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Photoredox-Catalyzed Hydroxymethylation of Heteroaromatic Bases

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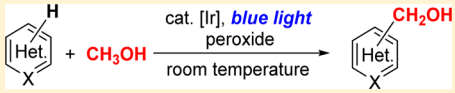
Supporting Information

ABSTRACT: We report the development of a method for room-temperature C−H hydroxymethylation of heteroarenes. A key enabling advance in this work was achieved by implementing visible light photoredox catalysis that proved to be applicable to many classes of heteroarenes and tolerant of diverse functional groups found in druglike molecules.



INTRODUCTION

Late-stage functionalization is a powerful tool for rapid exploration of structure−activity relationships (SAR) and for addressing numerous issues such as selectivity and metabolic stability that arise during the drug discovery process.[1] Late-stage functionalization capitalizes on the ubiquity of C−H bonds in organic compounds, bypassing the need for pre-functionalized synthetic handles in order to rapidly diversify lead structures. Heteroaromatic bases commonly found in biologically active compounds have been demonstrated to readily undergo C−H functionalization via their reactions with hydroxyalkyl, alkyl, aryl, trifluoromethyl, and acyl radicals through the well-known Minisci reaction.[2] Installation of the hydroxymethyl functional group (−CH_2OH) is particularly desirable as it can alter physical properties such as log *P* and solubility,[3] and through hydrogen-bonding interactions, the mode of binding of the pharmacophore. As such, a number of pharmaceuticals have incorporated this moiety (Figure 1). Moreover, a hydroxymethyl group can be used as a versatile point of diversification to access other target compounds.

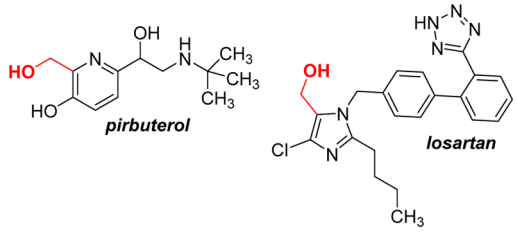
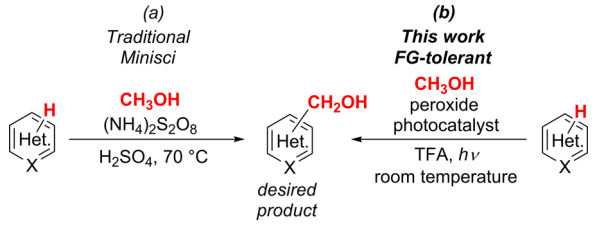


Figure 1. Marketed drugs that contain the hydroxymethyl moiety on heterocycles.

Minisci first demonstrated that hydroxymethyl radicals can be generated from methanol in the presence of ammonium persulfate, and that they react with heterocyclic bases under acidic conditions to yield hydroxymethylated products (Scheme 1a).[4] While these conditions are effective for simple heteroarenes, complex pharmacophores are often incompatible with elevated temperatures and an acidic, oxidizing medium.

Scheme 1. Methods for Hydroxymethylation of Heteroarenes: (a) Traditional Minisci Approach; (b) Photoredox-Catalyzed Method



More recent attempts at introducing the hydroxymethyl group have been made;[5] however, general reaction conditions effective for a wide variety of densely functionalized heteroarenes have not yet been developed.

Photoredox catalysis has become an increasingly powerful method for the mild and efficient generation of radicals for organic synthesis.[6] We previously reported an approach for generating alkyl radicals using a photoredox-mediated method.[7] By combining a photocatalyst and a peroxide, we demonstrated that controlled production of alkyl radicals could be achieved at room temperature, allowing a series of complex, biologically active compounds to be successfully alkylated. Similarly, MacMillan recently reported a photoredox catalyzed system for the addition of stabilized radicals, derived from ethers, to heteroarenes.[8,9] Herein, we demonstrate that an analogous photoredox approach can be implemented for the selective generation of hydroxymethyl radicals from methanol and their addition to heteroarenes (Scheme 1b).

RESULTS AND DISCUSSION

We first evaluated the activity of some commonly employed photocatalysts and a variety of oxidants for the hydroxymethylation of lepidine.[10] As shown in Figure 2, [Ir(dF-CF_3-

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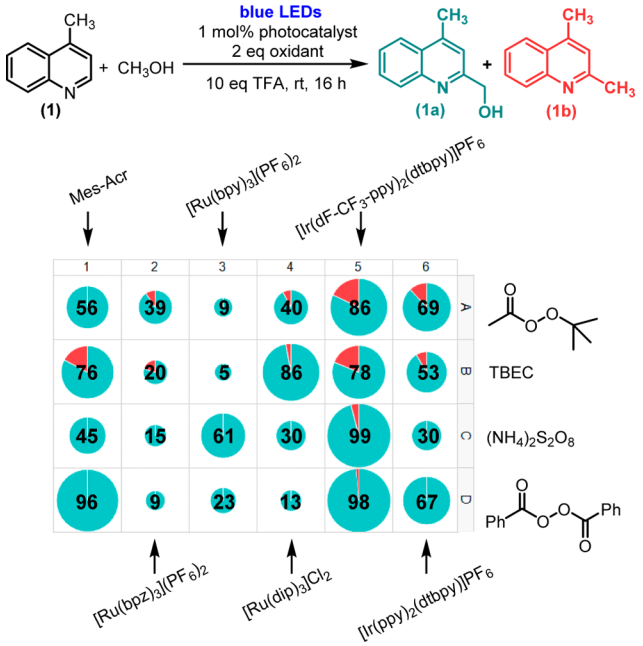


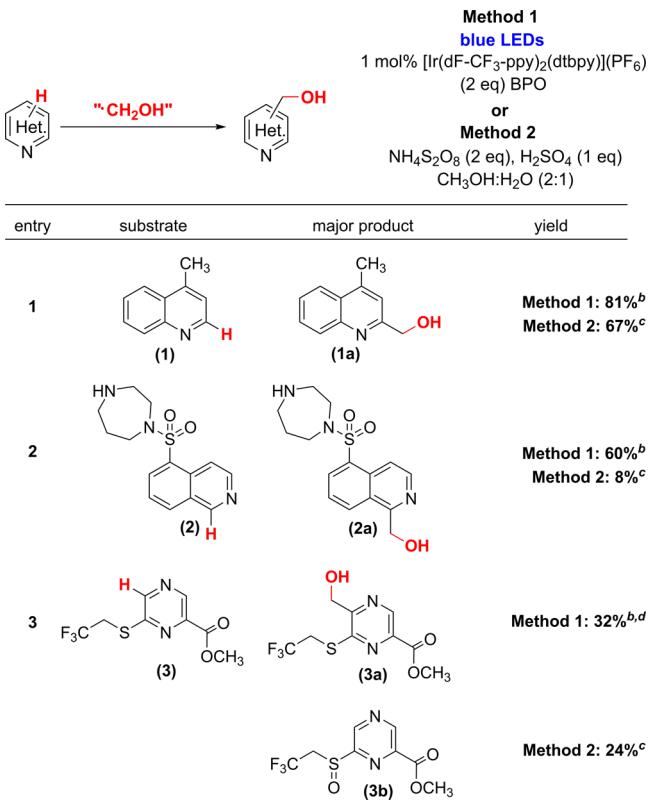
Figure 2. High-throughput optimization of photoredox-mediated hydroxymethylation of lepidine. Percent yields determined by UPLC–MS. Conditions: 5 μmol of lepidine, 10 μmol of oxidant, 1 mol % of photocatalyst, 50 μmol of TFA (10 equiv), 50 μL of methanol, 1 μmol of 4,4′-di-*tert*-butylbiphenyl (internal standard), blue LED, 16 h, room temperature under nitrogen atmosphere. See the Supporting Information for complete details. TFA = trifluoroacetic acid; Mes-Acr =10-methyl-9-(2,4,6-trimethylphenyl)acridinium perchlorate; bpy =2,2′-bipyridine; dF-CF_3-ppy =5-(trifluoromethyl)-2-(2,4-difluorophenyl) pyridine; dtbpy =4,4′-di*tert*-butyl-2,2′-bipyridine; bpz =2,2′-bipyrazine; ppy =2-phenylpyridine; dip =4,7-diphenyl-1,10-phenanthroline; TBEC = *tert*-butylperoxy 2-ethylhexyl carbonate.

ppy)$_2$(dtbpy)]PF_6 (column 5) was the most active photocatalyst for this reaction. *tert*-Butyl peracetate (TBPA), the peroxide determined to be successful in our previously reported methylation system, resulted in a mixture of the desired hydroxymethylated product (**1a**) and methylated product (**1b**) (row A).[11] Similarly, *tert*-butylperoxy 2-ethylhexyl carbonate, TBEC, provided a mixture of **1a** and **1b** (row B). Notably, ammonium persulfate and benzoyl peroxide (BPO) both provided **1a** in high yield and selectivity (rows C and D, respectively).[12]

The optimized conditions were compared to the conditions originally reported by Minisci (Table 1). When the relatively simple substrate lepidine was subjected to each set of conditions, both methods yielded product **1a** in high yields (81% and 67%, respectively). However, upon testing more complex substrates, the photocatalyzed method proved to be markedly more effective. The isoquinoline-containing drug fasudil provided the desired product in just 8% yield under Minisci's conditions, compared with a 60% yield of **2a** when subjected to our improved conditions. Additionally, pyrazine substrate **3** contains a thioether moiety that proved to be susceptible to oxidation, forming the sulfoxide compound **3b** under Minsici conditions. In contrast, this method yielded desired product **3a** in 32% yield with no oxidation product detected.

To evaluate the scope of the reaction, a variety of electron-rich and -poor heteroarenes[13] were selected and subjected to the optimized reaction conditions (Table 2). Substituted

Table 1. Comparison of Thermal and Photoredox-Catalyzed Hydroxymethylation[a]



[a]Isolated yields are reported. [b]Conditions: 0.175 mmol of substrate, 1 mol % of [Ir(dF-CF_3-ppy)$_2$(dtbpy)]PF_6, BPO (2 equiv), 133 μL of TFA (10 equiv), blue LED, rt, 16 h. [c]Conditions: 0.175 mmol of substrate, 0.35 mmol of $(NH_4)_2S_2O_8$ (2 equiv), 0.175 mmol of H_2SO_4 (1 equiv), 390 μL of CH_3OH/H_2O (2:1), 70 °C, 24 h. [d]Reaction time: 8 h.

pyridines (**4**, **5**) performed well, although mixtures of regioisomers were obtained when both ortho- and para-activated sites contained free C–H bonds. This method could be extended to the pyridine-containing diuretic torsemide (**6**), albeit in somewhat decreased yield. Substituted quinolines with a range of groups at the 4- (**1**, **7**, **8**) and 2-positions (**9**) were all suitable candidates for this reaction, providing up to 80% yield of the desired product. Notably, an aryl bromide substituent (**8**) was well tolerated. Similarly, isoquinoline substrates **2** and **10**[14] predominantly provided monohydroxymethylated products. Pyrazines (**3**, **11**) and pyrimidines were also competent substrates, with antifungal voriconazole (**12**) giving a 57% yield of **12a**/**12b**. Interestingly, fused pyrazine compound **13** provided the highest yield (28%) when ammonium persulfate was used as the oxidant combined with Lewis acid BF_3·OEt_2,[15] imidazoles,[16] benzimidazoles, and thiazoles (**14**–**18**) also underwent hydroxymethylation, as did pyrazolopyridazine **19**.

Unexpectedly, quinoxaline- and quinazoline-containing compounds **20** and **21** were methoxylated instead of hydroxymethylated under the reaction conditions (Table 3). Minor amounts of methoxylated byproducts were also observed with some pyridine- and imidazole-containing substrates.[13,16] Similarly, the pyridine ring in pioglitazone (**22**) was not functionalized when subjected to the reaction conditions, but instead a methoxy group was introduced at the benzylic

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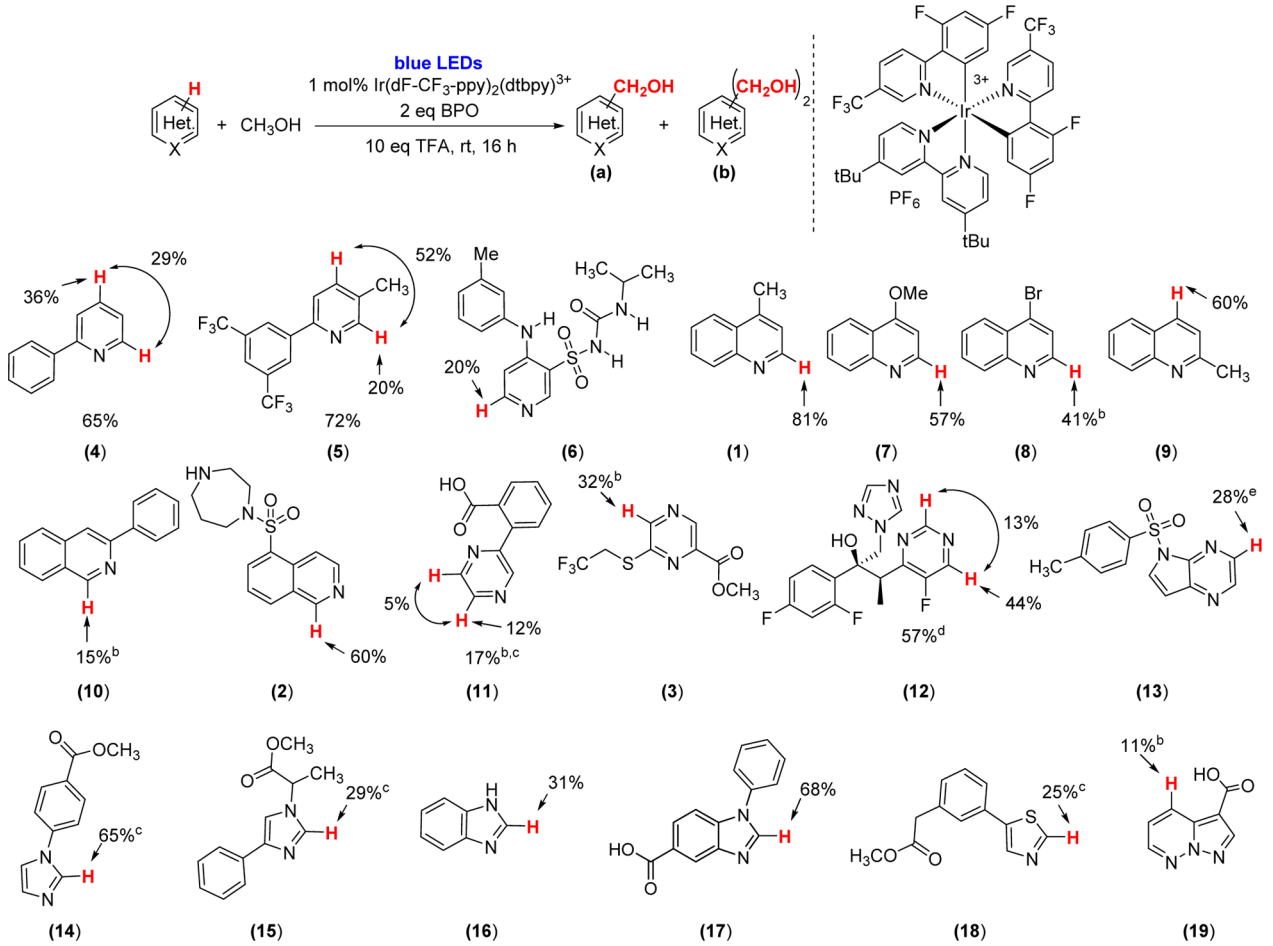
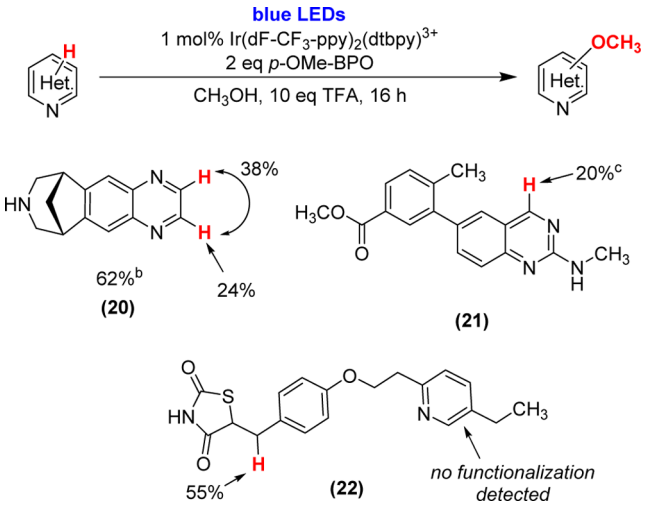
Table 2. Substrate Scope for the Hydroxymethylation of Heteroarenes[a]



[a]Isolated yields are reported. Conditions: 0.175 mmol of substrate, 1 mol % of $[Ir(dF\text{-}CF_3\text{-}ppy)_2(dtbpy)]PF_6$, BPO (2 equiv), 133 μL of TFA (10 equiv), blue LED, rt, 16 h. [b]Reaction time 8 h. [c]4 equiv of BPO used. [d]1 equiv of TFA used. [e]2 eq $NH_4S_2O_8$ used in place of BPO as oxidant; 3 equiv $BF_3{\cdot}OEt_2$ used in place of TFA, 8 h.

Table 3. Methoxylation of Quinazolines, Quinoxolines, And Activated Benzylic Positions[a]



[a]Isolated yields are reported. Conditions: 0.175 mmol of substrate, 1 mol % of $[Ir(dF\text{-}CF_3\text{-}ppy)_2(dtbpy)]PF_6$, *p*-MeO-BPO (2 equiv), 133 μL of TFA (10 equiv), blue LED, rt, 16 h. [b]$Ru(phen)_3Cl_2$ used as photocatalyst. [c]2 equiv of BPO used as oxidant.

position.[17] Optimization of this reaction revealed that methoxy-substituted benzoyl peroxide provided the highest yield of methoxylated product with both varenicline and pioglitazone. Further investigations into the origin of this alternate reaction pathway are currently underway.[18]

A number of heterocyclic compounds were not functionalized under the photoredox reaction conditions (Figure 3). Less active heterocycles for this chemistry include pharmaceutical compounds diflufenican (**23**), fenarimol (**24**), glipizide (**25**), and minaprine (**26**). Benzothiazoles (**27**, **28**) and electron-rich indole **29** were also unreactive under the reaction conditions.

A plausible mechanism for the hydroxymethylation reaction is proposed in Figure 4. Irradiation of Ir^{III} with blue light forms the excited state complex Ir^{III}*, which is subsequently oxidized by BPO to form Ir^{IV} and phenyl radical (step b). Phenyl radical can abstract a hydrogen atom from methanol (step c) to produce the nucleophilic hydroxymethyl radical. Addition to the activated position of a protonated heterocycle (step d)[19] generates the hydroxymethylated heterocyclic radical cation intermediate. In the final step, Ir^{IV} oxidizes this species to give the desired product, simultaneously turning over the catalyst (step e). Interestingly, during the preparation of this manuscript, MacMillan[20] reported a photocatalytic system whereby methanol can be used to methylate heteroaromatic bases.[21]

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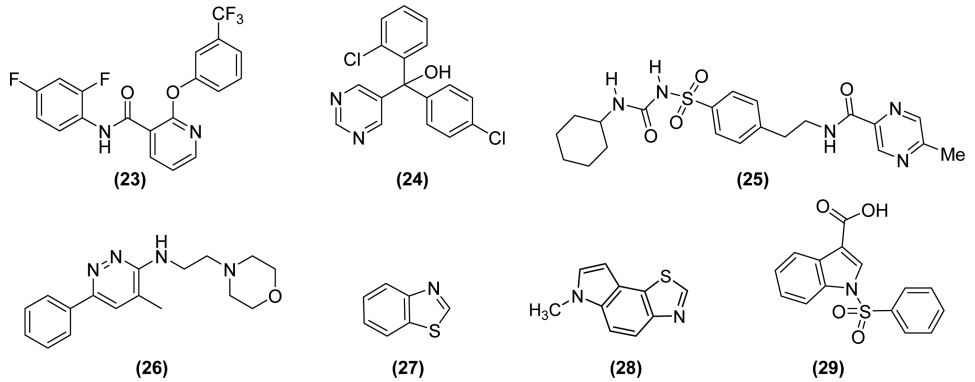


Figure 3. Substrates that are unreactive toward the reaction conditions.

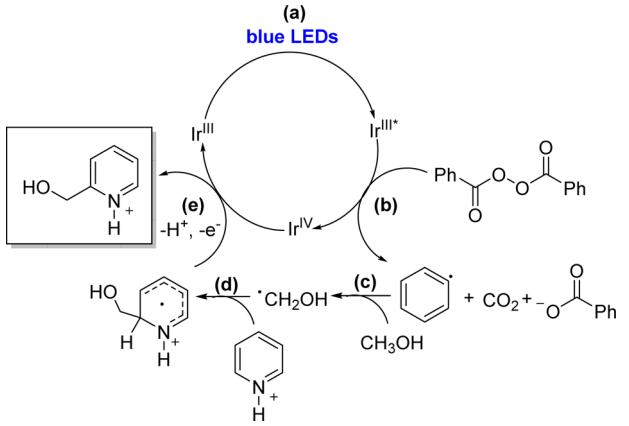


Figure 4. Proposed mechanism for photoredox-catalyzed hydroxymethylation.

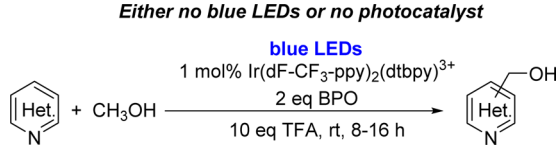
Similar to our putative mechanism shown in Figure 3, a hydroxymethylated radical cation intermediate is proposed. In this case, however, the key intermediate undergoes a spin-center shift with elimination of water, followed by reduction, to generate the methylated product, a consequence of the use of a thiol hydrogen-atom transfer reagent in place of a terminal oxidant.

Control experiments were performed to provide support for the proposed mechanism. When the reaction was performed in the dark with substrate **1** (Table 4, entry 1), no product was detected. Substrates **1**, **12**, and **14** were subjected to the reaction conditions without a photocatalyst using the 4 mA blue LED source that was used in the high-throughput screening experiments. In entries 2–4, <5% conversion to product was observed. However, when the amperage of the light source was increased to 1.3A, full conversion of **1** to **1a** was observed. There is precedent for this photoinduced transformation for electron-deficient quinolines and purine.[22] As shown in entries 6 and 7, the efficacy of the photoinduced reaction does appear to be substrate dependent. Partial conversion of substrate **12** was observed, and only a trace amount of **14a** was detected.

CONCLUSION

In summary, we have shown that visible light photoredox catalysis with BPO as terminal oxidant is able to effect the efficient hydroxymethylation of heterocyclic bases. This method shows applicability to a variety of different heterocycles and is tolerant of oxidation-prone functionalities. We anticipate that this strategy will prove more generally useful in the context of late-stage functionalization of drug-like molecules for the installation of this medicinally important functional group.

Table 4. Control Experiments for Photocatalyzed Hydroxymethylation Reaction[a]



entry	substrate	amperage of blue LEDs	variable removed	product detected	% conv[a]
1[b]	**1**	n/a	light	**1a**	>1
2[c]	**1**	4 mA	Ir	**1a**	<5
3[c,d]	**12**	4 mA	Ir	**12a**	<1
4[c]	**14**	4 mA	Ir	**14a**	<5
5[b]	**1**	1.3 A	Ir	**1a**	>99
6[b,d]	**12**	1.3 A	Ir	**12a**	37
7[b]	**14**	1.3 A	Ir	**14a**	<5

[a]All conversions determined by comparing the UV response of starting material and products using UPLC analysis. [b]Reaction set up in a 4 mL vial using a 1.3 A blue LED lamp. Substrate (0.175 mmol, 1 equiv), BPO (0.350 mmol, 2 equiv), $[Ir(dF\text{-}CF_3\text{-}ppy)_2(dtbpy)]PF_6$ (1 mol %), TFA (10 equiv), MeOH (1.75 mL), 8–16 h, rt. [c]Reaction set up using a high-throughput microvial reaction plate with a 24 diode array of blue LEDs set at 4 mA for the entire plate. Substrate (5 μmol, 1 equiv), BPO (10 μmol, 2 equiv), $[Ir(dF\text{-}CF_3\text{-}ppy)_2(dtbpy)]PF_6$ (1 mol %), TFA (10 equiv), MeOH (50 μL), 8–16 h, rt. [d]1 equiv of TFA added.

EXPERIMENTAL SECTION

General Procedure for Photoredox-Catalyzed Hydroxymethylation. In an N_2-atmosphere glovebox, substrate (0.175 mmol), 85 mg of benzoyl peroxide (0.350 mmol, 2 equiv), 1.9 mg of $[Ir(dF\text{-}CF_3\text{-}ppy)_2(dtbpy)]PF_6$ (1.75 μmol, 0.01 equiv), 133 μL of TFA (1.75 mmol, 10 equiv), and MeOH (1.75 mL, 0.1 M) were added to a 4 mL vial containing a Teflon-coated stir bar and sealed with a pressure release septum. The vial was then removed from the glovebox and placed in a shallow, mirrored glass vacuum dewar and illuminated with a 1.3 A blue LED lamp for 16 h with magnetic stirring. To maintain the reaction temperature <30 °C, the reaction setup was cooled by a stream of compressed air. Upon completion, the reaction solvent was removed in vacuo and the residue redissolved in CH_2Cl_2 (5 mL). The organic layer was then washed with saturated sodium bicarbonate, separated, and dried over Na_2SO_4. The crude reaction mixture was purified via chromatography to obtain pure product(s). Chromatographic purification details are given with each individual compound.

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*(4-Methylquinolin-2-yl)methanol (**1a**).* The general procedure was followed using 23 μL of 4-methylquinoline (0.175 mmol). After workup, the crude reaction mixture was purified via silica gel column chromatography (gradient of 30−50% EtOAc in hexanes) to give **1a** (30 mg, 81%) as a white solid. ^{1}H NMR (CD_3OD, 500 MHz): δ 2.76 (s, 3H), 4.82 (s, 2H), 7.55 (s, 1H), 7.59 (ddd, *J* = 8.4, 6.7, 1.1 Hz, 1H), 7.73 (ddd, *J* = 8.5, 6.7, 1.2 Hz, 1H), 7.99 (dd, *J* = 8.5, 1.1 Hz, 1H), 8.08 (dd, *J* = 8.4, 1.2 Hz, 1H). ^{13}C NMR (CD_3OD, 125 MHz): δ 19.1, 66.1, 120.9, 125.3, 127.6, 128.9, 129.4, 131.0, 147.8, 148.1, 162.7. HRMS (ESI): found *m*/*z* 174.0912 $[M + H]^+$, calcd for $C_{11}H_{11}NO$ + H 174.0913.

*(5-Tosyl-5H-pyrrolo[2,3-b]pyrazin-2-yl)methanol Trifluoroacetate (**2a·TFA**).* The general procedure was followed using 63 mg of fasudil dichloride (0.175 mmol). After workup, the reaction mixture was purified using reversed-phase HPLC (Waters Sunfire Prep C18 OBDTM stationary phase; 10−40% gradient of ACN in H_2O; containing 0.05% TFA modifier) to yield **2a·TFA** (46 mg, 60%) as a white solid. ^{1}H NMR (CD_3OD, 600 MHz): δ 2.21−2.15 (m, 2H), 3.44−3.37 (m, 4H), 3.62 (t, *J* = 6.1 Hz, 2H), 3.80−3.76 (m, 2H), 5.54 (s, 2H), 8.06 (dd, *J* = 7.5, 8.5 Hz, 1H), 8.61 (d, *J* = 6.8 Hz, 1H), 8.64 (dd, *J* = 7.5, 1.0 Hz, 1H), 8.73 (dd, *J* = 8.5, 1.0 Hz, 1H), 8.87 (d, *J* = 6.8 Hz, 1H). ^{13}C NMR (CD_3OD, 150 MHz): δ 27.5, 45.8, 46.3, 48.2, 49.0, 61.8, 121.6, 127.7, 130.4, 133.0, 135.1, 136.2, 137.0, 137.4, 162.8. HRMS (ESI): found *m*/*z* 322.1197 $[M + H]^+$, calcd for $C_{15}H_{19}N_3O_3S$ + H 322.1220.

*Methyl 6-(Hydroxymethyl)-5-((2,2,2-trifluoroethyl)thio)pyrazine-2-carboxylate (**3a**).* The general procedure was followed using 44 mg of methyl 5-((2,2,2-trifluoroethyl)thio)pyrazine-2-carboxylate (0.175 mmol) and a modified reaction time of 8 h. After workup, the reaction mixture was purified via silica gel column chromatography (gradient of 10−20% EtOAc in hexanes) to give **3b** (16 mg, 32%) as a white solid. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 3.93 (s, 3H), 4.34 (q, J_{HF} = 10.4 Hz, 2H), 4.67 (d, J_{HH} = 5.8 Hz, 2H), 5.73 (t, J_{HH} = 5.8 Hz, 1H), 8.91 (s, 1H). ^{13}C NMR (DMSO-d_6, 150 MHz): δ 29.44 (q, J_{CF} = 32.5 Hz), 52.9, 62.5, 125.6 (q, J_{CF} = 276.1 Hz), 140.1, 140.2, 151.3, 156.8, 163.5. ^{19}F NMR (DMSO-d_6, 564 MHz): δ −64.95 (t, J_{FH} = 10.4 Hz, 3F). HRMS (ESI): found *m*/*z* 283.0374 $[M + H]^+$, calcd for $C_9H_9F_3N_2O_3S$ + H 283.0359.

*Methyl 5-((2,2,2-Trifluoroethyl)sulfinyl)pyrazine-2-carboxylate (**3b**).* Methyl 5-((2,2,2-trifluoroethyl)thio)pyrazine-2-carboxylate (44 mg, 0.175 mmol), $NH_4S_2O_8$ (80 mg, 0.350 mmol, 2 equiv), H_2SO_4 (9.3 μL, 0.175 mmol, 1 equiv), and 390 μL of CH_3OH/H_2O (2:1) were added to a 4 mL vial with a pressure release septum containing a Teflon-coated stir bar. The vial was then sealed and heated at 70 °C for 24 h. The solvent was removed in vacuo, and CH_2Cl_2 (5 mL) and saturated sodium bicarbonate (3 mL) were added. The organic layer was then separated and dried over Na_2SO_4, and the crude mixture was purified via silica gel column chromatography (gradient of 15−35% EtOAc in hexanes) to give **3b** (11 mg, 24%) as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 4.05 (s, 3H), 4.10 (dq, J_{HH} = 14.7 Hz, J_{HF} = 10.3 Hz, 1H), 4.26 (dq, J_{HH} = 14.7 Hz, J_{HF} = 10.5 Hz, 1H), 9.35 (s, 1H), 9.42 (s, 1H). ^{13}C NMR (126 MHz, CD_3OD) δ 54.0, 57.9 (q, J_{CF} = 29.0 Hz), 125.7 (q, J_{CF} = 277.6 Hz), 144.0, 146.2, 148.5, 159.7, 164.8. ^{19}F (470 MHz, CD_3OD) δ −62.05 (s, 1F). HRMS (ESI): found *m*/*z* 269.0199 $[M + H]^+$, calcd for $C_8H_7F_3N_2O_3S$ + H 269.0202.

*(2-Phenylpyridin-4-yl)methanol (**4a**) and (6-Phenylpyridine-2,4-diyl)dimethanol (**4b**).* The general procedure was followed using 25 μL of 2-phenylpyridine (0.175 mmol). After workup, the reaction mixture was purified via silica gel column chromatography (gradient of 15−65% EtOAc in hexanes) to give **4a** (12 mg, 36%) and **4b** (11 mg, 29%) as white solids. **4a**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 4.62 (d, *J* = 5.8 Hz, 2H), 5.49 (t, *J* = 5.8 Hz, 1H), 7.30 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.43 (tt, *J* = 7.3, 1.3 Hz, 1H), 7.51−7.47 (m, 2H), 7.87 (dd, *J* = 1.5, 0.8 Hz, 1H), 8.10−8.03 (m, 2H), 8.59 (dd, *J* = 5.0, 0.8 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 61.7, 117.4, 120.0, 126.5, 128.8, 129.0, 138.8, 149.3, 152.7, 155.8. HRMS (ESI): found *m*/*z* 186.0928 $[M + H]^+$, calcd for $C_{12}H_{11}NO$ + H 186.0913. **4b**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.64−4.60 (m, 4H), 5.42 (t, *J* = 5.8 Hz, 1H), 5.46 (t, *J* = 5.7 Hz, 1H), 7.44−7.39 (m, 2H), 7.51−7.45 (m, 2H), 7.73−7.69 (br s, 1H), 8.08−8.02 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 61.9, 64.5, 115.5, 116.3, 126.5, 128.6, 128.8, 138.8, 153.2, 154.8, 161.7. HRMS (ESI): found *m*/*z* 216.1034 $[M + H]^+$, calcd for $C_{13}H_{13}NO_2$ + H 216.1019.

*(2-(3,5-Bis(trifluoromethyl)phenyl)-5-methylpyridin-4-yl)-methanol Trifluoroacetate (**5a·TFA**) and (6-(3,5-Bis-(trifluoromethyl)phenyl)-3-methylpyridine-2,4-diyl)dimethanol Trifluoroacetate (**5b·TFA**).* The general procedure was followed using 53 mg of 5-(3,5-bis(trifluoromethyl)phenyl)-2-methylpyridine (0.175 mmol). After workup, the reaction mixture was purified using reversed-phase HPLC (Waters Sunfire Prep C18 OBDTM stationary phase; 30−80% gradient of ACN in H_2O; containing 0.05% TFA modifier) to yield **5a·TFA** (16 mg, 20%) and **5b·TFA** (43 mg, 52%) as white solids. **5a·TFA**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.28 (s, 3H), 4.62 (s, 2H), 8.15 (br s, 1H), 8.17 (s, 1H), 8.48 (s, 1H), 8.69−8.64 (br s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.8, 60.0, 117.8,121.9, 123.4 (q, J_{CF} = 273.6 Hz, 2C), 126.5, 130.9 (d, J_{CF} = 32.9 Hz, 2C), 131.1, 141.2, 149.8, 150.3, 151.1. ^{19}F (DMSO-d_6, 470 MHz) δ −61.35 (s, 6F). HRMS (ESI): found *m*/*z* 336.0826 $[M + H]^+$, calcd for $C_{15}H_{11}F_6NO$ + H 336.0818. **5b·TFA**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.27 (s, 3H), 4.64 (s, 2H), 4.70 (s, 2H), 8.13 (s, 1H), 8.16−8.14 (br s, 1H), 8.75−8.72 (br s, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 12.3, 60.3, 63.5, 117.2, 121.9, 123.5 (q, J_{CF} = 272.3 Hz, 2C), 126.5, 129.5, 130.8 (d, J_{CF} = 32.8 Hz, 2C), 141.3, 148.5, 151.3, 158.1. ^{19}F (DMSO-d_6, 470 MHz δ −61.22 (s, 6F). HRMS (ESI): found *m*/*z* 366.0934 $[M + H]^+$, calcd for $C_{16}H_{13}F_6NO_2$ + H 366.0923.

*6-(Hydroxymethyl)-N-(isopropylcarbamoyl)-4-(m-tolylamino)-pyridine-3-sulfonamide (**6a**).* The general procedure was followed using 61 mg of *N*-(isopropylcarbamoyl)-4-(*m*-tolylamino)pyridine-3sulfonamide (torsemide; 0.175 mmol). After workup, the reaction mixture was purified using supercritical fluid chromatography (Princeton Chromatography ppu (pyridyl propyl urea) stationary phase; $scCO_2$/MeOH, 5−45% gradient of MeOH) to yield **6a** (13 mg, 20%) as a white solid. Note: characterization reported for the TFA salt of **6a**. **6a·TFA**. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 1.03 (d, *J* = 6.6 Hz, 6H), 2.33 (s, 3H), 3.59−3.70 (m, 1H), 4.38−4.47 (br s, 2H), 5.39−5.54 (br s, 1H), 6.57 (d, *J* = 6.4 Hz, 1H), 7.05−7.13 (m, 4H), 7.35 (dd, *J* = 7.5, 7.6 Hz, 1H), 8.56 (s, 1H), 8.62−8.84 (br s, 1H), 10.22−11.59 (br s, 1H). ^{13}C NMR (DMSO-d_6, 150 MHz): δ 21.0, 22.4, 41.5, 63.3, 103.2, 118.6, 120.7, 124.2, 126.3, 129.5, 138.1, 139.3, 149.2, 149.8, 152.3, 165.7. HRMS (ESI): found *m*/*z* 379.1450 $[M + H]^+$, calcd for $C_{17}H_{22}N_4O_4S$ + H 379.1435.

*(4-Methoxyquinolin-2-yl)methanol (**7a**).* The general procedure was followed using 25 μL of 4-methoxyquinoline (0.175 mmol). After workup, the reaction mixture was purified via silica gel column chromatography (gradient of 35−50% EtOAc in hexanes) to give **7a** (19 mg, 57%) as a white solid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 4.06 (s, 3H), 4.66 (d, *J* = 5.7 Hz, 2H), 5.54 (t, *J* = 5.7 Hz, 1H), 7.14 (s, 1H), 7.51 (ddd, *J* = 8.2, 6.9, 1.0 Hz, 1H), 7.71 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.87 (dd, *J* = 8.4, 1.0 Hz 1H), 8.10 (dd, *J* = 8.2, 1.4 Hz, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 55.9, 64.9, 97.9, 119.8, 121.4, 125.1, 128.1, 129.7, 147.8, 162.0, 163.9. HRMS (ESI): found *m*/*z* 190.0876 $[M + H]^+$, calcd for $C_{11}H_{11}NO_2$ + H 190.0863.

*(4-Bromoquinolin-2-yl)methanol (**8a**).* The general procedure was followed using 36 mg of 4-bromoquinoline (0.175 mmol) with a modified reaction time of 8 h. After workup, the reaction mixture was purified via silica gel column chromatography (gradient of 15−30% EtOAc in hexanes) to give **8a** (17 mg, 41%) as a white solid. ^{1}H NMR (CD_3OD, 500 MHz): δ 4.84 (s, overlapping with water, 2H), 7.68 (ddd, *J* = 8.2, 7.0, 1.0 Hz, 1H), 7.81 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 8.01 (dd, *J* = 8.2, 1.2 Hz, 1H), 8.01 (s, 1H), 8.21 (dd, *J* = 8.3, 1.0 Hz, 1H). ^{13}C NMR (CD_3OD, 125 MHz): δ 66.7, 124.3, 127.9, 128.3, 129.1, 129.8, 132.2, 136.3, 149.1, 163.5. HRMS (ESI): found *m*/*z* 237.9875 $[M + H]^+$, calcd for $C_{10}H_8BrNO$ + H 237.9862.

*(2-Methylquinolin-4-yl)methanol (**9a**).* The general procedure was followed using 24 μL of 2-methylquinoline (0.175 mmol). After workup, the reaction mixture was purified via silica gel column chromatography (gradient of 30−55% EtOAc in hexanes) to give **9a** (18 mg, 60%) as a white solid. ^{1}H NMR (CD_3OD, 500 MHz): δ 2.71 (s, 3H), 5.12 (s, 2H), 7.53 (s, 1H), 7.54 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.71 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.96 (dd, *J* = 8.3, 1.3 Hz, 1H) 7.99

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(dd, J = 8.2, 1.2 Hz, 1H). ^{13}C NMR (CD_3OD, 125 MHz): δ 24.9, 61.7, 120.4, 124.4, 125.8, 127.3, 129.0, 130.9, 148.3, 149.9, 160.5. HRMS (ESI): found m/z 174.0903 $[M + H]^+$, calcd for $C_{11}H_{11}NO$ + H 174.0913.

*(3-Phenylisoquinolin-1-yl)methanol (**10a**), 4-Methoxy-3-phenylisoquinoline (**10b**), and (4-Methoxy-3-phenylisoquinolin-1-yl)methanol (**10c**).* The general procedure was followed using 3-phenylisoquinoline (0.175 mmol, 23 μL) and a modified reaction time of 8 h. After workup, the reaction mixture was purified using reversed-phase HPLC (Waters Sunfire Prep C18 OBDTM stationary phase; 10−40% gradient of ACN in H_2O; containing 0.05% TFA modifier) to give **10a** (6.0 mg, 15%), **10b** (0.1 mg, 0.2%), and **10c** (0.5 mg, 1%) as white solids. **10a**. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.38−8.33 (m, 2H), 8.29−8.25 (m, 2H), 8.04 (br d, J = 8.2 Hz, 1H), 7.78 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H), 7.66 (ddd, J = 8.3, 6.8, 1.2 Hz, 1H), 7.56−7.50 (m, 2H), 7.43 (tt, J = 7.4, 1.1 Hz, 1H), 5.48 (t, J = 5.6 Hz, 1H), 5.14 (d, J = 5.6 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 159.5, 147.9, 138.6, 136.9, 130.5, 128.7, 128.6, 127.6, 127.2, 126.5, 125.6, 125.1, 115.8, 63.8. HRMS (ESI): found m/z 236.1052 $[M + H]^+$, calcd for $C_{16}H_{13}NO$ + H 236.1070. **10b**. ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.23 (s, 1H), 8.21−8.17 (m, 2H), 8.09−8.04 (m, 2H), 7.87 (ddd, J = 8.4, 6.7, 1.1 Hz, 1H), 7.73 (ddd, J = 8.4, 6.7, 1.1 Hz, 1H), 7.55−7.50 (m, 2H), 7.44 (tt, J = 7.4, 1.2 Hz, 1H), 3.67 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6, obtained from 2D heteronuclear ^{1}H−^{13}C experiments (viz., HSQC and HMBC) due to limited isolated yield) δ 148.5, 148.2, 141.7, 137.7, 131.2, 131.0, 129.0, 128.8, 128.6, 128.5, 128.4, 127.8, 121.2, 60.9. HRMS (ESI): found m/z 236.1047 $[M + H]^+$, calcd for $C_{16}H_{13}NO$ + H 236.1070. **10c**. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.39 (d, J = 8.4 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.11−8.08 (m, 2H), 7.86 (ddd, J = 8.4, 6.8, 1.1 Hz, 1H), 7.73 (ddd, J = 8.4, 6.8, 1.2 Hz, 1H), 7.55−7.50 (m, 2H), 7.44 (tt, J = 7.4, 1.1 Hz, 1H), 5.43 (t, J = 5.6 Hz, 1H), 5.05 (d, J = 5.6 Hz, 2H), 3.66 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 155.2, 148.1, 139.9, 137.5, 131.7, 130.5, 128.9, 128.3, 128.1, 127.5, 126.7, 126.1, 121.7, 63.7, 61.2. HRMS (ESI): found m/z 266.1151 $[M + H]^+$, calcd for $C_{17}H_{15}NO_2$ + H 266.1176.

*2-(5-(Hydroxymethyl)pyrazin-2-yl)benzoic Acid (**11a**) and 2-(5,6-Bis(hydroxymethyl)pyrazin-2-yl)benzoic Acid (**11b**).* The general procedure was followed using 35 mg of 2-(pyrazin-2-yl)benzoic acid (0.175 mmol). After workup, the reaction mixture was purified using reversed-phase HPLC (Waters Sunfire Prep C18 OBDTM stationary phase; 10−35% gradient of ACN in H_2O; containing 0.05% TFA modifier) to yield **11a** (5 mg, 12%) and **11b** (2 mg, 5%) as tan solids. Note: The isolated sample of **11b** contained ammonium trifluoroacetate (0.13 equiv) impurity. **11a**. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 4.69 (s, 2H), 5.89−5.32 (br s, 1H), 7.58 (td, J = 7.3, 1.8 Hz, 1H), 7.68−7.61 (m, 2H), 7.83 (dd, J = 7.6, 1.3 Hz, 1H), 8.69 (d, J = 1.4 Hz, 1H), 8.71 (d, J = 1.4 Hz, 1H). ^{13}C NMR (DMSO-d_6, 150 MHz): δ 62.6, 129.0, 129.6, 130.3, 131.1, 132.6, 137.3, 141.1, 142.4, 152.1, 154.8, 169.0. HRMS (ESI): found m/z 231.0753 $[M + H]^+$, calcd for $C_{12}H_{10}N_2O_3$ + H 231.0764. **11b**. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 4.73 (s, 2H), 4.75 (s, 2H), 7.58 (ddd, J = 7.9, 6.6, 2.0 Hz, 1H), 7.70−7.63 (m, 2H), 7.84 (dd, J = 7.9, 1.1 Hz, 1H), 8.65 (s, 1H). ^{13}C NMR (DMSO-d_6, 150 MHz): δ 62.0, 62.2, 129.0, 129.5, 130.4, 131.2, 132.4, 137.0, 141.0, 151.1, 152.2, 152.5, 169.0. HRMS (ESI): found m/z 261.0857 $[M + H]^+$, calcd for $C_{13}H_{12}N_2O_4$ + H 261.0870.

*(2S,3R)-2-(2,4-Difluorophenyl)-3-(5-fluoro-6-(hydroxymethyl)-pyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol Trifluoroacetate (**12a·TFA**) and (6-((2R,3S)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1H-1,2,4-triazol-1-yl)butan-2-yl)-5-fluoropyrimidine-2,4-diyl)-dimethanol Trifluoroacetate (**12b·TFA**).* The general procedure was followed using 61 mg of varenicline (0.175 mmol) and 13 μL of TFA (0.175 mmol, 1 equiv). After workup, the reaction mixture was purified using reversed-phase HPLC (Waters Sunfire Prep C18 OBDTM stationary phase; 10−45% gradient of ACN in H_2O; containing 0.05% TFA modifier) to yield **12a·TFA** (38 mg, 44%) and **12b·TFA** (12 mg, 13%) as white solids. **12a·TFA**. ^{1}H NMR (CD_3OD, 600 MHz): δ 1.13 (d, J_{HH} = 7.1 Hz, 3H), 4.18 (dd, J_{HH} = 7.1, J_{HF} = 1.1 Hz, 1H), 4.37 (d, J = 14.3 Hz, 1H), 4.83 (d, J_{HF} = 1.7 Hz, 2H), 4.86 (d, J = 14.3 Hz, 1H), 6.88−6.84 (m, 1H), 7.01−6.95 (m, 1H), 7.51−7.45 (m, 1H), 7.73 (s, 1H), 8.50 (s, 1H), 8.96 (d, J_{HF} = 1.8 Hz, 1H). ^{13}C NMR (CD_3OD, 150 MHz): δ 15.8, 38.7, 58.5, 60.3, 78.7, 105.2 (t, J_{CF} = 26.4 Hz), 112.3 (d, J_{CF} = 20.4 Hz), 125.3 (d, $J_{C,F}$ = 21.5 Hz), 131.9, 145.8, 150.3, 154.4, 155.1 (d, J_{CF} = 260.6 Hz), 158.3 (d, J_{CF} = 21.9 Hz), 159.3 (d, J_{CF} = 20.8 Hz), 160.5 (d, J_{CF} = 240.8 Hz), 164.6 (d, J_{CF} = 239.3 Hz). ^{19}F NMR (CD_3OD, 564 MHz): δ −140.26 (s, 1F), −112.90 (t, J_{FH} = 7.9 Hz, 1F), −109.57 (d, J_{FH} = 8.4 Hz, 1F). HRMS (ESI): found m/z 380.1319 $[M + H]^+$, calcd for $C_{17}H_{16}F_3N_5O_2$ + H 380.1329. **12b·TFA**. ^{1}H NMR (CD_3OD, 600 MHz): δ 1.12 (d, J_{HH} = 7.1 Hz, 3H), 4.17 (dd, J_{HH} = 7.1, J_{HF} = 1.1 Hz, 1H), 4.39 (d, J_{HH} = 14.3 Hz, 1H), 4.85−4.81 (m, 5H), 6.87−6.91 (m, 1H), 7.03−6.98 (m, 1H), 7.56−7.51 (m, 1H), 7.65 (s, 1H), 8.41 (s, 1H). ^{13}C NMR (CD_3OD, 150 MHz): δ 16.0, 38.4, 58.5, 60.3, 65.5, 78.7, 105.2 (t, J_{CF} = 26.9 Hz), 112.3 (d, J_{CF} = 20.9 Hz), 125.5 (d, J_{CF} = 21.3 Hz), 131.9, 145.9, 150.6, 154.0 (d, J_{CF} = 262.1 Hz), 158.3 (d, J_{CF} = 20.4 Hz), 159.5 (d, J_{FC} = 21.5 Hz), 160.4 (d, $J_{C,F}$ = 246.6 Hz), 164.5 (d, J_{CF} = 234.5 Hz), 165.3. ^{19}F NMR (CD_3OD, 470 MHz): δ −137.40 (s, 1F), −112.76 (t, J_{FH} = 7.9 Hz, 1F), −109.42 (d, J_{FH} = 8.4 Hz, 1F). HRMS (ESI): found m/z 410.1419 $[M + H]^+$, calcd for $C_{18}H_{18}F_3N_5O_3$ + H 410.1435.

*(5-Tosyl-5H-pyrrolo[2,3-b]pyrazin-2-yl)methanol (**13a**).* The general procedure was followed using 48 mg of 5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazine (0.175 mmol), 65 μL of BF_3OEt_2 (0.525, 3 equiv), and 80 mg of $NH_4S_2O_8$ (0.350 mmol, 2 equiv) with a modified reaction time of 8 h. After workup, the reaction mixture was purified via silica gel column chromatography (gradient of 25−50% EtOAc in hexanes) to give **13a** (13 mg, 28%) as a white solid. Note: Characterization data are reported for the TFA salt of **13a·TFA**. **13a·TFA**. ^{1}H NMR (CD_3OD, 500 MHz) δ 2.36 (s, 3H), 4.78 (s, 2H), 6.82 (d, J = 4.1 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H), 8.16 (d, J = 4.1 Hz, 1H), 8.47 (s, 1H). ^{13}C NMR (CD_3OD, 125 MHz) δ 21.7, 64.6, 107.2, 129.2, 131.2, 132.9, 136.4, 138.4, 141.6, 142.0, 147.8, 154.1. HRMS (ESI): found m/z 304.0757 $[M + H]^+$, calcd for $C_{14}H_{13}N_3O_3S$ + H 304.0750.

*Methyl 4-(2-(Hydroxymethyl)-1H-imidazol-1-yl)benzoate (**14a**).* The general procedure was followed using 35 mg of methyl 4-(1H-imidazol-1-yl)benzoate (0.175 mmol) and benzoyl peroxide (0.700 mmol, 168 mg, 4 equiv). After workup, the reaction mixture was purified via silica gel column chromatography (gradient of 70%−100% EtOAc in hexanes) to give **14a** (26 mg, 65%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.89 (s, 3H), 4.44 (d, J = 5.5 Hz, 2 H), 5.48 (t, J = 5.5 Hz, 1 H), 7.04 (s, 1H), 7.51 (s, 1H), 7.75 (d, J = 8.4 Hz, 2H), 8.09 (d, J = 8.4 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 52.3, 55.2, 121.3, 124.6, 127.9, 128.6, 130.4, 141.3, 146.9, 165.5. HRMS (ESI): found m/z 233.0913 $[M + H]^+$, calcd for $C_{12}H_{12}N_2O_3$ + H 233.0921.

*2-(2-(Hydroxymethyl)-4-phenyl-1H-imidazol-1-yl)propanoic Acid (**15a**) and 2-(5-Methoxy-4-phenyl-1H-imidazol-1-yl)propanoic Acid (**15b**).* The general procedure was followed using 40 mg of methyl 2-(2-(hydroxymethyl)-4-phenyl-1*H*-imidazol-1-yl)propanoate (0.175 mmol) and benzoyl peroxide (0.700 mmol, 168 mg, 4 equiv). After workup, the reaction mixture was purified using reversed-phase HPLC (Waters Sunfire Prep C18 OBDTM stationary phase; 10−40% gradient of ACN in H_2O; containing 0.05% TFA modifier) to give **15a** (7.6 mg, 29%) and **15b** (0.4 mg, 2%) as white solids. **15a**. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.87−7.74 (m, 2H), 7.73 (s, 1H), 7.35−7.30 (m, 2H), 7.17 (tt, J = 7.4, 1.3 Hz, 1H), 5.13 (q, J = 7.2 Hz, 1H), 4.54 (d, J = 13.0 Hz, 1H), 4.49 (d, J = 13.0 Hz, 1H), 1.66 (d, J = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 172.2, 147.6, 138.2, 134.6, 128.4, 126.0, 124.0, 115.1, 55.9, 53.6, 18.1. HRMS (ESI): found m/z 247.1052 $[M + H]^+$, calcd for $C_{13}H_{14}N_2O_3$ + H 247.1077. **15b**. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.78−7.68 (m, 2H), 7.38 (s, 1H), 7.37−7.32 (m, 2H), 7.13 (tt, J = 7.4, 1.3 Hz, 1H), 4.30 (q, J = 7.3 Hz, 1H), 3.74 (s, 3H), 1.52 (d, J = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6; chemical shifts were obtained from 2D ^{1}H−^{13}C heteronuclear NMR experiments (viz., HSQC and HMBC) due to limited isolated yield): δ 173.2, 142.8, 134.6, 130.2, 128.4, 125.1, 124.1, 120.6, 61.4, 54.2, 19.2. HRMS (ESI): found m/z 247.1051 $[M + H]^+$, calcd for $C_{13}H_{14}N_2O_3$ + H 247.1077.

*(1H-Benzo[d]imidazol-2-yl)methanol (**16a**).* The general procedure was followed using 36 mg of benzimidazole (0.175 mmol). After

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workup, the reaction mixture was purified via silica gel column chromatography (gradient of 60−100% EtOAc in hexanes) to give **16a** (8 mg, 31%) as a white solid. ^{1}H NMR (CD_3OD, 500 MHz): δ 4.83 (s, 2H), 7.19−7.23 (m, 2H), 7.51−7.55 (m, 2H). ^{13}C NMR (CD_3OD, 125 MHz): δ 59.1, 115.9, 123.6, 139.5, 156.4. HRMS (ESI): found m/z 149.0706 $[M + H]^+$, calcd for $C_8H_8N_2O$ + H 149.0709.

*2-(Hydroxymethyl)-1-phenyl-1H-benzo[d]imidazole-5-carboxylic Acid (**17a**).* The general procedure was followed using 48 mg of 1-phenyl-1*H*-benzo[d]imidazole-5-carboxylic acid (0.2 mmol). After workup, the reaction mixture was purified using reversed-phase HPLC (Waters Sunfire Prep C18 OBDTM stationary phase; 5−30% gradient of ACN in H_2O; containing 0.05% TFA modifier) to yield **17a** (52 mg, 68%) as a white solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 4.68 (s, 2H), 7.33 (d, J = 8.7 Hz, 1H), 7.62−7.71 (m, 5H), 7.95 (dd, J = 8.7, 1.5 Hz, 1H), 8.31 (d, J = 1.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 55.8, 110.8, 119.7, 125.2, 125.9, 126.8, 129.5, 130.0, 134.2, 138.3, 155.9, 157.9, 158.3, 167.3. HRMS (ESI): found m/z 269.0924 $[M + H]^+$, calcd for $C_{15}H_{12}N_2O_3$ + H 269.0921.

*Methyl 2-(3-(2-(Hydroxymethyl)thiazol-5-yl)phenyl)acetate (**18a**).* The general procedure was followed using 31 mg of methyl 2-(3-(thiazol-5-yl)phenyl)acetate (0.133 mmol) and a modified reaction time of 8 h. After workup, the reaction mixture was purified using reversed-phase HPLC (Waters Sunfire Prep C18 OBDTM stationary phase; 20−70% gradient of ACN in H_2O; containing 0.05% TFA modifier) to yield **18a** (11 mg, 25%) as a white solid. ^{1}H NMR (CD_3OD, 500 MHz) δ 3.70 (s, 3H), 3.71 (s, 2H), 4.84 (s, 2H), 7.27 (m, 1H) 7.38 (t, J = 7.7 Hz, 1 H), 7.54 (m, 2H), 7.96 (s, 1H). ^{13}C NMR (CD_3OD, 125 MHz) δ 41.6, 52.7, 62.6, 126.5, 128.8, 130.6, 130.7, 133.0, 137.0, 138.8, 140.8, 173.9, 174.8. HRMS (ESI): found m/z 264.0704 $[M + H]^+$, calcd for $C_{13}H_{13}NO_3S$ + H 264.0689.

*6-(Hydroxymethyl)pyrazolo[1,5-b]pyridazine-3-carboxylic Acid (**19a**).* The general procedure was followed using 29 mg of pyrazolo[1,5-*b*]pyridazine-3-carboxylic acid (0.175 mmol) with a modified reaction time of 8 h. After workup, the reaction mixture purified using supercritical fluid chromatography (Princeton Chromatography ppu (pyridyl propyl urea) stationary phase; $scCO_2$/MeOH, 5−30% gradient of MeOH) to yield **19a** (4 mg, 11%) as a white solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 5.10 (s, 2H), 5.68 (br s, 1H), 7.54 (d, J = 4.8 Hz, 1H), 8.46 (s, 1H), 8.59 (d, J = 4.8 Hz, 1H), 12.66 (br s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 60.4, 105.4, 115.2, 132.2, 143.1, 143.9, 145.3, 163.5. HRMS (ESI): found m/z 194.0546 $[M + H]^+$, calcd for $C_8H_7N_3O_3$ + H 194.0560.

*2-Methoxy-7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine (**20a**) and 2,3-Dimethoxy-7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine (**20b**).* The general procedure was followed using 54 mg of varenicline tartrate (0.150 mmol), 1.1 mg of $Ru(phen)Cl_2·H_2O$ (1.50 μmol, 0.01 equiv), 106 mg of 4-methoxybenzoic peroxyanhydride (0.350 mmol), and the lower wattage LED array (5 mA). After workup, the reaction mixture was purified using supercritical fluid chromatography (Princeton Chromatography ppu (pyridyl propyl urea) stationary phase; $scCO_2$/MeOH, 4−45% gradient of MeOH) to yield **20a** (13 mg, 24%) and **20b** (22 mg, 38%) as white solids. **20a**. ^{1}H NMR (CD_3OD, 500 MHz): δ 2.25 (d, J = 11.5 Hz, 1H), 2.53−2.43 (m, 1H), 3.34−3.29 (m, 2H), 3.53−3.47 (m, 2H), 3.64−3.59 (m, 2H), 4.11 (s, 3H), 7.87 (s, 1H), 7.97 (s, 1H), 8.47 (s, 1H). ^{13}C NMR (CD_3OD, 125 MHz): δ 40.0, 40.3, 42.1, 48.7, 54.5, 123.6, 124.7, 140.2, 140.5, 142.8, 142.9, 146.7, 159.6. HRMS (ESI): found m/z 242.1281 $[M + H]^+$, calcd for $C_{14}H_{15}N_3O$ + H 242.1288. **20b**. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.10 (d, J = 11.4 Hz, 1H), 2.62−2.39 (m, 1H), 3.26 (d, J = 12.5 Hz, 2H), 3.45−3.37 (m, 2H), 3.53−3.47 (m, 2H), 4.14 (s, 6H), 7.68 (s, 2H). ^{13}C NMR (CD_3OD, 125 MHz): δ 40.1, 42.4, 48.7, 54.6, 122.7, 139.2, 143.3, 151.6. HRMS (ESI): found m/z 272.1411 $[M + H]^+$, calcd for $C_{15}H_{17}N_3O_2$ + H 272.1394.

*Methyl 3-(4-Methoxy-2-(methylamino)quinazolin-6-yl)-4-methylbenzoate (**21a**).* The general procedure was followed using 52 mg of methyl 4-methyl-3-(2-(methylamino)quinazolin-6-yl)benzoate (0.169 mmol) and the lower wattage LED array (5 mA). After workup, the reaction mixture was purified via silica gel column chromatography (gradient of 10%−25% ethyl acetate in hexanes) to give **21a** (26 mg, 20%) as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.12 (d, J = 5.0 Hz, 3H), 3.90 (s, 3H), 4.07 (s, 3H), 7.34 (d, J = 8.0 Hz, 1H), 7.56−7.59 (overlapping br s, 2H), 7.88 (t, J = 1.3 Hz, 1H), 7.92 (dd, J = 8.0, 1.9 Hz, 1H), 7.95 (d, J = 1.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.0, 28.6, 52.2, 54.1, 110.2, 123.9, 124.1, 128.0, 128.5, 130.7, 131.2, 134.5, 135.1, 141.3, 141.6, 152.2, 159.7, 167.3, 167.8. HRMS (ESI): found m/z 338.1512 $[M + H]^+$, calcd for $C_{19}H_{19}N_3O_3$ + H 338.1499.[23]

*5-((4-(2-(5-Ethylpyridin-2-yl)ethoxy)phenyl)(methoxy)methyl)-thiazolidine-2,4-dione Trifluoroacetate (**22a/b·TFA**) and (Z)-5-(4-(2-(5-Ethylpyridin-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione Trifluoroacetate (**22c·TFA**).* The general procedure was followed using 50 mg of 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione monohydrochloride (pioglitazone hydrochloride; 0.128 mmol), 77 mg of 4-methoxybenzoic peroxyanhydride (0.255 mmol), and the lower wattage LED array (5 mA). After workup, the reaction mixture was purified by reversed-phase HPLC (Waters Sunfire Prep C18 OBDTM stationary phase; 5−30% gradient of ACN in H_2O; containing 0.05% TFA modifier) to give a mixture of three compounds **23a-c·TFA** (52 mg, corrected total yield 68%). The ratio of **22a**:**22b**:**22c** in the purified sample was determined by ^{1}H NMR spectroscopy to be 48:18:34. Further purification yielded a sample of **22a/b·TFA** and a sample enriched in **22c** that facilitated NMR structure elucidation. **22a·TFA**. ^{1}H NMR (DMSO-d_6, 600 MHz) δ 1.22 (t, J = 7.5 Hz, 3H), 2.72 (q, J = 7.5 Hz, 2H), 3.17 (s, 3H), 3.35 (t, J = 6.2 Hz, 2H), 4.37 (t, J = 6.4 Hz, 2H), 4.88 (d, J = 3.3 Hz, 1H), 4.93 (d, J = 3.3 Hz, 1H), 6.94 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H), 7.77 (d, J = 8.1 Hz, 1H), 8.13 (dd, J = 8.1, 1.5 Hz, 1H), 8.63 (d, J = 1.5 Hz, 1H) 12.08 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 14.9, 24.8, 33.9, 56.8, 59.2, 65.9, 79.5, 114.6, 125.8, 127.8, 130.1, 139.8, 142.3, 143.1, 152.8, 158.1, 171.9, 174.0. HRMS (ESI): found m/z 387.1361 $[M + H]^+$, calcd for $C_{20}H_{22}N_2O_4S$ + H 387.1373. **22b·TFA**. ^{1}H NMR (DMSO-d_6, 600 MHz) δ 1.21 (t, J = 7.5 Hz, 3H) 2.72 (q, J = 7.5 Hz, 2H), 3.20 (s, 3H), 3.36 (t, J = 6.3 Hz, 2H), 4.45 (t, J = 6.3 Hz, 2H), 4.92 (d, J = 4.4 Hz, 1H), 5.20 (d, J = 4.4 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H), 7.73 (d, J = 8.3 Hz, 1H), 8.11 (dd, J = 8.3, 1.9 Hz, 1H), 8.61 (d, J = 1.9 Hz, 1H), 11.81 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 14.9, 24.8, 34.0, 56.5, 57.0, 66.3, 80.4, 113.9, 125.6, 127.6, 129.2, 139.6, 141.8, 143.6, 152.8, 158.1, 171.8, 173.3. HRMS (ESI): found m/z 387.1356 $[M + H]^+$, calcd for $C_{20}H_{22}N_2O_4S$ + H 387.1373. **22c·TFA**. ^{1}H NMR (DMSO-d_6, 600 MHz) δ 1.20 (t, J = 7.6 Hz, 3H) 2.68 (q, J = 7.4 Hz, 2H), 3.29 (t, J = 5.9 Hz, 2H), 4.44 (t, J = 6.4 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 7.57−7.52 (m, 3H), 7.74 (s, 1H), 7.92−7.86 (br s, 1H), 8.53−8.50 (br s, 1H), 12.06 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 15.1, 24.8, 35.1, 66.6, 115.4, 120.4, 124.5, 125.7, 131.7, 132.1, 138.6, 139.0, 145.7, 153.7, 160.0, 167.3, 167.9. HRMS (ESI): found m/z 355.1095 $[M + H]^+$, calcd for $C_{19}H_{18}N_2O_3S$ + H 355.1111.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00811.

General experimental methods, detailed tables of results, and NMR spectra for compounds **1a**−**22a**, **5b**, **10b**,**c**, **12b**, **15b**, and **20b** (PDF)

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(11) TBPA plays dual role as both an oxidant and methyl source for this reaction.
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(15) See the Supporting Information for more details on the applicability of these conditions to other substrates.
(16) Imidazole **15** also generated a minor methoxylated product (**15b**) that was isolated in low yield. See the Supporting Information and Table 3 for more information.
(17) The methoxylated product was obtained as a pair of diastereomers **22a**/**22b** (55% yield) mixed with the corresponding elimination product **22c** (28% yield). See the Supporting Information for more details.
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(23) $^{1}H/^{15}N$ HMBC data were key in characterizing the structure. Hydroxymethylation was ruled out by multiplicity edited HSQC, and the location of methoxylation was confirmed using $^{1}H/^{13}C$ HMBC data. See the Supporting Information for details.

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