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Ruthenium-Catalyzed C−H Selenylations of Benzamides

Wenbo Ma,*[a] Zhengyun Weng,[a] Xinyue Fang,[a] Linghui Gu,[a] Yupin Song,[b] Lutz Ackermann*[c]

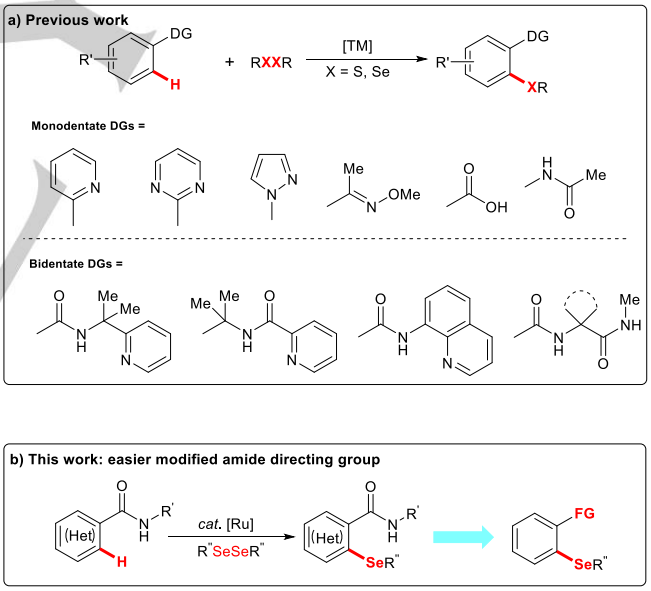
Abstract: A convenient and effective protocol for the ruthenium-catalyzed C−H selenylations of benzamides was achieved under mild reaction conditions. The robust ruthenium catalyst tolerated a wide range of functional groups and set the stage for the preparation for diversely decorated benzamides. The amide directing group could be transferred to carboxylic acid, aldehyde and tetrazoles. Preliminary mechanistic study indicated a base-assisted electrophilic-type substitution C−H activation event.

Introduction

Diaryl selenide scaffolds are important structural motifs that have attracted increasing interest as functional organic materials, drug candidates and biologically active compounds.[1] Furthermore, they also play an important role in fluorescent probes as well as coordination chemistry, and they are widely used in organic synthesis.[2] Therefore, the preparation of diaryl selenide scaffolds has attracted considerable interest in the past decades.[3] The traditional methods for their syntheses largely involved the use of electron-rich arenes or prefunctionalized aryl (pseudo)halides as the coupling partners.[4] However, most of these approaches usually required multi-step protocols under harsh reaction conditions, thus resulting in low overall yields with various functional groups being incompatible. In contrast, the transition-metal-catalyzed C−Se formation via direct C−H activation represents a powerful and reliable alternative due to its remarkable mild reaction conditions, broad substrate scope, step-economic fashion and environmental sustainability.[5]

In this context, transition metals such as palladium, rhodium, ruthenium, silver, nickel, cobalt and copper complex were explored as catalysts for the chelation-assisted C−H selenylations during the past decade.[6] Thereby, the chelation assistance regime could recently be expanded to pyrimidine,[7] pyrazole,[8] pyridine,[9] oxime,[10] carboxylate acid,[11] anilide[12] and bidentate auxiliaries.[13] These protocols provided efficient and convenient routes for the direct assembly of diaryl selenide scaffolds. (Scheme 1a) However, the desired mono-selenylated products were often accompanied by the difficult to remove diselenylated products,[14] with in some cases due to the poor regio-selectivity. Furthermore, many of these directing groups are difficult to remove or modify, thus limiting the further transformation in the complex compound synthesis. As a consequence, there is a continued strong demand for easily accessible and transformable directing group-assisted C−H. Amides are ubiquitous structural motifs which were widely found in numerous biologically active natural products and pharmaceutical compounds.[15] In addition, the amide group likewise represents a versatile functional group that can be easily converted into various useful functional groups, including tetrazoles, carboxylic acids or aldehydes.[16]

In continuation of our interest on the research of C−S and C−Se bond forming reactions using the ruthenium catalyzed C-H functionalization strategy,[12],[17] and considering the synthetic utility of amides, we herein report on the unprecedented ruthenium-catalyzed highly selective mono-selenylation of benzamides. (Scheme 1b)



Scheme 1. Transition-metal-catalyzed C−H Chalcogenations of Arenes

Results and Discussion

We commenced our studies by examining the reaction parameters for the envisioned direct C−H selenylation of benzamide (**1a**) with 1,2-diphenyldiselane (**2a**). Preliminary experiments indicated $[RuCl_2(p\text{-cymene})]_2$ as the appropriate catalyst, along with catalytic amount of $AgSbF_6$ and AgOTf as the additives at 100 °C for 20 h (Table 1, entry 1). Further optimization

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of the solvent indicated that TFE was the ideal reaction medium for this reaction, giving the desired product **3aa** in 88% yield (Table 1, Entry 8). Among various representative oxidants, including silver salts, copper acetate, $K_2S_2O_8$ and $PhI(OAc)_2$, AgOAc was found to be best, while the other oxidants led to inferior results. Remarkably, the absence of the $AgSbF_6$ and AgOTf additives resulted in unsatisfactory yields (Entries 19 and 20). A control experiment verified that the transformation did not occur in the absence of the ruthenium catalyst (Entry 21).

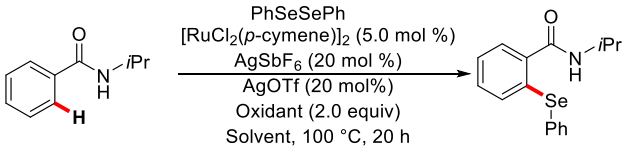
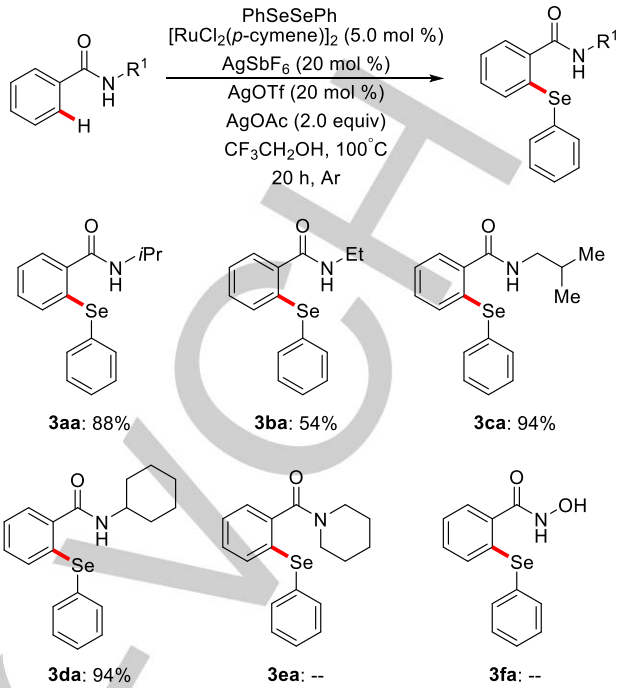


Table 1. Optimization of Ruthenium-Catalyzed C−H Selenylation[a]

Entry	Solvent	Oxidant	Yield[b]
1	toluene	AgOAc	23
2	DMF	AgOAc	trace
3	DMSO	AgOAc	17
4	1,4-Dioxane	AgOAc	21
5	DCE	AgOAc	trace
6	CH_3CN	AgOAc	trace
7	*t*-AmOH	AgOAc	trace
8	CF_3CH_2OH	AgOAc	88
9	CF_3CH_2OH	Ag_2CO_3	<10
10	CF_3CH_2OH	$AgNO_3$	<10
11	CF_3CH_2OH	Ag_2O	trace
12	CF_3CH_2OH	Ag_3PO_4	trace
13	CF_3CH_2OH	$AgOCCF_3$	17
14	CF_3CH_2OH	AgOPiv	37
15	CF_3CH_2OH	$Cu(OAc)_2$	--
16	CF_3CH_2OH	$PhI(OAc)_2$	--
17	CF_3CH_2OH	$K_2S_2O_8$	--
18	CF_3CH_2OH	AgOAc	20[c]
19	CF_3CH_2OH	AgOAc	20[d]
20	CF_3CH_2OH	AgOAc	59[e]
21	CF_3CH_2OH	AgOAc	--[f]

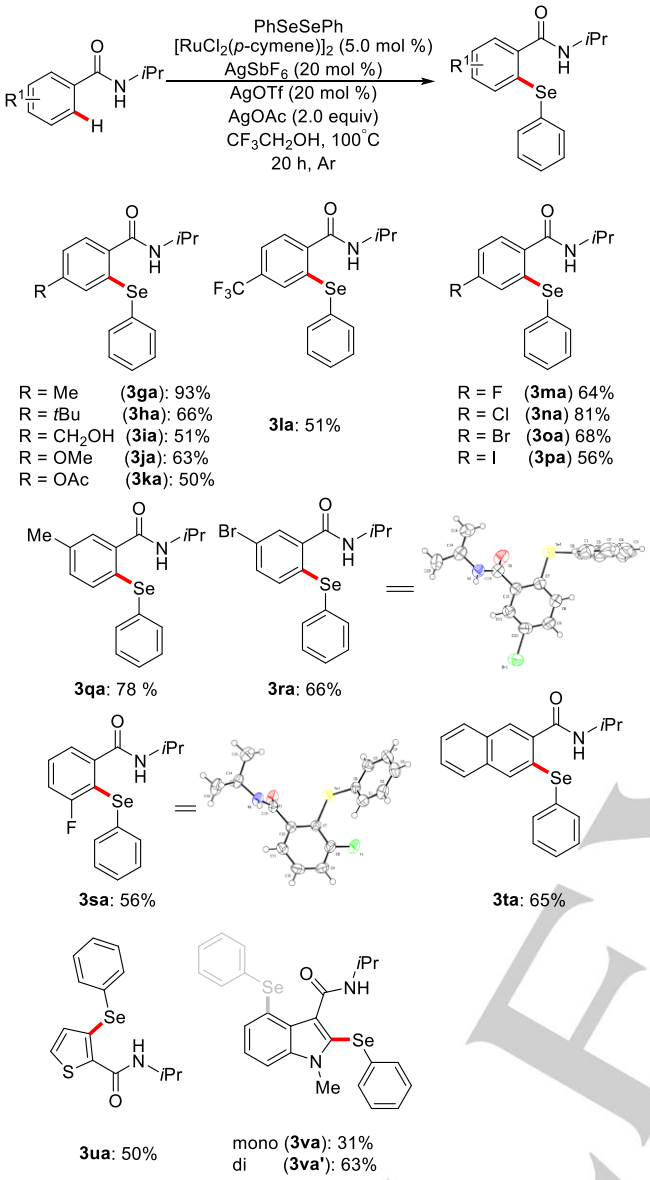
[a] Reaction conditions: amide **1a** (0.25 mmol), **2a** (0.50 mmol), Ruthenium catalyst (5 % mol), $AgSbF_6$ (20 % mol), AgOTf (20 mmol %), AgOAc (2.0 equiv), CF_3CH_2OH (2 mL). 100 °C under Ar for 20 h. [b] Isolated yield. [c]120 °C. [d] Without $AgSbF_6$. [e] Without AgOTf. [f] Without Ruthenium Catalyst.

Subsequently, we studied the effect exerted by the amide's *N*-substituent on the C−H selenylations (Scheme 2). Interestingly, the more sterically-hindered substituents, such as isopropyl-, (**1a**) 2-methylpropyl- (**1c**) and cyclohexyl- (**1d**), proved more effective as compared to the less congested analogue **1b**. *N*-hydroxybenzamide **1f** and tertiary amide **1e** failed to enable this reaction, thus indicated the key importance of the acidic N−H moiety for this transformation (Scheme 2).



Scheme 2. Effect Exerted by the N-substituent

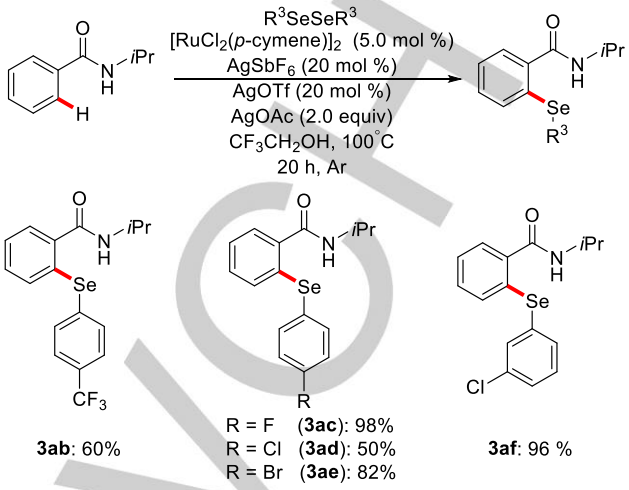
With the optimized catalytic system in hand, the reaction scope with respect to benzamide **1** was investigated by using 1,2-diphenyldiselane (**2a**) (Scheme 3). To our delight, the robust ruthenium catalyst was widely applicable, and, thus, proved to be tolerant of various important functional groups. Electron-rich benzamides, such as 4-methyl, 4-*tert*-butyl-, 4-hydroxymethyl-, 4-acetoxyl and 4-methoxylbenzamide efficiently reacted with 1,2-diphenyldiselane to give the selectively mono-selenylated benzamide products **3ga**-**3ka** in good to excellent yields. Electro-deficient groups, featuring halide functional groups, were well tolerated under the standard reaction conditions, providing the desired products **3la-3pa** with excellent levels of mono-selectivity. The unsymmetrical aromatic amides were also tested, and the C−H selenylations was largely influenced by steric interactions, giving the *mono*-selenylated products with excellent *regio*-selectivity. (**3qa** and **3ra**) On the contrary, *meta*-fluoro-substituted benzamide exclusively led to the selenylation at the C-2 position. The products **3ra** (CCDC 1853349) and **3sa** (CCDC 1853355) structure were further confirmed through single-crystal X-ray diffraction (XRD) analysis. As anticipated, the *N*-isopropyl-2-naphthamide (**1t**) reacted with 1,2-diphenyldiselane smoothly, furnishing the corresponding product **3ta** in 65% yield. It is important to note that the optimized ruthenium(II) catalyst was not restricted to the aryl-substituted amides. Indeed, the conversion of heterocyclic substrates, such as thiophene and indole derivatives, likewise proceeded efficiently, furnishing the *mono* and *di*-selenylated products in good yields. (**3ua** and **3va**)



Scheme 3. Scope of the C−H Selenylations of Benzamides **1**

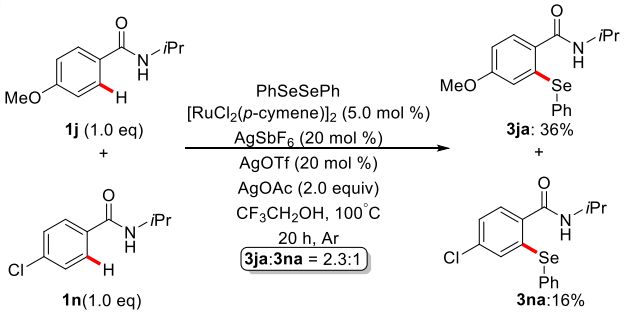
Subsequently, the substrate scope of C−H selenylation was further examined with differently substituted diaryldiselane. Gratifyingly, a diverse set of electron-withdrawing-substituted diaryl-diselanes smoothly reacted with benzamides, affording the desired product up to 98% yields (**3ac**). Particularly, the halide functional groups should prove invaluable for further manipulations by coupling reactions for the preparation of structurally-complex molecules. In contrast, the diaryl-diselane bearing electro-donating groups such as 4-methyl and 4-methoxyl were not compatible with the ruthenium catalysis regime.

To further demonstrate the synthetic utility of this robust ruthenium-catalyzed C−H selenylations, a gram-scale reaction was performed on 5 mmol scale between *N*-isopropylbenzamide (**1a**) and 1,2-diphenyldiselane (**2a**), delivering the desired selenylated product **3aa** in 75% isolated yield.

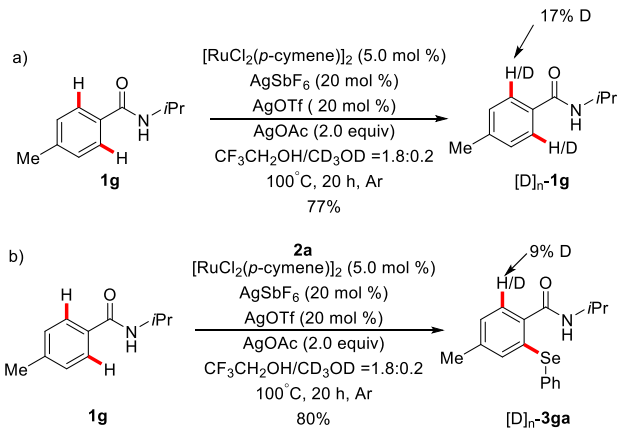


Scheme 4. C−H Selenylation with Diaryldiselane

In order to rationalize the mechanism of the amide-assisted ruthenium-catalyzed C−H selenylations, we performed intermolecular competition experiments between differently substituted amides **1**. The electron-rich arene was significantly more reactive than the electron-deficient one, indicating that the C–H bond activation involved a base-assisted intramolecular electrophilic-type substitution (BIES) event.[18] (Scheme 5) Subsequently, H/D exchange experiments were carried out with CD_3OD as the co-solvent. (Scheme 6) The results of H/D scrambling on the *ortho* positions of the aryl ring of the reisolated starting materials as well as the selenylated product indicated that the C–H bond activation step is reversible under the optimized reaction conditions

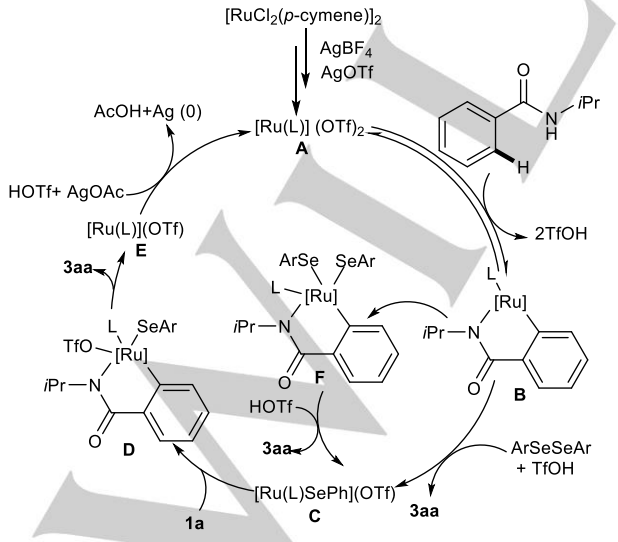


Scheme 5. Intermolecular Competition between Different Substituted Benzamide 1



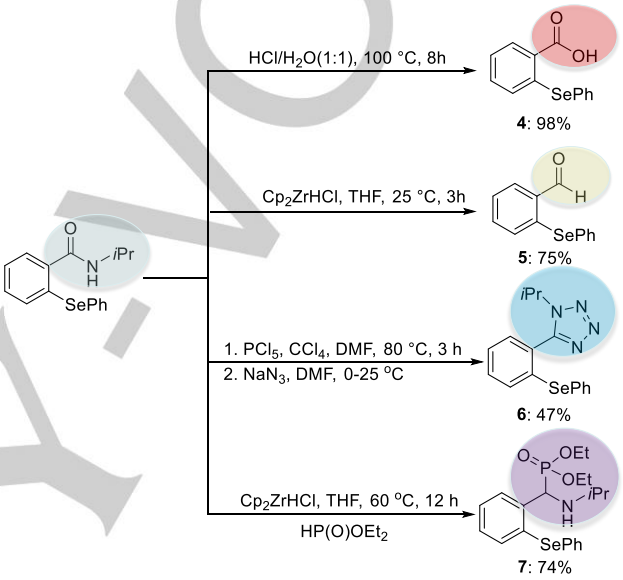
Scheme 6. H/D Exchange Experiment

Based on the mechanistic studies and previous literature,[9c, 10a,19] we proposed a plausible catalytic cycle for the Ru(II)-catalyzed C-H selenylation process in Scheme 7. The catalytic cycle is likely initiated by the removal of chloride from $[RuCl_2(p\text{-cymene})]_2$ in presence of $AgBF_4$ and AgOTf to provide an active cationic Ru(II) species **A**, followed by a reversible C–H bond activation of benzamide **1a**. The thus formed five-membered cycloruthenated compound **B** reacted with diarydiselane to afford the desired product **3aa** and realsed the intermediate **C.** Alternatively, the intermediated **B** react with diaryldiselane to give a Ru(IV) species **F** though a oxidative addition pathway followed by reductive elimination to afford the **3aa** and Ruthenium(II) species **C**. Subsequently, the intermediate **C** could participate in a second C–H activation process to form cycleruthenated species **D** again followed by reductive elimination to generate the target product **3aa** and ruthenium(I) **E,** which could be converted to active catalytic species Ru(II) in the presence of AgOAc and completed the cycle.



Scheme 7. Propost mechanism

Finally, we exploited the unique utility of the amide directing group for the late-stage derivatization of the thus-obtained selenylated product **3aa**. (Scheme 8). A variety of bio-relevant heterocycles and very useful functional groups such as carboxylate acid **4**, aldehyde **5**, tetrazole **6** and phosphite **7** [20] could be accessed in a step-economical fashion in moderate to excellent isolated yield under mild reaction conditions. Notably, the *ortho*-selenylated tetrazoles and aldehydes had thus far proven elusive structural motifs, bearing great potential for their future medicinal chemistry evaluation



Scheme 8. Modification of Products **3aa**

Conclusions

In conclusion, we have developed the unprecedentes ruthenium(II)-catalyzed C−H selenylations of benzamides with 1,2-diaryldiselanes though facile BIES C−H activation. A wide range of differently-substituted arylamides was efficiently converted under a robust ruthenium catalysis manifold, providing the *mono*-selenylated products in good to excellent yields. The amide group could be transformed into synthetcially useful aldehyde, carboxylate acid, tetrazole and phosphite derivatives in a step-economical fashion under mild reaction conditions. Detailed studies on the reaction mechanism and further development of direct selenylations are currently being pursued in our laboratory, and will be reported in due course.

Experimental Section

Ruthenium-Catalyzed C–H Selenylation with Substituted *N*-isopropylbenzamide: A suspension of *N*-isopropylbenzamide (**1a**) (40.7 mg, 0.25 mmol), 1,2-diphenyldiselane (**2a**) (156 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 5.0 mol %), $AgSbF_6$ (17.2 mg, 20 mol %), AgOTf (13

mg, 20 mol%) and AgOAc (83 mg 2.0 equiv) in CF_3CH_2OH (2.0 mL) was stirred under argon at 100 °C 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 (Hexane/DCE = 2:1, Hexane/EtOAc: 10/1) to yield **3aa** (70 mg, 88 %) as a white solid.

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Keywords: Ruthenium catalyst• C-H activation• Selenylation• Benzamide• Late-stage derivatization

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C−H Functionalizations:

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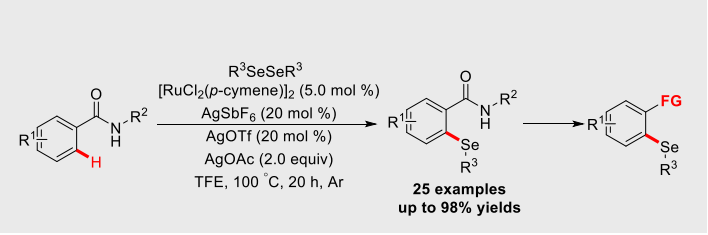
Ruthenium-Catalyzed C−H Selenylations of Benzamides



Ruthenium Catalyzed C-H Selenylations of Benzamide: The easily transformable amide directing groups assisted *ortho*-C-H selenylations of arenes with 1,2-diphenyldiselane by robust ruthenium catalyst were achieved with ample scope under mild reaction conditions. This general approach offered a straightforward access to various functional group substituted diarylselenide containing compounds. The plausible mechanism was proposed after the detailed mechanistic studies.