1	none	85
2	$CuCl_2$ instead of $Cu(OAc)_2$	0
3	$CuBr_2$ instead of $Cu(OAc)_2$	0
4	$Cu(TFA)_2$ instead of $Cu(OAc)_2$	0
5	CuI instead of $Cu(OAc)_2$	64
6	Li_2CO_3 instead of Na_2CO_3	55
7	K_2CO_3 instead of Na_2CO_3	trace
8	Cs_2CO_3 instead of Na_2CO_3	0
9	DMSO instead of NMP	60
10	CH_3CN instead of NMP	0
11	toluene instead of NMP	0
12	Phen (0.02 mmol) as additive	48
13	under N_2	0
14	no Na_2CO_3	0
15	no $Cu(OAc)_2$	0

[a]Reaction conditions unless specified otherwise: **1a** (0.6 mmol), Se_8 (0.6 mmol), **2a** (0.2 mmol), **3a** (0.3 mmol), catalyst (0.02 mmol), Na_2CO_3 (0.8 mmol), NMP (1.0 mL), under O_2 atmosphere, 120 °C, 18 h. [b]Isolated yield.

With the optimal reaction conditions in hand, we set out to explore the scope of amines which could be employed in this protocol (Scheme 2). It was found that an array of cyclic secondary amines were successfully engaged in this transformation, including thiomorpholine (**4b**), pyrrolidine (**4c**), and piperidine (**4f**−**4h**). Azepane (**4d**) was also a viable substrate and provided the desired product in good yield. We were pleased to find that unprotected 4-hydroxypiperidine (**4g**) could be alkenylarylselenated successfully to access 3-amino-4-selenomaleimide with high efficiency. Notably, a wide range of acyclic secondary amines were smoothly accommodated; *N*-methyl cyclohexylamine (**4e**) and *N*-methylpentylamine (**4i**) could be used as aminating reagents. In addition, *N*-methyl benzylamines (**4j**−**4l**) were feasible in the current reaction conditions, providing the corresponding products in excellent yields. However, primary alkyl amines, anilines, and electron-deficient amide could not take part in this transformation, indicating that the nucleophilicity of amines played an essential role in promoting the reaction.

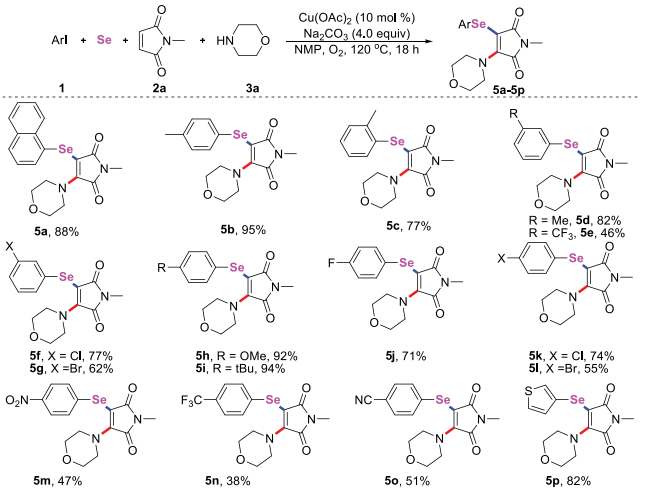
Scheme 2. Secondary Amines Scope[a]



[a]Reaction conditions: Table 1, entry 1. Isolated yields after column chromatography are given.

Subsequently, a variety of aryl iodides were examined under the current copper-catalyzed double C−Se bonds and C−N bond formation protocol, the results were summarized in Scheme 3. It was found that aryl iodides bearing electron-donating substituents (**5b**−**5d**, **5h**, and **5i**) displayed a higher

Scheme 3. Aryl Iodides Scope[a]



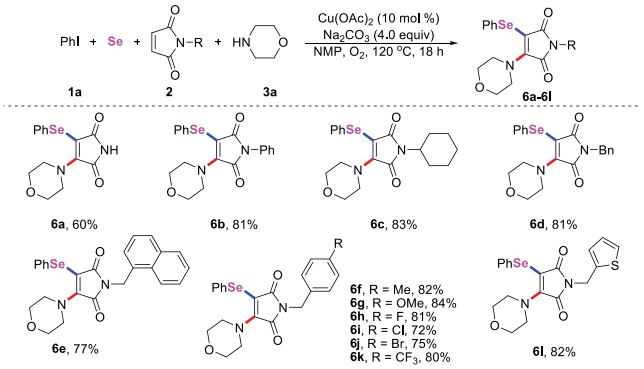
[a]Reaction conditions: Table 1, entry 1. Isolated yields after column chromatography are given.

DOI: 10.1021/acs.orglett.8b03980
Org. Lett. XXXX, XXX, XXX−XXX

reactivity than those with electron-deficient substituents (**5e**, **5m**−**5o**), implying that the efficiency of transformation is the hinge on the nature of substituents on the benzene ring. In addition, 2-iodonaphthalene (**5a**) proceeded smoothly and gave the corresponding product in excellent yield. Moreover, the sterically hindered substrate (**5c**) also worked well and produced the anticipated product in satisfactory yield. It is worth mentioning that typical functional groups, including methyl (**5b**−**5d**), trifluoromethyl (**5e**, **5n**), fluoro (**5j**), chloro (**5f**, **5k**), bromo (**5g**, **5l**), nitro (**5m**), and cyan (**5o**), were all well tolerated, providing a good opportunity for further transformation via well-developed cross-coupling reactions. Besides aryl iodides, 3-iodothiophene can also be utilized as a coupling partner for the current four-component cross-coupling reaction.

Next, we turned our attention to examining the viability of various maleimides under the optimal reaction conditions (Scheme 4). To our delight, free maleimide (**6a**) was a

Scheme 4. Maleimides Scope[a]



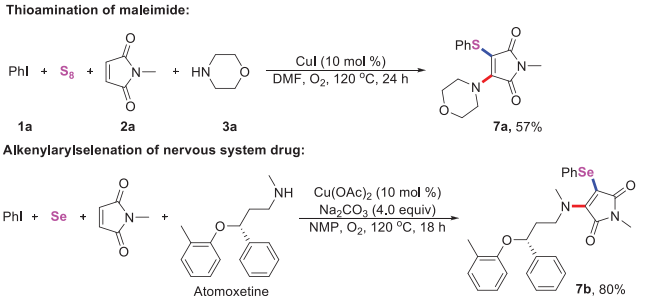
[a]Reaction conditions: Table 1, entry 1. Isolated yields after column chromatography are given.

competent substrate and gave the corresponding product in acceptable yield. Generally, *N*-substituted maleimides were readily aminophenylselenated to deliver the corresponding products in fair to good yields. The copper-catalyzed aminoarylselenation of maleimides displayed good functional group tolerance on the benzene ring of *N*-aryl maleimides, including methyl (**6f**), methoxy (**6g**), fuloro (**6h**), chloro (**6i**), bromo (**6j**), and trifluoromethyl (**6k**), providing a useful synthetic handle for further elaboration of selenium-containing products. Moreover, thiophene-substituted maleimide was also amenable to the current reaction conditions and afforded the target product in 82% yield.

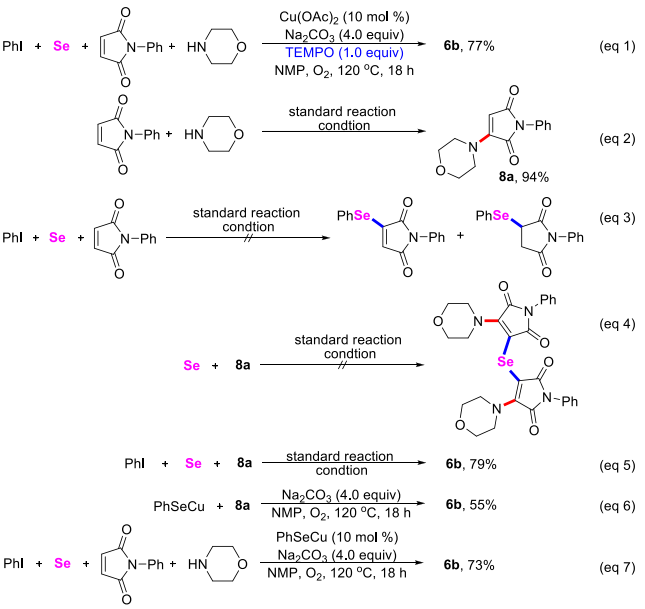
As shown in Scheme 5, the versatile application of the synthetic protocol was further demonstrated by employing S_8 powder as a sulfur source for the corresponding thioamination of maleimide to provide the corresponding product **7a** in 57% under slightly modified reaction conditions. This strategy provides additional evidence for the late-stage transformation of bioactive molecules, such as Atomoxetine,[12] a norepinephrine reuptake inhibitor, selectively alkenylarylselenated to give the expected product **7b** in excellent yield, making it of interest in selenium-containing pharmaceutical research.

To identify the reaction sequence of the four-component cross-coupling reaction via copper relay catalysis, some control experiments were designed, as shown in Scheme 6. First, we found that the addition of radical inhibitor did not significantly

Scheme 5. Thioamination of Maleimide and Late-Stage Alkenylarylselenation of Atomoxetine



Scheme 6. Preliminary Mechanism Investigation

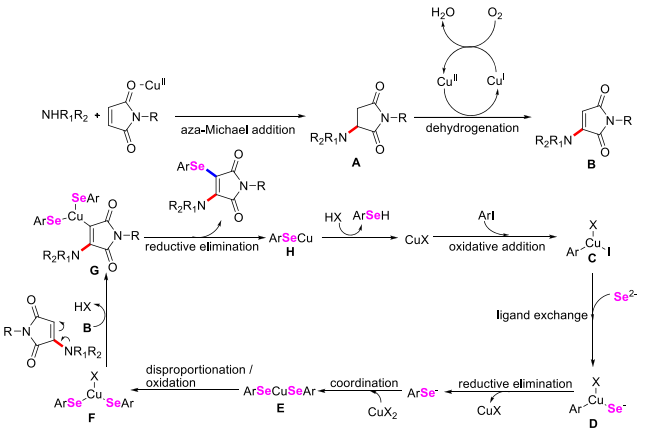


affect the efficiency of transformation (eq 1), which indicated a radical-mediated pathway could be ruled out. Second, oxidative amination product was isolated in 94% yield when *N*-phenylmaleimide was treated with morpholine under the optimized reaction conditions (eq 2). In contrast, when a mixture of iodobenzene, Se powder, and maleimide was stirred for 18 h, there was no seleno-Michael additiion product (eq 3). To further exclude the possibility of selenation of enaminone,[13] the reaction between Se powder and **8a** was also conducted (eq 4). Moreover, the product **6b** was obtained in 79% yield when the iodobenzene, Se powder, and **8a** were subjected to the standard reaction conditions (eq 5). On the basis of these results, we reasoned that enaminone is involved in this reaction and ArSeCu species may be the key intermediate, which was directly supported by the stoichiometric reactions between **8a** and PhSeCu[14] under an O_2 atmosphere (eq 6). Furthermore, the use of PhSeCu as catalyst led to a good yield of **6b** (eq 7). These results suggest that copper plays multiple roles in promoting this reaction.

On the basis of the above experimental observations, a plausible reaction mechanism for copper-catalyzed four-component cross-coupling is proposed in Scheme 7. First, aza-Michael addition and copper-catalyzed dehydrogenation of maleimides with secondary amines afford intermediate **B**.[15] In parallel, the oxidative addition of aryl iodides with copper catalyst to produce **C** and then species **C** undergoes ligand

DOI: 10.1021/acs.orglett.8b03980
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 7. Proposed Mechanism



exchange with Se^{2-} elemental Se to generate **D**. Next, **D** proceeds to reductive elimination to deliver $ArSe^-$ species, which with further coordination with copper catalyst provides the intermediate **E**, followed by disproportionation or oxidation to form **F**.[16] Subsequently, species **F** with **B** react to generate the key intermediate **G**,[17] Finally, intermediate **G** proceeds to reductive elimination to afford the corresponding product and release copper catalyst. However, an alternative pathway through the reaction of **B** with selenium ion intermediate to deliver product cannot be ruled out (for details, see the Supporting Information).

In conclusion, we have developed the first example of copper-catalyzed four-component cross-coupling of aryl iodides, Se powder, maleimides, and secondary amines, providing a concise and efficient pathway to access an array of difunctionalized maleimides. This protocol enables two C−Se bonds and C−N bond formation in one pot by addition of two different nucleophiles across the double bonds. Therefore, the current reaction significantly broadens the scope of existing difunctionalization reactions of electron-deficient alkenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03980.

^{1}H and ^{13}C NMR spectra of all new compounds and the experimental procedures (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (21602158), Zhejiang Provincial Natural Science Foundation (LY19B020011), State Key Laboratory of Structural Chemistry (No. 20170037), and the Opening Project of Zhejiang Provincial Top Key Discipline of Pharmaceutical Sciences (201723) is greatly appreciated.

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Org. Lett. XXXX, XXX, XXX−XXX