C–H Functionalization

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Direct α-Arylation of Ethers through the Combination of Photoredox-Mediated C–H Functionalization and the Minisci Reaction**

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Abstract: *The direct α-arylation of cyclic and acyclic ethers with heteroarenes has been accomplished through the design of a photoredox-mediated C–H functionalization pathway. Transiently generated α-oxyalkyl radicals, produced from a variety of widely available ethers through hydrogen atom transfer (HAT), were coupled with a range of electron-deficient heteroarenes in a Minisci-type mechanism. This mild, visible-light-driven protocol allows direct access to medicinal pharmacophores of broad utility using feedstock substrates and a commercial photocatalyst.*

Visible-light photoredox catalysis has recently emerged as a powerful tool for the functionalization of C–H and C–X bonds through numerous single-electron transfer (SET) pathways, a rapidly growing area of research that played a part in a large-scale renaissance of radical-based methodologies.[1] Recently, we sought to expand the types of organic molecules that can participate in photoredox-mediated C–H functionalization[2] by the exploitation of physical properties that are predictable across a wide range of structural classes (e.g., bond-dissociation energies (BDEs),[3] hydrogen-atom-transfer exchange constants,[4] and oxidation potentials; Figure 1). In previous work, we developed a photoredox organocatalytic C–H functionalization protocol that allows benzylic ethers to undergo selective α-oxy arylation (through radical–radical coupling) in the presence of functional groups that contain similar C–H bonds (e.g., amines, alcohols, and ethers with α-C–H functionality).[5] Herein, we report a photocatalytic mechanism that allows a complimentary class of organic molecules, namely dialkyl ethers, to formally undergo selective C–H bond functionalization and thereafter a Minisci-type coupling[6] with electron-deficient heteroarenes. This mild, visible-light-driven protocol enables the rapid conversion of feedstock ethers into α-oxy heteroarenes, an important and broadly employed pharmacophore in drug development.

Heteroaromatic moieties are undoubtedly among the most widespread constituents of pharmaceutical compounds.[7] Over the last decade, the direct C–H functionalization of heteroarenes has become a powerful and efficient transformation, with extensive applications in both medicinal and process chemistry.[8] Notably, the open-shell addition of alkyl groups to heteroarenes,[9] known as the Minisci reaction, has also enjoyed a broad scale re-adoption and application within drug discovery programs.[10] Recently, we questioned whether photoredox catalysis might be mechanistically coupled with the Minisci reaction to create a selective C–H functionalization/heteroarylation protocol that would convert cyclic and acyclic ethers to high-value pharmacophore adducts [Eq. (1), Figure 1]. When the use of nonfunctionalized ethers in the Minisci reaction was demonstrated in 1971, these exploratory studies required the use of metal salts or stoichiometric amounts of peroxides at high temperatures, a necessity that generally resulted in moderate or low yields and the production of a variety of radical-addition byproducts.[6] On this basis, we sought to develop a broadly useful α-oxyalkylation reaction that employs photoredox catalysis in conjunction with low-boiling feedstock ethers and mild conditions at room temperature. We hoped to develop

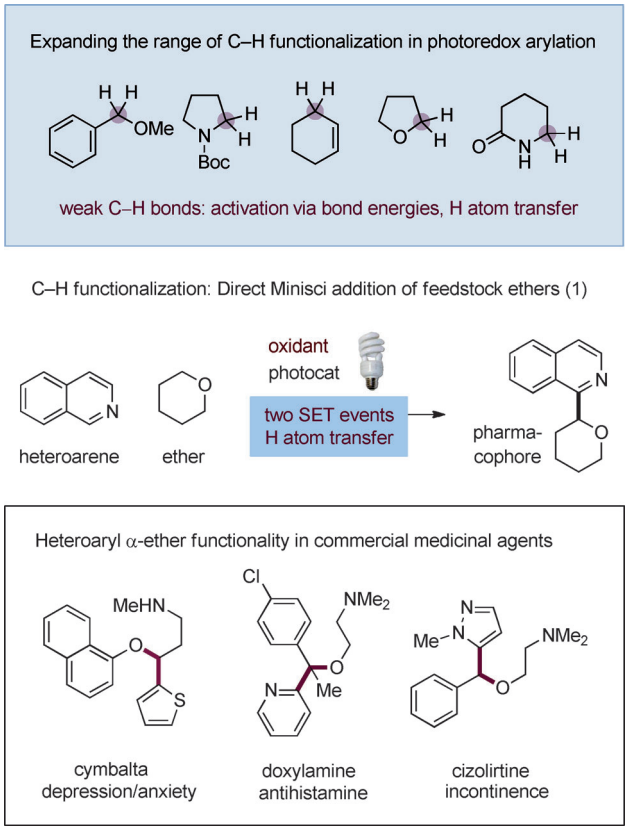

Figure 1. Photoredox-mediated C–H functionalization.

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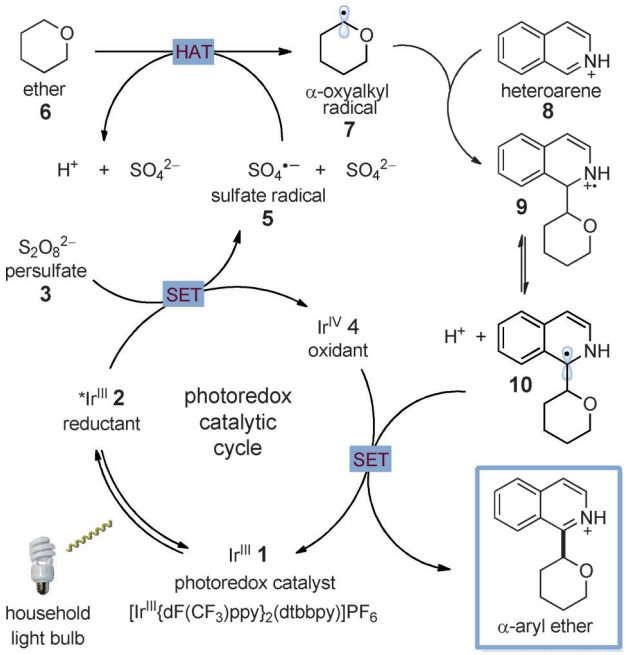
a complementary Minisci-type mechanism that enables a general, selective, and efficient C–H functionalization/heteroarylation reaction, and at the same time to deliver a protocol that can convert a broad range of cyclic and acyclic ethers to high-value pharmacophore adducts.

It has long been established that α-oxyalkyl radicals are relatively stable yet nucleophilic open-shell species that can readily react with electron-deficient substrates, such as olefins, imines, and heteroarenes.[11] However, the vast majority of photoredox-mediated C–H functionalization processes have been limited to α-alkyl- and α-aryl-substituted amines, while ethers and alcohols remain outside the scope of these SET/deprotonation pathways because of their comparatively high oxidation potentials (for THF, THP, and Et_2O, $E_{1/2}^{ox} > +2.4$ V vs. SCE in $MeCN/H_2O = 2:1$).[12] In an effort to expand the range of organic moieties that can participate in photocatalytic C–H functionalization (and to circumvent the limitations of an oxidation-potential-gated electron-transfer mechanism), we sought to employ a hydrogen-atom-transfer (HAT) pathway, that would allow hydrogen abstraction through photoredox catalysis in lieu of direct substrate oxidation. Previous studies in our group have shown that substrates that incorporate weak C–H BDEs, such as benzylic ethers, can be directly functionalized by the combination of an organocatalytic thiyl activation and photoredox catalysis.[5] In this study, we hypothesized that the intervention of a sulfate radical anion[13] should allow substrates that feature much stronger C–H BDEs, such as nonbenzylic dialkyl ethers, to be directly activated and thereafter employed in Minisci-type chemistry. Moreover, the successful application of this method would further demonstrate the utility of photoredox catalysis for medicinal chemistry.

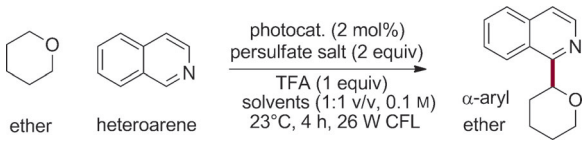
The mechanistic details of our proposed α-arylation of ethers are outlined in Scheme 1. Irradiation of photoredox catalyst $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (**1**) using visible light from a household light bulb at room temperature will produce a long-lived (2.3 μs) photoexcited state, $[*Ir^{III}\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (**2**).[14] Given that the resulting $*Ir^{III}$ species is a strong reductant ($E_{1/2}^{IV/*III} = -0.88$ V vs. SCE in $MeCN/H_2O = 2:1$),[12,15] we expected it to be capable of reducing the persulfate anion **3**[16] to afford $[Ir^{IV}\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (**4**), the sulfate dianion, and the sulfate radical anion (**5**).[13b] We presumed that the desired α-oxyalkyl radical **7** could then be generated through a HAT between the dialkyl ether **6** and the sulfate radical anion.[17] At this stage, we expected that the resulting α-oxyalkyl radical **7** would be sufficiently nucleophilic to add to the protonated electron-deficient heteroarene **8** in a Minisci-type pathway to afford the amine radical cation **9**. The cation **9**, upon loss of a proton, would give the α-amino radical **10**, which would undergo a second SET event with the oxidized photosystem **4** ($E_{1/2}^{IV/III} = +1.70$ V vs. SCE in $MeCN/H_2O = 2:1$)[12] to regenerate the ground state of photocatalyst **1** and furnish the desired α-aryl ether product.

The α-oxyalkyl radical **7** might be generated through two distinct mechanisms: 1) hydrogen-atom abstraction or 2) direct single-electron oxidation followed by deprotonation. While we cannot definitively rule out the latter possibility, we favor the proposed HAT pathway based on mechanistic evidence from the literature. Studies of the reaction of $SO_4^{\bullet-}$ and ethers by transient absorption spectroscopy,[18a] kinetic isotope effects,[18b] and correlation between BDEs and reaction rates[18c] are consistent with HAT as the operative mechanism. In the related case of alcohols, both ESR experiments[18b] and Minisci-type trapping reactions[13a] suggest that hydrogen abstraction, not SET/deprotonation, is the dominant pathway in the generation of α-oxyalkyl radicals mediated by sulfate radical anions.[19]



Scheme 1. Proposed mechanism for the α-arylation of ethers.

Table 1: Preliminary studies toward α-heteroarylation of ethers.

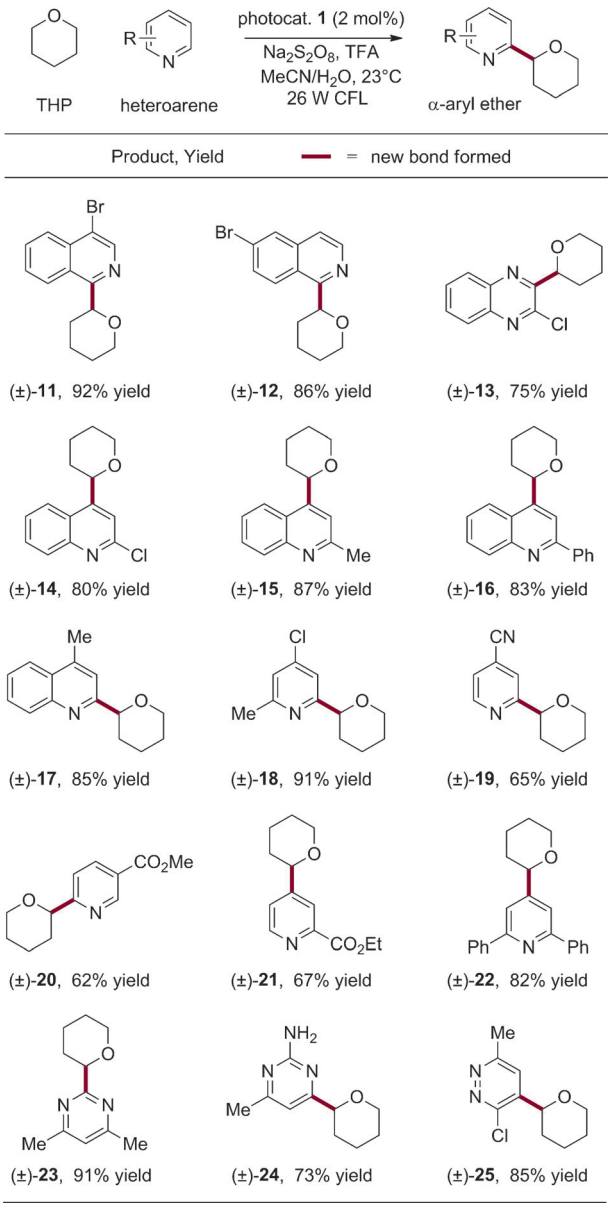


Entry	Photocatalyst	Persulfate salt	Solvents	Yield [%][a]
1	$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	$(NH_4)_2S_2O_8$	MeCN	68
2	$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	$(NH_4)_2S_2O_8$	$MeCN/H_2O$	77
3	$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	$K_2S_2O_8$	$MeCN/H_2O$	79
4	$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	$Na_2S_2O_8$	$MeCN/H_2O$	81
5	$[Ir(ppy)_3]$	$Na_2S_2O_8$	$MeCN/H_2O$	7
6	$[Ir(ppy)_2(dtbbpy)]PF_6$	$Na_2S_2O_8$	$MeCN/H_2O$	28
7	$[Ru(bpy)_3]Cl_2$	$Na_2S_2O_8$	$MeCN/H_2O$	22
8	$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	$Na_2S_2O_8$	$EtCN/H_2O$	88
9[b]	$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	$Na_2S_2O_8$	$EtCN/H_2O$	<1
10	none	$Na_2S_2O_8$	$EtCN/H_2O$	4

[a] Yield determined by ^1H NMR spectroscopy using 1,3-benzodioxole as the internal standard after work-up following the general procedure described in the Supporting Information. [b] Reaction performed in the absence of light. TFA = trifluoroacetic acid. CFL = compact fluorescent light.

Our examination of the proposed α-arylation of ethers began with tetrahydropyran (THP), isoquinoline, and a series of photocatalysts and persulfates (Table 1). To our delight, the desired α-arylation product was obtained in 68% yield using photocatalyst **1** in combination with $(NH_4)_2S_2O_8$ as the oxidant in MeCN under the irradiation of a 26 W household fluorescent light bulb (entry 1). The regioselectivity of the addition at the C1 position of isoquinoline was fully expected based on the previously described polar effect.[20] Notably, the addition of water allowed an increase in yield (entry 2, 77%), presumably in part because of the dissolution of the persulfate salt to generate a transparent biphasic reaction mixture, a measure that allows enhanced photon penetration. Changing the oxidant to $K_2S_2O_8$ improved the efficiency slightly, whereas the use of the more economical salt $Na_2S_2O_8$ provided the heteroarylation product in a superior yield of 81% (entries 3 and 4). An examination of several photocatalysts showed that photocatalyst **1** was most effective in this α-arylation protocol (entries 5–7). It is intriguing to consider that in comparison to $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (**1**), the less successful $[Ir(ppy)_3]$ and $[Ir(ppy)_2(dtbppy)]PF_6$ catalysts are more reducing at the $*Ir^{III}$ excited state, yet less oxidizing in the Ir^{IV} species, while $[Ru(bpy)_3Cl_2]$ exhibits a less reducing $*Ru^{II}$ species, yet more oxidizing Ru^{III} species.[21–23] As such, we speculate that matched redox potentials are essential for both SET events to be efficient, a scenario that requires a highly tuned photocatalyst with respect to its intrinsic redox window. As a second issue, we were aware that the α-C–H bonds of the ether product are weaker than those of the ether starting materials, which could lead to multiple arylation or product decomposition events.[6b] Indeed, we did observe oxidative dimerization of the arylation products in a small number of cases, however, with isoquinoline substrates, the use of EtCN as the reaction medium alleviated this issue (providing the desired adduct in 88% yield, entry 8). We hypothesize that EtCN, as a less polar solvent than MeCN, may be decreasing the different rates of electron transfer in our proposed mechanism. This would reduce the rate of production of the implicated radicals and at the same time suppress the formation of undesired by-products through higher-energy pathways. Given that the reduction potential of the persulfate anion is low,[16] we expected that this reagent would be unable to react with the substrate ethers without further activation. Indeed, the critical roles of the photocatalyst and light in this α-arylation method were demonstrated using control experiments, wherein minimal amounts of the desired product were detected in the absence of photoexcitation by visible light (entries 9 and 10).

Having identified the optimal conditions for this α-arylation protocol for ethers, we next focused on examining the scope of the heteroarene component (Scheme 2). A variety of electron-deficient heteroarenes readily coupled with THP in good to excellent yield at the most electrophilic site. Notably, bromo or chloro substituents at the C4 and C6 positions of isoquinoline are well tolerated, along with the C2 positions of both quinoxaline and quinoline (products **11**–**14**, 75–92% yields). Moreover, the use of 2-methyl- or 2-phenylquinoline resulted in the selective alkylation with THP at the C4 position, while 4-methylquinoline underwent coupling

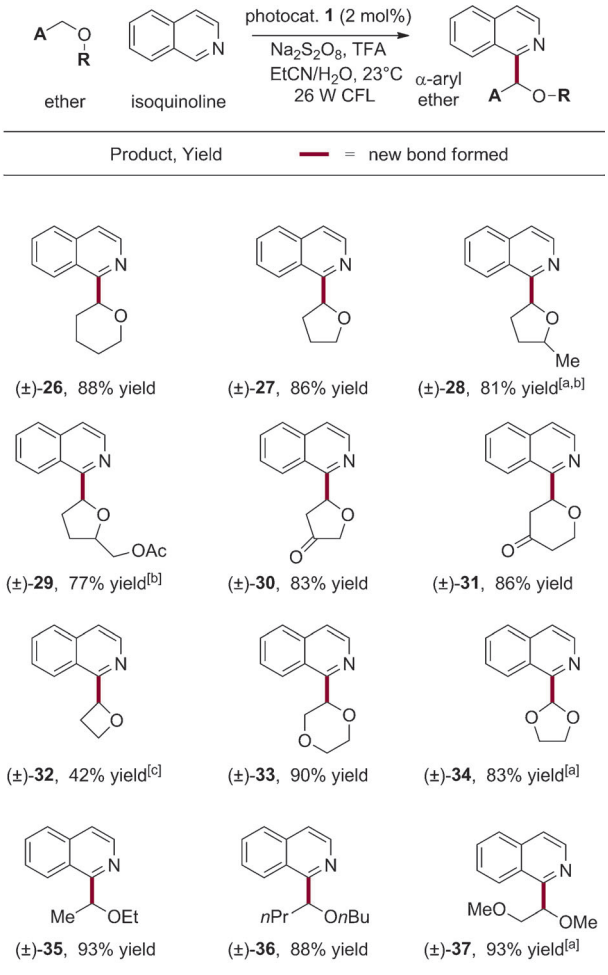


Scheme 2. Scope of heteroarenes in the Minisci ether addition. Yields are those of products isolated by column chromatography. A large excess of ether (25–50 equiv) is typically employed in these transformations. See the Supporting Information for experimental details.

exclusively at the C2 position (products **15**–**17**, 83–87% yields). It is important to note that various pyridine derivatives with electron-withdrawing groups reacted well in this ether-arylation protocol (products **18**–**22**, 62–91% yields). Dimethylpyrimidine readily participated in this coupling with THP at the C2 site in 91% yield (product **23**). It should be noted that the use of free amine substituents on the aromatic ring resulted in diminished reactivity toward the addition of the nucleophilic α-oxyalkyl radical. More specifically, the coupling of 2-amino-4-methylpyrimidine with THP required 48 h to reach full conversion, albeit in a useful 73% yield (product **24**). Again, high levels of regioselectivity were obtained with pyridazine-based heteroarenes, providing the

ortho-chloro-substituted alkylation adduct with almost complete site selectivity (product **25**, 85% yield).

Next, we explored the scope of the ether component in this α-heteroarylation protocol (Scheme 3). A range of cyclic and acyclic ethers were suitable coupling partners. Besides tetrahydropyran (product **26**, 88% yield), a series of tetrahydrofurans were amenable to direct addition with isoquinoline (products **27**–**29**, 77–86% yields). It should be noted, however, that for 2-methyltetrahydrofuran both the α-oxy methylene and α-oxy methine sites underwent arylation with approximately 4:1 regioselectivity for the less-hindered position (product **28**, 81% yield). With this result in mind, it is intriguing to consider that the use of tetrahydrofurfuryl acetate led to the arylation of α-methylene with complete regioselectivity, a remarkable finding given the three available α-oxy positions containing C–H bonds (product **29**, 77% yield). Moreover, the use of 3-oxotetrahydrofuran selectively



Scheme 3. Scope of ethers in the photoredox-mediated ether addition. Yields are those of products isolated by column chromatography. A large excess of ether (25–50 equiv) is typically employed in these transformations. See the Supporting Information for experimental details. [a] Regiomeric ratio (r.r.) determined by ^{1}H NMR spectroscopy. **28**: 3.5:1 r.r.; **34**: 3:1 r.r.; **37**: 2.3:1 r.r. [b] Diastereomeric ratio (d.r.) determined by ^{1}H NMR spectroscopy. **28**: 1.3:1 d.r.; **29**: 2:1 d.r. [c] MeCN used as the only solvent; 2 equiv of $(n\text{Bu})_4\text{NCl}$ added; no TFA added.

gave the C5-arylation product in the presence of a β-carbonyl group, effectively leaving the α-position of the carbonyl group untouched (product **30**, 83% yield). A similar level of regiocontrol and efficiency was achieved with 4-oxotetrahydropyran (product **31**, 86% yield). Recently oxetanyl moieties have emerged as a valuable new structural element in drug discovery.[24] However, at the present time, there are few synthetic methods that allow the facile introduction of oxetane in a direct and routine fashion into medicinal agents.[24,25] We initially found that the use of this strained ring system led to an oxetanyl radical that underwent ring-opening polymerization under our optimal aqueous/acidic conditions. Gratifyingly, when the coupling of oxetane and isoquinoline was carried out in MeCN (0.05 M) with the addition of $(n\text{Bu})_4\text{NCl}$ to help solubilize the persulfate anion, the desired product was obtained in a useful yield of 42% (product **32**). It should be noted that 1,4-dioxane is also amenable to this arylation protocol (product **33**, 90% yield), while 1,3-dioxolane provided the masked formyl analogue in 62% yield (product **34**, 83% yield, r.r. 3:1). The use of acyclic dialkyl ethers was also demonstrated by the use of the diethyl and dibutyl variants, both providing the heteroarylation adducts in excellent yield (product **35** and **36**, 93% and 88% yields, respectively). The coupling of diethyl ether is of particular interest, as its volatility (b.p. 35 °C) renders it incompatible with the temperatures required for thermal radical generation (80–90 °C).[6b,c] Moreover, dimethoxyethane underwent the arylation at both the methylene and methyl sites (r.r. 2.3:1) with high efficiency (product **37**, 93% yield).

In summary, we have developed a photoredox catalytic approach to the direct α-arylation of ethers with electron-deficient heteroarenes. This visible-light-promoted method shows a broad scope with regard to both the dialkyl ether and heteroarene substrates, providing consistently high yields of α-oxyalkylated arenes. Remarkably, this $C(sp^3)$–$C(sp^2)$ bond construction was achieved efficiently through C–H functionalization of both the coupling partners at room temperature, thereby allowing the coupling of even highly volatile ether substrates. We anticipate this new photoredox-mediated C–H functionalization/Minisci addition will find broad application in both the academic and pharmaceutical sciences.

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