C–H Functionalization Hot Paper

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Late-Stage Functionalization of Biologically Active Heterocycles Through Photoredox Catalysis**

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Abstract: *The direct C–H functionalization of heterocycles has become an increasingly valuable tool in modern drug discovery. However, the introduction of small alkyl groups, such as methyl, by this method has not been realized in the context of complex molecule synthesis since existing methods rely on the use of strong oxidants and elevated temperatures to generate the requisite radical species. Herein, we report the use of stable organic peroxides activated by visible-light photoredox catalysis to achieve the direct methyl-, ethyl-, and cyclopropylation of a variety of biologically active heterocycles. The simple protocol, mild reaction conditions, and unique tolerability of this method make it an important tool for drug discovery.*

The late-stage functionalization (LSF) of advanced synthetic intermediates and drug candidates has emerged as an important strategy for contemporary drug discovery.[1] Methods that enable direct manipulation of structural diversity without the need for pre-functionalized synthetic handles are among the most desirable to medicinal chemists. This approach compares favorably to a traditional de novo synthesis and holds promise for rapidly accelerating discovery timelines. Introducing small, inert functionality to a pharmacophore of interest relatively late in the discovery process may address problems associated with on- and off-target activity, metabolism, and pharmacokinetic profile. Fluoroalkyl substituents have traditionally been utilized as a fit-for-purpose solution due to their resistance toward oxidation by cytochrome P450 oxidases.[2] This benefit, however, often is negated by diminished physiochemical properties that ultimately affect other important ADME ("absorption, distribution, metabolism, and excretion") and safety attributes.[3] Small non-fluorinated alkyl substituents such as methyl, ethyl, and cyclopropyl may provide a viable alternative.[4] The methyl group in particular has been recognized as an important motif due to stereoelectronic effects that impact selectivity, improve potency, and offer insulation from enzyme metabolism.[5] However, despite the ubiquity and utility of small alkyl substituents in pharmaceuticals, to date no practical and general method has emerged to install these groups by C–H functionalization. Recent developments in radical-mediated addition of alkyl groups to arenes[6] and heteroarenes,[7] originally reported by Langlois[8] and Minisci,[9] have led to a renaissance in radical-based methodologies due to improvements in substrate scope and milder operating conditions. Herein, we report a visible-light mediated catalytic photoredox platform that efficiently installs alkyl groups into complex heteroarenes in the context of LSF.

Minisci et al. originally reported the alkylation of heteroaromatic bases through the silver-assisted decarboxylation of carboxylic acids in the presence of persulfate.[9] While these conditions are sufficient for simple heteroarenes, elevated temperatures and strong oxidants make them unsuitable for complex molecular architectures. Since this initial publication, numerous methods for generating alkyl radicals have emerged by the groups of Minisci,[10] Baran,[7] Molander,[11] and others[10] that have significantly increased the scope and generality of this strategy. Unfortunately, access to small unstable alkyl radicals such as Me, Et, and *c*-Pr using these protocols has not been realized in a synthetically meaningful sense.[12] In support of an on-going drug development strategy, we were interested in C–H functionalization of complex heterocycles with small alkyl substituents. Experimental evaluation of existing methods for the installation of a methyl group by radical functionalization highlighted a significant gap in current methodology, prompting us to initiate development of a more productive variant (Figure 1).

Our approach to this problem began with the hypothesis that slow, controlled generation of reactive radicals under photocatalytic conditions may reduce the incidence of undesired side reactions and allow productive pathways to dominate. We were encouraged by reports of the generation of ·Me from *tert*-butylperacetate (*t*BPA) by thermolysis, photolysis, or exposure to high-energy irradiation.[13] Since these conditions would likely be incompatible with late-stage compounds, we sought to develop a milder visible-light catalyzed method potentially applicable to LSF. Photoredox catalysis has recently emerged as a mild and efficient method for the generation of radicals, which exploits the unique

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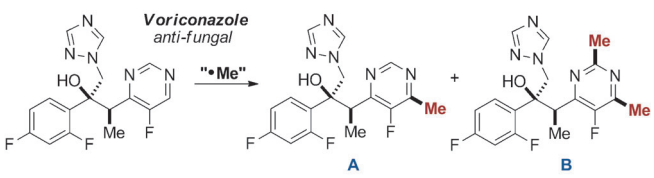

	Reagents:	Temperature	A/B	Yield[a]
Existing Methodology:	Me-BF_3K, $Mn(OAc)_3$, TFA,	50 °C	N/A	0%
	Me-SO_2-Zn-SO_2-Me, *t*BuOOH, TFA,	23 °C	N/A	0%
	AcOH, $AgNO_3$, $(NH_4)_2S_2O_8$, H_2SO_4,	70 °C	N/A	0%
	DMSO, H_2O_2, $FeSO_4$, H_2SO_4,	23 °C	N/A	6%
This Work:	*cat.* [Ir(dF-CF_3-ppy)$_2$(dtbpy)]PF_6 AcO*t*Bu, *hv*, TFA	23 °C	2.9:1	75%

Figure 1. Comparison of methods for radical methylation of voriconazole. Experiments performed on 50 mg scale according to published procedures. See Figure 3 for the structure of [Ir(dF-CF_3-ppy)$_2$(dtbpy)]PF_6. [a] Yield represents assay yield obtained by ultra performance liquid chromatography (UPLC) analysis of the crude reaction mixture using an internal standard. See Supporting Information for details.

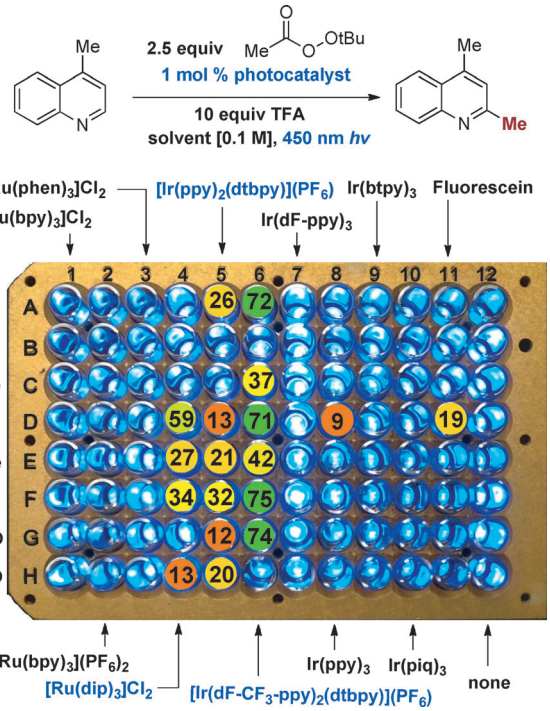

Figure 2. High-throughput experimentation enabled discovery of a room temperature photoredox catalyzed radical methylation. Experiments run on 10 μmol scale, 100 μL solvent, and 1 mol% photocatalyst at ambient temperature under nitrogen atmosphere. Numbers in table refer to % conversion based on UPLC-MS analysis of the crude reaction mixtures after addition of an internal standard. See Supporting Information for complete details. TFA = trifluoroacetic acid; ACN = acetonitrile; DMF = dimethylformamide; DMSO = dimethylsulfoxide; DCE = dichloroethane; phen = phenanthroline; bpy = bipyridine; ppy = 2-phenylpyridine; dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine; btpy = 2-(benzothiophenyl)pyridine; dF-ppy = 4,6-difluorophenylpyridine; dip = 4,7-diphenyl-1,10-phenanthroline; piq = 1-phenylisoquinoline.

photophysical properties of organic dyes and transition metal complexes.[14–15] Consistent with our longstanding interest in new reactivity and high-throughput experimentation,[16] we have established a reaction platform that allows photocatalyzed processes to be rapidly evaluated in parallel, using a 96-well-plate reactor engineered to allow each reaction to be irradiated independently by a single light-emitting diode (LED) at a specific wavelength.[17]

We chose lepidine as a model substrate to assess the generation of ·Me. A survey of 12 photocatalysts and 8 solvents and solvent mixtures with trifluoroacetic acid as an additive, identified a few unique catalyst/solvent combinations that provided significant conversion of lepidine to 2,6-dimethylquinoline at ambient temperature (Figure 2).

The cyclometalated Ir^{III} catalysts [Ir(dF-CF_3-ppy)$_2$(dtbpy)]PF_6 and [Ir(ppy)$_2$(dtbpy)]PF_6 are particularly reactive and have proven to be the most general in this process. No product was formed in a control well in the absence of catalyst or light. We were unable to generate ·Me from other *tert*-alkyl peroxides such as di-*tert*-butyl peroxide or *tert*-butylhydroperoxide. These data suggest the structure of *t*BPA, containing a carbonyl motif, is responsible for its unique reactivity. We reasoned that decomposition of *t*BPA might be initiated through a single electron-transfer event from the excited-state metal species Ir^{III}* to the low-lying π* orbital of the carbonyl, a pathway not accessible to other peroxides. The direct reduction of *t*BPA (*t*BPB, $E° = -1.95$ V vs SCE)[13c] by Ir^{III}* ($E° = -0.89$ V vs SCE) is thermodynamically challenging, however, proton-coupled electron transfer (PCET) under acidic conditions significantly lowers the barrier to reduction and may be kinetically feasible.[18] The unstable α-peroxy radical generated could decompose to acetic acid and *tert*-butoxy radical by homolytic cleavage of the weak O–O bond. Methyl radical likely is generated through β-scission of *tert*-butoxy radical, generating acetone as a by-product (Figure 3).[19] We propose that addition of ·Me to the protonated heterocycle followed by oxidation of the

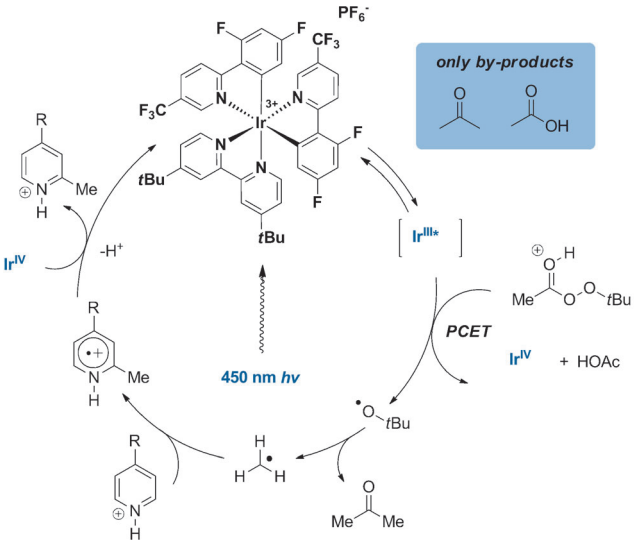

Figure 3. Proposed catalytic cycle for the photocatalyzed methylation of heterocycles with *t*BPA.

resultant amino-radical cation by Ir^{IV}, would furnish the desired product and regenerate the active catalyst species.

The low rate of peroxide decomposition in the absence of substrate further corroborates an electron-transfer mechanism making an energy-transfer sensitization mechanism for peroxide decomposition unlikely as the major pathway.[13c]

Due to the low molecular weight, benign by-products, and low cost of the reagent,[20] high reaction efficiency can be achieved without substantially impacting practicality or cost. Furthermore, in typical radical-based methods, slow addition of activating reagents is often necessary to avoid rapid heat generation due to the exothermic nature of the reactions and maintain low radical concentrations. Kinetic studies demonstrate the reaction rate in this photocatalyzed process to be entirely controlled by the intensity of light.[21] This provides a tool for exquisite control over the addition of radicals that is reliable and reproducible, especially on microscale in which slow addition is often unreliable. To evaluate the scope and assess the applicability of this technology as a LSF tool, we selected several medicinal and agrochemical compounds as a testing ground (Figure 4). As shown in Figure 4, blue light irradiation of a diverse collection of complex, highly elaborated molecules in the presence of a photocatalyst and *t*BPA provides good conversion to the respective methylated derivatives.[22] 6-Membered heterocycles such as pyridines, pyrazines, and pyrimidines react efficiently as well as some electron-rich 5-membered heterocycles (e.g. imidazole). Basic heterocycles are selectively methylated in preference to less basic motifs such as 1,3,4-triazole (see voriconazole). Selectivity for the 2- and 4-positions of the heteroaromatic rings is consistent with addition of a nucleophilic species to the protonated base. Due to the promiscuous nature of ·Me, multiple methylation events often occur when the reactions are allowed to reach completion, consistent with inherent competition of substrate with product. Most importantly, this transformation proceeds in the presence of common functionality such as basic amines, alcohols, amides, and esters without the need for protecting groups. Given the practicality of this approach with respect to generating ·Me, we were interested in expanding the scope to encompass additional small alkyl radicals. With the hypothesis that the tertiary alkoxy radical might selectively excise the most stable radical, we subjected fasudil (a potent vasodilator) to *tert*-amyl peracetate under identical reaction conditions and blue light. A single product was observed corresponding to the addition of ·Et (Figure 5), supporting our initial hypothesis regarding the nature of radical generation from alkyl peracetates.[23]

Extending the approach illustrated in Figure 5 to produce other alkyl radicals including ·*c*-Pr was impeded by the relative difficulty in synthesizing the required hydroperoxides. Ultimately our attention was diverted to an alternate radical source, i.e. biscyclopropanecarbonyl peroxide (CPO). Bis-carbonyl peroxides have been utilized extensively as radical initiators for a variety of transformations; however, their use as a direct source of alkyl radicals for C–H functionalization has been less widely explored,[24] most likely due to safety concerns arising from their thermal instability and shock sensitivity. An outlier in this class, CPO,

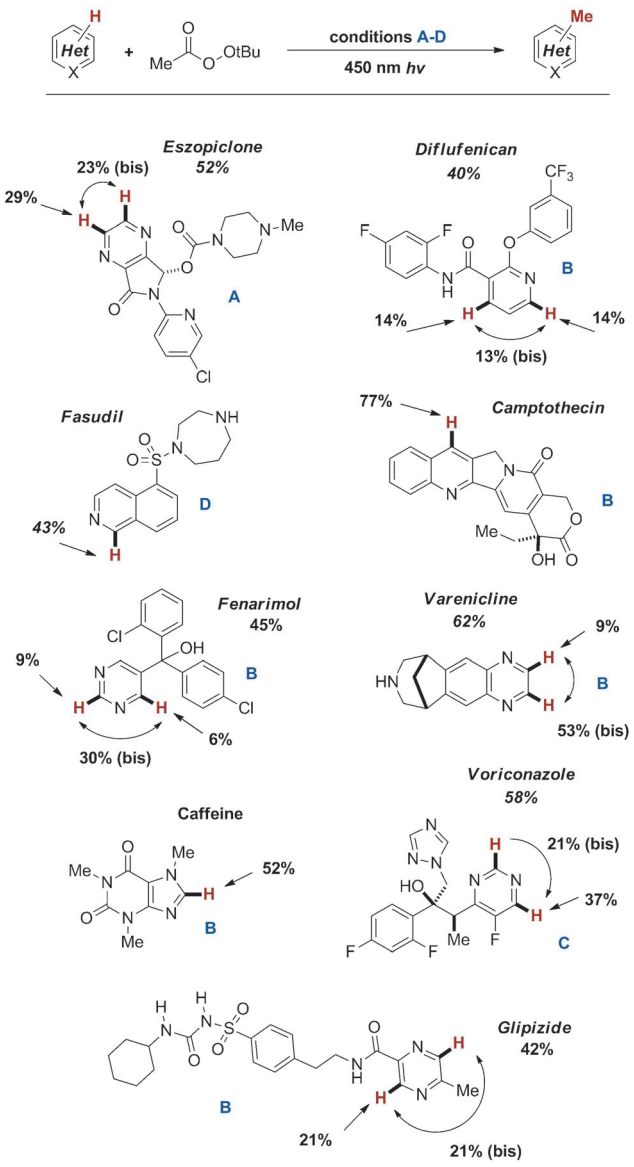

Figure 4. Methylation of complex medicinal and agrochemical agents. Yields represent isolated yields of methylated products after preparative HPLC of crude reaction mixture. Reactions performed with 2.5 equiv of *t*BPA. Conditions are as follows: Condition A, 1:1 AcOH:ACN (0.1 M), 1 equiv TFA, 2 mol% $[Ir(ppy)_2(dtbpy)]PF_6$; Condition B, 1:1 TFA:ACN (0.1 M), 2 mol% $[Ir(ppy)_2(dtbpy)]PF_6$; Condition C, 1:1 TFA:ACN (0.1 M), 2 mol% $[Ir(dF\text{-}CF_3\text{-}ppy)_2(dtbpy)]PF_6$; Condition D, 1:1 AcOH:ACN (0.1 M), 2 mol% $[Ir(dF\text{-}CF_3\text{-}ppy)_2(dtbpy)]PF_6$. See Supporting Information for experimental details.

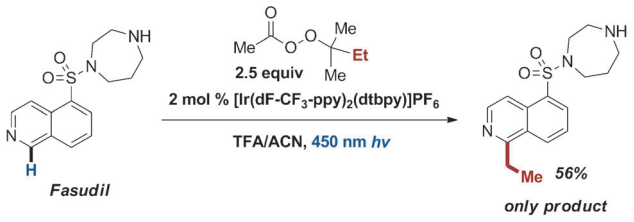

Figure 5. Generation of ·Et from *tert*-amyl peracetate. Ethyl radical is selectively generated from *tert*-amyloxy radical in the presence of fasudil leading to C–H ethylation of the isoquinoline motif.

is a bench-stable solid at ambient temperature,[25] presumably due to the disfavored thermal formation of the high-energy •*c*-Pr during homolysis.[26] However, we reasoned that single-electron transfer (SET) from an excited state metal complex to CPO should generate •*c*-Pr under mild conditions with concomitant release of CO_2. During our initial evaluation we discovered that this reagent can be decomposed easily using a set of conditions similar to that of *t*BPA. Complex heterocycles are smoothly alkylated with CPO providing high yields of the corresponding cyclopropyl-substituted derivatives (Figure 6). Addition of •*c*-Pr under these conditions follows similar regioselectivity patterns to •Me, alkylating preferentially in the 2- and 4-positions. Like *t*BPA, CPO proved to be a convenient source of radicals due to its low molecular weight, high stability, and benign decomposition products. This allows for simple and high purity isolation of the products directly by preparative-scale HPLC.

In summary, we have disclosed a novel mode of radical generation using visible-light photoredox catalysis that enables LSF of pharmaceutically important leads and drug candidates with benign and low-cost reagents. The uniquely mild conditions described for the generation of •Me, and other radicals, allow for efficient trapping in a complex setting and bridge an important gap in the area of Minisci-type C–H functionalizations. We anticipate that this method will expand the medicinal chemist's toolbox, allowing for rapid evaluation of profound methyl effects and providing expedient solutions for fast-moving therapeutic programs.

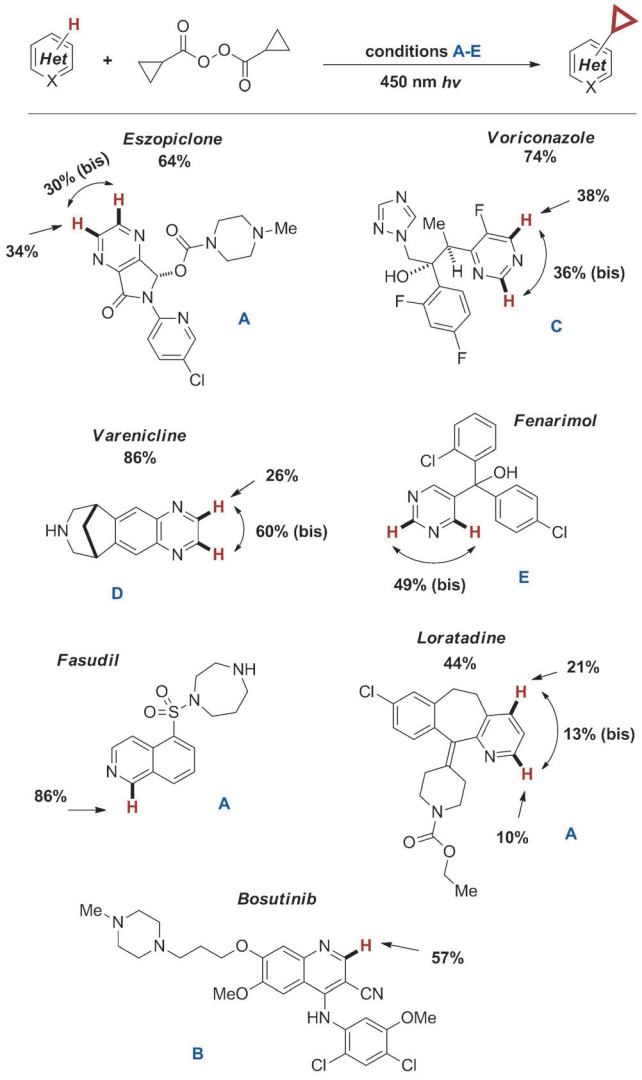

Figure 6. Cyclopropylation of complex medicinal and agrochemical agents. Late-stage compounds are efficiently cyclopropylated under visible-light irradiation in the presence of a photocatalyst. Yields represent isolated yields after preparative HPLC of crude reaction mixture. Reactions performed with 2.5 equiv CPO. Conditions are as follows: Condition A, 1:1 AcOH:ACN (0.1 M), 1 equiv TFA, 2 mol% $[Ir(ppy)_2(dtbpy)]PF_6$; Condition B, 1:1 TFA:ACN (0.1 M), 2 mol% $[Ir(ppy)_2(dtbpy)]PF_6$; Condition C, 1:1 TFA:ACN (0.1 M), 2 mol% $[Ir(dF\text{-}CF_3\text{-}ppy)_2(dtbpy)]PF_6$; Condition D, 1:1 TFA:ACN (0.1 M), 2 mol% $[Ru(dip)_3]Cl_2$; Condition E, 1 equiv (+)-CSA, ACN (0.1 M), 2 mol% $[Ir(dF\text{-}CF_3\text{-}ppy)_2(dtbpy)]PF_6$. See Supporting Information for experimental details.

Experimental Section

General procedure for the photoredox alkylation of heterocycles: To a 1 dram (4 mL) vial equipped with a pressure release septa (CG-4912–01) was added a magnetic stir bar, photocatalyst (0.02 equiv), substrate (50 mg) and solvent (0.1M) (generally 1:1 acetonitrile:TFA) followed by *tert*-butyl peracetate (50% solution in mineral spirits, 3.0 equiv) or similar peroxide. The solution is then degassed by subsurface nitrogen sparging for 5 min then irradiated with a 36W Kessil blue LED lamp until UPLC-MS analysis indicates complete consumption of starting material, or desired level of completion. After the reaction is complete, solvent is removed in vacuo then acetonitrile:water (1:1, 2 mL) is added and the crude mixture purified directly by mass-directed HPLC. Lyophilization of the fractions yields the desired products as TFA salts.

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[22] While UPLC-MS analysis of the crude reactions generally show no significant by-products, crude NMR experiments provide evidence for some polymerization. Isolated yields are consistently lower than assay yield presumably due to losses during repeated handling and fractionation of the crude material during purification. For example, voriconazole is methylated in 75% assay yield (Figure 1), while 58% isolated yield (Figure 4) is obtained.
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[25] Both dynamic scanning calorimetry experiments and dropweight testing was performed on this reagent in our laboratory. CPO does not appear to be shock sensitive and only decomposes violently above its melting point (80 °C) as a neat solid. The decomposition of CPO in organic solvent was found to be relatively non-energetic, commencing at 104 °C. While we feel this reagent is safe to handle in a laboratory setting organic peroxides should always be handled with extreme caution. See Supporting Information for DSC data.
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