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

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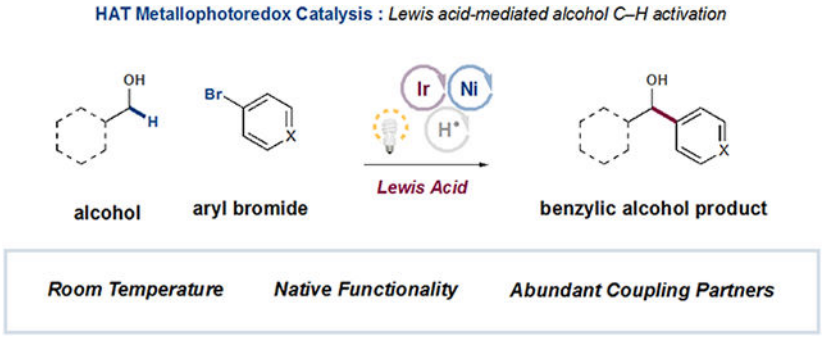
Abstract

The combination of nickel metallaphotoredox catalysis, hydrogen atom transfer catalysis, and a Lewis acid activation mode, has led to the development of an arylation protocol 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 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 technology facilitates rapid access to benzylic alcohols, an important motif in drug discovery. A 3-step synthesis of the Prozac exemplifies the utility of this new method.

Graphical Abstract

[**]The authors are grateful for financial support provided by the NIH General Medical Sciences (Grant NIHGMS (R01 GM103558–03), , and kind gifts from Merck, BMS, Janssen, and Eli Lilly.

Supporting information can be found under xxxxx



We report a method for C–C bond formation at the α-carbon of alcohols utilizing aryl halide electrophiles. This technology provides generic access to a broad range of benzylic and heteroaryl benzylic motifs which are widely represented in drug discovery and are useful building blocks for further derivatization. A new strategy for the selective functionalization of alcohols leveraging a Lewis acid additive is utilizing, to enable selective HAT at the α-carbon and supress competing C–O coupling.

Keywords

alcohols; photoredox catalysis; heterocycles; nickel; hydrogen atom transfer

It is well appreciated that alcohols represent one of the most ubiquitous functionalities found among organic molecules, 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 laboratories, 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 via 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 allow for the 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 protocol which allows for the chemoselective arylation of alcohols at the α-C–OH carbon atom in lieu of the more common oxygen-centered variant, without requiring pre-oxidation to the carbonyl.[7] 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. **Reaction Design.** From the outset, we recognized that the successful development of an α-alcohol arylation reaction via HAT and nickel catalysis would require a) chemoselective 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, b) 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 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, producing long-lived excited state complex *Ir(III) (**2**), a strong oxidant ($E_{1/2}^{red}$ [$*Ir^{III}/Ir^{II}$] = +1.21 V vs. SCE in MeCN).[10] Oxidation of 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, yielding 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**, furnishing 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 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 protocol began with exposure of *n*-hexanol, 4-bromobenzotrifluoride, photocatalyst **1**, $NiBr_2$•Me_4phen (**16**), along with 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**) was obtained (Table 1, entry 1, 3% yield). To expediently evaluate a large range of Lewis acid additives, we opted to optimize this coupling protocol utilizing high-throughput experimentation (HTE) (see SI for details). To this end, 24 Lewis acid additives were rapidly evaluated in a range of solvents utilizing this platform, 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 product 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, simplifying purification and increasing the overall yield of the transformation.[14]

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. Aryl halides bearing electron-withdrawing substituents such as trifluoromethyl, carboxymethyl, and sulfonamide, 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 in 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. 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 couple efficiently despite the 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 further demonstration of the utility of this α–hydroxy C–H arylation protocol, we sought to rapidly forge 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 utilizing our metallaphotoredox etherification protocol 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

The authors thank Tia Lee (Princeton University) for assistance in determining the excited state lifetime of photocatalyst **18**.

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[12]. The ground state redox potentials for this catalyst as well as spectrochemical data are available data are detailed in the Supporting Information. Photocatalyst 1 has a similar excited state lifetime vs. photocatalys 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 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 utilizing the same purification conditions as outlined in the Supporting information.

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

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

[17]. Secondary alcohols are not competent in this transformation at this time, leading to complete protodehalogenation of the arene and oxidation of one equivalent of the alcohol substrate. Efforts to expand the scope to include 2º alcohols are ongoing in our laboratory.

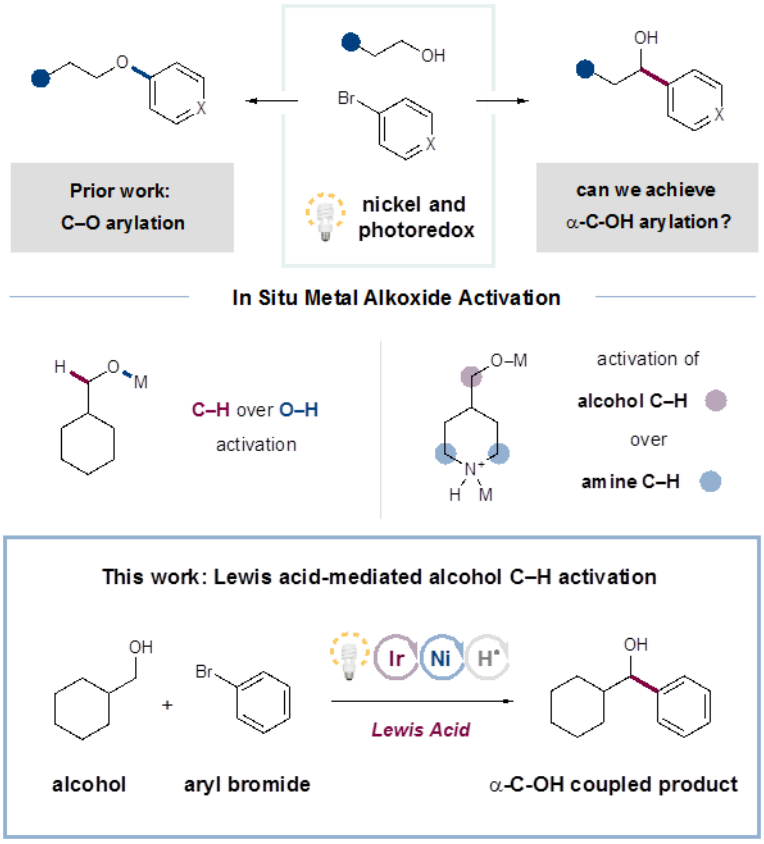


Figure 1.
The reactivity of alcohols.

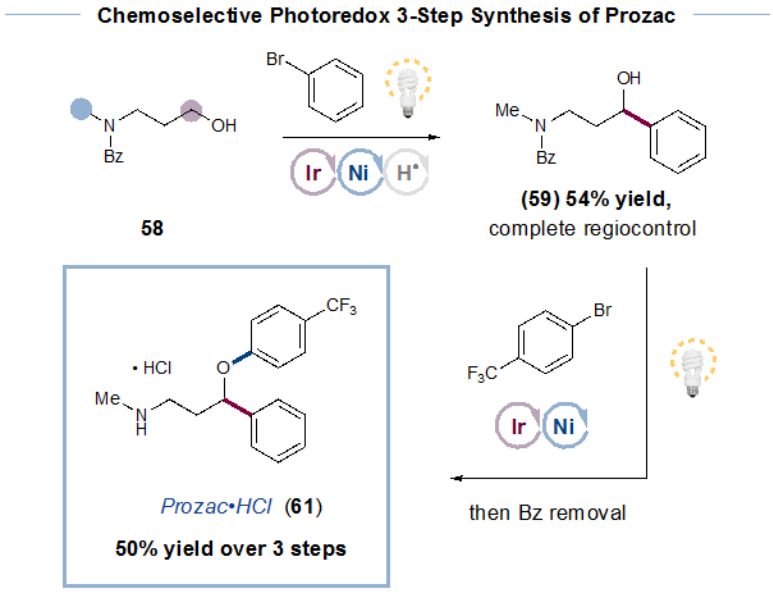
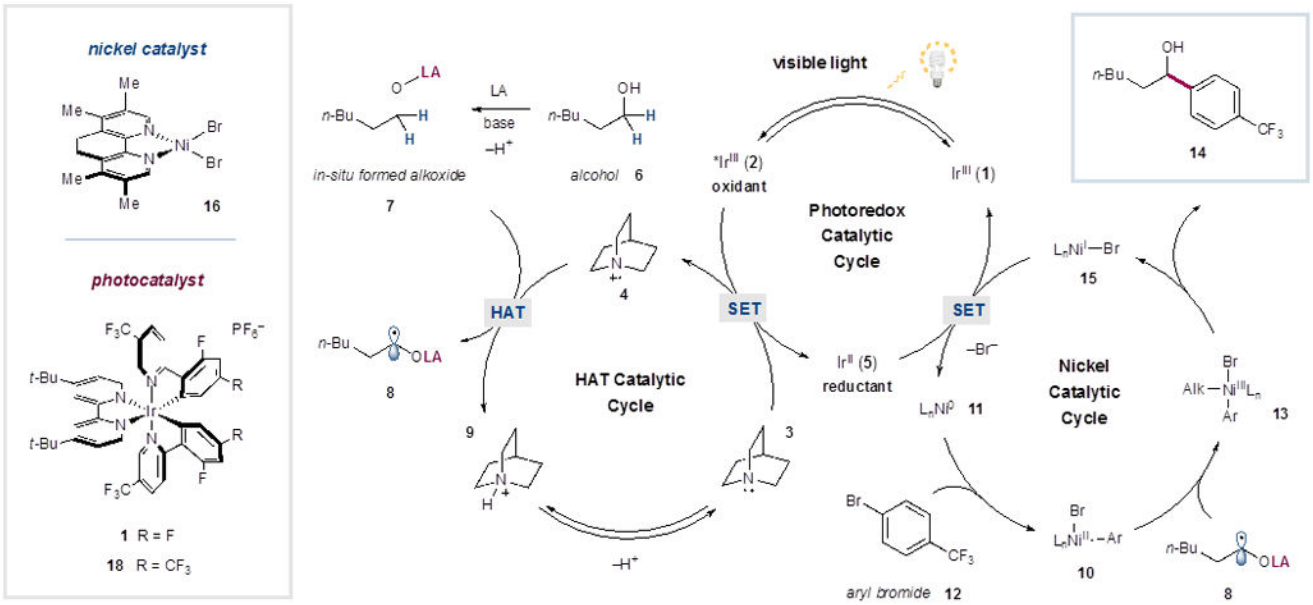


Figure 2.
Synthesis of Prozac. See Supporting Information for experimental details.

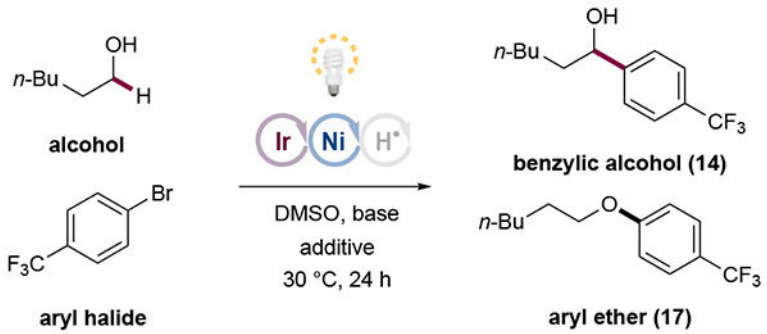


Scheme 1.

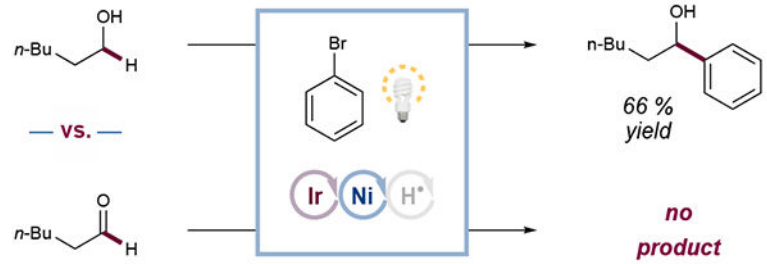
Proposed mechanism for the arylation of α-hydroxy C–H bonds via the merger of photoredox, HAT, and nickel catalysis

Table 1.

Optimization of Lewis acid mediated *C*- vs *O*-arylation.[a]



entry	addictive	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

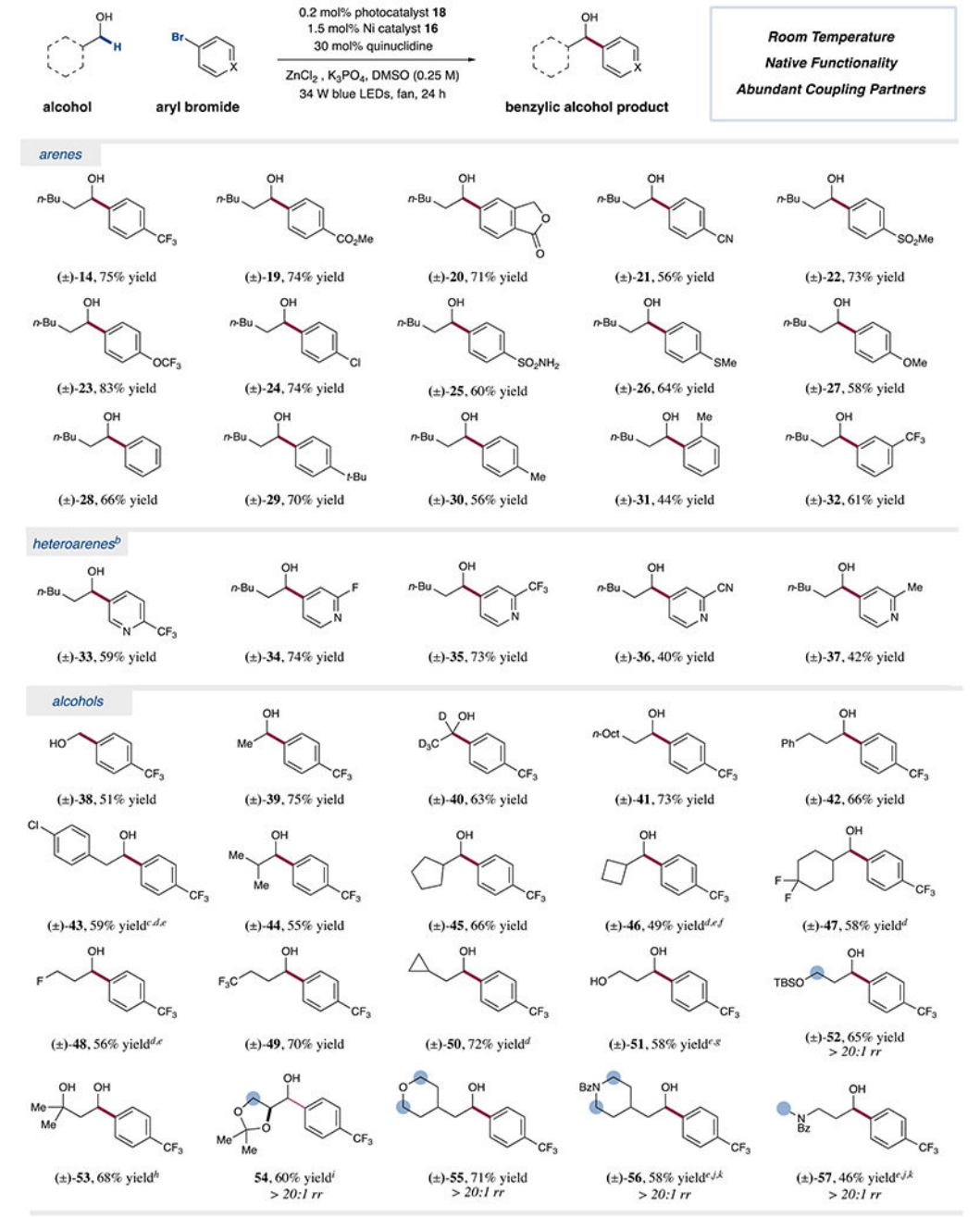
[d]Photocatalyst (0.2 mol%), $NiBr_2$•Me_4phen (1.5 mol%).

[e]Performed with photocatalyst **19**.

[f]3 equiv. of alcohol.

Table 2.

Scope of α-hydroxy C–H arylation via a triple catalysis mechanism. Tolerance of α-amino and α-ether C–H bonds.[a]



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[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 chromotography

[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**.