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Cu-Catalyzed Radical Selenylation of Olefin: A Direct Access to Vinyl Selenides

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Abstract. A method for the synthesis of vinyl selenides via Cu-catalyzed three-component reactions of arylboronic acids, Se powder and diarylethylenes has been developed. The reaction proceeds via addition of in situ generated selenium-centered radical to carbon-carbon double bond. This method highlights the use of easily accessible Se powder as selenium source in the construction of vinyl selenides for the first time.

Keywords: Selenylation; Olefin; Vinyl Selenides; Radical; Se powder

Selenium-containing compounds are gaining increasing attention due to their numerous applications in candidate drugs and agrochemicals, materials science as well as catalysis.^[1] Among them, vinyl selenides^[2] serve as important synthetic intermediates for the synthesis of vinyl synthons,^[3] versatile ethylene derivatives^[4] and heteroclyclic compounds.^[5] Considering their great importance, the development of efficient methods for the preparation of vinyl selenides has aroused significant interest of chemists. One of the synthetic methods relies on a Wittig-type reaction with PhSeCl as the selenium source (Scheme 1a).^[6] Transition-metal-catalyzed or light-promoted addition of selenium compounds including RSeSeR.^[7] RSeH^[8] and RSeZnCl^[9] to alkynes have also emerged as effective methods for the preparation of vinyl selenides (Scheme 1b). Another classical method to access vinyl selenides involves cross-coupling reactions between vinyl halides (or boronic acids or borates) with RSeSeR^[10] (or KSeCN^[11]) (Scheme 1c). Recently, ji's group developed a rhodium-catalyzed selenylation of Ntosylacrylamides with RSeSeR as the selenium source through N-tosylamide-assisted activation of the alkenyl C(sp²)-H bond, providing a regioselective access to (Z)- β -alkenyl selenides (Scheme 1d).^[12] Despite these achievements, certain issues associated with existing methods including harsh reaction conditions, the need for noble



Scheme 1 Diverse synthetic routes to vinyl selenides.

metals, the poor accessibility of the starting materials and selenium sources, continue to fuel research into the development of facile and efficient approaches for the preparation of vinyl selenides.

Although Se powder as a selenium source is inexpensive, available and bench-stable, it is indeed beyond the scope of current state-of-the-art methodologies for the construction of vinyl selenides probably due to its chemical inertness. On the other hand. Se powder as a selenium source has been successfully applied in the preparation of diaryl selenides via transition-metal-catalyzed reactions.^[13] In addition to transition-metal-catalyzed chemistry, the in-situ generated aryl radical enables the efficient activation of Se powder towards the generation of aryl selenium radical, as demonstrated by our group recently.^[14] Inspired by this work, we envisaged the possibility of extending the above-described strategy to the preparation of vinyl selenides, using Se powder as a selenium source. Specifically, we hoped to exploit the radical addition of aryl selenium radical

intermediates derived from arylboronic acids and Se powder to alkenes in combination with transitionmetal catalysis to access a series of vinyl selenides.

Ph

Table 1. Optimization of reaction conditions^[a]

			[M], ligand	Se
PhB(OH) ₂ +	Se +	sol ⁱ	vent, atmosphere	
1a	2a			3a 3a
entry	catalyst	solvent	temp (°C)	yield (%)
1	CuCl	DMSO	120	41
2	CuI	DMSO	120	50
3	Cu ₂ O	DMSO	120	46
4	CuCl ₂	DMSO	120	66
5	CuBr ₂	DMSO	120	70
6	Cu(OAc) ₂	DMSO	120	42
7	CuO	DMSO	120	53
8	Cu(OTf) ₂	DMSO	120	59
9	-	DMSO	120	0
10	CuBr ₂	DMF	120	63
11	CuBr ₂	DMA	120	59
12	CuBr ₂	NMP	120	0
13	CuBr ₂	THF	120	0
14	CuBr ₂	C ₂ H ₅ OH	120	0
15	CuBr ₂	toluene	120	0
16 ^[b]	CuBr ₂	DMSO	120	82
$17^{[b]}$	CuBr ₂	DMSO	80	0
18 ^[b]	CuBr ₂	DMSO	150	73
19 ^[bc]	CuBr ₂	DMSO	120	87
20 ^[c]	CuBr ₂	DMSO	120	74
21 ^[bd]	CuBr ₂	DMSO	120	59
22 ^[bce]	CuBr ₂	DMSO	120	15

^aReaction conditions: 1a (0.8 mmol), Se powder (0.8 mmol), 2a (0.4 mmol), catalyst (0.04 mmol), solvent (2.0 mL), under air, 120 °C, 12 h, isolated yields. ^[b]tricyclohexylphonium tetrafluoroborate (0.04 mmol) was used as ligand (L1). [c]Under O2. [d]Under N2. e5 mol% of CuBr₂ was used.

To test our idea, our initial effort focused on screening reaction conditions by choosing 1,1diphenylethlene, Se powder and phenyl boric acid as model substrates (Table 1). Gratifyingly, it was found that the three-component reaction conducted in DMSO under air at 120 °C using CuCl as a catalyst afforded the desired product **3a** with 41% yield (entry 1). Systematical screening for catalysts demonstrated that the use of CuBr₂ was the best choice and afforded the desired product 3a in 70% yield (entry 5), while other Cu salts led to moderate yields (entries 2-4 and 6-8). In the absence of Cu catalysts, the transformation was shut down (entry 9). Next, by screening various solvents (entries 10-15), no better results and even no formation of 3a were observed. We then turned our attention to screening a series of ligands (Table S1, see the supporting information). To our delight, the use of tricyclohexylphonium tetrafluoroborate (L1) as a ligand resulted in a dramatic increase in the yield of the desired product

3a (entry 16). Either reducing or increasing reaction temperature led to no observable improvements (entries 17 and 18). The replacement of air with O_2 atmosphere led to an increased yield (entries 19 and 20). In contrast, a negative effect was observed when the reaction was conducted under N_2 (entry 21). Lowing the catalyst loading greatly reduced the reaction efficiency (entry 22). Therefore, we chose the conditions of entry 19 as the standard reaction conditions where the reaction was performed in DMSO at 120 °C under O_2 in the presence of a catalytic system containing CuBr₂ and L1.

Table 2. Scope of arylboronic acids^[a]



^[a]Reaction conditions: 1 (0.8 mmol), Se powder (0.8 mmol), 2a (0.4 mmol), CuBr₂ (0.04 mmol), DMSO (2.0 mL), L1 (0.04 mmol), under O2, 12 h, 120 °C, isolated yields.

With the standard reaction conditions in hand, we sought to investigate the substrate scope with respect to boronic acids (Table 2). Arylboronic acids bearing halogen (1b-1g) and strong electron-withdrawing groups (1h and 1i) were well tolerated. It was also observed that both bromine and iodine substituents offer a good opportunity for further elaboration of the products (3f and 3g). The substrates containing electron-rich substituents such as isopropyl (1j), methyl (1k-1m), methoxy (1n and 1o) and trimethylsilyl (1p) groups were also amenable to the reaction conditions, affording the corresponding products in 40-76% yields. Moreover, it turned out that the substituents at the *meta* (1d and 1m) and para positions (1e and 1k) of the benzene ring gave better yield than those at the ortho position (1c and 11) probably due to steric hindrance. Remarkably, the sterically hindered substrate 1q could be converted to corresponding product **3q** in an acceptable yield. The bearing a fused substrate ring (1s)was accommodated by the standard reaction conditions. Nevertheless, in the case of heterocyclic boronic acids (1t and 1u) or alkylboronic acids (1v), no reactions took place, which could be attributed to the coordination of Cu catalyst with heteroatom.





^[a]Reaction conditions: **1a** (0.8 mmol), Se powder (0.8 mmol), **2** (0.4 mmol), CuBr₂ (0.04 mmol), DMSO (2.0 mL), L1 (0.04 mmol), under O₂, 12 h, 120 °C, isolated yields. ^[b]The ratio of *E*-isomer and *Z*-isomer, determined by GC-MS. ^[c]The ratio of *E*-isomer and *Z*-isomer, determined by ¹HNMP.



We then tested the substrate scope with respect to 1,1-diarylethylenes (Table 3). The reaction was highly tolerant of most functional groups such as halogen (**2a-2f**, **2j** and **2k**), methyl (**2g-2j**) and methylthio (**2l**) under the standard reaction conditions. In the case of asymmetric 1,1-diarylethylenes, a mixture of *E*-isomers and *Z*-isomers was obtained

with a ratio of 1:1 in most cases. Interestingly, good stereoselectivity was observed for the synthesis of product **4**I. Unfortunately, the substrate with multiple strong electron-rich substituents failed to give the desired product **4q**. Surprisingly, the reaction of *N*-phenylmethacrylamide, Se and PhB(OH)₂ afforded the unexpected addition product **4p** rather than vinyl selenide under standard conditions (Scheme 2). After

Table 4. The Reaction of $ArB(OH)_2$, Se powder and maleimide ^[a]



^[a]Reaction conditions: **1** (0.8 mmol), Se powder (0.8 mmol), **5** (0.4 mmol), CuBr₂ (0.04 mmol), DMSO (2.0 mL), L1 (0.04 mmol), under O₂, 12 h, 120 °C, isolated yields.

preliminary screening of ligands (Table S2), the yield of $4\mathbf{r}$ could be increased to 40% by using tri-*m*-tolylphosphane as a ligand.



Scheme 3. Control experiments. Standard conditions: $CuBr_2$ (0.04 mmol), DMSO (2.0 mL), L1 (0.04 mmol), under O_2 , 12 h, 120 °C, isolated yields.

In addition to 1,1-diarylethylenes, the feasibility of maleimides as the substrates in this protocol was assessed (Table 4). *N*-phenyl-substituted maleimide reacted well with various arylboronic acids to deliver the desired products in 28-72% yields (**6a-6j**). Furthermore, *N*-methyl-substituted maleimide proved to be a viable substrate (**5k**). Unfortunately, further examination on substrate scope led to no better results.^[15]



Scheme 4 A plausible mechanism.

To elucidate the reaction mechanism, a series of control experiments were performed (Scheme 3). A mixture of PhB(OH)₂ and Se powder was subjected to the standard conditions, leading to the formation of diphenyl diselenide in 87% yield (Scheme 3a). The absence of CuBr2 resulted in no formation of diphenyl diselenide, demonstrating the importance of CuBr₂ for this transformation (Scheme 3b). The same result was observed by the addition of TEMPO into the reaction between $PhB(OH)_2$ and Se powder, supporting a radical process (Scheme 3c). The reaction between diphenyl diselenide and 1.1phenylethylene proceeded well to afford the desired product 3a under the standard conditions (Scheme 3d), even or in the absence of CuBr₂ or L1 (Scheme 3e). The addition of tempo completely suppressed the formation of 3a, implying that the transformation involved a radical process (Scheme 3f). Interestingly, with PhSeBr also successfully reacted 1.1phenylethylene to afford 3a under the standard conditions (Scheme 3g).

In line with the above experimental results, a plausible mechanism for selenylation of 1,1diarylethylenes was postulated (Scheme 4). The reaction starts with the formation of aryl radical species **A** from the arylboronic acid in the presence of Cu(II) catalyst. Next, the in-situ generated aryl radical **A** enables the efficient activation of Se powder towards the generation of aryl selenium radical **B**, followed by dimerization to form diphenyl diselenide in a reversible manner. The addition of aryl selenium radical **B** to diarylethylene produces carbon-centred radical intermediate **C**. The resulting intermediate **C** then undergoes single electron transfer (SET) with Cu(II) to afford intermediate **D** which is deprotonated to give the desired product (Path I). According to this mechanism, the relatively poor stability of intermediates **C** and **D** may be responsible for the reaction failing when using other alkenes such as styrene and cyclohexene. Alternatively, aryl selenium radical **B** reacts with CuBr₂ to generate ArSeBr which adds to **2a** to give intermediate **F**. The resulting intermediate **F** then undergoes HBr elimination to provide the desired product (Path II).

In conclusion, we developed a facile and convenient method for the synthesis of vinyl selenides through Cu-catalyzed three-component radical reactions of arylboronic acids, Se powder and diarylethylenes. In particular, this method highlights the use of Se powder as selenium source in the construction of vinyl selenides for the first time. Key to the success of this method was the generation of an aryl selenium radical intermediate. In addition, the method offers a strategy for activating of Se powder by in-situ generated radicals, further expanding the use of Se powder in the preparation of organic selenium compounds.

Experimental Section

A 25 mL Schlenk tube equipped with a stir bar and O_2 atmosphere was charged with phenylboronic acid (0.8 mmol), selenium (0.8 mmol), 1, 1-phenylethylene (0.4 mmol), tricyclohexylphonium tetrafluoroborate (L1) (0.04 mmol), CuBr₂ (0.04 mmol) and 2 mL DMSO. The tub was fitted with a rubber septum, then the septum was replaced by a Teflon screwcap. The reaction mixture was stirred at 120 °C for 12 h. After cooling down, the reaction mixture was diluted with 10 mL of ethyl ether, filtered through a pad of silica gel, followed by washing the pad of the silica gel with the same solvent (20 mL), concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel to provide the corresponding product.

Acknowledgements

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COMMUNICATION

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