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Copper-Catalyzed 8-Aminoquinoline-Directed Selenylation of Arene and Heteroarene C−H Bonds

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Supporting Information

ABSTRACT: An efficient copper-catalyzed/-mediated and 8-aminoquinoline-assisted arylselenylation of inert C−H bonds of (hetero)arenes with readily available diselenides has been reported. The reaction is scalable and tolerates a wide spectrum of functional groups to deliver diarylselenides in very high yields (up to 98%). Application of this methodology to the facile synthesis of thiophene-fused selenochromone was demonstrated.

Molecules embracing carbon−selenium−carbon connectivity, so-called organoselenides, have occupied a prominent position in medicinal chemistry and drug discovery.[1] Particularly, the diaryl selenide scaffolds are often found in drug candidates displaying a broad range of bioactivities (Figure 1).[2]

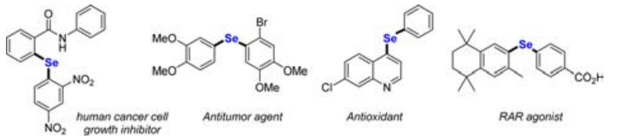
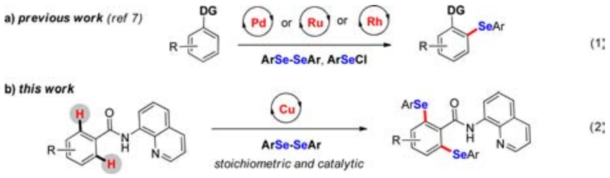


Figure 1. Examples of biologically active diaryl organoselenides.

Furthermore, they also have important applications to functional organic materials and play a pivotal role in organic synthesis as useful intermediates and catalysts.[3] As a result, much attention has been paid toward the development of novel synthetic protocols for organoselenides.[4]

Among the various established approaches, synthesis of organoselenides through transition-metal-catalyzed direct C−H bond functionalization is very attractive.[5] However, direct selenylation of an inert aryl C−H bond is increasingly challenging due to the strong coordinating property of the organoselenium compounds.[6] Successes have primarily been achieved with precious palladium, ruthenium, and rhodium catalysts (Scheme 1, eq 1).[7] In contrast, utilization of inexpensive first-row-transition metals for such a transformation is very rare. Attempts have been made with nickel catalysts, albeit in a single substrate.[8] Except the reactions of electron-rich nucleophilic aromatic compounds,[9] at present, there is no general report of direct selenylation of inert aryl C−H bonds en route to diaryl selenides using abundant copper catalysts.

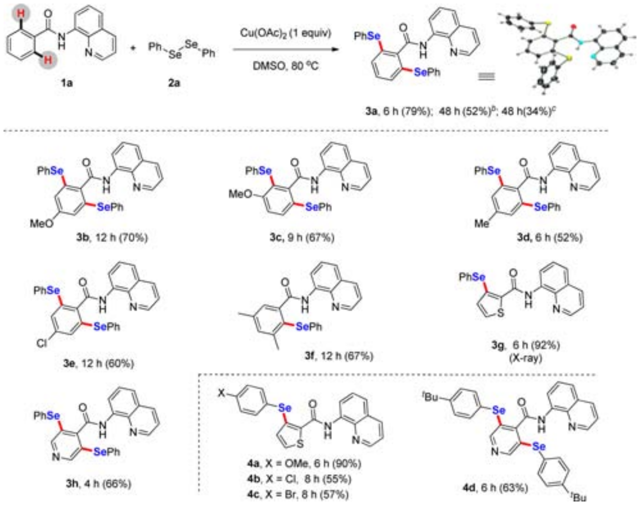
Scheme 1. Transition-Metal-Catalyzed Arylselenylation of $C(sp^2)$−H Bonds



Herein, we report an efficient copper-catalyzed and -mediated *ortho*-selenylation of (hetero)arenes with readily available diselenides under mild conditions by using an easily removable 8-aminoquinoline directing group (Scheme 1, eq 2).

Our study began by evaluating the reaction of 8-aminoquinoline amide **1a** with commercially available diphenyl diselenide **2a** as the selenium source (Scheme 2). To our delight, when the mixture of **1a** and **2a** in DMSO was exposed

Scheme 2. Copper Promoted Selenylation of Benzamides[a]



[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $Cu(OAc)_2$ (1 equiv), DMSO (3 mL), 80 °C. Yields of isolated products are given. [b] $Cu(OAc)_2$ (50 mol %) was used. [c] $Cu(OAc)_2$ (20 mol %) was used.

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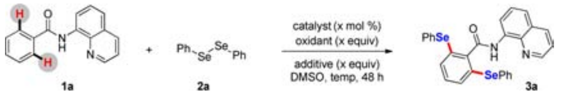
to stoichiometric copper acetate at 80 °C, *ortho*-diselenylation proceeded cleanly to deliver **3a** in 79% isolated yield. The structure of the product **3a** was unambiguously confirmed by X-ray analysis.[10] Lowering the amount of $Cu(OAc)_2$ to 0.5 and 0.2 equiv reduced the yields of the product, even after prolonging the reaction time.

Under this condition, various aromatic **1b–f** and heteroaromatic **1g,h** amides having electron-donating and -withdrawing substituents efficiently took part in the reaction to deliver the desired products in good to excellent yields (Scheme 2). Interestingly, a *meta*-disubstituted amide gave only monoselenylation product **3f** in 67% yield. Other substituted diselenides are also equally suitable for this reaction and produced highly functionalized selenides in high yields (**4a–d**).

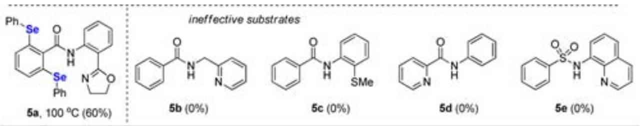
Although copper acetate is inexpensive and this reaction condition is mild and efficient, we envisaged that a catalytic version of the present protocol will have wider significance in modern organic synthesis and, thus, sought to render the reaction catalytic. Consequently, we conducted the reaction of amide **1a** and **2a** using 20 mol % $Cu(OAc)_2$ as the catalyst and Ag_2CO_3 as an oxidant (Table 1). Gratifyingly, with this catalytic protocol, expected product **3a** was obtained in 48% isolated yield after 48 h (Table 1, entry 1). The reaction efficiency was improved in the presence of the potassium fluoride additive to give a 62% yield (Table 1, entry 2).[11] Consequently, other fluorides were examined; however, a deleterious effect was observed (Table 1, entries 3–5). Further screening of other copper catalysts (Table 1, entries 6–9), oxidants (Table 1, entries 10–11), and solvents (Table 1, entries 12–14) also gave inferior results. The reaction temperature was determined to be a very crucial parameter for this reaction. When the reaction was performed at 130 °C, the yield was dropped to 52% (Table 1, entry 15). When the temperature was decreased to 80 °C, the reaction yield was increased to 72% (Table 1, entry 16). Further reduction of the reaction temperature, however, attenuated the formation of **3a** (Table 1, entry 17). The reaction completely failed in the absence of $Cu(OAc)_2$, and the yield also reduced dramatically without Ag_2CO_3 (Table 1, entries 18–19). When Ag_2CO_3 was replaced with K_2CO_3, the desired product was obtained in 24% yield (Table 1, entry 20). These observations demonstrate that the presence of both the copper catalyst and Ag_2CO_3 are essential and Ag_2CO_3 is possibly playing the role of oxidant.

Table 1. Optimization of Catalytic Reaction Conditions[a]



entry	catalyst	oxidant	additive	temp (°C)	yield (%)[b]
1	$Cu(OAc)_2$	Ag_2CO_3	–	100	48
2	$Cu(OAc)_2$	Ag_2CO_3	KF	100	62
3	$Cu(OAc)_2$	Ag_2CO_3	CsF	100	33
4	$Cu(OAc)_2$	Ag_2CO_3	Selectfluor	100	28
5	$Cu(OAc)_2$	Ag_2CO_3	$(PhSO_2)_2NF$	100	42
6	$Cu(OTf)_2$	Ag_2CO_3	KF	100	43
7	$CuBr_2$	Ag_2CO_3	KF	100	50
8	CuCl	Ag_2CO_3	KF	100	56
9	CuOAc	Ag_2CO_3	KF	80	52
10	$Cu(OAc)_2$	$K_2S_2O_8$	KF	80	trace
11	$Cu(OAc)_2$	Ag_2O	KF	80	53
12[c]	$Cu(OAc)_2$	Ag_2CO_3	KF	80	56
13[d]	$Cu(OAc)_2$	Ag_2CO_3	KF	80	trace
14[e]	$Cu(OAc)_2$	Ag_2CO_3	KF	80	trace
15	$Cu(OAc)_2$	Ag_2CO_3	KF	130	52
16	**$Cu(OAc)_2$**	**Ag_2CO_3**	**KF**	**80**	**72**
17	$Cu(OAc)_2$	Ag_2CO_3	KF	60	14
18	–	Ag_2CO_3	KF	80	0
19	$Cu(OAc)_2$	–	KF	80	30
20	$Cu(OAc)_2$	–	KF, K_2CO_3	80	24

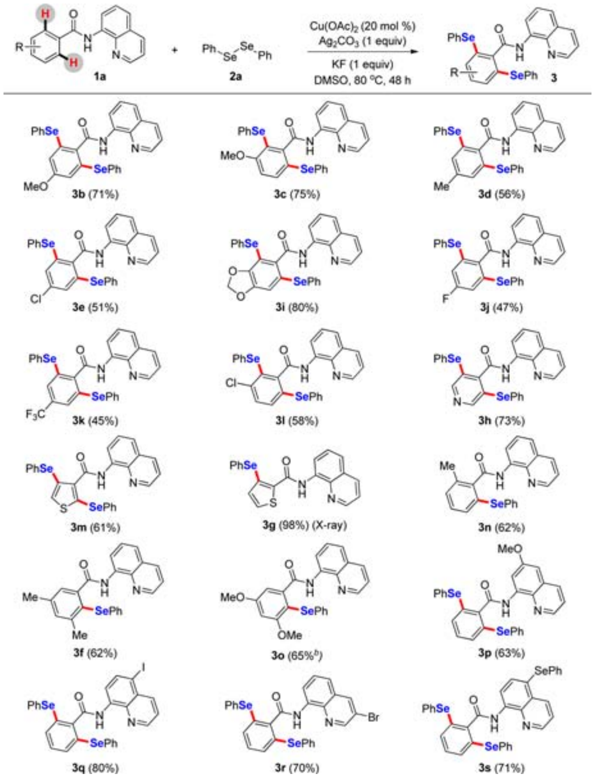
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $Cu(OAc)_2$ (20 mol %), oxidant (0.2 mmol), solvent (3 mL), 48 h. [b] Isolated yields. [c] Solvent was DMF. [d] Solvent was dioxane. [e] Solvent was toluene.



The reaction was also tested with other directing groups.[5i,j] The 8-aminoquinoline motif appeared to be more effective under the current conditions with benzamide derivatives; with the exception of the amino-phenyl-oxazole directing group introduced by Yu (**5a**), other structurally related coordinating groups failed to promote the reaction (**5b–d**) (Table 1).

With the optimized catalytic reaction conditions in hand, the scope of this method was then investigated (Scheme 3). The reaction is quite general for a wide range of substituted 8-aminoquinoline amides. Various benzamides bearing electron-donating and electron-withdrawing groups were all compatible, but electron-rich substrates showed better reactivity to give

Scheme 3. Reaction Scopes with Respect to Amides[a]



[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $Cu(OAc)_2$ (20 mol %), Ag_2CO_3 (0.2 mmol), KF (0.2 mmol), DMSO (3 mL), 48 h. Yields of isolated products are given. [b] Diselenylation product was isolated in 18% yield.

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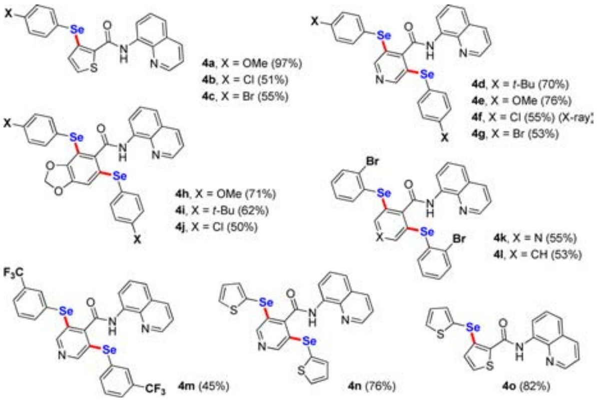
higher yields (**3b–l**). The reaction afforded difunctionalization products even with *meta*-substituted amides **3c,l**. The methodology was successfully applied to carboxamides bearing six- and five-membered heteroaryl substituents such as pyridine **3h** and thiophene **3g,m** to render desired products in good to excellent yields (up to 98%).

As anticipated, *ortho*-substituted benzamide produced monoselenylation (**3n**). Interestingly, 3,5-disubstituted benzamides also gave preferably monoselenylated products (**3f,o**), which could be attributed to steric effect. Furthermore, substrates having methoxy, halogens, and selenium functionalities in the quinoline ring were also suitable (**3p–s**) and smoothly produced the desired products in high yields (63–80%).

The reaction efficiency of different diselenides was also evaluated (Scheme 4). Various diaryl diselenides with electron-donating and -withdrawing groups could efficiently participate in the reaction to deliver the corresponding selenylated products in good yields (**4a–m**). For instance, the diaryl diselenides with methoxy and *tert*-butyl substituents at the *para*-position of the aryl ring generally produced the desired products in very high yields (**4a**, **4d–e**, and **4h–i**). Importantly, halogen substituents in the diselenides was tolerable (**4b–c**, **4f–g**, **4j**, **4k–l**), which are a useful synthetic handle for further functionalization to complex molecules. In the case of a *meta*-CF_3-substituted diaryl diselenide, selenylated product **4m** was obtained in moderate yield. Besides aromatic diselenides, the heteroaromatic diselenide such as 2,2′-dithienyl diselenide showed good reactivity rendering heteroaromatic seleno ethers in high yields (**4n–o**). These heterocyclic compounds with a higher number of selenium bridges are expected to be valuable for material science.

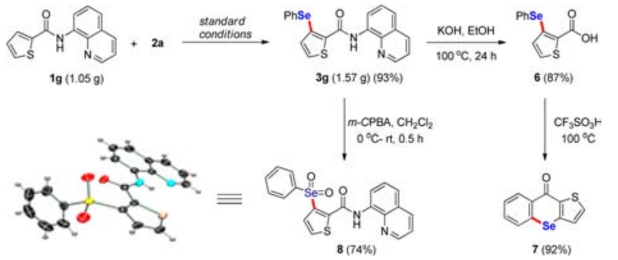
Scheme 4. Reaction Scopes with Respect to Diaryl Diselenides[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $Cu(OAc)_2$ (20 mol %), Ag_2CO_3 (0.2 mmol), KF (0.2 mmol), DMSO (3 mL), 48 h. Yields of isolated products are given.

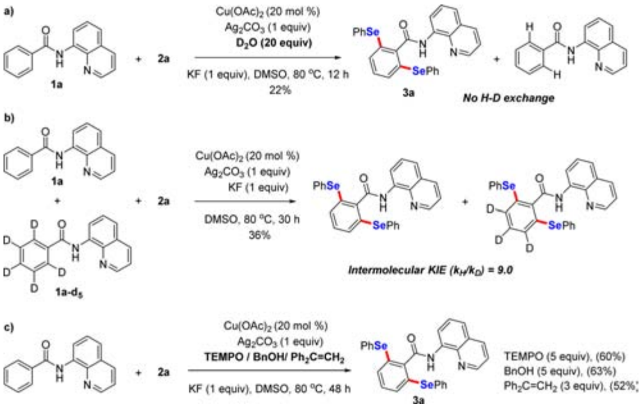
To evaluate the reaction efficacy, we have executed the reaction on a gram scale with amide **1g** (Scheme 5). The efficiency of a small scale reaction was retained upon scale-up delivering **3g** in 93% yield. Furthermore, the amide bond can be easily cleaved in one step to obtain free acid **6**, which was efficiently converted to novel thiophene-fused selenochromone **7** by treating with triflic acid in excellent yield. Further, exposure of the compound **3g** to *m*-CPBA at low temperature gave unsymmetrical selenone **8** in very high yield (74%).

Scheme 5. Gram Scale Synthesis and Functionalization of Selenylation Product



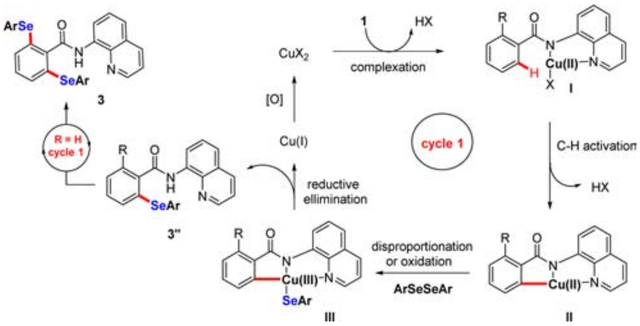
In order to probe the reaction mechanism various controlled experiments were performed (Scheme 6). When the selenylation reaction was conducted in the presence of D_2O under typical reaction conditions, no deuterium incorporation was detected in the recovered starting material or the product, validating the cleavage of the C–H bond is irreversible (Scheme 6a). The intermolecular kinetic isotope effect revealed $k_H/k_D = 9.0$, which implies that C–H bond breaking is likely involved in the rate-determining step (Scheme 6b). Further, in the presence of radical scavengers such as TEMPO, benzyl alcohol, and 1,1-diphenylethylene, a significant amount of product **3a** was isolated (Scheme 6c). These results refute the involvement of radical species in the reaction pathway.

Scheme 6. Control Experiments



While mechanistic clarification must await further study, based on the preceding discussion and previous literature reports, a plausible reaction mechanism is outlined in Scheme 7.[5] After complexation of **1** with a copper catalyst, Cu(II)-aryl species **II** is produced via a basic ligand (acetate/carbonate) promoted concerted-metalation–deprotonation (CMD) path-

Scheme 7. Plausible Reaction Mechanism



way. The C,N,N-pincer type Cu(III)-aryl intermediate **III** is formed by disproportionation/oxidation and simultaneous transfer of aryl selenium functionality. Subsequent, reductive elimination leads to the monoselenylated product **3′′** with the formation of Cu(I) species. The active Cu(II) catalyst is generated by oxidation to continue the catalytic cycle. The product **3″** (R = H) undergoes the catalytic *cycle 1* for a second time to produce the diselenylation product **3**.

In conclusion, we have unfolded the first copper-catalyzed/mediated direct selenylation of (hetero)arenes directed by a removable bidentate auxiliary. This protocol is operationally simple and scalable and displays a broad substrate scope with high functional group compatibility, delivering diarylselenides in very high yields (up to 98%). Preliminary mechanistic studies suggest that a basic ligand-enabled, irreversible, rate-determining CMD step is most likely to be involved in this process. Application of this methodology to the facile synthesis of a thiophene-fused selenochromone was demonstrated.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01420.

Complete experimental details, characterization data for the prepared compounds (PDF)
Crystallographic data (CIF, CIF, CIF, CIF)

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Notes

The authors declare no competing financial interest.

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