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Selective Hydrogen Atom Abstraction through Induced Bond Polarization: Direct α-Arylation of Alcohols through Photoredox, HAT, and Nickel Catalysis

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Abstract: *The combination of nickel metallaphotoredox catalysis, hydrogen atom transfer catalysis, and a Lewis acid activation mode, has led to the development of an arylation method for the selective functionalization of alcohol α-hydroxy C–H bonds. This approach employs zinc-mediated alcohol deprotonation to activate α-hydroxy C–H bonds while simultaneously suppressing C–O bond formation by inhibiting the formation of nickel alkoxide species. The use of Zn-based Lewis acids also deactivates other hydridic bonds such as α-amino and α-oxy C–H bonds. This approach facilitates rapid access to benzylic alcohols, an important motif in drug discovery. A 3-step synthesis of the drug Prozac exemplifies the utility of this new method.*

Alcohols represent one of the most ubiquitous functionalities found among organic molecules, and typically found in nature in the form of sugars, steroids, and proteins, while synthetic variants are found across a broad range of pharmaceutical agents.[1] With respect to their reactivity profiles, alcohols commonly function as oxygen-centered nucleophiles via their lone pairs, or alternatively as a source of protons due to the extensive polarization of O–H bonds. In contrast, the use of unactivated alkyl alcohols (C–OH) as a source of carbon-centered nucleophiles remains relatively unknown.[2] Recently, a number of research groups, including our own, have demonstrated that the combined action of photoredox and nickel catalysis can deliver a broad range of C–C and C–X bond-forming transformations.[3,4] As part of these studies, we have further recognized that native functionality can be readily harnessed as coupling partners in transition-metal catalysis, an attractive finding given the widespread availability of these biomass feedstocks. Recently, we demonstrated that electron-rich C–H bonds adjacent to amine and ether functionalities can serve as useful precursors to carbon-centered radicals through hydrogen atom transfer (HAT) with catalytically generated aminium radical cations.[5] In those abstraction/coupling studies, selectivity is governed by well-established polar effects in the key HAT event, which allows kinetically controlled functionalization of hydridic C–H bonds in the presence of much weaker, polarity-mismatched C–H bonds.[6] With this in mind, we recently sought to develop a catalytic HAT/cross-coupling reaction that would selectively target α-alcohol C–H bonds in the presence of a wide range of strong, weak, hydridic, acidic, and/or neutral C–H or O–H bonds. By leveraging this HAT manifold, we hypothesized that it would be feasible to develop a method that enables the chemoselective arylation of alcohols at the α-C–OH carbon atom in lieu of the more common oxygen-centered variant,[7] without requiring pre-oxidation to the carbonyl. Herein, we describe the successful execution of these design ideals and provide a mechanistically unique approach to the construction of benzylic alcohols from aryl halides and aliphatic alcohols (Figure 1).

From the outset, we recognized that the successful development of an α-alcohol arylation reaction through HAT and nickel catalysis would require 1) chemoselective

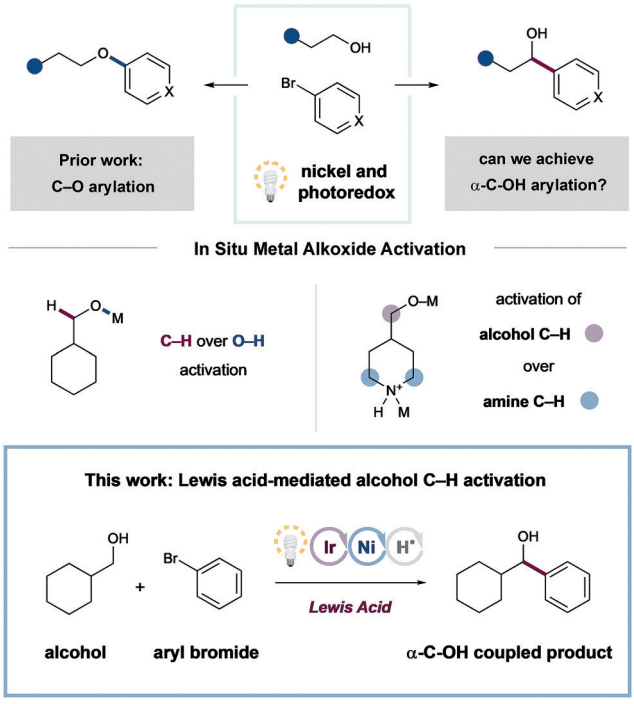

Figure 1. The reactivity of alcohols.

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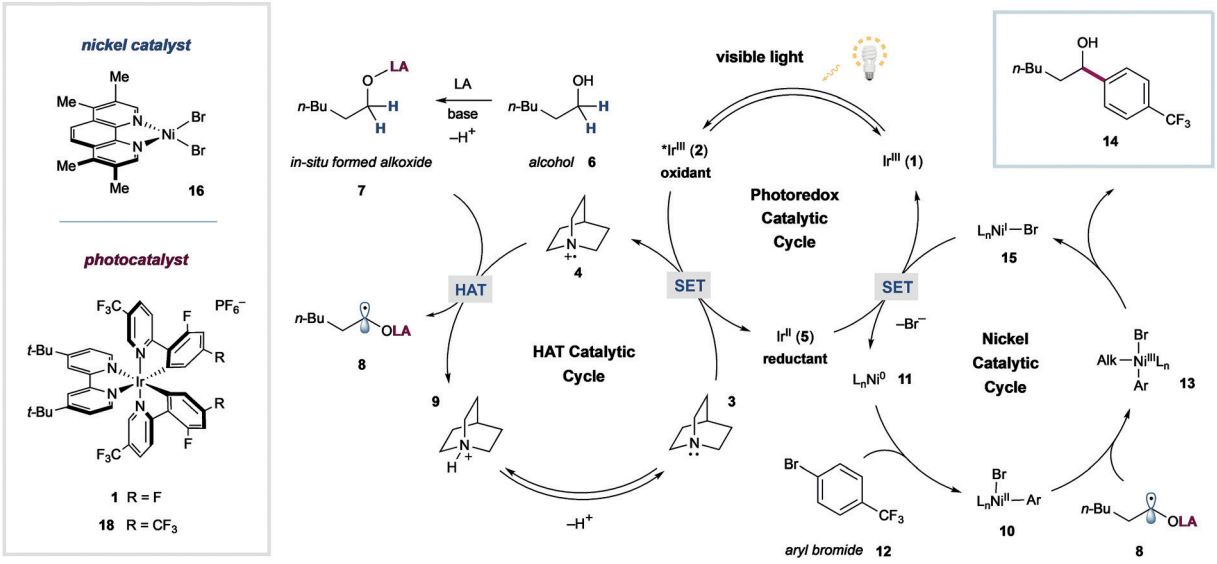
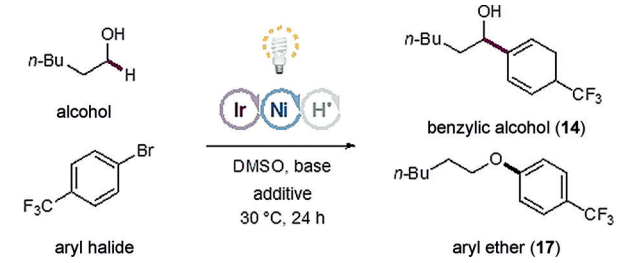
formation and coupling of an α-C–OH carbon-centered radical in the presence of α-CH-amines and other electron rich C–H bonds, and 2) comprehensive suppression of the more common C–O arylation mechanism—a pathway that readily operates under the influence of photoredox and nickel catalysis.[2b] Based on our prior work utilizing hydrogen-bond donors to selectively activate alcohols,[5a] we hypothesized that exposure of alcohol coupling partners to Lewis acids in the presence of a base should lead to metal alkoxide systems that exhibit greatly enhanced hydridic character at the α-alkoxy C–H positions. As a consequence, we anticipated that any subsequent HAT events would be dramatically accelerated at these α-alkoxy carbons if we were to use polarity-matched ammonium radical cations to perform the hydrogen abstraction step.[8] In contrast, the same Lewis acids are known to datively coordinate to electron-rich amines (without deprotonation), which retards the rate of HAT at the resulting α-ammonium-metal C–H bond due to concomitant loss of hydridic character. With respect to the question of C- versus O-arylation chemoselectivity, we felt that judicious selection of Lewis acid would lead to a metal alkoxide species that might not readily participate in transmetalation with the key Ni^{II}aryl catalytic intermediate, a critical step towards suppressing the possibility of aryl ether formation.[9]

Our mechanistic hypothesis (Scheme 1) begins with photoexcitation of the Ir^{III} photocatalyst $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (**1**) with visible light to produce the long-lived excited-state complex $*Ir^{III}$ (**2**), which is a strong oxidant ($E_{1/2}^{red}$ $[*Ir^{III}/Ir^{II}] = +1.21$ V vs. SCE in MeCN).[10] Oxidation of the HAT catalyst quinuclidine (**3**) by the excited state of the photocatalyst should be facile ($E_p[Quinuclidine^{\bullet+}/Quinuclidine] = +1.1$ V vs. SCE in MeCN), delivering the radical cation **4** and Ir^{II} complex **5**.[11] Concomitantly in solution, a Lewis acid can coordinate to the alcohol substrate **6**, such that an inorganic base can facilitate deprotonation to yield the Lewis acid bound alkoxide **7**. The quinuclidinium radical cation **4** is electronically matched to abstract an electron-rich hydrogen atom from the α-alkoxy position of in situ formed alkoxide **7** to furnish α-alkoxy radical **8**.[11] The Ni^{II} aryl halide complex **10**, generated as a result of oxidative addition of Ni^0 **11** into aryl halide **12**, can intercept the α-alkoxy radical **8** to generate the Ni^{III}-aryl,alkyl species **13**. Subsequent reductive elimination should furnish benzylic alcohol **14** and Ni^I complex **15**. Finally, single-electron transfer between the reduced Ir^{II} state of the photocatalyst **5** and Ni^I species **15** should close both catalytic cycles simultaneously. At this stage, the quinuclidinium ion **9** would then be deprotonated by a stoichiometric inorganic base to regenerate the quinuclidine HAT catalyst (**3**). Our investigation into this new alcohol coupling method began with exposure of *n*-hexanol, 4-bromobenzotrifluoride, photocatalyst **1**, $NiBr_2{\cdot}Me_4phen$ (**16**), and stoichiometric quinuclidine **3** (to function as both the HAT catalyst and base) to a blue LED lamp. As expected, significant amounts of the ether alcohol product (**14**) were obtained (Table 1, entry 1, 3% yield). To expediently evaluate a large range of Lewis acid additives, we opted to optimize this coupling method by utilizing high-throughput experimentation (HTE; see the Supporting Information for details). To this end, 24 Lewis acid additives were rapidly evaluated in a range of solvents, with zinc salts and DMSO proving to be uniquely effective in comprehensively suppressing ether formation (entries 2 and 3). By reducing the quinuclidine loading to 30 mol% and introducing an inorganic base, significant improvements in efficacy were observed (entries 4–6). Finally, changing the photocatalyst to the more oxidizing $Ir[FCF_3(CF_3)ppy]_2(dtbbpy)PF_6$ (**18**) ($E_{1/2}^{red}$ $[*Ir^{III}/Ir^{II}] = +1.25$ V vs. SCE in MeCN) led to a further increase in yield (entry 7).[12] In all cases, a small amount of a ketone byproduct was observed, likely formed as a result of the in situ oxidation of alcohol product **14**.[13] The ketone can be readily reduced to the desired alcohol product, thereby simplifying purification and increasing the overall yield of the transformation.[14]

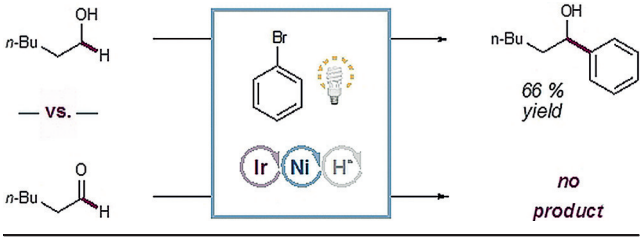


Scheme 1. Proposed mechanism for the arylation of α-hydroxy C–H bonds through a combination of photoredox, HAT, and nickel catalysis.

Table 1: Optimization of Lewis acid mediated C- versus O-arylation.[a]



Entry	Additive	Base	% Yield (**alcohol**/ether)[b]
1	None	quinuclidine	**3**/54
2	$ZnCl_2$	quinuclidine	**44**/0
3	$ZnBr_2$	quinuclidine	**48**/0
4	$ZnCl_2$	NaOH	**66**/0
5	$ZnCl_2$	K_3PO_4	**60**/0
6	$ZnBr_2$	K_3PO_4	**52**/0
7[c,d,e]	$ZnCl_2$	K_3PO_4	**74**/0
8[c,d,e,f]	$ZnCl_2$	K_3PO_4	**65**/0



[a] Performed on a 10 μmol scale with photocatalyst **1** (0.5 mol%), $NiBr_2$·Me_4phen (0.5 mol%), quinuclidine (30 mol%), aryl halide (1.0 equiv), alcohol (5.0 equiv), additive (1.5 equiv), base (1.0 equiv) in DMSO (0.25 M). [b] Yield determined by UPLC or ^{1}H NMR analysis. [c] Reaction conducted on 0.3 mmol scale. [d] Photocatalyst (0.2 mol%), $NiBr_2$·Me_4phen (1.5 mol%). [e] Performed with photocatalyst **19**. [f] 3 equiv of alcohol.

Control experiments demonstrated that the photocatalyst, nickel catalyst, quinuclidine, and visible-light irradiation were all requisite components.[15] Finally, decreasing the equivalents of alcohol did not lead to a substantial decrease in efficiency (entry 8). Notably, when the analogous aldehyde (hexanal) was subjected to the optimized reaction conditions, none of the desired alcohol or ketone where obtained.[15]

With optimized conditions in hand, we next evaluated the scope of this transformation (Table 2). Aryl halides bearing electron-withdrawing substituents such as trifluoromethyl, carboxymethyl, and sulfonamide groups, delivered the corresponding benzylic alcohols in excellent yields (**14**, **19**–**25**, 56–83% yield). Electron-neutral and electron-rich aryl bromides also performed well in this transformation (**26**–**30**, 56–70% yield). Importantly, *ortho* and *meta* substitution are tolerated (**31** and **32**, 44% and 61% yield, respectively). Moreover, 3- and 4-chloropyridines delivered the corresponding heteroarylated alcohols with good efficiency (**33**–**37**, 40–74% yield). Interestingly, these substrates required the use of magnesium chloride as the Lewis acid additive.[16]

We next examined the scope of this transformation with respect to the alcohol component (Table 2). Remarkably, the simplest carbinol, methanol, can be employed in this transformation, furnishing the corresponding benzylic alcohol (**38**, 51% yield). Simple aliphatic alcohols are generally competent substrates for this C–H arylation (**14** and **39**–**41**, 63–75% yield). Moreover, deuterated ethanol furnishes the corresponding phenethyl alcohol in good yield (**40**, 63% yield). Alcohols containing weak benzylic C–H bonds are exclusively functionalized at the α-hydroxy position (**42** and **43**, 66 and 59% yield, respectively). Acyclic and cyclic β,β-disubstituted alcohols also perform well (**44**–**47**, 49–66% yield). A variety of alcohols bearing γ-electron-withdrawing groups also coupled efficiently despite inductive deactivation of the α-hydroxy C–H bonds towards HAT in these substrates (**47**–**49**, 56–70% yield). Notably, protected and unprotected diols were competent coupling partners in this transformation, furnishing monoarylated products exclusively (**51**–**53**, 58–68% yield). Finally, a variety of heteroatom-containing alcohols, which possess multiple hydridic C–H bonds, furnished the products with exclusive functionalization at the α-hydroxy C–H position (**54**–**57**, 46–71% yield).[17]

As a further demonstration of the utility of this α-hydroxy C–H arylation method, we sought to rapidly construct the medicinal agent Prozac (Figure 2). Indeed, subjecting protected *N*-methyl propanolamine (**58**) to the optimized coupling conditions with bromobenzene delivered benzylic alcohol **59**. The ethereal linkage present in the drug molecule was then constructed by utilizing our metallaphotoredox etherification method to deliver **60**, which following deprotection furnished Prozac·HCl in 50% overall yield and in only three steps from a simple, protected amino alcohol. Perhaps most notable is the chemo- and regioselectivity (>20:1) for the desired C–C coupling reaction at the α-alcohol C–H position without ether formation or arylation of the α-methyl amine.

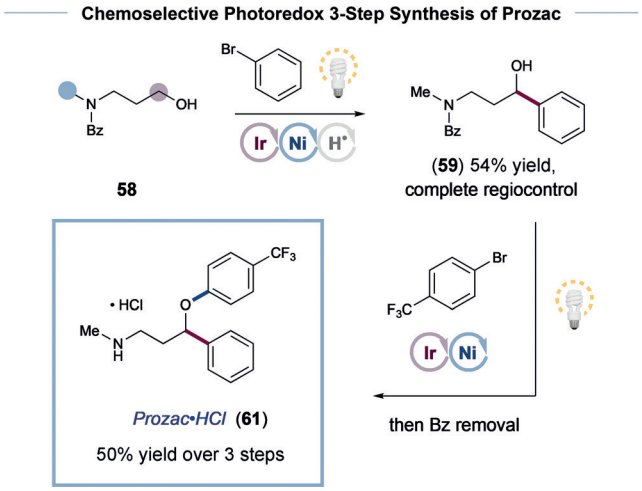
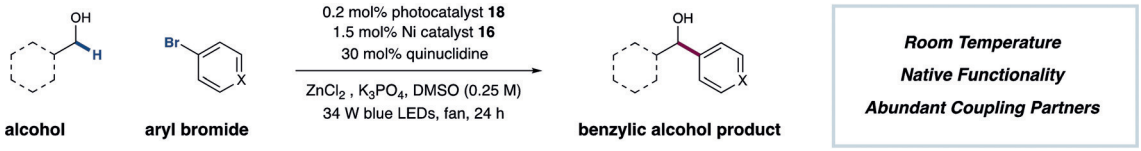
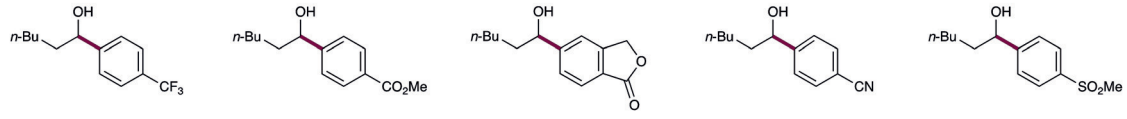


Figure 2. Synthesis of Prozac. See the Supporting Information for experimental details.

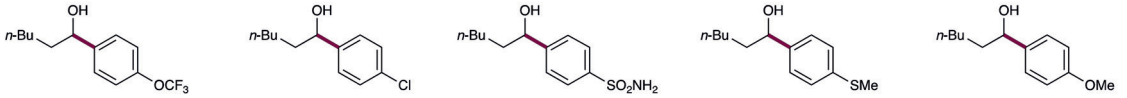
Table 2: Scope of the α-hydroxy C–H arylation, including tolerance of α-amino and α-ether C–H bonds.[a]



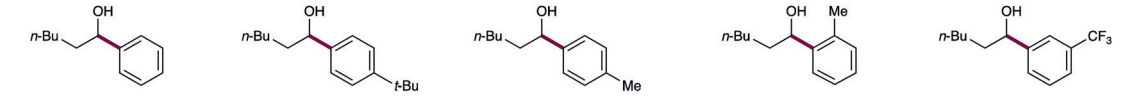
arenes



(±)-**14**, 75% yield; (±)-**19**, 74% yield; (±)-**20**, 71% yield; (±)-**21**, 56% yield; (±)-**22**, 73% yield

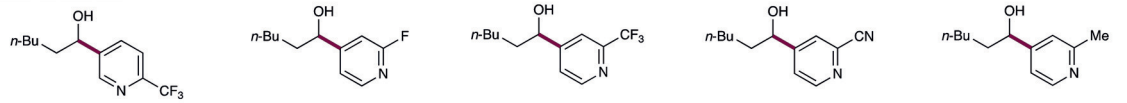


(±)-**23**, 83% yield; (±)-**24**, 74% yield; (±)-**25**, 60% yield; (±)-**26**, 64% yield; (±)-**27**, 58% yield



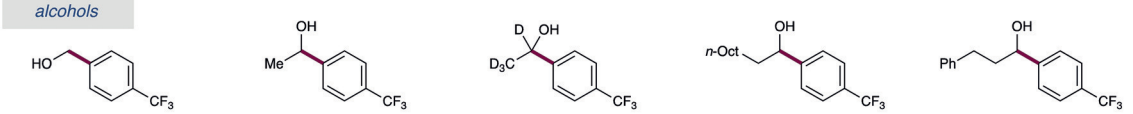
(±)-**28**, 66% yield; (±)-**29**, 70% yield; (±)-**30**, 56% yield; (±)-**31**, 44% yield; (±)-**32**, 61% yield

heteroarenes[b]

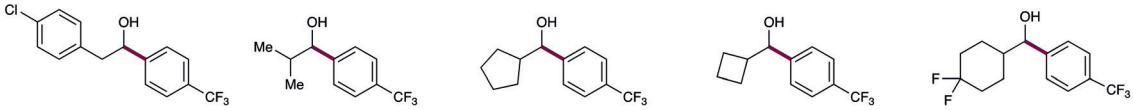


(±)-**33**, 59% yield; (±)-**34**, 74% yield; (±)-**35**, 73% yield; (±)-**36**, 40% yield; (±)-**37**, 42% yield

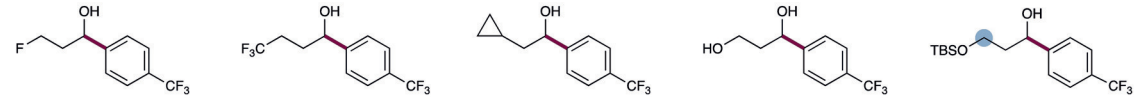
alcohols



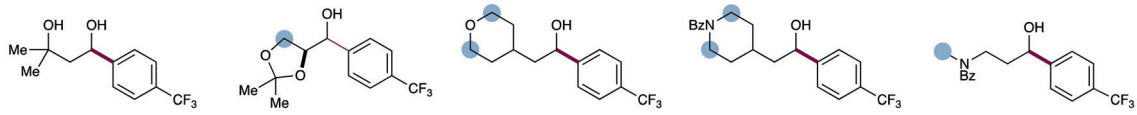
(±)-**38**, 51% yield; (±)-**39**, 75% yield; (±)-**40**, 63% yield; (±)-**41**, 73% yield; (±)-**42**, 66% yield



(±)-**43**, 59% yield[c,d,e]; (±)-**44**, 55% yield; (±)-**45**, 66% yield; (±)-**46**, 49% yield[d,e,f]; (±)-**47**, 58% yield[d]



(±)-**48**, 56% yield[d,e]; (±)-**49**, 70% yield; (±)-**50**, 72% yield[d]; (±)-**51**, 58% yield[e,g]; (±)-**52**, 65% yield, > 20:1 rr



(±)-**53**, 68% yield[h]; **54**, 60% yield[i], > 20:1 rr; (±)-**55**, 71% yield, > 20:1 rr; (±)-**56**, 58% yield[e,j,k], > 20:1 rr; (±)-**57**, 46% yield[e,j,k], > 20:1 rr

[a] Performed with photocatalyst **19** (0.2 mol%), Ni catalyst **16** (1.5 mol%), quinuclidine (30 mol%), aryl halide (1.0 equiv), alcohol (5.0 equiv), $ZnCl_2$ (1.5 equiv), potassium tribasic phosphate (1.0 equiv) on a 1.0 mmol scale in an 8 mL vial using DMSO as solvent (0.25 M) for 24 hours; yield after isolation by column chromatography. [b] 2 equiv $MgCl_2$, 3 mol% quinuclidine. [c] 1 mol% photocatalyst **19**. [d] 50 mol% quinuclidine. [e] 48 hours. [f] 2 mol% photocatalyst **19**. [g] 5 mol% quinuclidine. [h] 20 mol% quinuclidine. [i] 1:1 mixture of diastereomers. [j] 3.0 equiv of alcohol. [k] 2 mol% Ni catalyst **16**.

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Conflict of interest

The authors declare no conflict of interest.

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[12] The ground-state redox potentials for this catalyst as well as spectrochemical data are detailed in the Supporting Information. Photocatalyst **1** has a similar excited-state lifetime versus photocatalyst **1** (2.0 μs vs. 2.3 μs).

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[14] The ketone product was reduced with NaBH4 in the same vessel. In all cases, the ketone product constituted less than 8% of the aryl halide derived product in the crude mixture (6:1 to >20:1 ratio of ketone/alcohol), and reduction to the desired benzylic alcohol was conducted to increase the yield of desired product. Product **14** can be obtained in 70% yield without the reductive work-up by utilizing the same purification conditions as outlined in the Supporting information.

[15] See the Supporting Information for details. When the aldehyde was subjected to the optimized reaction conditions, aldehyde products where observed by ^{1}H NMR and GS–MS analysis.

[16] We attribute the improved efficiency observed with heteroarene coupling partners when utilizing magnesium salts to the higher oxophilicity of magnesium compared to zinc. See Ref. [9].

[17] Secondary alcohols are not competent in the current transformation; they lead to complete protodehalogenation of the arene and oxidation of one equivalent of the alcohol substrate. Efforts to expand the scope to include 2° alcohols are ongoing.

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