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## Photoelectrochemical C–H Alkylation of Heteroarenes with Organotrifluoroborates

#### Hong Yan, Zhong-Wei Hou and Hai-Chao Xu\*

**Abstract:** A photoelectrochemical method for the C–H alkylation of heteroarenes with organotrifluoroborates has been developed. The merger of electrocatalysis and photoredox catalysis provides a chemical oxidant-free approach for the generation and functionalization of alkyl radicals from organotrifluoroborates. A variety of heteroarenes are functionalized using primary, secondary and tertiary alkyltrifluoroborates with excellent regio- and chemoselectivity.

Organic electrochemistry, which employs traceless electricity to promote reactions, is an enabling and green synthetic technology and have been gaining increasing traction.<sup>[1]</sup> The electrochemical generation of alkyl radicals dates back in 1847 when Kolbe reported the decarboxylative dimerization of carboxylic acids.<sup>[2]</sup> However, application of alkyl radicals generated on the electrode surface in intermolecular functionalization reactions has been hampered by undesirable pathways of the alkyl radicals such as over-oxidation to carbocations, radical-radical dimerization (Kolbe reaction), and reaction with the electrode surface that causes electrode passivation.<sup>[3]</sup> The use of a redox catalyst to generate the alkyl radicals in the bulk solution can overcome some of the abovementioned problems (Scheme 1a).<sup>[4]</sup> However, overoxidation to carbocations are still difficult to avoid because the commonly employed radical precursors have higher oxidation potentials than many alkyl radicals, especially tertiary alkyl radicals and those with  $\alpha$ -stablization groups such as  $\pi$ -systems and heteroatoms.[3e,5,6]

Photoredox catalysis has emerged as a versatile technology for the generation of reactive radical species.<sup>[7]</sup> Because of the transient nature of the redox active excited state of the photocatalyst and the organic radical species, overoxidation of alkyl radicals usually does not occur under photochemical conditions. Compared with the extensively investigated redox neutral transformations, photochemical net oxidation reactions are less explored and generally rely on the use of stoichiometric chemical oxidants.<sup>[7]</sup> In this context, visible light-promoted Minisci alkylation of heteroarenes using oxidizing reagents such as peroxydisulfate  $(S_2O_8^{2-})$  salts<sup>[8a,b]</sup> and hypervalent iodine<sup>[8c-e]</sup> have been extensively studied because of the importance of heteroarenes in chemistry and biology.

With our continued interest in organic radical chemistry,<sup>[9]</sup> we envision the merger of organic electrochemistry and photoredox catalysis for the development of oxidative radical reactions

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(Scheme 1b).<sup>[10]</sup> The proposed photoelectrochemical method, which combines the reagent-free feature of electrochemistry and the versatility of photochemistry in radical formation, can potentially provide a platform for the development of enabling and sustainable synthetic methodologies. Herein, we report an unprecedented photoelectrochemical C–H alkylation reaction of heteroarenes with organotrifluoroborates (Scheme 1c).<sup>[11]</sup> These reactions are compatible with the introduction of pimary, secondary and tertiary alkyl groups to heteroarenes and proceed in an oxidizing reagent-free fashion.



Scheme 1. Reaction design.

Organotrifluoroborates, which are stable and easily available, have been demonstrated to be excellent precursors for alkyl radical species.<sup>[8a,12]</sup> Particularly, Molander and coworkers have employed these reagents in photoredox-mediated C-H alkylation of heteroarenes.<sup>[8a]</sup> We began our study by optimizing the photoelectrochemical conditions for the alkylation of lepidine (1) with potassium isopropyltrifluoroborate 2 (Table 1). The electrolysis was conducted with a constant current in an undivided cell equipped with a reticulated vitreous carbon (RVC) anode and platinum plate cathode. A 20 W blue LED was employed as the light source. The optimal reaction mixture consisted organic dye [Mes-Acr<sup>+</sup>]ClO<sub>4</sub><sup>-</sup> (3)<sup>[13]</sup> as the catalyst (5 mol %) and TFA (1 equiv) as the acid additive, in a mixed solvent of MeCN/H<sub>2</sub>O (2:1) at RT. Under these conditions, the desired C-H alkylation product 4 was isolated in 87% yield (entry 1). Light (entry 2), electricity (entry 3) and the catalyst (entry 4) were critical for success and the absence of any of these elements led to the recovery of most of 1. Other catalysts such as [Ir(dF(CF<sub>3</sub>)ppy)<sub>2</sub>(dtbbpy)](PF<sub>6</sub>) (entry 5) and 4CzIPN<sup>[14]</sup> (entry 6) were less efficient probably because of the lower reduction potentials of their corresponding excited state compared to that of 3. Increasing the current from 2 mA to 4 mA (entry 7) or 6 mA (entry 8) led reduced conversion and current efficiency suggesting the importance of synchronizing the electrocatalytic and photocatalytic steps. A good yield of 80% was still obtained when the supporting electrolyte Et<sub>4</sub>NBF<sub>4</sub> was omitted (entry 9). Although stringent removal oxygen was not

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necessary, the yield of **4** decreased to 63% when the reaction was conducted under air (entry 10).

Table 1. Optimization of reaction conditions.<sup>[a]</sup>



Entry	Deviation from standard conditions	Yield [%] <sup>[b]</sup>
1	none	87 <sup>[c]</sup>
2	no light	4 (75)
3	no electricity	14 (82)
4	no <b>3</b>	5 (95)
5	[Ir(dF(CF <sub>3</sub> )ppy) <sub>2</sub> (dtbbpy)](PF <sub>6</sub> ) as catalyst	43 (34)
6	4CzIPN as catalyst in CH <sub>3</sub> CN/H <sub>2</sub> O (11:1)	56 (36)
7	4 mA, 5 h	68 (21)
8	6 mA, 3.4 h	52 (38)
9	no Et <sub>4</sub> NBF <sub>4</sub>	80
10	under air	63

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol), MeCN (4 mL), H<sub>2</sub>O (2 mL), Et<sub>4</sub>NBF<sub>4</sub> (0.3 mmol), argon, RVC anode, Pt cathode, 2 mA ( $j_{anode} \approx 0.03$  mA cm<sup>-2</sup>), blue LED (450 nm), 10 h (2.5 F mol<sup>-1</sup> based on **1**). [b] Yield determined by <sup>1</sup>H-NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. Unreacted **1** in parenthesis. [c] Isolated yield.





The substrate scope regarding the heteroarenes were next investigated (Scheme 2). The photoelectrochemical C-H functionalization reaction tolerated many heteroarenes such as 4- or 2-substituted quinolines (5-9), isoquinoline (10), acridine (11), phenathridine (12), phthalazine (13), guinazolinone (14), benzothiazole (15), Imidazo[1,2-b]pyridazine (16), and purine (17). All the heterocycles underwent monoalkylation with excellent regioselectivity except for phthalazine that afforded bisalkylation product.<sup>[8]</sup> In addition, bioactive compounds such as voriconazole (18), camptothecin (19), fasudil (20) and guinine (21) underwent regio- and chemoselective monoalkylation. The secondary amine moiety embedded in fasudil and the tertiary amine moiety of quinine, which were sensitive to oxidative decomposition, remained intact during the photoelectrochemical C-H alkylation probably because these basic functionalities were protonated under the acidic reaction conditions.



**Scheme 2.** Scope of heteroarenes. Reaction conditions: Table 1, entry 1, 10 h (2.5 F mol<sup>-1</sup> based on heteroarene) unless otherwise mentioned. [a] Reaction with 3 equiv of **2**. [b] Reaction with potassium cyclohexyltrifluoroborate. [c] Reaction with 3 equiv of TFA.

The scope of organotrifluoborate was subsequently explored using lepidine 2 or 2-phenylquinoline as the coupling partner (Scheme 3). A variety of acyclic (22) and cyclic (23-29) organotrifluoroborates secondary participated in the photoelectrochemical C-H alkylation reaction including those bearing a ketone carbonyl (27), a Boc-protected amine (28), or a cyclic ether (29). α-Alkoxyl and tertiary alkyl radicals are oxidized at potentials much lower than the organotrifluoborates and thus are prone to undergo overoxidation to carbocations.[3e,6] Pleasingly, α-alkoxyl (30–33) and tertiary (34-39) organotrifluoroborates also reacted successfully under modified conditions using either increased loading of the catalyst 3 or 4CzIPN as the catalyst.

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Scheme 3. Scope of organotrifluoroborate. Reaction conditions: Table 1, entry 1, 2–9 F mol<sup>-1</sup> (based on heteroarene). [a] 3 equiv of organotrifluoroborate. [b] 20 mol % of 3. [c] Reaction with 5 mol % 4CzIPN as catalyst in MeCN/H<sub>2</sub>O (11:1), 65 °C.



1,4-Dihydropyridines, which are prepared in one step from aldehydes, have been employed as alkyl radical precursors.<sup>[15]</sup> Preliminary results showed that 1,4-dihydropyridine **40** could

also serve as an effective alkylation reagent under the photoelectrochemical conditions [Eq. (1)]. Moreover, the photoelectrochemical alkylation reaction was applicable to promote the oxidative addition-cyclization cascade of acrylamide **41**, leading to the formation of oxindole **43** [Eq. (2)]. Together, these results suggested potentially broad applications of the photoelectrochemical protocol in promoting oxidative radical reactions.



Scheme 4. Mechanistic proposal. Potentials (*E*) vs saturated calomel electrode (SCE).

A possible mechanism for the electrochemical C-H akylation reaction has been proposed (Scheme 4). Irradiation of the organic dye Mes-Acr+ (3) leads to its highly oxidizing excited state 3\* (E<sup>red</sup> = 2.06 V vs SCE in MeCN).<sup>[13a]</sup> Single electron transfer (SET) between 3\* and the organotrifluoroborate results in the acridinyl radical Mes-Acr and an alkyl radical.[8a,16] The stable radical Mes-Acr<sup>-[13b,c]</sup> is oxidized at the anode surface to regenerate the ground-state catalyst 3. On the other hand, the alkyl radical reacts with the protonated heteroarene to give the radical cation I, which loses a proton to give the C-radical intermediate II.<sup>[17]</sup> II needs to lose an electron to afford the final product. However, this radical is probably not oxidized on the anode surface because it is not expected to have a lifetime long enough for it to travel to the electrode.[18] The oxidation potential of II can be estimated using the reduction potential of protonated quinoline 4 [ $E_{p/2}^{red}$  = -1.19 V vs SCE in MeCN/H<sub>2</sub>O (2:1)]. Hence, it is thermodynamically favorable for II to lose an electron to the ground-state catalyst 3 ( $E_{p/2}^{red} = -0.57 \text{ V vs SCE in MeCN}^{[13b]}$  to form the final functionalized heteroarene product. At the cathode, protons are reduced to generate H<sub>2</sub>, obviating the need for electron and proton acceptors for the C-H alkylation reaction.

In summary, we have developed a chemical oxidant-free C– H alkylation reaction of heteroarenes with organotrifluoroborates by merging photoredox catalysis and electrocatalysis. Under the photoelectrochemical conditions, alkyl radicals are efficiently generated and participate readily in intermolecular oxidative transformations without overoxidation to carbocations. Application of the photoelectrochemical protocol to promote other oxidative radical reactions are ongoing in our laboratory.

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**Keywords:** electrochemistry • photoelectrochemistry • oxidation • radical reaction • C–H alkylation

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Page No. – Page No. Photoelectrochemical C–H Alkylation of Heteroarenes with Organotrifluoroborates

A photoelectrochemical method has been developed for the C–H alkylation of heteroarenes with organotrifluoroborates under oxidizing reagent-free conditions. A variety of heteroarenes are functionalized with 1°, 2° and 3° alkyl groups with excellent regio- and chemoselectivity.