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Electrochemical S-vinylation of sulfinamides with β -bromostyrenes†

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We present an electrochemical method for sulfoximine synthesis via radical cross-coupling of sulfonimidoyl and styryl radicals, generated from sulfinamides and bromostyrenes. This approach enables the efficient synthesis of vinyl sulfoximines, including bioactive-tethered derivatives, in moderate to good yields.

Sulfoximine-containing molecules have gained significant attention in medicinal chemistry due to their unique structural features, including a stereogenic center at the sulfur atom and a small, hydrophilic core.¹ These compounds exhibit diverse biological properties; for example as a proline-rich tyrosine kinase inhibitor (A),² cyclin-dependent kinases (CDK) inhibitors (B),³ or CYP24 hydroxylase inhibitor (C).⁴ Beyond their pharmaceutical applications, sulfoximines have also been employed as pesticides in crop protection.⁵ Given their widespread importance in drug discovery and agrochemicals, the development of efficient and sustainable synthetic methodologies to access sulfoximines remains a crucial research goal. Several strategies have been explored for sulfoximine synthesis. One of the most common approaches involves the amination of sulfoxides using aminating reagents.^{6–9} However, such approach is often limited by the need for stoichiometric oxidants and low substrate tolerance, restricting its broader applicability.⁷ More recently, radical methodologies have emerged as promising alternatives for sulfoximine synthesis.^{10–13} Bolm¹¹ and Gau¹² reported methods using sulfonimidoyl radicals, generated from sulfonimidoyl chloride or fluoride.

Electrochemical synthesis—the use of electric current to mediate redox transformations in organic synthesis—has witnessed a

renaissance in recent years and is developing as an inherently green and sustainable method to access radical intermediates under precise reaction conditions.^{13,14} In this context, Ling and co-workers developed an electrochemical approach that generates sulfonimidoyl radicals *in situ* via paired electrolysis, enabling vinyl sulfoximine synthesis.¹⁵ Against the background of recent developments in sulfoximine synthesis and our interest in this research area,¹⁶ we herein present a modified electrochemical approach that circumvents the need for DBU and triethylamine salts. Our protocol employs carbonate salts as the sole additive, enabling the efficient synthesis of vinyl sulfoximines under ambient conditions (Scheme 1).

Initially, we investigated the reaction of sulfinamide **1a** with β -bromostyrene (**2a**) under electrochemical conditions, using a graphite electrode and K₂CO₃ as the base. To our delight, the desired product **3a** was formed in 41% yield (Table 1, entry 1). With this positive result we then proceeded to screen other solvents, yet both THF or methanol gave inferior results. On increasing the ratio of water, a sharp decrease in the yield of **3a** was observed (Table 1, entry 4). We next went for evaluation of organic and inorganic bases; using pyridine and KOH as base the product **3a** was formed only in traces while Na₂CO₃ or K₃PO₄ gave **3a** in 39% and 33%, respectively (Table 1, entries 5–8). When the reaction was performed in presence of electrolytes in acetonitrile, the product **3a** was not detected (Table 1, entry 9); similarly, a significant decrease in the yield of **3a** was observed under aerobic conditions (Table 1, entry 10). Changing the cathode to Ni plate resulted in a significant increase in the yield of the desired product **3a**, which could be isolated in 77% yield (Table 1, entry 11). The reaction failed to deliver the product in absence of electric current indicating the necessity of electricity. Further, on increasing or decreasing the reaction current does not provide a better than at 3 mA (Table 1, entry 12).

We first investigated the substrate scope (Scheme 2) by varying the sulfinamide (**1**). Both pivoyl and benzoyl protecting groups were well tolerated in this transformation; however, the benzoyl-protected sulfinamide yielded product **3c** in only 22%,

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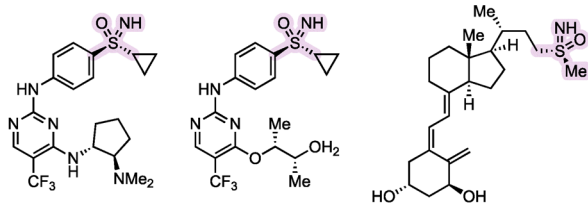
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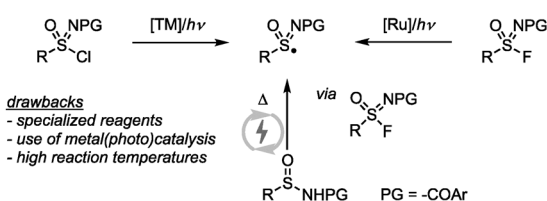
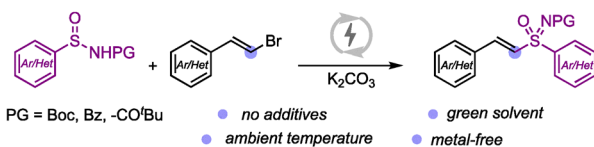


A Selected bioactive sulfoximines



A proline-rich tyrosine kinase B CDK inhibitor C CYP24 hydrolase inhibitor

B Previous work on the generation of sulfoximido radicals to access sulfoximines

C Our work on electrochemical radical cross-coupling of sulfinamides with β -bromostyrene

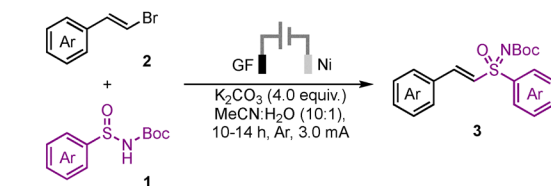
Scheme 1 Biologically relevant sulfoximines bearing molecules and strategies for the generation of sulfoximido radicals.

Table 1 Optimization of reaction conditions^a

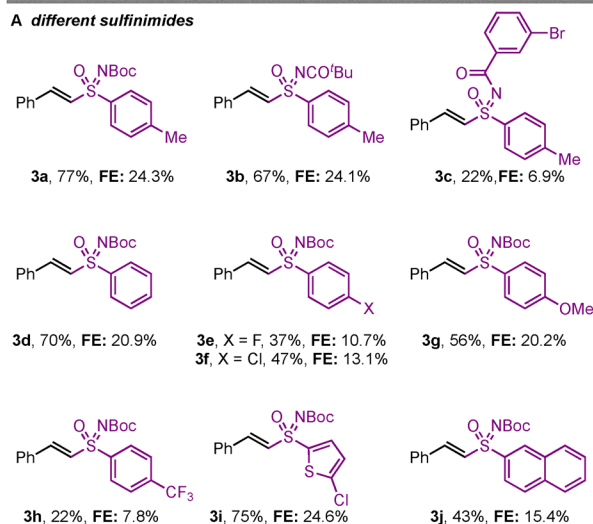
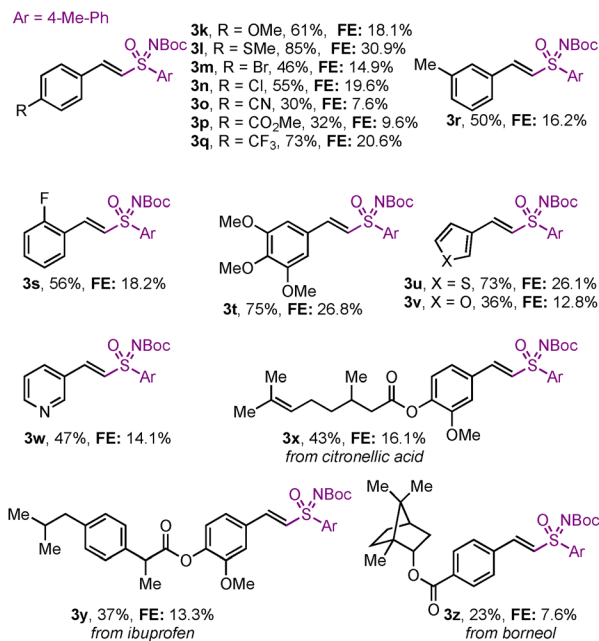
Entry	Variation from condition	Yield [%] of 3a
1	None	41
2	THF : H ₂ O	39
3	MeOH : H ₂ O	Traces
4	MeCN : H ₂ O (1 : 5)	13
5	Pyridine instead of K ₂ CO ₃	Traces
6	KOH instead of K ₂ CO ₃	Traces
7	Na ₂ CO ₃ instead of K ₂ CO ₃	39
8	K ₃ PO ₄ instead of K ₂ CO ₃	33
9	TBAI, TBClO ₄ , TBABF ₄ in MeCN	—
10	Under air	14
11	Ni as cathode	84 (77) ^b
12	No current	NR
13 ^c	At 5 mA/1 mA current	75/63

^a Reaction conditions: **1a** (0.1 mmol), **2a** (3.0 equiv.) and K₂CO₃ in MeCN : H₂O (10 : 1, 2.0 mL) under argon. ¹H NMR yields were calculated using mesitylene as internal standard. ^b Isolated yield. ^c Nickel as cathode.

whereas the Boc- and pivoly-protected variants afforded products **3a** and **3b** in significantly higher yields of 77% and 67%, respectively.



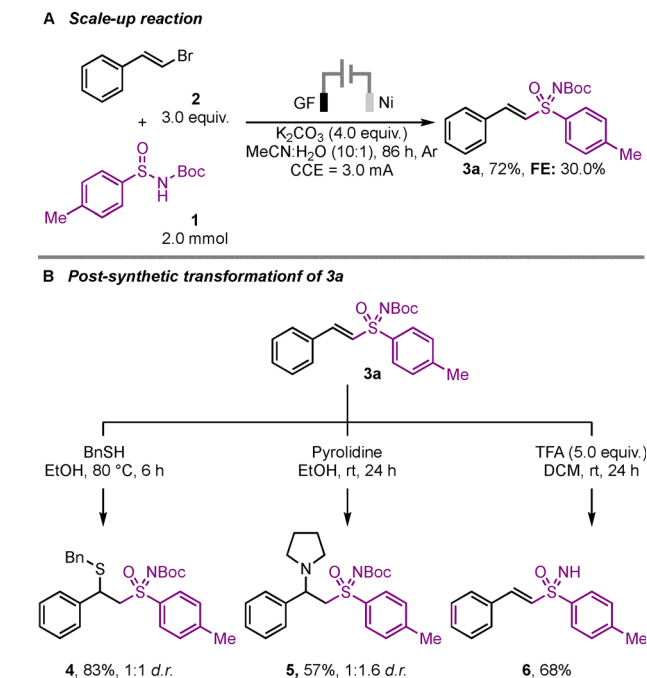
A different sulfinamides

B different β -bromostyrene

Scheme 2 Substrates scope; **1** (0.2 mmol), **2** (3.0 equiv.) and K₂CO₃ (4.0 equiv.) in MeCN : H₂O (10 : 1, 2.0 mL) were electrolyzed at 3 mA CCE using GF (anode) and Ni (cathode) under argon. FE = faradaic efficiency.

Next, we explored the effect of the aryl ring substitutions on the sulfinamide. A wide range of substituents, including electron-donating, electron-withdrawing groups, and halogens, were well-tolerated. Phenylsulfinamide yielded product **3d** in 70%. Halogenated sulfinamides produced **3e** and **3f** gave slightly lower yields, whereas the methoxy-substituted sulfinamide gave product **3g** in 56%. Notably, mono-CF₃-substituted

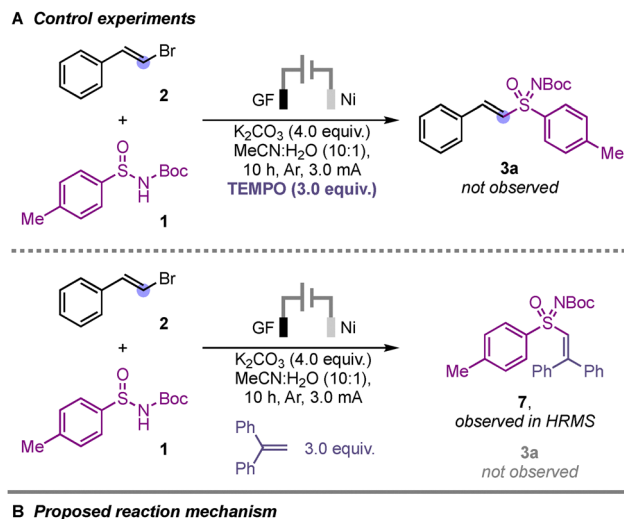




Scheme 3 Scale up reaction and post-synthetic transformations.

arylsulfonamide provided product **3h** in only 22% yield, while 3,5- CF_3 and CN-substituted sulfonamides failed to generate the corresponding sulfoximines (see ESI[†]). The presence of two CF_3 groups (see, ESI[†]) at the meta positions of the sulfonamide failed to provide the desired product, possibly due to their strong electron-withdrawing nature. Similarly, substitutions at the *ortho* position *e.g.* Cl or Me, (see ESI[†]) did not yield the corresponding sulfoximines, which may be attributed to steric hindrance. The thiophene-derived sulfonamide afforded product **3i** in a good yield of 75%, whereas the naphthalene analogue provided **3j** in 43%. We then assessed the influence of the substituents on the aryl ring of bromo styrene **2**. The reaction tolerated diverse substitution patterns, including electron-donating, electron-withdrawing groups, and halogens, affording the respective products in moderate to good yields. Electron-donating groups positively influenced the yields (**3k**, **3l**), while halogenated substrates led to moderate yields (**3m**, 46%; **3n**, 55%). Strongly electron-withdrawing substituents such as CN and CO_2Me gave **3o** and **3p** in lower yields (30% and 32%, respectively), whereas CF_3 -substituted styrene gave **3q** in an excellent 73% yield. *meta*- and *ortho*-substituted bromostyrenes reacted efficiently, delivering products **3r** (50%) and **3s** (56%). The tri-methoxy-substituted bromostyrene provided **3t** in 75% yield. Additionally, heterocyclic bromostyrenes were well tolerated; pyridine- and furan-containing derivatives gave products **3w** and **3v** in lower yields, while the thiophene analogue afforded **3u** in 73%. Finally, bioactive tethered bromostyrene derivatives were also compatible, yielding products **3x–3z** in moderate yields. The observed faradaic efficiencies (6.9–30.9%) are relatively low, which may be due to competitive hydrogen evolution resulting from water present in the reaction medium.

To demonstrate the applicability of the developed electrochemical protocol, a scale up reaction at 2 mmol scale were



Scheme 4 Control experiment and possible reaction mechanism.

performed under the standard reaction condition to provide the desired product in 72% yield (Scheme 3A). Additionally, Michael addition reaction of **3a** with thiol and pyrrolidine have been performed and the products **4** and **5** were isolated in 83% and 57% yield, respectively (Scheme 3B). Furthermore, the Boc-protecting group could be easily removed under acidic condition to deliver the free sulfoximine **6** (Scheme 3B).

We then performed several control experiments to get insight into the reaction mechanism (Scheme 4A). When the reaction was performed using TEMPO as radical quencher the reaction failed to provide the product **3a** suggesting the radical nature of the reaction. Further, using 1,1-diphenyl ethene as radical trapping agent, we observed the formation of the adduct **7**. Based on these control experiments and previous literature reports,¹⁷ we postulated that the sulfonamide anion **8** undergoes anodic oxidation to generate the *N*-centred radical intermediate which could undergo electronic rearrangement to generate the sulfonimidoyl radical **9** (Scheme 4B). At the cathode, the bromostyrene undergoes one-electron reduction to generate the styryl radical **10**, which finally undergoes radical cross coupling with **9** to provide the sulfoximine **3a** (Scheme 4B).

In conclusion, we have demonstrated the application of electrochemistry to access vinyl sulfoximines through a radical



cross-coupling of the sulfonimidoyl and styryl radicals under metal- and additive-free conditions. The developed protocol successfully delivered a variety of sulfoximine derivatives in moderate to good yields. This strategy was further applied to synthesize bioactive tethered vinyl sulfoximines in moderate yields. Additionally, the synthetic applicability of the protocol was demonstrated through a scale-up reaction and subsequent post-synthetic modifications.

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Data availability

All experimental data, and detailed experimental procedures are available in the ESI.†

Conflicts of interest

There are no conflicts to declare.

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