OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

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Electrochemical Aminoselenation and Oxyselenation of Styrenes with Hydrogen Evolution

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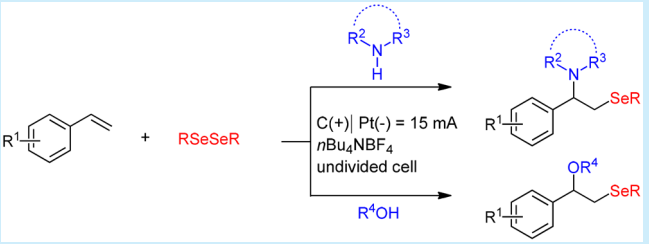
Supporting Information

ABSTRACT: The use of additive-free conditions is an ideal approach to prepare organoselenium reagents from readily available unsaturated substrates. Thus, we report the electro-induced aminoselenation and oxyselenation of styrenes without any acids or oxidants as additives. This transformation is compatible with various functional groups, which leads to vicinal difunctionalized organoselenium compounds. Our strategy improves the potential of this protocol for use in the pharmaceutical industry. Based upon the preliminary mechanism studies, we propose two possible pathways.



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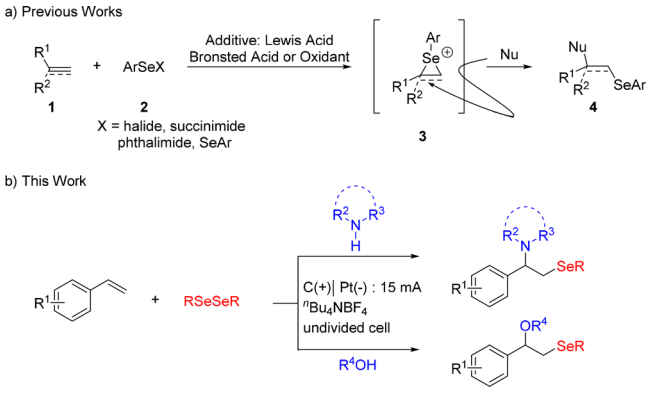
Organoselenium reagents have demonstrated important biological activities and versatile utilities in which phenylseleno compounds are widely used for organic synthesis.[1] The oxidative difunctionalization of easily available unsaturated substrates (alkenes, alkynes or allenes) is a useful method to build up this ubiquitous scaffold. Various Lewis acids,[2] Brønsted acids,[3] or oxidants[4] have been used for the introduction of arylseleno functionality into an unsaturated substrates **1** with a variety of arylseleno derivatives **2** (*N*-arylselenophthalimide, diaryl diselenide, arylselenohalide, or arylselenosuccinimide) as shown in Scheme 1a. Mechanistic studies showed that additives activated seleno reagent **2** to facilitate the formation of seleniranium ion **3** and subsequent addition with nucleophiles generated vicinal difunctional compounds **4**.

Scheme 1. Preparation of Organoselenium Reagents via Difunctionalization of Unsaturated Compounds



In particular, the aminoselenation and oxyselenation of olefins have attracted our attention. Despite major progress in the field, the use of excess of acids, oxidants, or transition-metal catalysts was required in previous reports in which the generation of undesirable and toxic byproducts was unavoidable. The emerging electrosynthesis has been recognized as an effective alternative for oxidants or reductants and minimized byproduct formation.[5] Inspired by the recent development of electrochemical alkene difunctionalization[6] pioneered by the Lin group, we launched electrochemical oxidative amino- and oxyselenation projects (Scheme 1b) to avoid extra additives which turned out to be a more environmentally benign and economical approach.

At the outset of our studies, we explored the aminoselenation of styrene (**1a**) with benzotriazole (**5a**) and diphenyl diselenide (**2a**) under different reaction parameters. After considerable efforts, optimal yield of product **6a** was obtained in 80% yield under constant current (15 mA) for 4 h in the presence of $^{n}Bu_4NBF_4$ and CH_3CN/1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) = 8:2 as the cosolvent (Table 1, entry 1). HFIP could be used to stabilized radicals. On the contrary, the yield was slightly diminished by using CH_3CN only (entry 2). Among a variety of supporting electrolytes, $^{n}Bu_4NClO_4$ and $^{n}Bu_4NPF_6$ demonstrated lower efficiency compared to $^{n}Bu_4NBF_4$ (33−35% yield, entries 3 and 4). In

Received: December 20, 2018

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DOI: 10.1021/acs.orglett.8b03274
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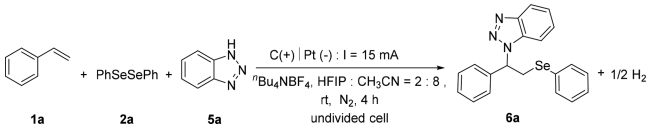
Table 1. Optimization Study for the Electrochemical Aminoselenation of Styrene[a]



entry	variation from the standard reaction conditions	yield[b] (%)
1	none	80
2	CH_3CN (10 mL) instead of HFIP/CH_3CN	61
3	$^nBu_4NClO_4$ instead of $^nBu_4NBF_4$	35
4	$^nBu_4NPF_6$ instead of $^nBu_4NBF_4$	33
5	Pt(+)|Pt(−) instead of C(+)|Pt (−)	42
6	C(+)|C(−) instead of C(+)|Pt(−)	60
7	6 mA instead of 15 mA, 4 h	62
8	12 mA instead of 15 mA, 4 h	73
9	40 °C instead of rt	60
10	no electricity, N_2	NR

[a]Standard reaction conditions: Pt plate (15 mm × 15 mm × 0.3 mm) cathode, graphite rod anode (Φ 6 mm), constant current = 15 mA, **1a** (0.5 mmol), **2a** (0.25 mmol), **5a** (0.5 mmol), $^nBu_4NBF_4$ (0.2 mmol), HFIP (2 mL), CH_3CN (8 mL), room temperature, 4 h (4.6 F/mol), undivided cell. [b]Yield of isolated product.

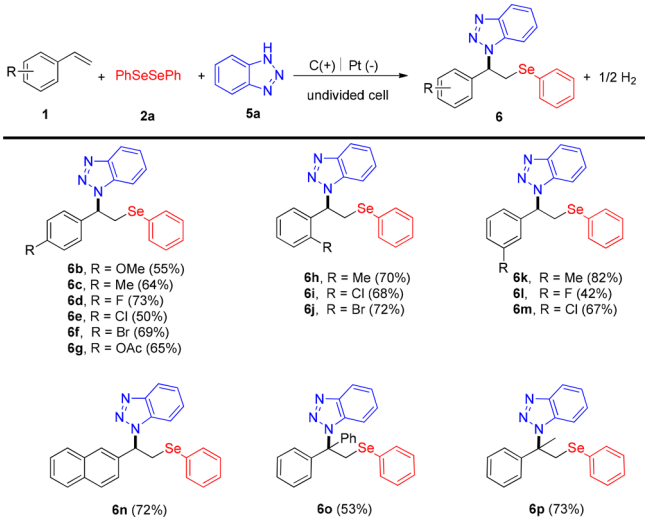
order to test the electrode effect, platinum plates or graphite rods (Φ 6 mm) were applied for both electrodes and furnished compound **6a** in 42−60% yields (entries 5 and 6). Furthermore, changing the operating current (6 mA or 12 mA) was proved to be less efficient as well (62−73%, entries 7 and 8). When the temperature was raised to 40 °C, **6a** was observed in 60% yield only. Control experiments showed that no desired product was generated without electricity (entry 10).

With the optimized reaction conditions in hand, we examined electronic and steric effects for this reaction with various styrene derivatives as shown in Scheme 2. Styrenes bearing electron-rich and -deficient substitution at the *para*-, *meta*-, and *ortho*-positions **1b−m** reacted efficiently with benzotriazole (**5a**) and diphenyl selenide (**2a**) to afford the desired products **6b−m** in 42−82% yield. It is noteworthy that all valuable electrophilic functional groups, such as fluoro, chloro, bromo, or ester substitutions, are well tolerated. Furthermore, vinylnaphthalene (**1n**), 1,1-diphenylethylene (**1o**), and *α*-methylstyrene (**1p**) were used as substrates to render the desired products **6n−p** in moderate to good yield (53−73%).

Electrochemical alkene difunctionalization was further probed with various amino sources, such as benzotriazole **5b**, saccharin (**5c**), pyrazole **5d−e**, and sulfamide (**5f**), affording the corresponding *β*-amido selenides **6q−u** (Scheme 3) in reasonable yields (35−64%). We were pleased to discover that anilines **5g,h** were applicable under the reaction conditions, and the desired amidoselenides **6v,w** could be obtained in 73 and 64% yield, respectively. In addition, aliphatic diselenides also led to the desired products **6x,y** in moderate to good yields. This reaction therefore represents a breakthrough to the limited intermolecular selenide difunctionalization and improves the potential of this protocol for use in the pharmaceutical industry.

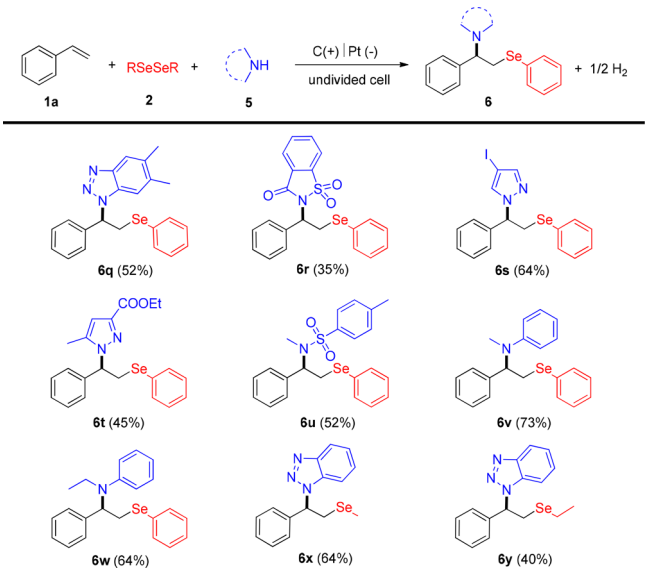
In consideration of the remarkably broad substrate scope displayed by the electrochemical conditions, we performed this transformation with several other nucleophiles including carboxylic acids, water, and alcohols (Scheme 4, **7a−l**).

Scheme 2. Substrate Scope of Electrochemical Aminoselenation[a]



[a]Standard reaction conditions: Pt plate (15 mm × 15 mm × 0.3 mm) cathode, graphite rod anode (Φ 6 mm), constant current = 15 mA, **1a** (0.5 mmol), **2a** (0.25 mmol), **5a** (0.5 mmol), $^nBu_4NBF_4$ (0.2 mmol), HFIP (2 mL), CH_3CN (8 mL), room temperature, 4 h (4.6 F/mol), undivided cell. [b]Yield of isolated product.

Scheme 3. Electrochemical Aminoselenation with Various Amino Nucleophiles and Diselenide[a]

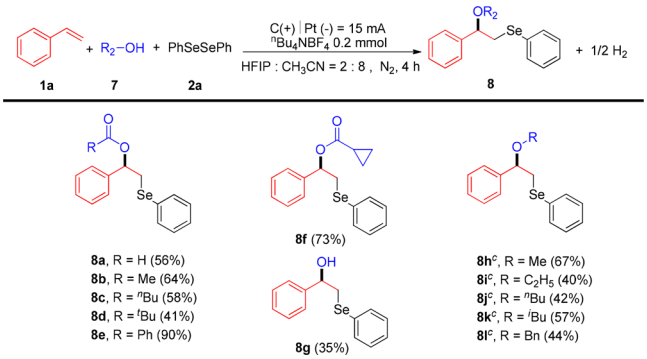


[a]Standard reaction conditions: Pt plate (15 mm × 15 mm × 0.3 mm) cathode, graphite rod anode (Φ 6 mm), constant current = 15 mA, **1a** (0.5 mmol), **2** (0.25 mmol), **5** (0.5 mmol), $^nBu_4NBF_4$ (0.2 mmol), HFIP (2 mL), CH_3CN (8 mL), room temperature, 4 h (4.6 F/mol), undivided cell. [b]Yield of isolated product.

Formic acid (**7a**), acetic acid (**7b**), butyric acid **7c,d**, benzoic acid (**7e**), and cycloproylcarboxylic acid **7f** proved to be very good nucleophiles for this transformation, affording the corresponding products **8a−f** in 41−90% yield. Notably, when benzoic acid was used as the nucleophile, the desired product **8e** was obtained in 90% yield. However, when water was used as the nucleophile, only 35% of the corresponding product **8g** was isolated. Encouraging by these results, we have

DOI: 10.1021/acs.orglett.8b03274
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Electrochemical Oxyselenation with Various Oxy-nucleophiles[a]



[a]Standard reaction conditions: Pt plate (15 mm × 15 mm × 0.3 mm) cathode, graphite rod anode (Φ 6 mm), constant current = 15 mA, **1a** (0.5 mmol), **7** (1 mL) (**7d–f** 10 equiv), diphenyl selenide **2a** (0.25 mmol), $^{n}Bu_4NBF_4$ (0.2 mmol), HFIP (2 mL), CH_3CN (8 mL), room temperature, 4 h (4.6 F/mol), undivided cell. [b]Yield of isolated product. [c] Using CH_3CN (10 mL) as solvent only.

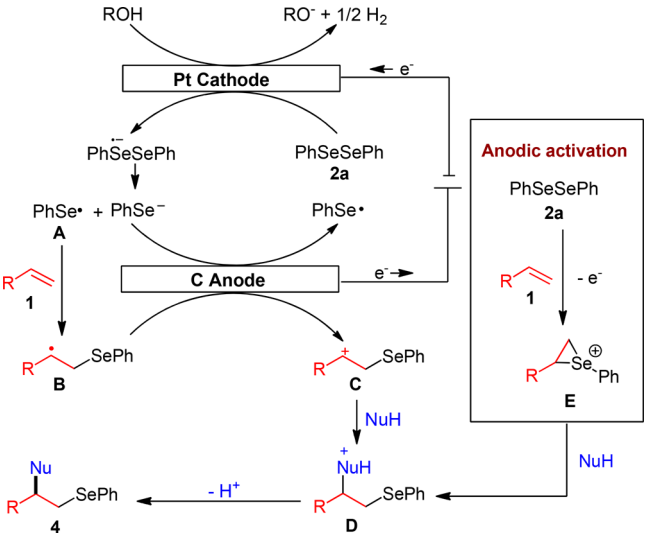
extended the scope of this oxyselenation to various alcohols **7h–l** and obtained the desired products **8h–l** in moderate yields (40–67%). Low conversion of starting materials was the main reason for reactions in lower yields.

To gain some insight into the reaction mechanism, three substrates were conducted in cyclic voltammetry experiments (Figure S1). An obvious oxidation peak of substrate **1a** could be observed at 2.25 V (Figure S1, red line), while there was no obvious oxidation peak for benzotriazole (**5a**). Moreover, the diphenyl diselenide (**2a**) demonstrated an oxidation peak at 1.88 V (Figure S1, blue line). A reduction peak of diphenyl diselenide (**2a**) was observed at −1.74 V under the reaction solvent system (Figure S2, blue line). Therefore, the diphenyl diselenide (**2a**) may involve in both oxidation and reduction processes in the catalytic cycle.

On the basis of our mechanistic studies and literature reports,[7] the proposed mechanism of electrochemical oxidative amino- and oxyselenation of styrenes is depicted in Scheme 5.

The reaction might be initiated by the formation of seleno radical **A** and selenium anion via cathodic reduction.

Scheme 5. Proposed Reaction Mechanism



Thereafter, radical addition of **A** to alkene provides radical **B** in good regioselectivity. Subsequently, further anodic oxidation, nucleophilic attack as well as deprotonation leads to the formation of product **4**. Alternatively, we cannot rule out the pathway that diphenyl diselenide (**2a**) undergoes anodic oxidation followed by the formation of the cyclic selenium intermediate **E**,[8] which reacts with NuH to form the final product.

We have developed highly efficient electrochemical amino-selenation and oxyselenation reactions which can run at room temperature without any hazardous additives (acids, oxidants, or transition metals). This provides a green way for the synthesis of phenylselenenylated molecules. In the amino-selenation, secondary phenylalkyl amines can act as a reaction component to generate aminated products which are difficult to make via known methods. Further applications of electrochemical difunctionalization of olefins are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03274.

Experimental procedure, characterization data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (21702081, 21702150), China Postdoctoral Science Foundation (BX201600114, 2016M602340), and Jiangxi Provincial Education Department Foundation (GJJ160325).

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