Activation of C–H Bonds via the Merger of Photoredox and Organocatalysis: A Coupling of Benzylic Ethers with Schiff Bases

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ABSTRACT: The photoredox-mediated coupling of benzylic ethers with Schiff bases has been accomplished. Direct benzylic C–H activation by a combination of a thiol catalyst with an iridium photocatalyst and subsequent radical–radical coupling with secondary aldimines affords a variety of β-amino ether products in good to excellent yields. Mechanistic studies suggest that a reductive quenching pathway of the photocatalyst is operable.

The direct and controlled C–H functionalization of sp³-hybridized carbons has become a challenging goal in modern synthetic organic chemistry.¹ In this context, our laboratory has recently introduced a protocol that allows the activation and subsequent arylation of benzylic C–H bonds via the cooperative action of a photoredox catalyst and a thiol organocatalyst (eq 1).² This transformation relies on the coupling of two catalytically generated radicals: an arene radical anion formed by reduction of an aryl nitrile, and a benzyl ether radical generated by thiol-mediated hydrogen atom abstraction from benzylic ethers. Moreover, we postulate that the thiol organocatalyst undergoes oxidative proton-coupled electron transfer (PCET)³ in the presence of photoexcited catalysts to generate the requisite thiyl radical⁴ that can selectively cleave the C–H bond of benzylic ethers.⁵ This photoredox–organocatalysis C–H functionalization mechanism exploits several established physical properties (e.g., bond dissociation energies (BDEs),⁶ hydrogen atom transfer exchange constants,⁷ and oxidation potentials) that are predictable across a wide range of reaction classes. Herein we translate this general C–H functionalization concept to the direct coupling of benzyl ethers with secondary aldimines to afford β-amino ethers in one step (eq 2). This new radical–radical coupling protocol employs readily available substrates, a visible light source, and the combination of a thiol catalyst and photocatalyst.

The β-amino ether functionality is a widespread motif in synthetic organic chemistry. However, the synthesis of these structural units is often challenging and typically requires multiple steps, organometallic reagents, and immoderate reaction conditions.⁸ With this in mind, we questioned whether photoredox catalysis would allow the concurrent generation of α-benzylic ether radical 1 (via oxidation) and α-amino radical anion 2 (via reduction) prior to a critical heterocoupling of these two highenergy species (eq 2). Importantly, this new multi-catalysis reaction mechanism would be organocatalytic, redox-neutral, as well as atom-economical and should provide an unprecedented and non-classical C=C disconnection that will find utility in the fields of medicinal chemistry and organic molecule construction.

Design Plan. The proposed catalytic cycle of our new light-driven redox transformation is depicted in Scheme 1.¹⁰ It has long been established that the photoredox catalyst IrIII(ppy)₂(dbbpy)PF₆ (3) will be photoexcited to the *Ir³⁺ state...
state 4 by visible light irradiation with a household light bulb or blue LEDs. Excited species 4 can function as an oxidant ($E^{1/2}_{1/2} = +0.66$ V vs SCE in MeCN) and can be quenched by the thiol catalyst methyl thioglycolate (6) to produce Ir$^{III}$ppy$_2$(dtbbpy) (5), as well as thyl radical 7.

Although the oxidation potential of typical thiols ($E^{1/2}_{1/2} = +0.85$ V vs SCE for cysteine) should render this electron transfer unfavorable, we expect that the addition of a weakly basic additive (K$_2$HPO$_4$ or LiOAc) would facilitate the formation of thyl radical 7 via a concerted PCET event. In order to close the photoredox cycle, Ir$^{II}$ species 5 ($E^{1/2}_{1/2} = -1.51$ V vs SCE) should be reduced to the N-aryl imine 8 ($E^{1/2}_{red} = -1.98$ V vs SCE for R = Ar = Ph) under the reaction conditions via a single-electron transfer (SET) event to afford the $\alpha$-amino radical anion 9. With respect to BDEs, thyl radical 7 should readily abstract a hydrogen atom from benzyl ether substrate 10 ($\alpha$-C–H BDE = 85.8 kcal/mol for benzyl methyl ether) and to complete the organocatalytic cycle. We assume the resulting benzyl radical 11 will rapidly combine with $\alpha$-amino radical anion 9 to afford the desired $\beta$-amino ether product. This critical C–C bond-forming step should be facilitated by the persistent radical effect, wherein species 9 is a long-lived open-shell species that does not readily homodimerize, thereby enabling a highly selective radical–radical heterocoupling event.

Although a radical–radical coupling is proposed we are aware that an addition of benzylic radical 11 into imine 8 followed by reduction of the N-centered radical is also feasible. However, we consider this pathway as unlikely since imine dimer and imine reduction byproducts have been observed in certain cases.

**Results.** The proposed ether–imine coupling was first evaluated with a series of established photoredox catalysts (Table 1). Initially we found that irradiation of benzyl methyl ether, imine 12, methyl thioglycolate (6), and K$_2$HPO$_4$ with visible light in the presence of Ir(ppy)$_3$, or Ru(bpy)$_3$Cl$_2$, resulted in no observable yield of the desired 1,2-amino ether product (entries 1 and 2). Fortunately, however, use of the heteroleptic catalyst Ir(ppy)$_2$(dtbbpy)PF$_6$ (3) provided the desired $\beta$-amino ether in 42% yield (entry 3). The efficiency of this heteroradical coupling was further improved by irradiating the photocatalyst with blue LEDs (entry 4, 75% yield). Notably, the use of n-Bu$_4$NOAc as a more operationally convenient additive at the 10 mol% level resulted in diminished yields (entry 5, 55% yield), we found that the use of the soluble LiOAc (entry 6, 22% yield). These results are consistent with the requirement of a soluble base that enables a concerted PCET mechanism for the formation of thyl radical 7 (Scheme 1). We recognize that a stepwise pathway may also be operable, wherein deprotonation of the thiol catalyst could precede the oxidation of the resulting thiolate anion (mechanistic studies are ongoing to delineate between these two pathways). As an effective alternative to the hygroscopic n-Bu$_4$NOAc, we have established LiOAc (entry 8) as a more operationally convenient additive at 10 mol% loading (entry 9). In addition, we have found that DMA is the superior medium for this process while solvents such as MeCN or DMSO are also competent (entries 10 and 11, 73% and 70% yield). Finally, control experiments verified the requirement of light, an organocatalyst, and a photocatalyst, as no product was observed in the absence of these components (entries 12–14).

**Reaction Scope.** With the optimal coupling conditions in hand, we next sought to determine the scope of aldimines that can be employed in this new radical–radical heterocoupling protocol. As shown in Table 2, electronically "neutral" imines...
(entry 1, 77% yield), as well as electron-rich arenes, increase the overall coupling efficiency (entries 2−4, 79−85% yield). We rationalized that electron-rich α-amino radicals are more nucleophilic and thereby more rapidly react with benzylic radical 11, resulting in generally higher yields. In addition, bicyclic arenes, such as naphthalene (entry 5, 85% yield) the heteroaromatic quinoline (entry 6, 58% yield) are well tolerated.

With respect to the aniline-derived moiety of the imine, we found that strongly electron-donating and -withdrawing groups have a deleterious effect on overall reaction yield (entries 7 and 8, 61% and 56% yield); yet, high efficiency is achieved when halogen atoms are introduced at the para-positions (entries 9 and 10, both 84% yield). Also, aldimines that incorporate a CF3 group or pyridine-based heteroaromatics were found to be viable coupling partners for this redox process (entries 11−14, 58−75% yield).

Next we focused on expanding the range of benzylic ethers in this dual catalysis protocol (Table 3). To our delight we found that electron-rich ethers give the desired products in high yield (entry 1, 85% yield), along with para-, meta-, and ortho-substituted arenes (entries 1−4, 73−85% yield). With respect to the potential for broad application, it is important to recognize...
that a variety of protecting groups are well tolerated in this C−C bond forming process (entries 5−8, 70−82% yield). Moreover, cyclic ethers such as phthalane and isochromane are useful substrates, further demonstrating the versatility of this photoredox reaction (entries 9−11, 62−75% yield). Perhaps most notably, a wide range of heteroaromatic-containing ethers can be readily implemented using these reaction conditions (entries 12−14, 45−54% yield), an important consideration with respect to medicinal chemistry applications.

During the course of these studies, we rationalized that the rate of this transformation is likely dependent on the number of photons penetrating the reaction vessel and is therefore dependent on the illumination surface area. Thus, we investigated the progress of this transformation with respect to the size and nature of the reaction containers employed. It was shown that the typical reaction with N-phenyl imine 12 and benzyl methyl ether was slowest (22 h) in a standard reaction vial (as used in Tables 1−3). Indeed, when the same transformation was conducted in an NMR tube, the reaction proceeded with a significantly faster reaction rate with complete product formation determined at 14 h. However, the fastest protocol we have achieved thus far for this β-amino ether formation (6 h to completion) has been accomplished by maximizing the surface area via the use of PFA tubing as a reaction vessel.18 These results clearly demonstrate that (i) this transformation as currently performed is photon-limited with respect to the overall rate and (ii) it will likely be well suited to reaction scale-up via flow protocols.

Last, to provide further mechanistic insight into the pathway of this new photoredox coupling, we have conducted a series of Stern−Volmer quenching studies19 with Ir(ppy)2(dbbpy)PF6 (3), benzalaniline, butyl thioglycolate (41),20 and n-Bu4NOAc as a soluble additive.21 As shown in Figure 1, these investigations clearly demonstrate the thiyl catalyst 41 can indeed quench the excited photocatalyst, but only in the presence of the acetate base (no quenching was observed by the thiyl in the absence of acetate). In addition, benzalaniline quenches the excited photocatalyst only to a minor extent,19 suggesting that a reductive quenching pathway is likely.

**ASSOCIATED CONTENT**

# Supporting Information
Procedures and spectral data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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**Notes**

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

Financial support was provided by NIH/NIAMS (RO1 GM103558-03), and kind gifts from Merck and Amgen. D.H. is grateful for financial support from the German Research Foundation (DFG).

**REFERENCES**


