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Metal-Free-Visible Light C−H Alkylation of Heteroaromatics via Hypervalent Iodine-Promoted Decarboxylation

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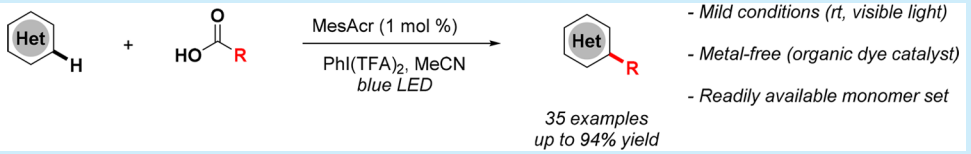
Supporting Information

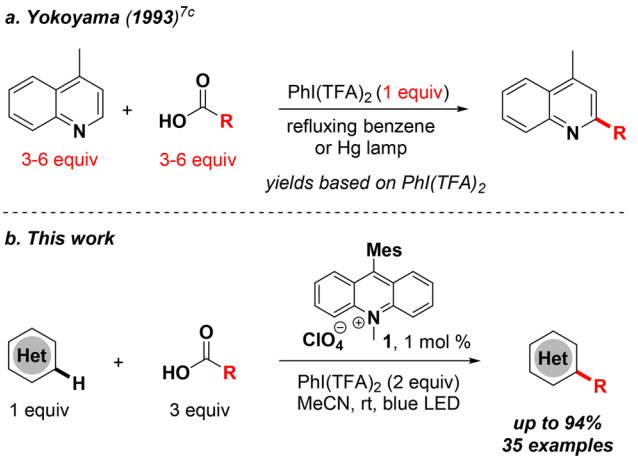


ABSTRACT: A metal-free photoredox C−H alkylation of heteroaromatics from readily available carboxylic acids using an organic photocatalyst and hypervalent iodine reagents under blue LED light is reported. The developed methodology tolerates a broad range of functional groups and can be applied to the late-stage functionalization of drugs and drug-like molecules. The reaction mechanism was investigated with control experiments and photophysical experiments as well as DFT calculations.

The C−H alkylation of heteroaromatics remains a formidable challenge in synthetic organic chemistry. Such functionalization is nonetheless remarkably useful, and it has become one of the most sought after strategies for the rapid late-stage diversification of pharmaceuticals.[1] The most ubiquitous method for C−H alkylation of heteroaromatics was pioneered by Minisci who used carboxylic acids to generate alkyl radicals in the presence of silver nitrate, ammonium persulfate, and sulfuric acid at elevated temperatures.[2] Due to the harsh conditions, variable yields, and practical limitations in library format, the past decade has seen a surge in alternative thermal reaction conditions showcasing a variety of coupling partners.[3]

Photoredox catalysis has become a powerful methodology in synthetic organic chemistry.[4] New photoredox Minisci conditions that take advantage of the mild generation of alkyl radicals at room temperature have arisen.[5] These protocols however still display recurrent limitations such as the use of expensive metal photocatalysts (iridium or gold),[5b,c,e−j] a large excess of coupling partner (up to 10 equiv), and the requirement to prepare either the coupling partner[5d,e,g,i,j] or the photocatalyst.[5f] To our surprise, no photoredox protocol had been developed for carboxylic acids, a broadly available monomer set. During the preparation of this manuscript, however, decarboxylative couplings were reported[5h,l,m] using, for instance, an iridium catalyst in the presence of a persulfate oxidant under visible light. Instead, our method uses the more soluble and under-utilized hypervalent iodine reagents.[6,7] These reagents were utilized in Minisci transformation under refluxing benzene or ultraviolet light (mercury lamp, Scheme 1a) albeit with a large excess of the heteroaromatic and the carboxylic acid coupling partners (3−6 equiv).[7c]

Scheme 1. Hypervalent Iodine Dicarboxylates in Minisci Transformations



Herein, we report the first metal-free and visible light-promoted C−H alkylation of heteroaromatics using hypervalent iodine dicarboxylates at room temperature. Our method leverages the broad range of commercially available carboxylic acids and a catalytic amount of an organic dye: 9-mesityl-10-methyl acridinium (**1**, MesAcr, Scheme 1b).[5d,8,9] Our mechanistic studies suggest a mechanism that is distinct from recent literature.[5h,m]

At the outset of our studies, we selected lepidine (**2**) as the limiting substrate (1 equiv) and isobutyric acid (**3**, 5 equiv) to

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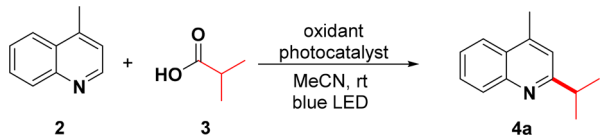
optimize the reaction conditions under blue LED light irradiation (λ_{max} = 455 nm). Bis(acetoxy)iodobenzene (BAIB, 3 equiv) was used as a starting point along with the use of trifluoroacetic acid (10 equiv) in acetonitrile (Table 1; see

Table 1. Reaction Conditions Optimization



entry[a,b]	catalyst (1 mol %)	oxidant (2 equiv)	yield (%)[c,d]
1	$Ru(bpz)_3(PF_6)_2$	$PhI(OAc)_2$	29
2	$[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$	$PhI(OAc)_2$	78 (76)
3	MesAcr	$PhI(OAc)_2$	86 (86)
4	MesAcr	PhIO	9
5	MesAcr		91
6	MesAcr	$PhI(OPiv)_2$	48
7	**MesAcr**	**$PhI(TFA)_2$**	**97 (94)**[e]

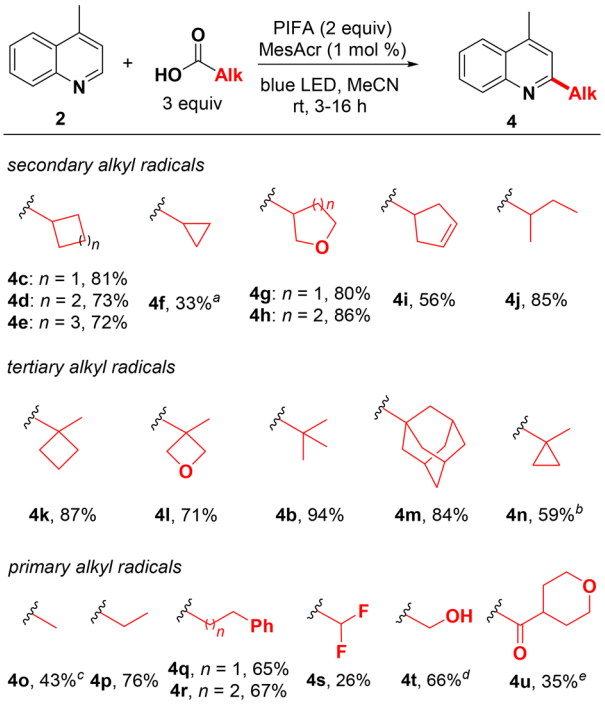
[a]General conditions: lepidine **2** (1 equiv), isobutyric acid **3** (3 equiv), oxidant (2 equiv), MeCN (0.1 M), 32 W blue LED light, rt, 16 h. [b]TFA (5 equiv) was added. [c]NMR yields using mesitylene as external standard. [d]Isolated yields are shown in parentheses. [e]No TFA was added.

Supporting Information (SI) for the full optimization study). Our initial screening tested a range of well-known metal photocatalysts (iridium-, ruthenium-, and copper-based). We were pleased to see the formation of desired isopropylated lepidine **4a** in 29% yield with $Ru(bpz)_3(PF_6)_2$ (entry 1).

The conversion of lepidine improved significantly with iridium catalysts (up to 78%), even though incomplete conversion remained an issue (entry 2). We then turned our attention to organic dyes (fluorescein, Eosin Y, and acridinium derivatives), and we were pleased to find that 9-mesityl-10-methyl acridinium **1** (MesAcr) increased the yield to 86% (entry 3). In order to avoid the competing methylation pathway, due to the radical decomposition of the acetoxy-ligated iodine reagent, we explored other oxidants such as oxone, TBHP, persulfate, and other hypervalent iodine derivatives (entries 4–7). Iodosobenzene led to poor conversion (9%, entry 4) while IBX derivative **5** improved the yield to 91% (entry 5). However, the poor solubility of the latter in acetonitrile and the requirement for its preparation made this oxidant a less attractive option. As expected, $PhI(OCOt\text{-}Bu)_2$ led to a mixture of the desired product (**4a**) and *tert*-butylated lepidine analogue (**4b**; see Scheme 2) in 48% and 52% yields, respectively. Finally, we decided to use bis(trifluoroacetoxy)iodo benzene (PIFA) to avoid the complication of forming undesired alkylated products and to bypass adding additional trifluoroacetic acid to the reaction mixture. This modification led to full conversion of lepidine to isopropylated lepidine **4a** in 94% isolated yield (97% GC yield, entry 7). Solvent screening confirmed that the best results were obtained with acetonitrile.

With the optimized conditions in hand, we explored the substrate scope with commercially available carboxylic acids that were selected based on the type of alkyl radicals they generate (e.g., primary, secondary, tertiary radicals; Scheme 2). Consistent with our preliminary results obtained with

Scheme 2. Carboxylic Acid Scope



[a]51% recovered starting material. [b]40% recovered starting material. [c]AcOH was used as solvent, and $PhI(OAc)_2$, as oxidant. [d]MeOH was used as solvent. [e]40% recovered starting material and less than 10% of alkylated product were observed.

isobutyric acid, other α-branched carboxylic acids that form secondary alkyl radicals reacted smoothly under the reaction conditions. Cyclobutyl, cyclopentyl, and cyclohexyl analogues (**4c–e**) were isolated in 81%, 73%, and 72% yields, respectively. In contrast, addition of the smaller cyclopropyl group suffered from poor conversion and afforded cyclopropylated lepidine **4f** in a low 33% yield with 38% of unreacted lepidine. This reactivity is consistent with the known instability of cyclopropyl radicals, hence resulting in the unproductive consumption of the carboxylic acid coupling partner. Cyclic ethers (tetrahydrofuran **4g** and tetrahydropyrane **4h**) were installed efficiently (80%, 86%) while the presence of an unsaturation (cyclopentenyl) decreased the yield slightly (**4i**, 56% versus **4d**, 73%). Finally, an acyclic secondary radical also reacted well to form **4j** (85%). Tertiary alkyl groups such as methyl cyclobutyl (**4k**), methyl oxetane (**4l**), *tert*-butyl (**4b**), and adamantyl (**4m**) were incorporated to lepidine in similar good yields. As expected from the superior relative stability of tertiary radicals over secondary radicals, the methyl cyclopropyl group was installed in an increased 59% isolated yield (versus 33% for **4f**) along with 40% recovered lepidine.

Finally, the more challenging linear carboxylic acids that form primary radicals were used successfully, leading to excellent yields considering their high reactivity. A solvent and oxidant swap (acetonitrile to acetic acid; PIFA to BAIB) allowed us to maximize the formation of methylated lepidine **4o** obtained in an excellent 43% yield. In addition, our reaction conditions in acetonitrile worked smoothly for longer chains: ethyl (**4p**, 76%), phenyl ethyl (**4q**, 65%), and phenyl propyl (**4r**, 67%). It is worth noting that the good yield of **4q** demonstrates the advantage of using the carboxylic acid monomer set since other monomers such as homoallylic bromides or iodides used by

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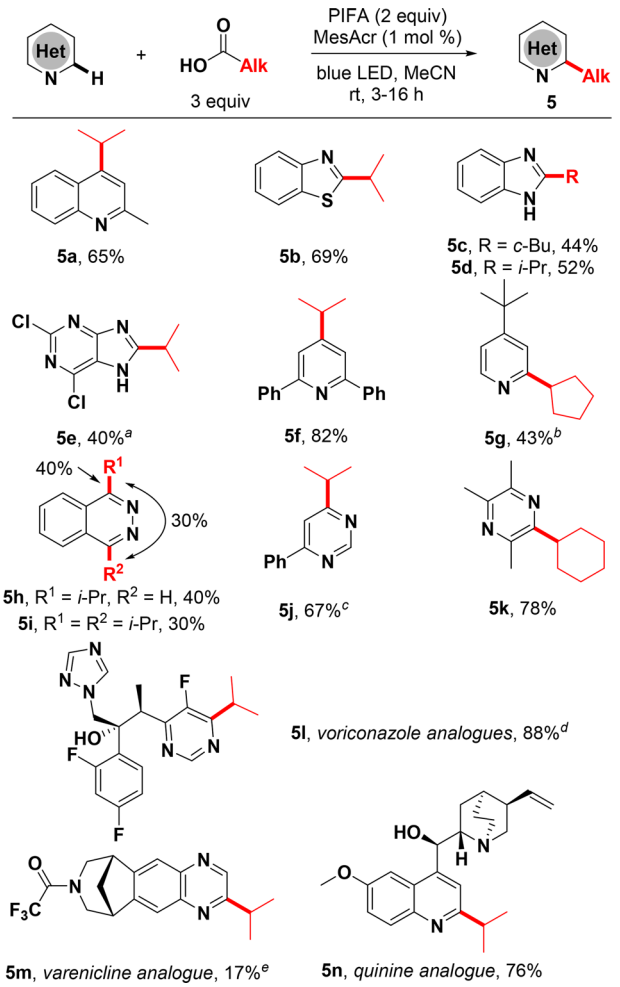
recent photoredox protocols decompose readily under the reaction conditions to form styrenes.[5a,c,d] As expected, the more electrophilic difluoromethyl radical reacted in a lower yield (**4s**, 26%). Another solvent swap (acetonitrile to methanol) enabled hydroxymethylation to occur smoothly (**4t**, 66%). We hypothesized that the alkyl radical generated from isobutyric acid abstracted the methanol α-oxy proton by analogy to the mechanism reported by DiRocco in the photocatalyzed hydroxymethylation of heteroarenes.[5c,10] Finally, acylation of lepidine was exemplified by using 2-oxo-2-(tetrahydro-2*H*-pyran-4-yl)acetic acid to give ketone **4u** in 35% isolated yield.

We then selected a range of simple and complex electron-deficient heteroaromatics in order to explore functional group tolerance (Scheme 3).

Scheme 3. Scope of the Heteroaromatics and Drugs



[a]49% recovered starting material. [b]Minor amount of bis-alkylated product was observed. [c]The product was isolated as a 4:1 mixture in favor of the mono- versus the bis-alkylated product. [d]Monoalkylated and bis-alkylated pyrimidine analogues were isolated in 77% and 11% isolated yields, respectively. [e]55% recovered starting material.

For instance, the C4 position of quinaldine and the most electrophilic C2 positions of benzothiazole, benzimidazole, and 2,6-dichloro purine provided alkylated products **5a**, **5b**, **5c**, **5d**, and **5e** in moderate to good yields (40−69%). Incomplete conversion of the starting heterocycles accounted for the modest yields. Other heteroaromatic products such as pyridines (**5f**, **5g**), phthalazines (**5h**, **5i**), pyrimidine (**5j**), and pyrazine (**5k**) were also obtained in good yields. Three drugs (voriconazole, varenicline, and quinine) were selected to test our protocol as a late-stage C−H functionalization. To our delight, the isopropyl analogue (**5l**) of antifungal voriconazole was isolated in 77% isolated yield along with 11% of the bis-alkylated drug analogue (not shown; second alkylation occurred at the C2 position of the pyrimidine). The conversion of the trifluoroacetamide precursor of varenicline, a smoking cessation drug, successfully gave isopropylated analogue **5m** in 17% yield. The antimalarial drug quinine also yielded the desired alkylated product (**5n**) in 76% yield. Together, these results demonstrate that this catalytic system tolerates a variety of functional groups such as secondary alcohols, olefins, tertiary amines, aryl ethers, and other heterocycles.

Unlike the photoredox Minisci mechanism proposed for iridium or ruthenium photocatalysts,[5h,m] the photoactivated catalyst *(MesAcr$^+$) is unable to reduce the hypervalent iodine dicarboxylate adduct due to its high redox potential (E^*_{red} > +2.0 V), leaving the origin of this reduction elusive. To better understand the reactivity of *(MesAcr$^+$) under the reaction conditions, we carried out a series of steady-state and time-resolved Stern−Volmer quenching experiments (see the SI). While the direct oxidation of an alkyl carboxylate by *(MesAcr$^+$) under basic conditions is well precedented,[11] it has not been reported under acidic conditions and cannot be assumed under our reaction conditions. The species responsible for the reduction of *(MesAcr$^+$) thus far remains unclear. We believe inefficient oxidation of trace carboxylate or neutral heteroaromatic may be sufficient to generate small amounts of MesAcr· as part of an initiation step. The inefficient nature of this oxidation could explain the low quantum efficiency of this process (*vide infra*). Once reduced, the MesAcr· is able to transfer an electron to the hypervalent iodine adduct (Scheme 4), to initiate the proposed catalytic cycle and regenerate the MesAcr$^+$ photocatalyst. The hypervalent iodine radical anion, $[PhI(O_2CR)_2]^{\bullet-}$, is expected to rapidly collapse leading to the formation of the alkyl radical R·. Using high-level DFT calculations (CPCM(ACN)/B3LYP/6-311++g-(2d,2p)+LanL2DZ with extra diffuse and polarization for iodine; see the SI for details), the collapse of the radical anion $[PhI(O_2CR)_2]^{\bullet-}$ was found to be highly favorable with no significant energy barriers found at this level of theory. Overall, the proposed catalytic cycle is thermodynamically favorable (ΔG_{cycle} = −83.15 kcal/mol) and each individual step is thermodynamically feasible.

We experimentally validated the proposed single electron transfer (SET) step between lepidine's neutral α-amino radical and PIFA by cyclic voltammetry (see the SI). In acetonitrile, the reduction potential of protonated lepidine and PIFA were −1.34 V and −0.527 V vs ferrocene, respectively. Both half reactions therefore predict a very favorable SET reaction with a +2.05 V driving force.

Since this reaction appears to proceed via a chain reaction, the quantum yield of the reaction was measured using a Ru(bpy)$_3$ and diphenylanthracene (DPA) actinometer according to the literature.[12] While our analysis suggests a chain reaction, we obtained a low overall quantum yield of ∼0.18 at the start of the reaction. This discrepancy is likely due to an inefficient initiation step (e.g., inefficient oxidation of a carboxylate) and/or inefficient chain propagation. A rapid termination was ruled out since the quantum yield was slightly higher at higher light intensity.

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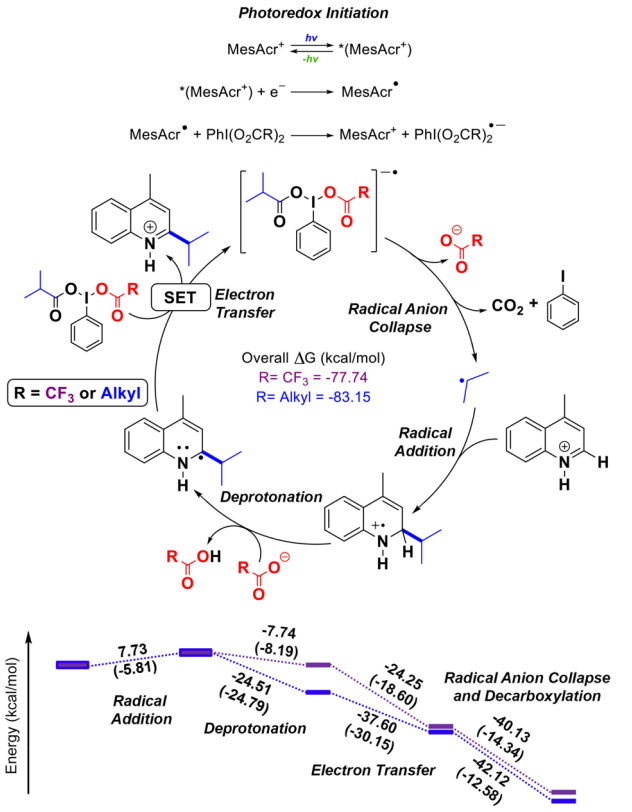
Scheme 4. Proposed Mechanism and DFT-Calculated ΔG_{rx} (ΔH_{rx} in Parentheses) for Each Step of the Catalytic Cycle



We report herein a metal-free photoredox C−H functionalization of heteroarenes using an acridinium photocatalyst and hypervalent iodine reagents under blue LED light. This light-initiated chain reaction occurs under mild reaction conditions and uses the broad and readily available carboxylic acid monomer set. A range of functional groups are well tolerated (olefins, alcohols, ethers, tertiary amines), and the method is applicable to late-stage functionalization of complex molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01085.

Full experimental details (PDF)

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Notes

The authors declare no competing financial interest.

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