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Palladium-Catalyzed Distal C–H Selenylation of 2-Aryl Acetamides with Diselenides and Selenyl Chlorides

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Abstract: A convenient and effective method of palladium-catalyzed C–H selenylation of the 2-aryl acetamides assisted with removable 8-aminoquinoline with readily available diselenides and selenyl chlorides has been developed. This selenylation reaction is scalable and tolerates a wide range of functional groups, providing a straightforward way of the preparing unsymmetrical diaryl selenides and dibenzoselenepinone. Preliminary mechanistic studies indicated that a single-electron transfer type mechanism and facile C–H metalation are operative.

Keywords: Palladium catalyst; C–H selenylation; Removable directing group; 2-Aryl acetamides; Single-electron transfer.

Introduction

Unsymmetrical diaryl chalcogenide scaffolds are useful building blocks that frequently appear in many drug candidates and natural products.[1] For example, aryl chalcogenide derivatives displayed promising bioactivities ranging from antitumor, antioxidant, anti-inflammatory, antibacterial, antiviral activities. (**Figure 1**).[2] In addition, aryl chalcogenide compounds have extensive applications in functional materials, organic catalysis, synthetic chemistry and fluorescent probes.[3] Thus, the preparation of organic molecules containing diaryl chalcogenide motifs has received considerable interest in recent years. Traditional methods to access unsymmetrical diaryl sulfides and diaryl selenides mainly rely on cross-coupling reactions of pre-functionalized staring materials or direct electrophilic substitutions of electron-rich aromatic compounds with thiols/disulfides or diselenides.[4] Moreover, most of these reactions are performed under harsh or strongly-basic reaction conditions and resulted in a narrow substrate scope. Therefore, a general, rapid, and highly regioselective method for the construction of C−Se and C−S bonds is highly desirable.

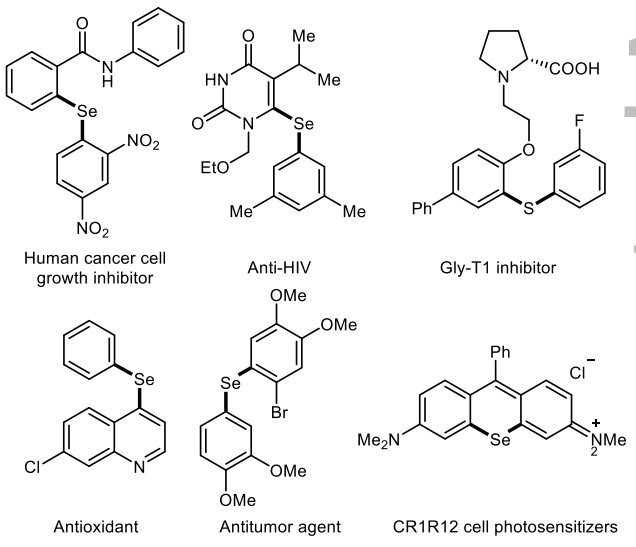
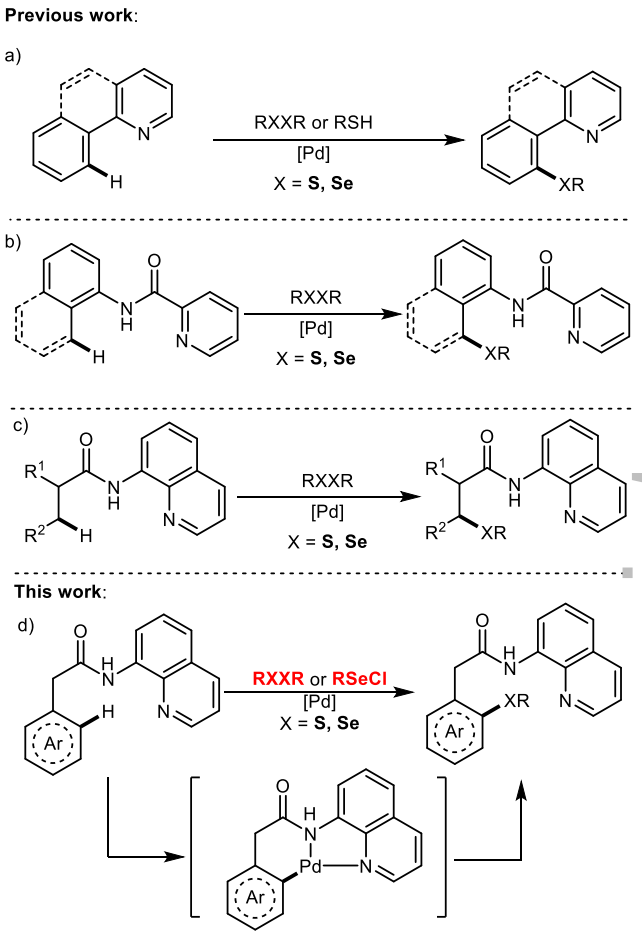


Figure 1. Representative related bioactive molecules.

In the past few decades, transition metal-catalyzed directed C−H chalcogenation has emerged as a powerful and effective strategy for the construction of S- or Se-containing structures in pharmaceuticals and materials due to its remarkable potential for step economy and environmental sustainability.[5] These catalytic reactions usually require directing groups

pre-installed in the starting materials to govern the reactivity and regioselectivity. In this context, lots of efforts has been made to develop diverse directing groups, which enable the successful transformation.[6] As early as 2014, Nishihara and Li reported the first palladium-catalyzed aryl C−H thiolation with diaryl disulfides directed by pyridine group.[7] Subsequently, Law, Wong and Anbarasan further extended the substrate scope with different chalcogenide reagents under the palladium catalysis (**Scheme 1a**).[8] Our group then disclosed the selective *ortho*-thiolation and selenylation of *N*-arylsulfonamides with disulfides and diselenides *via* weak coordination.[9] Nishihara and coworkers developed a palladium-catalyzed *peri*-selective C−H chalcogenation of naphthylamines with the assistance of picolinamide bidentate directing groups.[10] Inspired by this work, more recently, Xie's group further achieved the γ-C(sp^3)−H chalcogenation of alkylamines with diaryl disulfides and diselenide in good yield (**Scheme 1b**).[11] Furthermore, Maiti's group reported palladium-catalyzed the more challenging C(sp^3)−H chalcogenation with the assistance of 8-aminoquinoline directing groups, which provides a generally useful method for structural modifications of α-amino acids (**Scheme 1c**).[12] Nevertheless, despite significant progress in palladium-catalyzed aryl C(sp^2)−H and aliphatic C(sp^3)−H chalcogenation, the distal *ortho*-chalcogenation of phenylacetic acid derivatives has been rarely reported so far.

More recently, our group reported a ruthenium(II)-catalyzed distal chalcogenation of aromatic C(sp^2)−H bonds with diselenides and disulfides through weak coordination.[13] However, these reactions require excess diselenide or disulfide reagents and additional additives for complete conversion. Furthermore, only *para*- and *meta*-substituted 2-aryl acetamides and electron-deficient diselenides were compatible with this catalytic reaction. The more steric hindrance 2-aryl acetamides and electron-efficient diselenide substrates also remains a challenge. In continuation of our work [14] and those of others on the catalytic synthesis of unsymmetrical diaryl selenides, herein, we disclose the efficient palladium (II)-catalyzed *ortho*-selenylations of synthetically useful aryl acetic amide with readily available diaryl diselenides or phenylselenyl chloride *via* distal C−H bond activation process. (**Scheme 1d**)



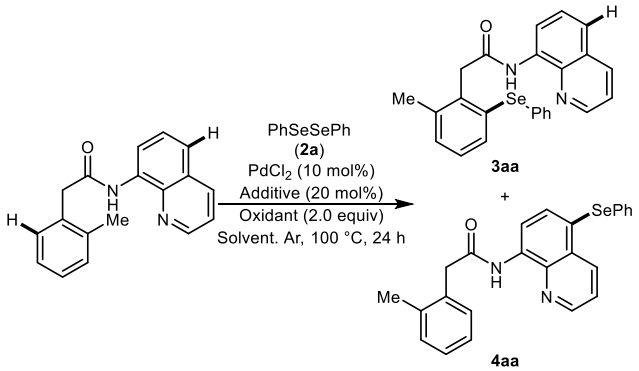
Scheme 1 Directing group assisted palladium-catalyzed C−H chalcogenations.

Results and Discussion

Our exploration was commenced by examining the reaction parameters for the envisioned direct C–H selenylation of *N*-(quinolin-8-yl)-2-(*o*-tolyl)acetamide (**1a**) with diphenyl diselenide (**2a**) under palladium catalysis. The desired product **3aa** was obtained in 32% yield in the presence of 2 equiv. Ag_2CO_3 in DMF at 100 ℃ without any additives (Entry 1, Table 1). The addition of AgOTf significantly increased the yield to 66%. Substituting TfOH as additive gave a comparable yield of the desired product along with 11% side product **4aa** under the standard conditions (Entry 3). To our delight, the combination of AgOTf and TfOH as co-additives in this catalytic reaction resulted in 80% of desired product. Further experimental results on oxidant screening revealed that Ag_2CO_3 gained the best performance, while other silver salts such as AgOAc, Ag_2O, AgOPiv and dipotassium peroxymonosulfate resulted in unsatisfactory yields. (Entries 6-10). Among various representative solvents, including DMF, DMSO, toluene, 1,4-dioxane, TFE, HFIP and trifluorotoluene, DMF turned out to have better reactivity than others, affording the selenylated product **3aa** in 80 % yield,

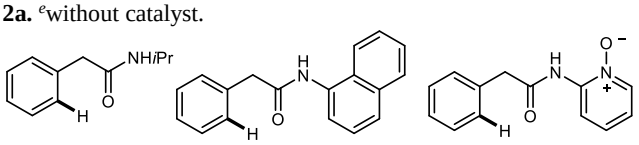
while the other solvents led to inferior results. Remarkably, reducing the amount of the diaryl diselenide coupling partners to 1.2 equivalence, gave the desired product **3aa** in 94% yield along with 6% side products **4aa** (Entry 19). However, further decreasing the diaryl diselenide loading to 1.0 equivalence significantly affected the chemical yield. (Entry 20) Control experiments verified that the selenylation reaction did not occur in the absence of the palladium catalyst or silver oxidant. (Entries 11 and 21).

Table 1. Optimization of various reaction parameters[a]



Entry	Oxidant	Additive	Solvent	Yield% **3aa/4aa**
1	Ag_2CO_3	---	DMF	32/0
2	Ag_2CO_3	AgOTf	DMF	66/0
3	Ag_2CO_3	TfOH	DMF	69/11
4	Ag_2CO_3	AgOTf+TfOH	DMF	80/18
5	Ag_2CO_3	AgOTf+TfOH	DMF	79/16[b]
6	AgOAc	AgOTf+TfOH	DMF	66/6
7	Ag_2O	AgOTf+TfOH	DMF	64/5
8	AgOPiv	AgOTf+TfOH	DMF	68/17
9	$K_2S_2O_8$	AgOTf+TfOH	DMF	58/14
10	$CuBr_2$	AgOTf+TfOH	DMF	0/74
11	--	AgOTf+TfOH	DMF	trace
12	Ag_2CO_3	AgOTf+TfOH	DMSO	--
13	Ag_2CO_3	AgOTf+TfOH	Toluene	--
14	Ag_2CO_3	AgOTf+TfOH	DCE	20/5
15	Ag_2CO_3	AgOTf+TfOH	dioxane	trace
16	Ag_2CO_3	AgOTf+TfOH	TFE	70/5
17	Ag_2CO_3	AgOTf+TfOH	HFIP	29/1
18	Ag_2CO_3	AgOTf+TfOH	$PhCF_3$	70/6
19	Ag_2CO_3	AgOTf+TfOH	DMF	94/6[c]
20	Ag_2CO_3	AgOTf+TfOH	DMF	48/6[d]
21	Ag_2CO_3	AgOTf+TfOH	DMF	--[e]

[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.40 mmol), $PdCl_2$ (10 mol %), Additive (20 mol %), TfOH (5 μL), solvent (2.0 mL), 100 C, 24 h, under Ar. [b] TfOH (10 μL). [c]1.2 equiv **2a**. [d]1.0 equiv **2a.** [e]without catalyst.



Scheme 2 Unreactive substrates

To clarify the necessity of the 8-aminoquioline as the bidentate directing group, a series of phenyl acetamides (**I**–**III**) in which the 8-aminoquinoline group was replaced by a different directing groups, such as isopropylamine, 1-naphthylamine or 2-aminopyridine-*N*-oxide were subjected to the optimized reaction conditions. No selenylated products were observed indicated that the 8-aminoquinoline directing group was essential for this transformation (Scheme 2).

Having established the optimal reaction conditions, we set out to investigate the substrate scope of this selenylation reaction by examining various benzamide derivatives. As shown in Scheme 3, benzamides bearing electron-donating groups such as -Me or -OMe, on the *ortho*-position were selenylated smoothly, providing the corresponding *mono*-selenylated products in 94% and 45% yields (**3aa** and **3ba**). The *meta*-substituted benzamides also proceeded efficiently at the less sterically encumbered C–H bonds, affording the desired products in good yields with excellent regioselectivity (**3ca**-**3ea**). Furthermore, 1-naphthyl- and 2-naphthyl- substituted substrates reacted smoothly to give the corresponding products in 50% and 83% yields respectively (**3fa** and **3ga**). The **1h** also participated in the reaction, however, the yields were somewhat lower (**3ha**). Gratifyingly, heterocyclic substrate **1i** was also selenyated efficiently and afford the desired product in 49% isolated yield (**3ia**). However, the 3-substituted thiophene substrate and more challenging alkenyl C(sp^2)–H and aliphatic C(sp^3)–H bonds were not compatible with the palladium catalysis regime (**3ja**-**3la**). Note that attempts to activate heteroaryl, naphthyl, and *ortho*-substituted aryl C–H bonds by the previous report on ruthenium(III) catalyst assisted by simple amide directing groups have, unfortunately, met with limited success and only resulted in unsatisfactory yields. [13]

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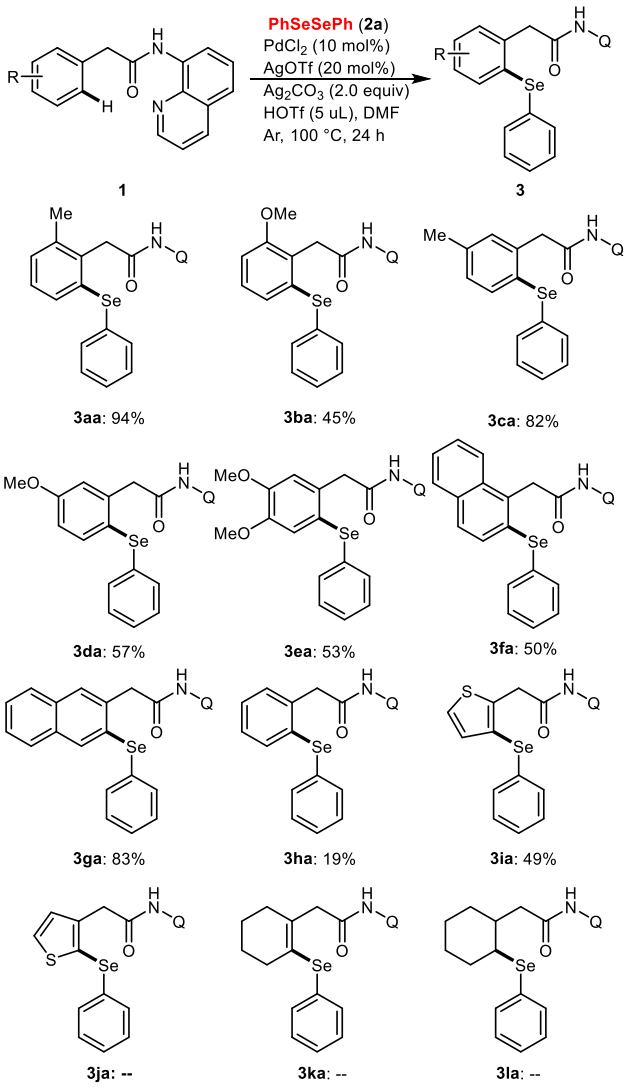
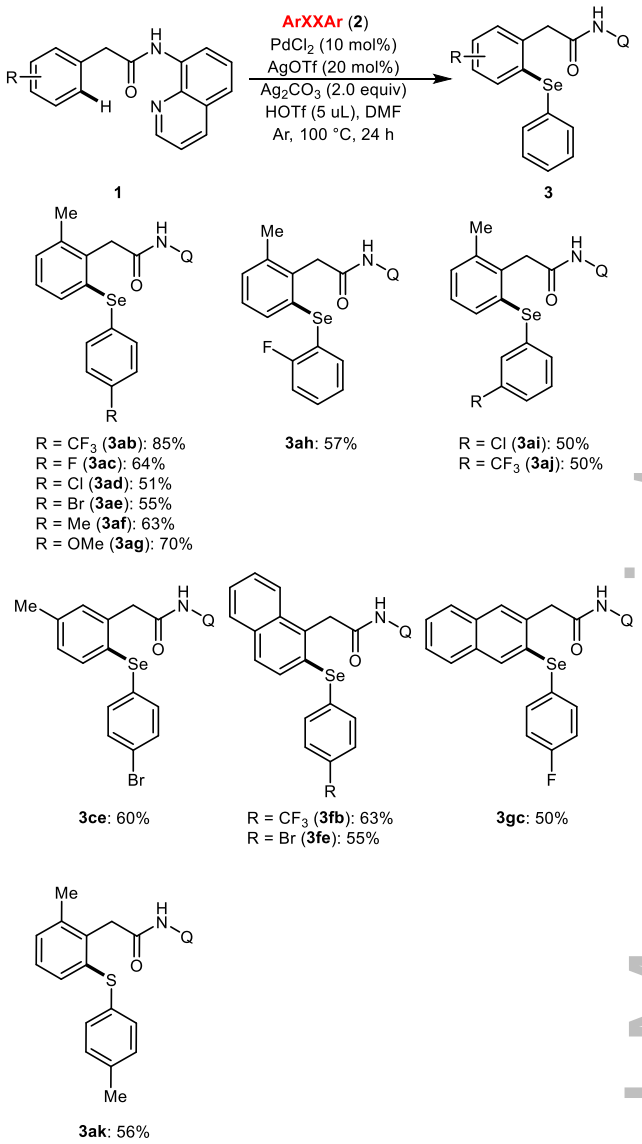


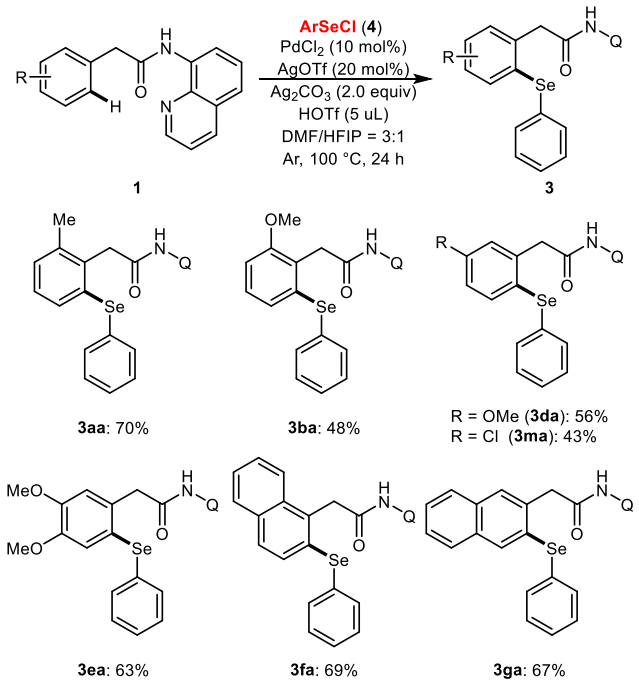
Scheme 3 Palladium-catalyzed C−H selenylations with different substituted 2-aryl acetamides.



Scheme 4. Investigation of diaryl diselenide scope.

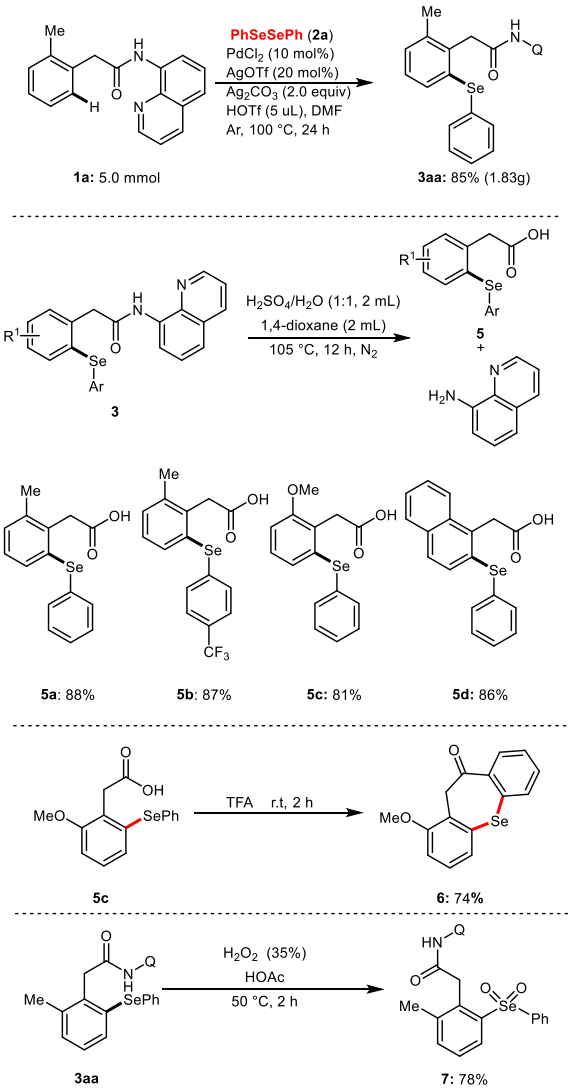
Subsequently, a wide range of substituted diaryl diselenides was evaluated under the optimized reaction conditions. As depicted in **Scheme 4**, diaryl diselenides bearing either electron-withdrawing (**2b**−**2e, 2h-2j**) or electron-donating groups (**2f**−**2g**) on *para*-, *meta*- or *ortho*-position showed high reactivity under the optimized conditions to give the selected *mono*-selenylated products in medium to high yields. Importantly, various functional groups such as halogen and methoxyl were also well tolerated under this palladium catalysis condition, giving the possibility to further functionalize the selenylated products. Notably, 1,2-di-*p*-tolyldisulfide could be employed as a suitable coupling partner and afforded the thiolated product **3ak** in synthetically useful yield.

Encouraged by the successful distal selenylation reaction with diaryl diselenide as coupling partners, the more challenging phenylselenenyl chlorides (**4**)[15] were also tested under the palladium catalysis. As anticipated, differently substituted 2-aryl acetamides showed good reactivity, furnishing the desired products **3aa**−**3ba** and **3da**−**3ga** with high levels of positional selectivity. It is worth pointing out that the *meta*-chloro substituted benzamide also proved to be a suitable substrate in this selenylation, although only give the selective *mono*-selenylated product in moderate yields owing to incomplete conversion.



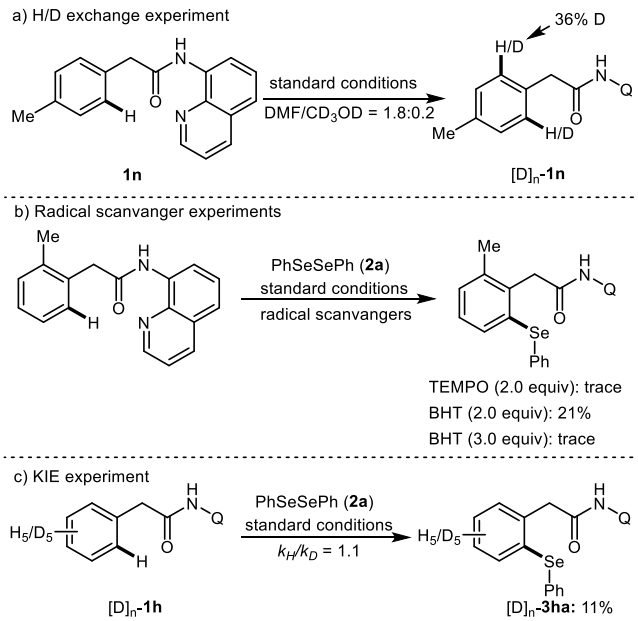
Scheme 5. Substrate scope of palladium-catalyzed selenylation with phenylselenenyl chlorides.

To further demonstrate the practicality of this palladium-catalyzed C−H selenylation, a gram-scale reaction with 5.0 mmol of **1a** and **2a** was carried out, and the selenylated product **3aa** was delivered in a slightly lower isolated yield of 85%. In addition, the 8-aminoquinoline could be easily removed in the presence of H_2SO_4 in 1,4-dioxane at 105°C under argon, to provide the corresponding *ortho*-selenylated 2-arylacetic acids (**5a**-**5d**) in excellent yields. Notably, the 8-aminoquinoline was also recovered in over 80% yield. Furthermore, the thus obtained *ortho*-selenylated 2-arylacetic acid was treated with TFA at room temperature to give the biologically relevant dibenzoselenepinone moiety **6** in 74% yield through an intramolecular cyclization process. Finally, the selenylated product **3aa** could be selectively oxidized to selenone **7** in the presence of hydrogen peroxide in 78% yield.



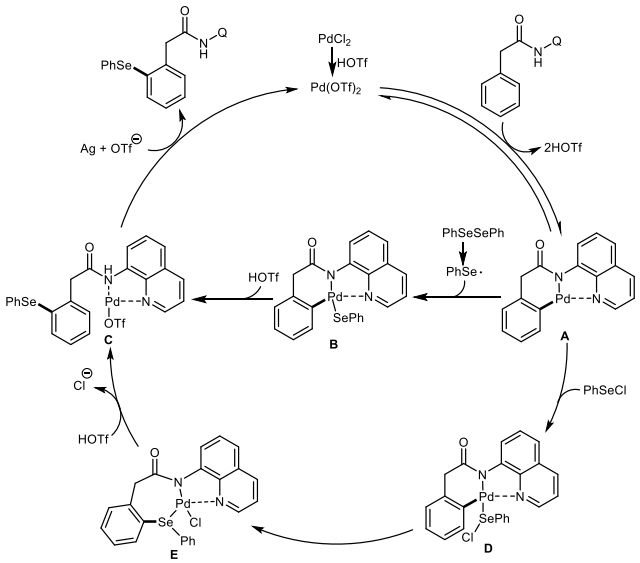
Scheme 6. Diversification of the selenylated products.

Considering the high catalytic activity of the robust palladium catalyst, we conducted a set of control experiments to gain insights into the reaction mechanism. First, when the selenylation was conducted with CD_3OD as cosolvent under the standard reaction condition, around 36% deuterium was incorporated at the *ortho*-position of recovered starting material, thus indicating that the C−H bond cleavage is reversible. (**Scheme 7a**) Furthermore, the addition of typical radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) significantly suppressed the catalyst's efficacy and did not produce the desired product (**Scheme 7b**), suggesting that a single electron transfer (SET)- type mechanism likely being in force here. A kinetic isotope effect (KIE) of 1.1 through intermolecular competitive C−H selenylation of **1h** and isotopically labeled [D_5]-**1h** with **2a** implying that the C−H cleavage might not be involved in the rate-determining step (**Scheme 7c**).



Scheme 7. Mechanistic Studies

On the basis of experimental evidence discussed above and previous literature reports [12],[16] we proposed a plausible mechanism outlined in **Scheme 8**. Initially, the activated palladium catalyst coordinated to the *N*, *N* bidentate ligand to give a six membered cyclopalladated intermediate **A** through a reversible C−H bond activation process. Subsequent oxidation by a selenyl radical generated palladium (III) **B**, followed by reductive elimination to afford the *ortho*-selenylated product. Besides, the intermediate **A** could also coordinate with PhSeCl, followed by nucleophilic displacement of the Cl by the Pd−C(aryl) bond cleavage to give species **E.** Finally, reductive elimination released the coupling product with the regeneration of the active palladium catalyst in the presence of silver oxidant.



Scheme 8. Proposed catalytic cycle.

Conclusion

In conclusion, we have developed a novel and facile method of palladium-catalyzed distal C−H selenylations of 2-aryl acetic acid derivatives directed by a removable 8-aminoquinolines bidentate auxiliary. This protocol demonstrates scalable, excellent regioselectivity and good functional group tolerance, and delivered unsymmetrical diaryl selenides in good yields (up to 94%). Considering the multi-bioactivity of the diaryl diselenide and dibenzoselenepinone derivatives, further applications of this strategy for the preparation or diversification of complex molecules and pharmaceuticals are currently in progress in our laboratory

Experimental Section

A suspension of substituted *N*-(quinolin-8-yl)-2-(*o*-tolyl)-acetamide (**1**) (1.0 equiv, 0.20 mmol), 1,2-diphenyldiselane (**2**) (1.2 equiv, 0.24 mmol) or phenylselenenyl chloride (**4a**) (2.0 equiv, 0.4 mmol), $PdCl_2$ (4 mg, 10 mol %), Ag_2CO_3 (110 mg, 0.4 mmol), AgOTf (10 mg, 20 mol %) and HOTf (5 μL) in DMF (2.0 mL) or mixture solvent (DMF:HFIP = 3:1) was stirred under argon at 100 ℃ for 24 h. At ambient temperature, the reaction mixture was quench with H_2O (10 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvents in *vacuo*, the crude product was purified by column chromatography on silica gel (Petroleum ether/DCM: 2/1→1/1) to yield product **3**.

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FULL PAPER

Palladium-Catalyzed Distal C–H Selenylation of 2-Aryl Acetamides with Diselenides and Selenyl Chlorides

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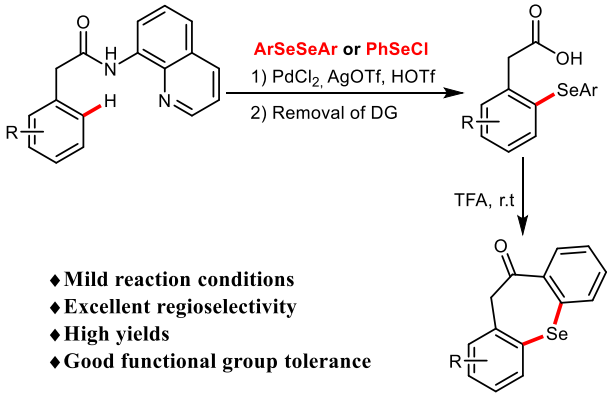

- **Mild reaction conditions**
- **Excellent regioselectivity**
- **High yields**
- **Good functional group tolerance**