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Communication

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# Electrophotocatalytic C–H Functionalization of Ethers with High Regioselectivity.

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**ABSTRACT**: The highly regioselective electrophotocatalytic C-H functionalization of ethers is described. These reactions are catalyzed by a trisaminocyclopropenium (TAC) ion in a mild electrochemical potential with visible light irradiation. Ethers undergo oxidant-free coupling with isoquinolines, alkenes, alkynes, pyrazoles, and purines with typically high regioselectivity for the less-hindered α-position. The reaction is proposed to operate via hydrogen atom transfer (HAT) from the substrate to the photoexcited TAC radical dication, thus demonstrating a new reactivity mode for this electrophotocatalyst.

Over recent decades, the functionalization of unactivated C–H bonds has been established as a process of great value to organic synthesis.[1] Among the oldest of strategies to achieve such transformations, hydrogen atom transfer (HAT) has served as the key initiating step for a wide range of important processes.[2,3] Because the rate of hydrogen abstraction from a C–H bond depends both on the bond dissociation enthalpy (BDE) and polar effects in the transition state, C-H bonds in different environments (e.g. allylic, benzylic, α-oxy, and α-acyl positions) display large differences in reactivity. [4, 5] Consequently, great success has been achieved for the selective activation of chemically distinct C–H bonds via HAT processes. However, regioselective activation of chemically similar C–H bonds remains a significant challenge.[4,6] As a prime example, the Minisci reaction, [7] which involves the addition of a radical to heteroarenes, has proven to be a useful tool for building molecular complexity.[8,9] While this strategy has been shown to be efficient for the construction of bioactive molecules,[10] many examples of this reaction require the use of stoichiometric amount of peroxides and suffer from poor regiocontrol due to the strong similarity of nearly equivalent C-H bonds (Scheme 1A).[8,11] In pioneering work, MacMillan first reported the direct α-arylation of ethers by the combination of photoredox-catalyzed C–H activation and Minisci reaction.[8b] However, for a non-symmetric substrate such as 2-methyltetrahydrofuran, only a 3.5:1 regioselectivity between α-positions was observed. Later, a direct $K_2S_2O_8$-promoted cross-dehydrogenative coupling reaction was reported by Singh,[8c] but the elevated temperature (120 °C) of the method resulted in an even lower 1.6:1 regioselectivity. In 2017, Wang reported a N-hydroxysuccinimide-mediated procedure which achieved only a 2:1 regioselectivity for the same product.[8f] Recently, a system involving Cu/Selectfluor enabled high regioselectivity in one example, although 2.0 equiv. of expensive Selectfluor was required to serve as the HAT acceptor.[8g] Thus, the development of a highly regioselective, catalytic platform for Minisci-type functionalization of ethers remains an open challenge.

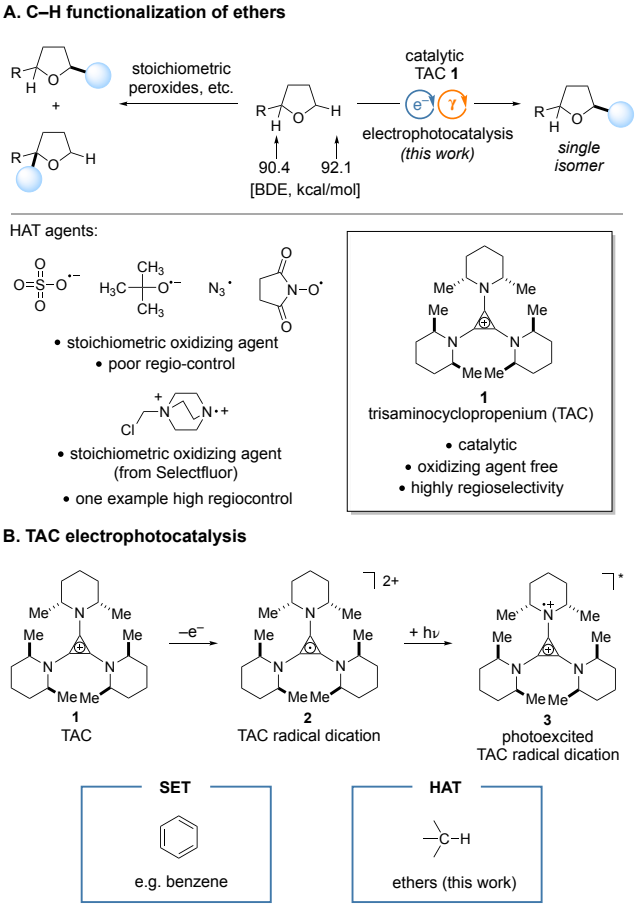
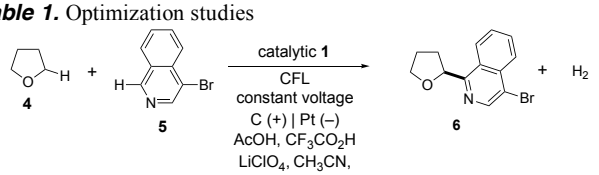



***Figure 1.*** Electrophotocatalysis with a trisaminocyclopropenium radical dication (a) HAT process. (b) SET process.

We recently reported a potent electrophotocatalytic system[12] involving trisaminocyclopropenium ion (TAC) **1**.[13] In this process, the colorless TAC electrophotocatalyst was converted by anodic oxidation at mild potential to the open-shell, photoabsorptive TAC radical dication **2**, followed by photoexcitation to produce **3** (Fig. 1B). The photoexcited TAC radical dication **3** was found to be sufficiently potent ($E_{red}$ = 3.33 V vs. SCE) to oxidize benzene and other unactivated arenes via single electron transfer (SET).[13a] Importantly,

calculations demonstrated that **3** has aminyl radical cation character on one of the nitrogen substituents. We thus envisioned that this intermediate might also be an effective HAT acceptor and thereby enable a diverse menu of transformations initiated by this alternative activation event. Furthermore, because it is known that H• transfer reactions are very sensitive to steric effects,[14] we reasoned that the hindered nature of the TAC might enable highly regioselective reactions between chemically similar but sterically differentiated C–H bonds. In this Communication, we show that TAC **1** is indeed an effective electrophotocatalyst for highly regioselective ether C–H bond functionalizations.

***Table 1.*** Optimization studies




| entry | **1** (mol%) | $E_{cell}$ (V) | other | yield (%)[a,b] |
|---|---|---|---|---|
| 1 | 5 | 1.5 | – | 42 |
| 2 | 5 | 1.5 | no light | <5 |
| 3 | 5 | – | no current | <5 |
| 4 | 5 | 1.5 | no catalyst | <5 |
| 5 | 5 | 1.5 | no TFA | 8 |
| 6 | 8 | 1.5 | – | 82 (80)[c] |
| 7 | – | 3.0 | direct electrolysis | messy |
| 8 | 8 | 1.0 | lower voltage | <5 |
| 9 | 8 | 1.5 | 1.6 g scale | 72 |
| 10 | 8 | 1.5 | 2-Me-THF (**7**) substrate | 56 (55)[c] |

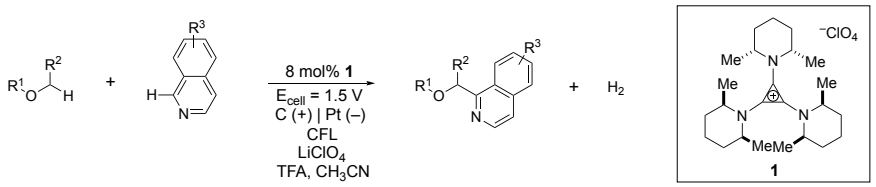
[a] See SI for detailed procedures. Reactions performed under constant voltage (CV) conditions with light irradiation for 18 h (entries 1-5) or 36 h (entries 6-10) at rt. [b] Yields determined by $^1$H NMR spectroscopy. [c] Yield of isolated product.

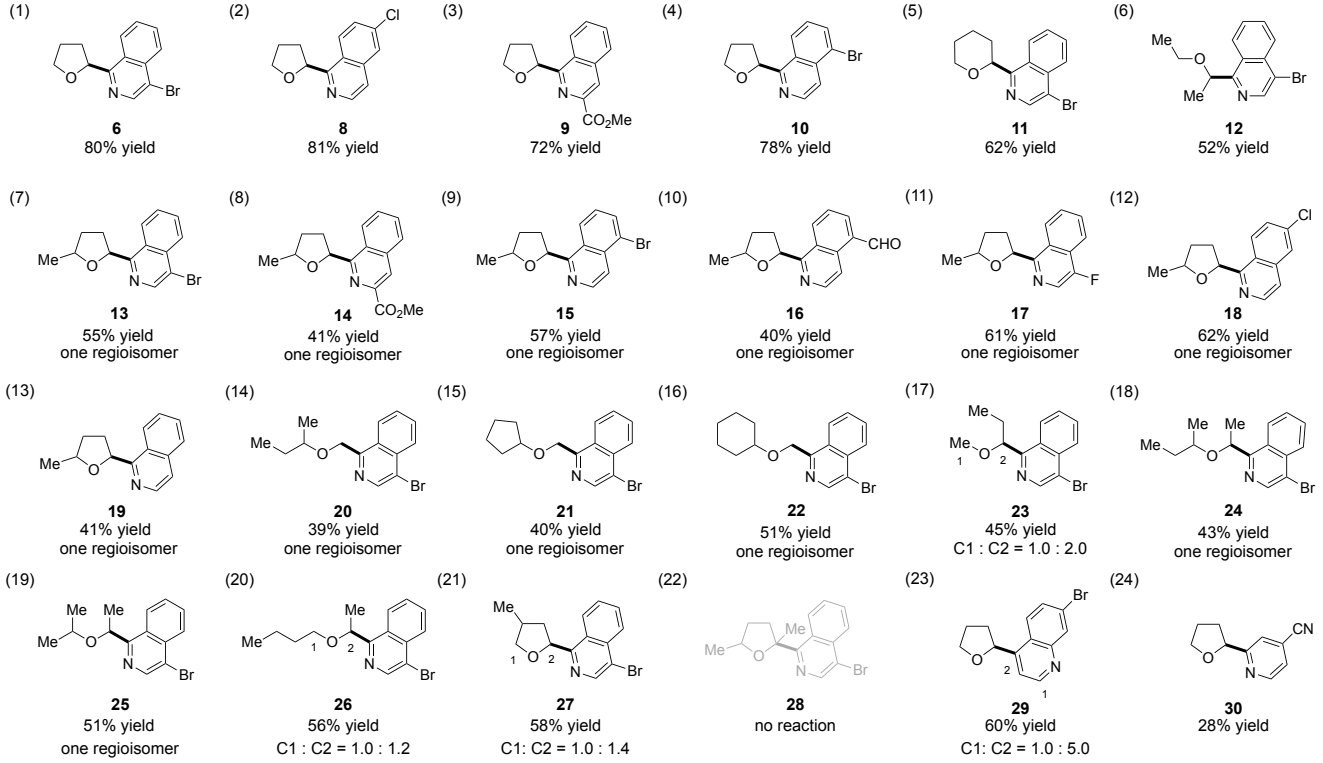
We first examined the electrophotocatalytic coupling of THF (**4**) and 4-bromoisoquinoline (**5**) (Table 1). By subjecting these reactants to 5 mol% **1** with a 1.5 V constant voltage undivided cell and visible light irradiation from a white light compact fluorescent light (CFL) in the presence of $LiClO_4$, acetic acid, and $CF_3CO_2H$, a 42% yield of the Minisci product **6** was obtained. To probe whether the process was actually electrophotocatalytic, we eliminated the light, electricity, and catalyst in turn (entries 2-4) and found that each component was necessary, with only trace product (≤5% yield) otherwise observed.[15] The yield was also significantly diminished without the addition of $CF_3CO_2H$ (entry 5), presumably because the protonation of isoquinoline is necessary for facile addition. Further optimization (see supporting information for details) of the conditions involving a slightly higher catalyst loading (8 mol%) and longer reaction time of 36 h led to an 82% yield of adduct **6** (entry 16). Importantly, when we attempted the same reaction by direct electrolysis using up to 3.0 V constant voltage, the coupling product **6** was observed by $^1$H NMR as part of a complex mixture of multiple, unidentified products (entry 7, see also supporting information). Lower voltages (e.g. $E_{cell}$ = 1.0 V) did not affect this reaction (entry 8). To demonstrate the preparative potential of this method, we conducted a large-scale reaction (8 mmol), from which 1.6 g of the product could be obtained (entry 10). Finally, we also examined these optimized conditions using a non-symmetric ether, 2-methyltetrahydrofuran (**7**) (entry 10), which led to a 55% isolated yield of the corresponding adduct as a single regioisomer.

With these optimized conditions, we explored some of the scope of this process. In addition to the formation of **6** (Table 2, entry 1), a variety of other isoquinoline partners could be utilized, giving rise to adducts **8-10** bearing halogens and ester functionality in various positions in moderate to good yields (entries 2-4). Other cyclic and acyclic ethers like tetrahydropyran and diethyl ether also led to the coupled products **11** and **12** in 62% and 52% yields respectively (entries 5-6).

Next, we sought to further explore the crucial issue of regioselectivity. As shown in Table 1, 2-methyltetrahydrofuran (**7**) delivered regioisomerically pure products **13-18** with a variety of functionalized isoquinoline reactants (entries 7-12). Isoquinoline itself also participated with high regioselectivity and moderate yield (entry 13). Other acyclic ethers were also shown to lead to single isomers with moderate to good yields (entries 14-20). It is worth noting that this procedure resulted in significant regioselectivity of primary over tertiary C-H bonds (entries 14-16), with only the primary C–H functionalized products **20-22** detected. However, in the competition between primary and secondary C–H bonds, the reaction mainly occurred at the secondary position (entry 17). In this case, the greater stability of the intermediate secondary carbon radical presumably outweighed the steric difference between the two positions. These conditions also showed excellent regioselectivity of tertiary versus secondary C-H bonds (entries 18 and 19), with only the secondary C-H bonds undergoing reaction. For substrates with only slightly different steric environments, however, essentially no regioselectivity was observed (entries 20-21). Notably, no reaction was observed for 2,5-dimethyltetrahydrofuran, which only has tertiary α-C-H bonds (entry 22). In terms of other azole partners, we observed a reasonably efficient reaction with a quinoline partner (entry 23) and a low efficiency with a pyridine substrate (entry 24). Other species examined (e.g. pyrimidine, quinoxaline, indole) did not react under these conditions.

***Table 2.*** Electrophotocatalytic C–H functionalization of ethers with isoquinolines and other azoles.[a,b,c]

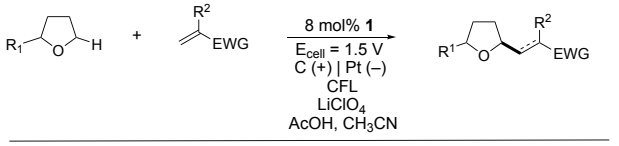


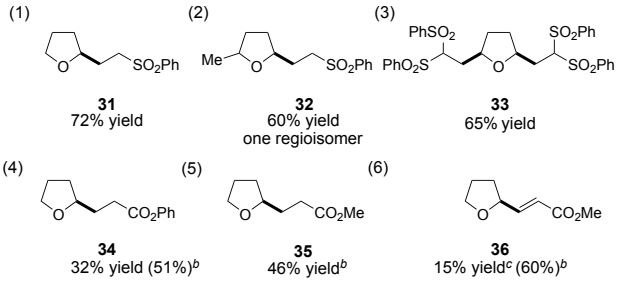




[a] 2 mL ether used. See SI for detailed procedures. Reactions performed under constant voltage (CV) with light irradiation for 36 h at rt. [b] Isolated yields. [c] Diastereomeric ratio (d.r.) determined by $^1$H NMR spectroscopy. **14**: 1:1.6 d.r.; **13**, **18**: 1:1.1 d.r.; **15**: 1:1.2 d.r.; **16**, **17**, **19**: 1:1.0 dr.

To further explore the scope of this electrophotocatalytic process, we examined the use of other radical acceptors (Table 3). We initially chose to explore vinyl sulfones because of their synthetic versatility by oxidative or reductive removal of the phenylsulfonyl groups. In the case of phenyl vinyl sulfone, adduct **31** was isolated in 72% yield (entry 1). An "on-off" experiment demonstrated that this was not a radical chain process (see supporting information). Once again, 2-methyltetrahydrofuran led to a single regioisomeric product **32** resulting from HAT from the less hindered α-position (entry 2). Interestingly, the 2,5-disubstituted ether **33** was produced as the major product when 1,1-bis(phenylsulfonyl)ethylene was used as the acceptor (entry 3). We speculate that ion-pairing of the mono-substituted product conjugate base with the cationic TAC catalyst may accelerate the second functionalization. In addition, moderate yields of adducts **34** and **35** could be obtained with acrylate esters (entries 4 and 5). Finally, a propargylic ester led to the formation of the α, β-unsaturated product **36** in 60% yield as 1:1 mixture of olefin isomers (entry 6).

***Table 3.*** Electrophotocatalytic C–H functionalization of ethers with alkenes and alkyne.[a]



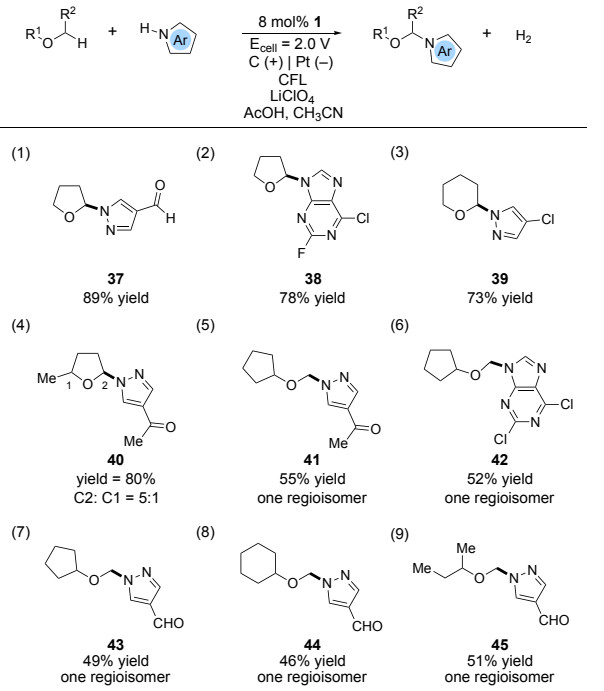




[a] 2 mL ether used. Yields determined for purified products. [b] $^1$H NMR yields [c] *E/Z* = 1:1.

In addition to the C-C bond coupling reactions shown above we also found that C-N bond formation was possible (Table 4). The conditions employed were similar to those previously described, but with acetic acid instead of trifluoroacetic acid

and a cell potential of 2.0 V.[16] First, 4-formylpyrazole (entry 1) and a halogenated purine (entry 2) reacted with THF to deliver adducts **37** and **38** in high yields. Tetrahydropyran could also be functionalized in good yield (entry 3). In the case of 2-methyltetrahydrofuran, we again observed the selective coupling at the less-hindered position, leading to adduct **40** in 80% yield as a 5:1 mixture of regioisomers. Notably, a related photocatalytic method was reported to produce only the C1 isomer for a similar reaction of this substrate.[16a] Meanwhile, we found other substrates also reacted with complete selectivity for the less-hindered C–H bonds (entries 5-9).

***Table 4.*** Electrophotocatalytic C–H functionalization of ethers with azoles.[a]




[a] 2 mL ether employed. Yields determined for purified products.

A mechanistic rationale for these electrophotocatalytic reactions is shown in Figure 2A. The TAC cation **1** undergoes electrochemical oxidization ($E_{OX}$ = 1.26 V vs. SCE) to generate radical dication **2**. Photoexcitation then leads to intermediate **3** bearing aminyl radical cation character. Hydrogen atom transfer from the ether substrate **7** to **3** generates the corresponding radical **46** along with the protonated TAC dication **47**. In support of the HAT step, we observed a kinetic isotopic effect (KIE) of $k_{H/D}$ = 3.0.[8f] We propose that steric encumbrance arising from the intermediate **3**, which is effectively locked in the conformation with all methyls in the axial position,[13] dictates the regioselective abstraction of the less hindered hydrogen atom. Once formed, **46** can react with isoquinoline **5** to produce intermediate radical **48**, which is followed by a second oxidation (likely via **3**) and loss of proton to furnish the product **12**. Meanwhile, deprotonation of dication **47** regenerates the TAC catalyst **1** to close the catalytic cycle. It should be emphasized that controlled ether functionalizations of this type by direct electrolysis can be challenging because the radical intermediates (e.g. **46**) are more easily oxidized than the substrates, yet the anode provides the capacity for multiple sequential oxidation events. In contrast, the electrophotocatalytic approach maintains only a low concentration of active oxidant, which presumably increases the lifetime of the radical enough that it can undergo productive one-electron chemistry.

As a final note, we recognize that, while the C–C coupling reactions shown in Tables 2 and 3 surely occur via ether radical intermediates (e.g. **46**), the azole couplings shown in Table 4 are mechanistically ambiguous. While they might also proceed via somophilic addition of the azole **50** to the same type of radical intermediate **49** followed by oxidation (Figure 2B, path a), it is conceivable that oxidation to the corresponding oxocarbenium ion **52** followed by nucleophile addition of the azole **50** is the operative pathway (path b). As evidence that this latter pathway is plausible, we found that the use of benzyl alcohol (**53**) led to acetal **54** (Figure 2C), the formation of which must have proceeded via oxocarbenium ion **52**. Thus, it appears that this electrophotocatalytic strategy enables the functionalization of ethers via both one and two electron pathways using closely related conditions.

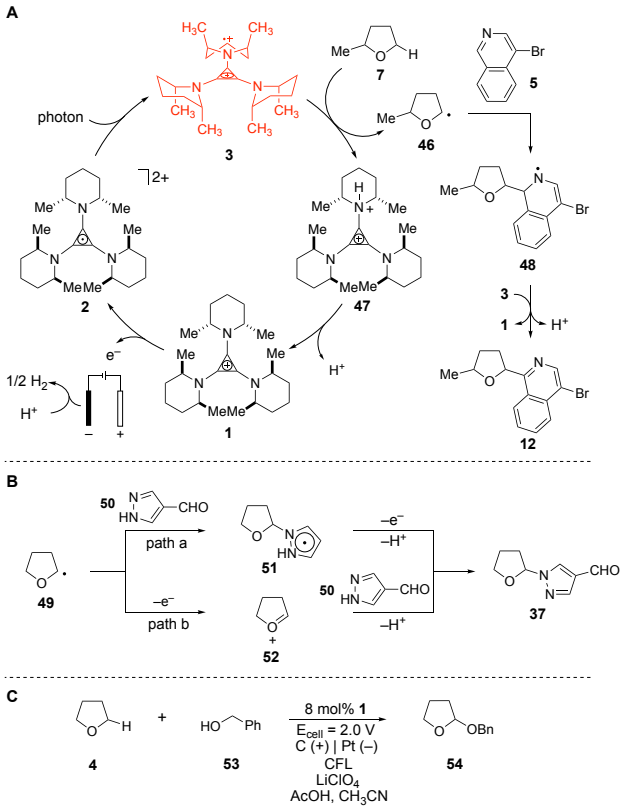



**Figure 2**. A. Mechanistic rationale for electrophotocatalytic Minisci reaction. B. Alternative pathways for azole coupling. C. Formation of acetal **54**.

In summary, an electrophotocatalytic C–H functionalization of ethers with high regioselectivity has been developed. The TAC **1** was shown to operate as a single-component HAT electrophotocatalyst. Through the combination of electrical and photochemical energy, this system obviates the need for an external oxidizing agent, while the catalyst structure enables high regioselectivities

based on steric differentiation of chemical similar bonds. This study thus realizes catalysis and high regioselectivity in the same system for these useful reactions.

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**Supporting Information Available:** Experimental procedures and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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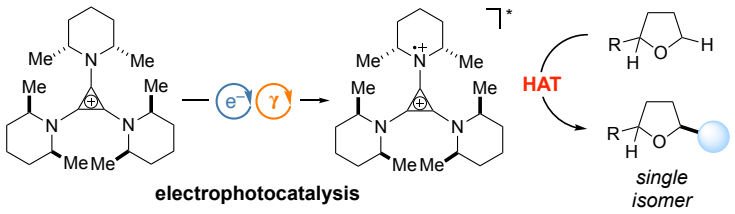
15. The THF should be pure and oxygen excluded because THF-peroxide contaminants can be converted to the same product without irradiation.

16. For related methods, see: (a) Zhang, L.; Yi, H.; Wang, J.; Lei, A. Visible-Light Mediated Oxidative C–H/N–H Cross-Coupling between Tetrahydrofuran and Azoles Using Air. *J. Org. Chem.* **2017**, *82*, 10704-10709. (b) Wu, J.; Zhou, Y.; Chiang, C.-W.; Lei, A. Electro-oxidative C(sp3)–H Amination of Azoles via Intramolecular Oxidative C(sp3)–H/N–H Cross-Coupling. *ACS Catal*. **2017**, *7*, 8320-8323.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