Organic LETTERS

Letter

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Rh(III)-Catalyzed Selenylation of Arenes with Selenenyl Chlorides/Diselenides via C−H Activation

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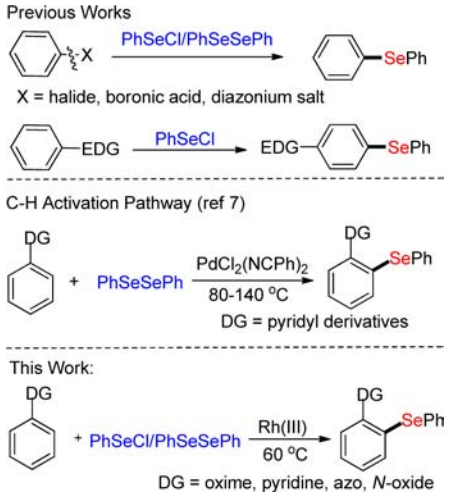
Supporting Information

ABSTRACT: Rh(III)-catalyzed, chelation-assisted C−H activation and selenylation of arenes has been achieved. Arenes bearing oxime, azo, pyridyl, and *N*-oxide chelating groups are viable substrates, and electrophilic selenyl chlorides and diselenides are used as selenylating reagents. The catalytic system is highly efficient under mild conditions over a broad range of substrates with excellent functional group tolerance.

The C−Se bond represents an important linkage in organic compounds[1] and is widely found in drug candidates, biological molecules, and even functional organic materials.[2] Thus, synthesis of compounds with a C−Se linkage has attracted increasing attention for many years. Over the past decades, a large number of synthetic methods have been developed to construct various organoselenium compounds with potential biological activities. These methods are mainly limited to the coupling of prefunctionalized aryl substrates (aryl halides,[3] aryl boronic acids,[4] or aryl diazonium salts[5]) or electron-rich aryl compounds.[6] Therefore, to overcome these limitations, introduction of a selenyl group via direct functionalization of C−H bonds would constitute a more straightforward and attractive alternative. Recently, while our work was in progress, Nishihara and co-workers reported the first Pd-catalyzed direct activation and selenylation of inert C−H bonds of arenes using diselenides (Scheme 1).[7] However, their catalytic systems are only efficient for arenes bearing pyridyl and derivatives as directing groups with the reaction temperature being up to 140 °C, which may limit the synthetic applications of the method.

Scheme 1. Representative C−Se Coupling Reactions



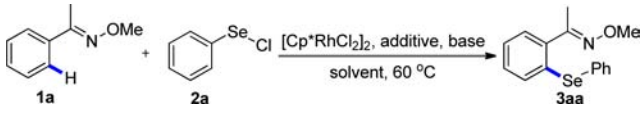
On the other hand, transition metals,[8] especially Rh(III) complexes,[9] have been recently extensively employed as useful and efficient catalysts for C−H bond activation and subsequent construction of diversified carbon−heteroatom (N, S, O, and halogen) bonds. Thus, rhodium(III) catalysts are known to effectively complement other transition metals in the functionalization of C−H bonds in terms of activity, selectivity, substrate scope, and functional-group tolerance.[10] Although rhodium(III)-catalyzed efficient C−H activation−sulfenylation has been realized by Y. Li and co-workers,[11] to the best of our knowledge, there is still no report on the related C−Se bond formation via a Rh(III)-catalyzed C−H activation process. This transformation could be more challenging because the product may pose stronger inhibition. Having noted that Glorius and Yu independently reported Rh(III)-catalyzed amination of arenes using electrophilic *N*-chloroamine reagents,[12] we reasoned that selenylation using electrophilic selenium sources might be realizable. We now report our findings on the efficient coupling of arenes with selenenyl chlorides/diselenides under relatively mild conditions.

We initiated our investigation with the optimization studies on the selenylation of oxime **1a** using the commercially available phenylselenenyl chloride **2a** catalyzed by 4 mol % of $[Cp^*RhCl_2]_2$ in the presence of $AgSbF_6$ (1.5 equiv) and CsOAc (1.2 equiv) in THF solvent, and the desired product **3aa** was obtained in 87% yield (Table 1, entry 1). The electrophilicity of the silver salt seems to play an important role because essentially no product formation was observed when AgOAc was used (entry 2). The superstoichiometric amount of $AgSbF_6$ also seems necessary, and a decrease of the amount to 0.16 equiv led to essentially no reaction (entry 3). Screening of the solvents showed THF to be optimal, while a lower isolated yield or simply no reaction was obtained when the

Received: November 6, 2014
Published: December 17, 2014

dx.doi.org/10.1021/ol503231p | *Org. Lett.* 2015, 17, 58−61

Table 1. Optimization of the Reaction Conditions[a]



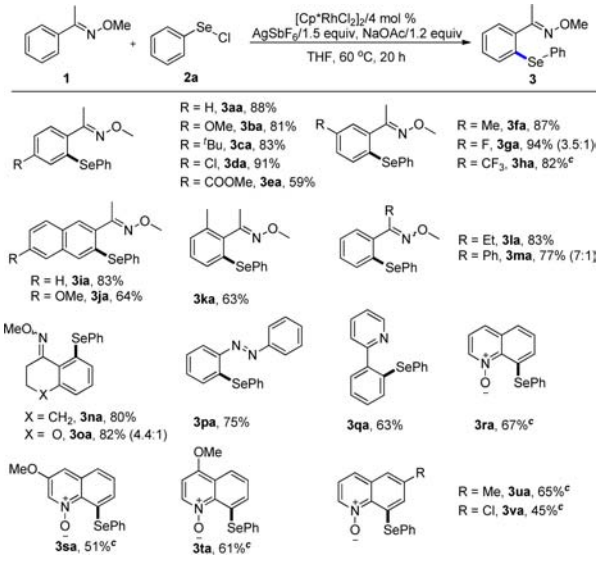
entry	additive/equiv	base/equiv	solvent	yield[b]
1	$AgSbF_6$/1.5	CsOAc/1.2	THF	87%
2	AgOAc/1.5	CsOAc/1.2	THF	trace
3	$AgSbF_6$/0.16	CsOAc/1.2	THF	trace
4	$AgSbF_6$/1.5	CsOAc/1.2	DCM	83%
5	$AgSbF_6$/1.5	CsOAc/1.2	DCE	75%
6	$AgSbF_6$/1.5	CsOAc/1.2	MeCN	trace
7	$AgSbF_6$/1.5	CsOAc/1.2	dioxane	trace
8	$AgSbF_6$/1.5	NaOAc/1.2	THF	88%[c]
9	$AgSbF_6$/1.5	Na_2CO_3/1.2	THF	72%
10	$AgSbF_6$/1.5	NaOAc/1.2	THF	30%[d]
11	–	NaOAc/1.2	THF	n.d.
12	$AgSbF_6$/1.5	–	THF	n.d.
13	$AgSbF_6$/1.5	NaOAc/1.2	THF	n.d.[e]
14	$AgSbF_6$/1.5	NaOAc/1.2	THF	84%[f]
15	$AgSbF_6$/1.5	NaOAc/1.2	THF	23%[g]
16	$AgSbF_6$/1.5	CsOAc/1.2	THF	61%[h]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mol), $[Cp^*RhCl_2]_2$ (4 mol %), silver additive, base, solvent (3 mL), 60 °C, 20 h, sealed tube under N_2. [b]GC yield. [c]Isolated yield after column chromatography. [d]30 °C. [e]No $[Cp^*RhCl_2]_2$ was used. [f]Diphenyl diselenide (0.24 mmol) was used as the selenylating reagent. [g]Phenylselenyl bromide (0.24 mmol) was used as the selenylating reagent. [h][Ru(*p*-cymene)-Cl_2] (4 mol %) was used as the catalyst.

reaction was performed in other solvents such as DCM, DCE, MeCN, and 1,4-dioxane (entries 4–7). Screening of the base indicated that NaOAc is the best choice (entries 8–9). Lowering the reaction temperature to 30 °C gave rise to a much lower yield (entry 10). Control experiments also revealed that no desired product was detected when the catalyst, additive, or base was omitted (entries 11–13). Furthermore, diphenyl diselenide exhibited similar efficiency under the same conditions, affording product **3aa** in 84% yield (entry 14). However, a reaction using phenylselenenyl bromide afforded **3aa** in only 23% GC yield (entry 15). In addition, switching the rhodium catalysts to [Ru(*p*-cymene)Cl_2]$_2$ under otherwise the same conditions afforded product **3aa** in only 61% GC yield (entry 16), indicative of the superiority of Rh(III) catalysis for this reaction. Attempts to extend the reaction to a larger scale using 1.0 mmol of **1a** under the optimal conditions met with difficulty and only a 37% yield was isolated.

Having identified the optimal conditions, the scope and limitations of this system were explored next (Scheme 2). When *O*-Me oxime was used as a directing group for the coupling with selenenyl chloride **2a**, introduction of various substitutions into the *para*-position of the phenyl ring was well tolerated, and the corresponding products were isolated in 59–91% yields with excellent *ortho* selectivity. While slightly electron-deficient (**3da**) and -rich arenes (**3ba**, **3ca**) were selenylated under the standard conditions in good yields, a relatively lower yield (59%) was obtained when a stronger electron-withdrawing group was introduced into the *para*-position of the backbone (**3ea**, CO_2Me). To further scrutinize the regioselectivity, the coupling reactions of *meta*-Me and -CF_3 substituted oximes were performed and the C–H functionalization occurred exclusively at the less hindered *ortho* position in 87% (**3fa**) and 82% (**3ha**) yields, respectively. Successful selenylation of the naphthalene

Scheme 2. Scope of Arene Substrates[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (1.5 equiv), NaOAc (1.2 equiv), THF (3 mL), 60 °C, 20 h, sealed tube under N_2. [b] Isolated yield after column chromatography. [c] 80 °C.

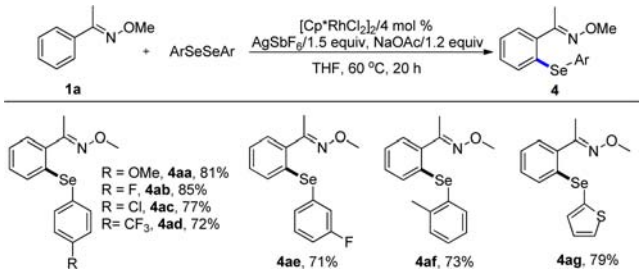
scaffolds was also accomplished to afford products in 83% and 64% yields (**3ia**, **3ja**). In contrast, the coupling of the *meta*-fluoro-substituted oxime produced two inseparable regioisomeric products in a ratio of 3.5:1 on the basis of ^1H NMR analysis. Introduction of an *ortho* substituent is well-tolerated as in the isolation of product **3ka** in 63% yield, which indicates tolerance of the steric bulkiness of the *o*-Me group. The reaction also tolerated various substitutions at the imine moiety (**3la**–**3oa**). Moreover the selenylation reaction is not restricted to oxime substrates, and arenes bearing other directing groups such as azo and pyridyl also underwent smooth couplings, albeit with slightly lower yields (**3pa** and **3qa**). To our delight, quinoline *N*-oxides also gave smooth coupling (80 °C) at the C-8 position in moderate yields (**3ra**–**3va**). We noted that C–H activation at the C-8 position of quinoline *N*-oxides is less common than at the C-2 position, and only a few examples have been recently reported.[13]

To demonstrate the scope of diselenide substrates, different readily synthesized diselenides were applied as substrates to couple with oxime **1a**. Thus, symmetric diselenides with electron-donating and -withdrawing substituents in the arene ring all reacted smoothly with good efficiency (**4aa**–**4ag**, Scheme 3).

Several experiments have been performed to probe the reaction mechanism. Two competition experiments were used to determine the electronic preference of the reaction. When an equimolar mixture of 4-Cl oxime (**1d**) and 4-^{t}Bu oxime (**1c**) was allowed to compete under the standard conditions in the coupling with PhSeCl or PhSeSePh, the electron-rich oxime exhibited higher reactivity in both cases with ratios being 6:1 and 9:1, respectively (Scheme 4). These experimental data seem to agree with an electrophilic selenylation pathway. To probe the C–H activation process, the kinetic isotope effect (KIE) has been measured and the initial rate kinetic isotope studies revealed a KIE value of 2.3 (Scheme 4), which indicated that the C–H cleavage was probably involved in the rate-limiting step. Moreover, when cyclometalated Rh(III) complex **5** was

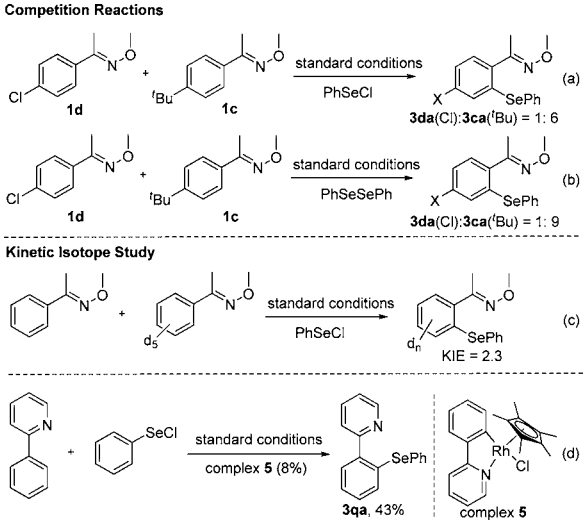
dx.doi.org/10.1021/ol503231p | *Org. Lett.* 2015, 17, 58–61

Scheme 3. Scope of Diselenide Substrates[a]



[a]Reaction conditions: **1a** (0.2 mmol), diaryl diselenide (0.24 mol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (1.5 equiv), NaOAc (1.2 equiv), THF (3 mL), 60 °C, 20 h, sealed tube under N_2. [b] Isolated yield after chromatography.

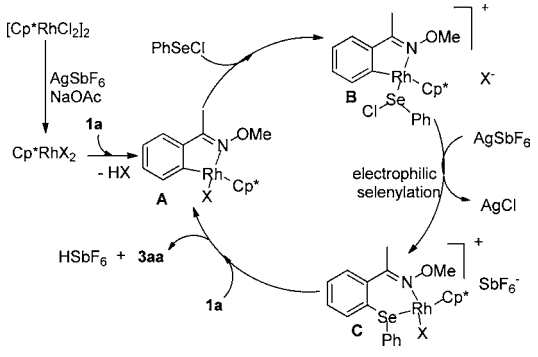
Scheme 4. Mechanistic Studies



designated as a catalyst precursor, the coupling of 2-phenylpyridine and phenylselenenyl chloride afforded product **3qa** in 43% yield, indicating the relevancy of C−H activation.

To account for the transformation, a proposed catalytic cycle for the C−Se coupling using PhSeCl is given in Scheme 5 on the basis of the above results and the previous literature.[12,13] C−H activation of the arene substrate gives a rhodacyclic intermediate **A**. Coordination of the selenium is followed by nucleophilic displacement of the Cl by the Rh−C(aryl) bond (electrophilic selenylation), and this chloride abstraction is likely assisted by the silver salt which may play a dual role in both substrate

Scheme 5. Proposed Reaction Mechanism



activation and catalyst activation.[13,14] Coordination of oxime **1a** to **C** and subsequent C−H activation release the coupling product with the regeneration of the cyclometalated rhodium complex **A**. However, at the current stage we cannot exclude the Rh(III)−Rh(V) pathway in which the Se−Cl bond oxidatively adds to a Rh(III) species.[15]

In summary, we have achieved the first Rh(III)-catalyzed direct selenylation of arenes under chelation assistance with readily available electrophilic selenenyl chlorides or diselenides as selenylating reagents. The reaction occurred via a C−H activation pathway, and different arenes bearing oxime, azo, pyridyl, and *N*-oxide directing groups are viable substrates. The catalytic reactions are highly efficient under mild conditions over a broad range of substrates with excellent functional group tolerance. This reaction provides new entries to the synthesis of diaryl selenoethers. Efforts to expand the utility of this coupling and to design other related catalytic systems are ongoing in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, and copies of NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Dalian Institute of Chemical Physics, Chinese Academy of Sciences, and the NSFC (21272231 and 21472186) for financial support. X.L. conceived and designed the experiments.

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