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C-H Functionalization of Heteroarenes Using Unactivated Alkyl Halides through Visible-Light Photoredox Catalysis under Basic Conditions

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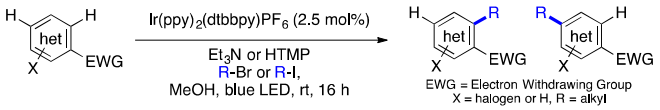
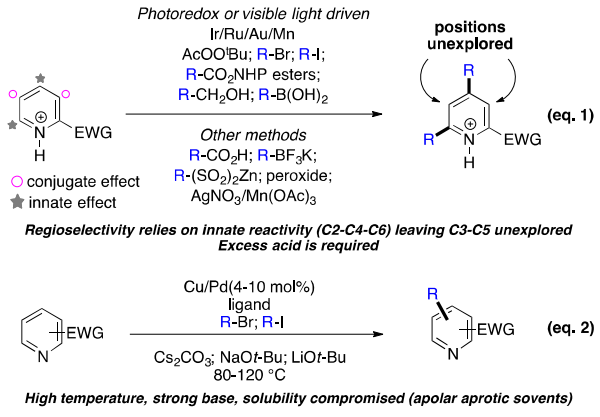


ABSTRACT: A C-H functionalization of electron-deficient heteroarenes using commercial unactivated alkyl halides through reductive quenching photoredox catalysis has been developed. Mainstream approaches rely on the use of an excess of strong acids that result in regioselectivities dictated by the innate effect of the protonated heteroarene, leaving functionalization of other carbons unexplored. We report a mild method under basic conditions that allows access to previously underexplored regioselectivities by relying on a combination of conjugate and halogen *ortho*-directing effects. Overall this methodology gives quick access to a variety of alkylated heteroarenes that will be of interest to medicinal chemistry programs.

INTRODUCTION

Metal-catalyzed cross-coupling reactions have emerged as highly useful and widely applicable methods for accessing structurally diverse heterocyclic compounds via carbon-carbon bond formation. As a result, these methods have profoundly influenced both drug design and organic synthesis fields.[1] However, typical synthetic strategies rely on the simultaneous use of functional groups such as aryl halides and organometallic monomers (e.g. boronic acids or esters, Grignard reagents, etc.) leading to lengthy and/or tedious synthetic optimizations and may leave certain substitution patterns unexplored. There is therefore, a need for new and robust approaches that allow rapid access to a wider variety of functionalized heteroarenes *via* simplification of the Csp^2-Csp^3 and Csp^2-Csp^2 couplings strategies. Towards this end, C-H functionalization chemistry has emerged as a powerful and efficient tool to perform transformations that allow direct and convergent syntheses of highly substituted cores with successful application to singleton synthesis, parallel array synthesis, and late stage modification of lead molecules.[2,3] The incorporation of small structural modifications on heteroarene rings (e.g. small alkyl groups) can provide medicinal chemists the ability to introduce new vectors for structure-based drug design as well as alter physicochemical properties for the purposes of enhancing potency, and improving target selectivity, solubility, and metabolic stability.[4,5] Recently, academic and industrial laboratories have increasingly reported multiple C-H functionalizations of heteroarenes which rely on the innate reactivity of the protonated electron-deficient heteroarenes.[6,7,16–22,8–15] For instance, protonation of a heteroarene, such as pyridine, (Scheme 1, eq. 1) activates the C2, C4 and/or C6 positions increasing its ability to react with nucleophilic radicals. However, the regioselectivity of the functionalization is dictated by the innate effect of the heteroarene and the necessity of using an excess of strong acid, rendering the exploration of the remaining carbons unexplored (e.g. C3 and C5).[12,16,18,21]

Scheme 1: C-H Functionalization of Heteroarenes



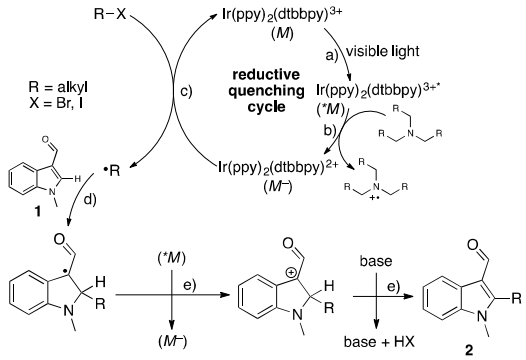
In theory, innate reactivity and its resulting regioselectivity induced from the preactivation of the core by protonation may be bypassed by favoring and enhancing the conjugate reactivity and the halogen *ortho*-directing effect under basic conditions. To date, few examples of alkylation of heteroarenes in basic conditions have been reported in the literature (Scheme 1, eq. 2).[6,23–26] These methods, though useful, however suffer

from several limitations. For instance, alkylation reactions are usually not compatible with primary alkyl groups and rely on the use of strong bases at elevated temperature, sometimes in nonpolar aprotic solvents (e.g. toluene, trifluorobenzene, etc.) with occasionally high catalyst loads (up to 10 mol%), which may lead to complications such as decomposition, and/or poor solubility of common heteroarenes.

RESULTS AND DISCUSSION

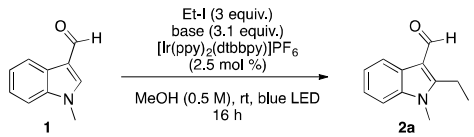
Recently, our research lab has demonstrated[27–29] an increasing interested in photoredox technologies[6,30–34] that led us to investigate new methodologies around the C-H functionalization of π electron-deficient systems which would give access to uncharted chemical space. As a starting point, we elected alkyl halides as suitable sources of alkyl radicals due to their broad commercial availability and previous successful applications.[8,9] Interestingly, radical generation from the reduction of alkyl halides using iridium photoredox catalysis has been understudied and is limited to few reports (halide reduction, amide formation, intramolecular cyclization and borylation).[34–38] Furthermore, we reasoned that only a selection of iridium catalysts could be powerful enough to efficiently reduce alkyl halides *via* either reductive or oxidative quenching cycles. In general, the reductive quenching pathway allows access to stronger reduction potential for the catalyst (e.g. $E_{1/2}^{II/III}$= -2.19 V, -1.51 V versus saturated calomel electrode (SCE) for *fac*-$Ir(ppy)_3$ and $Ir(ppy)_2(dtbbpy)$ respectively)[34] versus the oxidative quenching cycle (e.g. $E_{1/2}^{III*/IV}$= -1.73 V, -0.96 V versus SCE for *fac*-$Ir(ppy)_3$ and $Ir(ppy)_2(dtbbpy)$ respectively).[35] Cognizant of the strengths and weaknesses of both catalytic pathways, we initiated an unprecedented intermolecular C-H functionalization of heteroarenes using unactivated alkyl halides through visible-light photoredox catalysis. As a test experiment, we designed an alkylation of indole **1** with ethyl iodide and tributylamine using both catalytic scenarios: *fac*-$Ir(ppy)_3$[35,37] (Table 1, entry 1) or $Ir(ppy)_2(dtbbpy)$[36] (Table 1, entry 2). Pleasingly, we found that $Ir(ppy)_2(dtbbpy)$ with a sacrificial reductant (e.g. tributylamine) was a better candidate for the C-H functionalization reaction.

Scheme 2: Proposed mechanism for the C-H Functionalization of indole 1



We believe the reaction to proceed *via* the following proposed mechanism (Scheme 2): a) excitation of the catalyst ground state (*M*) to the excited state (**M*), b) electron transfer from the tertiary amine to (**M*) resulting in the formation of a highly reductant iridium species (*M*⁻), c) formation of the alkyl radical from the reduction of the carbon halogen bond ($E_{1/2}^{red}$ = -1.67 V versus SCE for ethyl iodide)[30] and completion of the catalytic cycle with the regeneration of the catalyst ground state (*M*), d) addition of the alkyl radical to C2 of indole **1**, e) oxidation of the subsequent radical by another reductive quenching cycle to deliver the desired C2 functionalized indole **2** *via* a carbocation intermediate. This proposed mechanism may be supported by previous report[36] and the radical formation was confirmed *via* radical clock (see supporting information) and TEMPO control experiments (Table 1, entry 14). In addition, further experiments using trifluoroacetic acid, or without added amine (Table 1, entry 13), led to no conversion, highlighting the importance of the tertiary amine as a reductant in the catalytic pathway.

Table 1: Optimization of the reaction conditions[a]



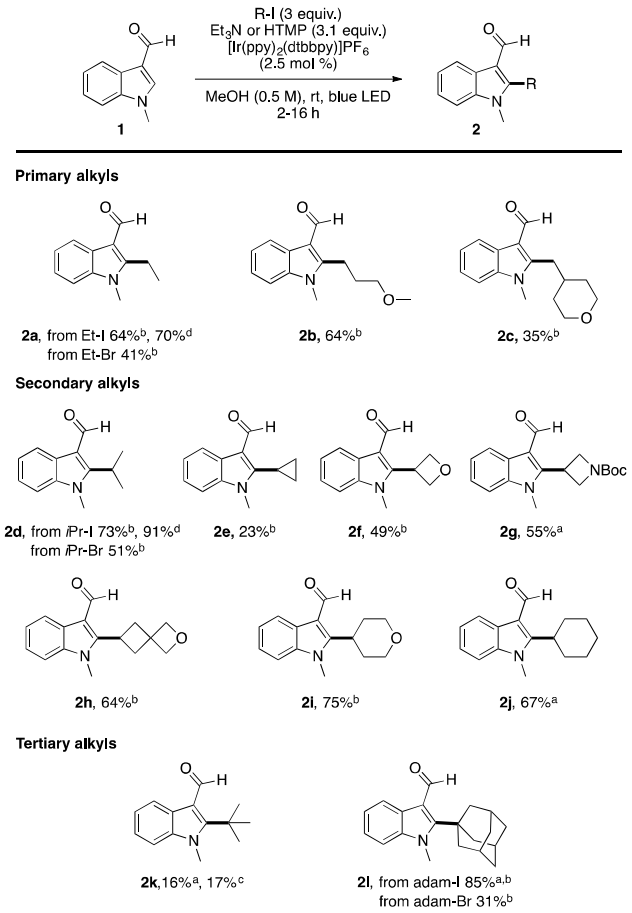
Entry	Base	Different from above	Conversion[b] (yield)[c]
1	Bu_3N	*Fac*-$Ir(ppy)_3$	42%
2	Bu_3N	-	92% (59%)
3	Et_3N	-	86% (54%)
4	DIPEA	-	78% (49%)
5	Cy_2NH	-	76%
6	quinuclidine	-	8%
7	2,6-lutidine	-	4%
8	HTMP	-	**92% (64%)**
9	Et_3N	MeCN	43%
10	Et_3N	DMSO	14%
11	Et_3N	DCE	30%
12	Et_3N	DMF	22%
13	no base	-	0%
14	Et_3N	3 eq. TEMPO	0%
15	Et_3N	dark	0%
16	Et_3N	no catalyst	12%

[a] Reactions performed with 2x40W blue LEDs. [b] Conversions analyzed by ^{1}HNMR with 1,4-dinitrobenzene as internal standard. [c] Isolated yields.

After a quick screen of bases (Table 1, entries 3-8) and solvents (Table 1, entries 9-12), we found that optimal conditions were obtained when using 3.1 equivalents of 2,2,6,6-tetramethylpiperidine (HTMP), 3 equivalents of alkyl iodide, and 2.5 mol% of $[Ir(ppy)_2(dtbbpy)]PF_6$ at room temperature in methanol under blue LED irradiation for 16 h (supporting information). Overall, Et_3N, Bu_3N or HTMP showed similar efficiency, however reactions using HTMP often gave a cleaner profile and slightly improved yields. This may be explained by the absence of acidic α-protons adjacent to the *N*-centered radical cation that could potentially create undesired side reactions.[30] With our best conditions in hand, we screened the scope of the reaction with primary, secondary and tertiary alkyl halides and indole **1** (Scheme 3). We were delighted to find that the reaction works with primary, secondary and tertiary alkyl radicals, and is not limited to alkyl iodides but is also compatible with alkyl bromides, albeit with slightly reduced efficiency (~20% lower yields for primary **2a** and secondary **2d** radicals and 50% with tertiary radicals **2d**). The latter result greatly broadens the availability of commercial

alkyl radical precursors, particularly if the corresponding alkyl iodide is not available. Another advantage of using basic conditions, compared to acidic conditions, allows the introduction of acid-sensitive groups (e.g. oxetanes, Boc carbamates, spirocyclic systems, aldehydes) with great efficiency (**2f**, 49%; **2h**, 64%; **2g**, 55%). In addition, we confirmed that yields could be increased (up to 20%, see **2a**, **2d**) when the reaction was performed with the Penn OC Photoreactor M1[39] compared to a 2x40W blue LED setup.

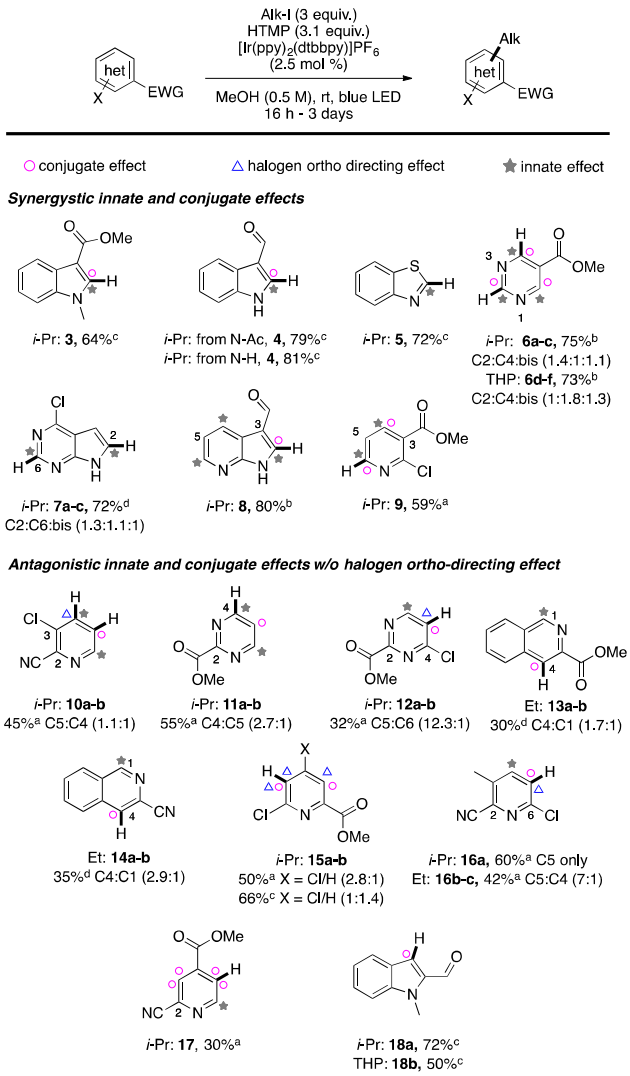
Scheme 3: C-H Functionalization of indole 1 using primary, secondary and tertiary alkyl radicals



[a] Reaction performed with Et_3N using 2x40W blue LEDs. [b] Reaction performed with HTMP using 2x40W blue LEDs. [c] Reaction performed with Et_3N using Penn OC Photoreactor M1 at maximum light intensity and ventilation speed. [d] Reaction performed with HTMP using Penn OC Photoreactor M1 at maximum light intensity and ventilation speed.

Finally, we were interested in evaluating our optimized reaction conditions with a variety of heteroarenes and alkyl iodides. Only a few reports have fully explored the regioselectivities of the C-H functionalization of heteroarenes under acidic conditions.[12,16,18,21] These reports generally heavily rely on the innate effect, accentuated by the protonation of the cores with strong acids. Surprisingly, the regioselectivities for the C-H functionalization of heteroarenes under basic conditions have not been reported. Based on our results, we believed that under basic conditions, divergent regioselectivities would be favored by promoting conjugate and halogen *ortho*-directing effects and attenuating the innate effect. The alkylation regioselectivity accounting for predicted innate, conjugate and halogen *ortho*-directing effects for a variety of heterocycles are depicted and corresponding symbols in Scheme 4. Interestingly we found that naturally electron-deficient cores (indole, benzothiazole, isoquinoline, pyrimidine) required none or a minimum of electronic activation by either the presence of a halogen (Cl atom) or an electron-withdrawing group (EWG: aldehyde, nitrile, ester) in order to react. In addition, we found that pyridines were more reluctant to convert and usually required further activation (EWGs and/or Cl atom). Furthermore, both halides and EWGs may play a dual role by electronically activating the heteroarenes and may also serve as functional handles for subsequent derivatizations. As predicted, when combining conjugate and innate effects, excellent yields were observed (**3** to **9**, 59-81% yields). It is worth noting that higher yield and opposite regioselectivity were obtained compared with previous report[12] when pyrimidine **6** was used with *i*-Pr radical, emphasizing our hypothesis on attenuated innate reactivity under basic conditions. Remarkably, pyrrolopyrimidine **7** could be functionalized at C2 and/or C6 with 72% yields overall. In theory, this would allow a medicinal chemist to vary three positions sequentially at C2, C4 and C6 (coupling reactions) by controlling the reaction conditions. In addition, combined conjugate and innate effects seem to prevail against solely innate effects: 7-azaindole **8** was selectively functionalized at C2 versus the electron-deficient C4/C6 with 80% yield. We have also verified that steric hindrance plays a role in regioselectivity: pyridine **9** was exclusively functionalized at C6 against C4. Notably, we confirmed that innate effect could be attenuated when competing with conjugate and halogen *ortho*-directing effects without loss of efficiency (**10-18**, 30-72% yields). This allowed access to vectors that are difficult to obtain *via* classic C-H functionalization reactions (e.g. acidic conditions that are mainly governed by innate effect regioselectivity). Interestingly, pyridine **10** which was reported to be unreactive under C-H functionalization[12] performed well under our reaction conditions giving a mixture (1:1.1) of C4 (combined innate/halogen *ortho*-directing effects) versus C5 (conjugate effect) in 45% yield. Concerning naturally π electron-deficient pyrimidine **11**, innate effect seems to be more prevalent than conjugate effect (2.7:1 ratio), however it could be bypassed when competing with the combined conjugate/halogen *ortho*-directing effects with an excellent 12.3:1 ratio (**12**). Remarkably, unprecedented C4 functionalization of isoquinolines **13** and **14** could be obtained benefitting from the conjugate effect against innate effect. In general, isoquinolines are exclusively alkylated at C1 (innate effect) under acidic conditions.[18] Another confirmation of how steric hindrance plays a role in regioselectivity is observed when comparing ester isoquinoline **13** (1.7:1, C4/C2 ratio) versus nitrile isoquinoline **14**, (2.9:1 C4/C2 ratio). Pleasingly, C3 or C5 π electron-rich carbons of pyridines **15-17** and indole **18** could be successfully functionalized (30-72% yield). This is exceptional because the synergy between the conjugate and halogen *ortho*-directing effects could efficiently override the innate effect allowing the exploration of a chemical space which was difficult to access by other means. It is also important to mention that for highly π electron-deficient systems (e.g. **15**), partial reduction of the chloride atom could be observed. This reduction was accentuated when pyridine **15** was used with the Penn OC Photoreactor M1 (1:1.4, Cl/H ratio, **15a-b**) compared to a 2x40W blue LED setup (2.8:1, Cl/H ratio, **15a-b**). We believe that greater light intensity and thermal activation may be the major factors with this side reaction.

Scheme 4: C-H Functionalization of heteroarenes



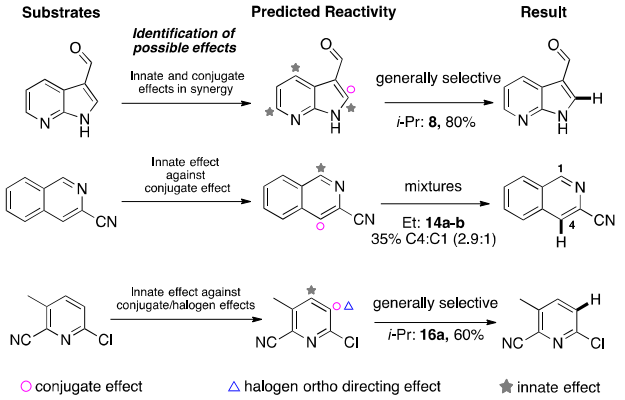
[a] Reaction performed for 16 h with HTMP using 2x40W blue LEDs. [b] Reaction performed for 16 h with HTMP using 2x40W blue LEDs and 2 equiv. of alkyl iodide. [c] Reaction performed for 16 h with HTMP using Penn OC Photoreactor M1 at maximum light intensity and ventilation speed. [d] Reaction performed for 72 h with HTMP using 2x40W blue LEDs.

In order to build confidence on the outcome of the reactions, a predicted model is depicted within scheme 5. First, it is important to identify the most prevalent forces that drive regioselectivity such as the innate and conjugate effects. In general, when both are combined, high selectivity and excellent yields are obtained. However, when opposed to each other, a mixture of compounds is often observed that may vary depending on the nature of the heteroarene used for the reaction (more or less π electron-deficient). Then, you may consider halogen *ortho*-directing effect that increases reactivity and selectivity when it is combined with another effect. In addition, steric effect may also play a role and may help discriminate multiple possible sites of alkylation.

CONCLUSION

In conclusion, we have developed an unprecedented, mild photoredox C-H functionalization of heteroarenes under basic conditions. Our method allows the introduction of small alkyl groups, including acid sensitive groups, on carbons that are usually not functionalized using existing acidic conditions. In addition, we found that pre-activation of the heteroarenes with EWGs or Cl atom was needed to increase reactivity and help with the control of the regioselectivity. These groups also play a dual role by providing useful functional handles for further derivatizations. Finally, this highly convergent method utilizes abundant and commercially available alkyl halides that allow quick exploration of vector for drug design, rendering this methodology highly complementary to other C-H functionalizations that usually require the synthesis of the alkyl radical precursors (NHP esters, alkyl boronic acids, sulfinates, etc.).

Scheme 5: Predictive model for regioselectivity



EXPERIMENTAL SECTION

General Information: $[Ir(ppy)_2(dtbbpy)]PF_6$ was purchased from Sigma Aldrich and stored at -20 °C. All other reactants were obtained commercially from various suppliers and stored accordingly. Reactions were done in either the lights setup (2 x 40W, 420 nm Kessil LED A160WE lights, intensity set to max, color dial completely counterclockwise, Chemglass stir plate and small desk fan) or the reactor setup (Penn OC reactor M1, 420 nm). Separations were done using a CombiFlash Rf+ Lumen Automated Flash Chromatography System with 200 mL/min max flow, 200 psi, with integrated ELSD and 200-400 nm UV variable wavelength detector and a 40g HP Silica RediSep Rf gold column. Thin layer chromatography (TLC) was performed using 250 µm silica gel plates. TLC plates were visualized using an ultraviolet lamp. Solvents were evaporated by either Biotage V10 touch or rotary evaporator. ^1H NMR and ^{13}C NMR spectra were recorded on a Brunker 400 MHz, 101 MHz spectrometer. Spectra are internally referenced to residual solvent signals ($CDCl_3$ δ = 7.26 (^1H) and 77.16 (^{13}C) or DMSO δ = 2.50 (^1H) and 39.52 (^{13}C)). Data for ^1H NMR are reported according to the following conventions: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quintet, br = broad, and combinations thereof), coupling constant J (Hz), integration. Low-Resolution Mass Spectrometry analyses were conducted on Waters Acquity UPLC (Acquity Binary Solvent Manager, 2777C-Autosampler, Acquity PDA, Acquity ELS and Acquity Column Manager) and Waters Acquity SQ systems from Waters Corporation, Milford, MA. Signal acquisition conditions included: Waters Acquity HSS T3, 2.1mmx50mm, C18, 1.7µm; Column Temperature 60 °C as the column; 0.1% formic acid in water (v/v) as the mobile phase A; 0.1% formic acid in acetonitrile (v/v) as the mobile phase B; 1.25mL/min as the flow and ESCI (ESI+/-, APCI+/-), 100-2000m/z scan, 0.4sec scan time, Centroid as the MS method. High Resolution

Mass spec data was collected on a Thermo QExactive, with an Orbitrap mass analyzer and with a Waters Acquity UPLC on the front end. Chromatography was done on a Waters CSH C18 column, 1.7 um, 2.1x150 mm. Mobile phase A was water with 0.2% Formic Acid. Mobile phase B was acetonitrile with 0.2% Formic Acid. The gradient began at 2% B, increased to 100% B over 3 min, held for 1 minute at 100% B, followed by a 1 min re-equilibration at 2% B. The flow rate was 0.35 mL/min throughout. Mass spec full scan positive mode was employed for all samples. The full scan mass resolution was set to 140,000. UV spectral data was collected from 220 to 350 nm.

Procedure 1: 1 equiv. of heteroarene (if solid), 3 equiv. of alkyl halide (if solid) and 2.5 mol% of $[Ir(ppy)_2(dtbbpy)]PF_6$ were added to a vial (1 dram, ~3.7 mL), 15x45mm, 13-425 thread with red pressure relief cap Chemglass vial. The vial was purged for 5 minutes under vacuum and was filled with nitrogen gas. Then MeOH (0.5 mL), 3.1 equiv. of Et_3N and 1 equiv. of the heteroarene (if liquid) were successively added under N_2 atmosphere. The nitrogen line was removed and 3 equiv. of alkyl halide (if liquid) was added. The vial was irradiated under blue LED light and stirred overnight at room temperature at 1,000 RPM with a small cooling fan (approx. 16 hours). In addition, NMR yield can be obtained after the completion of the reaction by adding to the vial 0.25 equiv. of 1,4-dinitrobenzene and by comparing the reference peak integration at 8.44 ppm in $CDCl_3$ and one of the product(s) aromatic peaks. The volatiles were evaporated using a V10 Biotage system. If the resulting product contains one or several basic nitrogens, a basic workup is required using partition between a saturated solution of sodium bicarbonate and DCM, otherwise, the crude mixture was loaded onto a 40g gold ISCO column using Hexane/Ethyl Acetate (100:0 to 0:100) as eluents to yield desired product(s).

Procedure 2: Same as Procedure 1, however HTMP (3.1 equiv.) was used instead of Et_3N.

Procedure 3: Same as Procedure 1, however the Penn OC M1 photoreactor (setup 2) was used instead of irradiation by blue LED lights (setup 1). The photoreactor was set to max LED light (100%), max stir speed (2,000RPM), and max fan speed (5,200RPM).

Procedure 4: Same as Procedure 1, however HTMP (3.1 equiv.) was used instead of Et_3N and the photoreactor (setup 2) was used instead of the lights (setup 1). The photoreactor was set to max LED light (100%), max stir speed (2,000RPM), and max fan speed (5,200RPM).

Procedure 5: Same as Procedure 1, however HTMP (3.1 equiv.) was used instead of Et_3N and 2 equiv. of alkyl halide was used instead of 3 equiv.

Procedure 6: Same as Procedure 1, however HTMP (3.1 equiv.) was used instead of Et_3N and the reaction was ran for 3 days instead of 16 hours.

Compound Characterizations

2-ethyl-1-methyl-indole-3-carbaldehyde (**2a**). Synthesized using procedure 4, 70% yield (32.8 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.14 (s, 1H), 8.24 – 8.22 (m, 1H), 7.28 – 7.22 (m, 3H), 3.70 (s, 3H), 3.09 (q, *J* = 7.6 Hz, 2H), 1.30 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 184.0, 154.2, 136.9, 125.0, 122.7, 122.4, 120.1, 112.4, 110.4, 29.6, 17.0, 14.7.HRMS (ESI), m/z: calculated for $C_{12}H_{14}NO$ $[M+H]^+$: 188.1075, found: 188.1073.

2-(3-methoxypropyl)-1-methyl-indole-3-carbaldehyde (**2b**). Synthesized using Procedure 2, 64% yield, (37.0 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.18 (s, 1H), 8.32 – 8.24 (m, 1H), 7.39 – 7.27 (m, 3H), 3.76 (s, 3H), 3.40 (t, *J* = 5.8 Hz, 2H), 3.36 (s, 3H), 3.26 – 3.18 (m, 2H), 1.96 (ddt, *J*= 8.3, 7.3, 5.8 Hz, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 184.5, 151.2, 137.2, 125.9, 123.3, 123.0, 121.1, 114.3, 109.5, 70.8, 58.8, 30.0, 29.8, 21.1. HRMS (ESI), m/z: calculated for $C_{14}H_{18}NO_2$ $[M+H]^+$: 232.1338, found: 232.1338.

1-methyl-2-(tetrahydropyran-4-ylmethyl)indole-3-carbaldehyde (**2c**). Synthesized using Procedure 2, 35% yield (22.5 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.16 (s, 1H), 8.36 – 8.20 (m, 1H), 7.33 (m, 3H), 4.04 – 3.87 (m, 2H), 3.77 (s, 3H), 3.44 – 3.22 (m, 2H), 3.17 – 3.01 (m, 2H), 1.95 – 1.83 (m, 1H), 1.66 – 1.58 (m, 2H), 1.57 – 1.42 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 184.4, 149.3, 137.2, 125.9, 123.5, 123.2, 121.0, 115.0, 109.6, 67.9 (2C), 36.6, 33.1 (2C), 31.8, 30.3. HRMS (ESI), m/z: calculated for $C_{16}H_{20}NO_2$ $[M+H]^+$: 258.1494, found: 258.1491.

2-isopropyl-1-methyl-indole-3-carbaldehyde (**2d**). Synthesized using Procedure 4, 91% yield (45.8 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.38 (s, 1H), 8.35 (dd, *J* = 6.2, 2.7 Hz, 1H), 7.33 – 7.27 (m, 3H), 3.81 (s, 3H), 3.73 (hept., *J* = 7.4 Hz, 1H), 1.55 (d, *J* = 7.2, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 184.7, 156.3, 137.2, 126.2, 123.3, 123.1, 121.7, 113.7, 109.4, 31.1, 26.2, 22.6 (2C). HRMS (ESI), m/z: calculated for $C_{13}H_{16}NO$ $[M+H]^+$: 202.1232, found: 202.1231.

2-cyclopropyl-1-methyl-indole-3-carbaldehyde (**2e**). Synthesized using Procedure 2, 23% yield (11.4 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.43 (s, 1H), 8.41 – 8.25 (m, 1H), 7.35 – 7.20 (m, 3H), 3.88 (s, 3H), 2.01 (tt, *J* = 8.4, 5.6 Hz, 1H), 1.36 – 1.16 (m, 2H), 1.07 – 0.84 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 185.7, 151.6, 136.8, 125.2, 123.7, 123.2, 122.2, 115.6, 109.3, 30.7, 6.6 (2C), 6.1. HRMS (ESI), m/z: calculated for $C_{13}H_{14}NO$ $[M+H]^+$: 200.1075, found: 200.1075.

1-methyl-2-(oxetan-3-yl)indole-3-carbaldehyde (**2f**). Synthesized using Procedure 2, 49% yield (26.3 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.19 (s, 1H), 8.33 – 8.23 (m, 1H), 7.37 – 7.27 (m, 3H), 5.25 – 5.17 (m, 2H), 5.04 – 4.93 (m, 3H), 3.83 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 184.1, 147.7, 137.4, 126.1, 123.9, 123.3, 121.1, 114.8, 109.6, 76.5 (2C), 32.6, 30.9. HRMS (ESI), m/z: calculated for $C_{13}H_{14}NO_2$ $[M+H]^+$: 216.1025, found: 216.1027.

Tert-butyl-3-(3-formyl-1-methyl-indol-2-yl)azetidine-1-carboxylate (**2g**). Synthesized using Procedure 1, 55% yield (43.2 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.22 (s, 1H), 8.28 – 8.12 (m, 1H), 7.35 – 7.20 (m, 3H), 4.59 – 4.35 (m, 3H), 4.26 – 4.15 (m, 2H), 3.79 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 184.1, 156.2, 148.0, 137.3, 126.0, 123.9, 123.3, 121.1, 115.0, 109.6, 80.4, 30.9, 56.0-55.0 (broad, 2C) 28.4 (3C), 25.3. HRMS (ESI), m/z: calculated for $C_{18}H_{23}N_2O_3$ $[M+H]^+$: 315.1709, found: 315.1708.

1-methyl-2-(2-oxaspiro[3.3]heptan-6-yl)indole-3-carbaldehyde (**2h**). Synthesized using Procedure 2, 64% yield (40.8 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.10 (s, 1H), 8.29 – 8.17 (m, 1H), 7.27 – 7.12 (m, 3H), 4.82 (s, 2H), 4.58 (s, 2H), 3.69 – 3.59 (m, 1H), 3.57 (s, 3H), 2.90 – 2.75 (m, 2H), 2.70 – 2.56 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 184.6, 152.3, 137.0, 126.1, 123.5, 123.0, 121.6, 114.8, 109.3, 84.3, 82.0, 40.9, 40.0 (2C), 30.9, 27.6. HRMS (ESI), m/z: calculated for $C_{16}H_{18}NO_2$ $[M+H]^+$: 256.1338, found 256.1341.

1-methyl-2-tetrahydropyran-4-yl-indole-3-carbaldehyde (**2i**). Synthesized using Procedure 2, 75% yield (45.6 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.34 (s, 1H), 8.34 – 8.23 (m, 1H), 7.28 – 7.18 (m, 3H), 4.24 – 4.02 (m, 2H), 3.76 (s, 3H), 3.59 – 3.43 (m, 3H), 2.38 – 2.16 (m, 2H).1.79 – 1.70 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 184.5, 152.3, 137.1, 126.1, 123.5, 123.1, 121.4, 114.1, 109.6, 68.5 (2C), 34.3 (2C), 32.1, 31.3. HRMS (ESI), m/z: calculated for $C_{15}H_{18}NO_2$ $[M+H]^+$: 244.1338, found: 244.1336.

2-cyclohexyl-1-methyl-indole-3-carbaldehyde (**2j**). Synthesized using Procedure 1, 67% yield (40.4 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.40 (s, 1H), 8.52 – 8.25 (m, 1H), 7.29 – 7.09 (m, 3H), 3.76 (s, 3H), 3.24 – 3.13 (m, 1H), 2.02 – 1.88 (m, 4H), 1.84 (m, 2H), 1.50 – 1.28 (m, 4H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 184.9, 155.4, 137.0, 126.2, 123.3, 123.0, 121.8, 114.1, 109.5, 37.5, 33.0, 31.1, 27.1 (2C), 25.9 (2C). HRMS (ESI), m/z: calculated for $C_{16}H_{20}NO$ $[M+H]^+$: 242.1545, found: 242.1545.

2-tert-butyl-1-methyl-indole-3-carbaldehyde (**2k**). Synthesized using Procedure 3, 17% yield (9.1 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.68 (s, 1H), 8.57 – 8.51 (m, 1H), 7.34 – 7.27 (m, 3H), 3.97 (s, 3H), 1.71 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.4, 156.1, 138.0, 126.5, 123.6, 123.2, 123.0, 116.0, 109.0, 35.9, 34.1, 32.2 (3C). HRMS (ESI) failed after multiple attempts, LCMS was used instead, m/z: calculated for $C_{14}H_{18}NO$ $[M+H]^+$: 216.1, found: 216.5.

2-(1-adamantyl)-1-methyl-indole-3-carbaldehyde (**2l**). Synthesized using Procedure 2, 85% yield (62.3 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.73 (s, 1H), 8.57 – 8.50 (m, 1H), 7.32 – 7.27 (m, 3H), 4.05 (s, 3H), 2.41 – 2.35 (m, 6H), 2.25 – 2.17 (m, 3H), 1.89 – 1.83 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.9, 155.8, 138.0, 126.6, 123.4, 123.0, 122.8, 116.2, 109.0, 42.4 (3C), 39.4, 36.4 (3C), 34.7, 28.5 (3C). HRMS (ESI), m/z: calculated for $C_{20}H_{24}NO$ $[M+H]^+$: 294.1858, found: 294.1859.

Methyl 2-isopropyl-1-methyl-indole-3-carboxylate (**3**). Synthesized using procedure 4, 64% yield (37.0 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.14 – 8.06 (m, 1H), 7.34 – 7.28 (m, 1H), 7.26 – 7.19 (m, 2H), 4.44 (hept, *J* = 7.3 Hz, 1H), 3.93 (s, 3H), 3.84 (s, 3H), 1.47 (d, *J* = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.6, 153.8, 137.0, 126.7, 122.3, 121.9, 121.8, 109.2, 103.1, 50.9, 31.7, 25.2, 20.3 (2C). HRMS (ESI), m/z: calculated for $C_{14}H_{18}NO_2$ $[M+H]^+$: 232.1338, found: 232.1335.

2-isopropyl-1H-indole-3-carbaldehyde (**4**). Synthesized using procedure 4, 79% (from N-Ac, 37.0 mg), 81% (from N-H, 37.9 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.27 (s, 1H), 8.53 (s, 1H), 8.35 – 8.19 (m, 1H), 7.48 – 7.32 (m, 1H), 7.33 – 7.19 (m, 2H), 3.82 (hept, *J* = 7.0 Hz, 1H), 1.46 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 184.4, 156.1, 134.8, 126.3, 123.6, 123.0, 121.3, 113.2, 111.0, 26.0, 22.8 (2C). HRMS (ESI), m/z: calculated for $C_{12}H_{14}NO$ $[M+H]^+$: 188.1075, found: 188.1074.

2-isopropyl-1,3-benzothiazole (**5**). Synthesized using Procedure 4, 72% yield (31.9 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.85 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.45 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.34 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 1H), 3.43 (hept, *J* = 6.9 Hz, 1H), 1.48 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 178.7, 153.3, 134.8, 126.0, 124.7, 122.7, 121.7, 34.2, 23.1 (2C). HRMS (ESI), m/z: calculated for $C_{10}H_{12}NS$ $[M+H]^+$: 178.0690, found: 178.0687.

Methyl 2-isopropylpyrimidine-5-carboxylate and Methyl 4-isopropylpyrimidine-5-carboxylate (**6a-b**). Synthesized using Procedure 5, inseparable by column chromatography, 51% yield (23.0 mg). C-2:C-4 (1.4:1). ^{1}H NMR (400 MHz, Chloroform-*d*) Major: δ 9.18 (s, 2H), 3.95 (s, 3H), 3.28 (hept, *J* = 6.9 Hz, 1H), 1.35 (d, *J* = 6.9 Hz, 6H). Minor: δ 9.20 (s, 1H), 9.04 (s, 1H), 3.94 (s, 3H), 3.88 (hept, *J* = 6.7 Hz, 1H), 1.28 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) Major: δ 179.3, 164.6 (2C), 158.3, 121.4, 52.6, 38.1, 21.66 (2C). Minor: δ 176.4, 165.6, 160.3, 158.5, 123.1, 52.8, 32.3, 21.71 (2C). HRMS (ESI), m/z: calculated for $C_9H_{13}N_2O_2$ $[M+H]^+$: 181.0977, found: 181.0975.

Methyl 2,4-diisopropylpyrimidine-5-carboxylate (**6c**). Synthesized using Procedure 5, 24% yield (13.3 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.98 (s, 1H), 3.92 (s, 3H), 3.87 (hept, *J* = 6.8 Hz, 1H), 3.21 (hept, *J* = 6.9 Hz, 1H), 1.33 (d, *J* = 6.9 Hz, 6H), 1.27 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 177.4, 176.2, 166.1, 151.2, 119.9, 52.5, 37.9, 32.4, 21.73 (2C), 21.65 (2C). HRMS (ESI), m/z: calculated for $C_{12}H_{19}N_2O_2$ $[M+H]^+$: 223.1441, found: 223.1444.

Methyl 2-tetrahydropyran-4-ylpyrimidine-5-carboxylate and methyl 4-tetrahydropyran-4-ylpyrimidine-5-carboxylate (**6d-e**). Synthesized using procedure 5, inseparable by column chromatography, 44% yield (24.4 mg), C-4:C-2 (1.8:1). ^{1}H NMR (400 MHz, Chloroform-*d*) Major: δ 9.23 (s, 1H), 9.11 (s, 1H), 4.08 (m, 2H), 3.96 (s, 3H), 3.86 (tt, *J* = 11.7, 3.9 Hz, 1H), 3.62 – 3.49 (m, 2H), 2.14 – 1.91 (m, 3H), 1.75 – 1.66 (m, 1H). Minor: δ 9.21 (s, 2H), 4.08 (m, 2H), 3.96 (s, 3H), 3.62 – 3.49 (m, 2H), 3.20 (tt, *J* = 10.5, 4.7 Hz, 1H), 2.14 – 1.91 (m, 3H), 1.75 – 1.66 (m, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) Major: δ 173.7, 165.2, 160.4, 158.7, 123.0, 67.9 (2C), 52.9, 39.9, 31.25 (2C). Minor: δ 176.2, 164.5, 158.3, 121.4, 67.8 (2C), 52.7, 44.6 31.27 (2C). HRMS (ESI), m/z: calculated for $C_{11}H_{15}N_2O_3$ $[M+H]^+$: 223.1083, found: 223.1077.

Methyl 2,4-di(tetrahydropyran-4-yl)pyrimidine-5-carboxylate (**6f**). Synthesized using procedure 5, 21% yield (16.1 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.11 (s, 1H), 4.16 – 4.05 (m, 4H), 3.95 (s, 3H), 3.93 – 3.85 (m, 1H), 3.59 (td, *J* = 11.3, 2.2 Hz, 4H), 3.20 (tt, *J* = 11.6, 4.3 Hz, 1H), 2.16 – 1.99 (m, 4H), 1.96 (t, *J* = 7.9 Hz, 2H), 1.76 – 1.67 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 174.8, 174.0, 165.0, 158.2, 120.5, 67.9 (2C), 67.7 (2C), 52.8, 43.8, 39.9, 31.2 (2C), 31.1 (2C). HRMS (ESI), m/z: calculated for $C_{16}H_{23}N_2O_4$ $[M+H]^+$: 307.1652 found: 307.1652.

4-chloro-6-isopropyl-7-methyl-pyrrolo[2,3-d]pyrimidine (**7a**). Synthesized using Procedure 6, 27% yield (14.1 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 6.34 (s, 1H), 3.82 (s, 3H), 3.12 (hept, *J* = 6.8 Hz, 1H), 1.38 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 152.3, 150.5, 150.2, 149.9, 117.5, 94.2, 28.8, 26.3, 22.2 (2C). HRMS (ESI), m/z: calculated for $C_{10}H_{13}ClN_3$ $[M+H]^+$: 210.0793, found: 210.0794.

4-chloro-2-isopropyl-7-methyl-pyrrolo[2,3-d]pyrimidine (**7b**). Synthesized using Procedure 6, 24% yield (12.5 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.11 (d, *J* = 3.5 Hz, 1H), 6.52 (d, *J* = 3.5 Hz, 1H), 3.86 (s, 3H), 3.25 (hept, *J* = 6.9 Hz, 1H), 1.38 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.7, 152.2, 151.9, 129.3, 115.1, 99.2, 37.5, 31.5, 22.2 (2C). HRMS (ESI), m/z: calculated for $C_{10}H_{13}ClN_3$ $[M+H]^+$: 210.0793, found: 210.0795.

4-chloro-2,6-diisopropyl-7-methyl-pyrrolo[2,3-d]pyrimidine (**7c**). Synthesized using Procedure 6, 21% yield (13.2 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.26 (s, 1H), 3.80 (s, 3H),

3.23 (hept, *J* = 6.9 Hz, 1H), 3.09 (hept, *J* = 6.8 Hz, 1H), 1.38 (d, *J* = 6.9 Hz, 6H), 1.37 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.7, 153.1, 150.3, 149.2, 115.0, 93.7, 37.5, 28.6, 26.2, 22.28 (2C), 22.27 (2C). HRMS (ESI), m/z: calculated for $C_{13}H_{19}ClN_3$ $[M+H]^+$: 252.1262, found: 252.1261.

2-isopropyl-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (**8**). Synthesized using Procedure 5, used DCM/EtOAc (100:0 to 0:100) as eluents rather than Hexane/EtOAc with the same gradient, 80% yield (37.6 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.68 (s, 1H), 10.30 (s, 1H), 8.66 (dd, *J* = 7.8, 1.6 Hz, 1H), 8.45 (dd, *J* = 4.9, 1.3 Hz, 1H), 7.32 (dd, *J* = 7.8, 4.9 Hz, 1H), 3.91 (hept, *J* = 7.0 Hz, 1H), 1.62 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 184.3, 158.1, 148.8, 143.3, 130.7, 119.7, 118.8, 111.7, 26.2, 23.0 (2C). HRMS (ESI), m/z: calculated for $C_{11}H_{13}N_2O$ $[M+H]^+$: 189.1028, found: 189.1021.

Methyl 2-chloro-6-isopropyl-pyridine-3-carboxylate (**9**). Synthesized using Procedure 2, 59% yield (31.4 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 (d, *J* = 7.9 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 3.92 (s, 3H), 3.07 (hept, *J* = 6.9 Hz, 1H), 1.29 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.5, 165.2, 149.5, 141.0, 123.8, 119.0, 52.8, 36.3, 22.2 (2C). HRMS (ESI), m/z: calculated for $C_{10}H_{12}ClNO_2$ $[M+H]^+$: 214.0635, found: 214.0629.

3-chloro-5-isopropyl-pyridine-2-carbonitrile (**10a**). Synthesized using Procedure 2, 24% yield (10.8 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.47 (d, *J* = 2.0 Hz, 1H), 7.68 (d, *J* = 1.9 Hz, 1H), 3.03 (hept, *J* = 6.9 Hz, 1H), 1.31 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 149.5, 148.2, 135.9, 135.2, 130.7, 115.1, 32.0, 23.3 (2C). HRMS (ESI), m/z: calculated for $C_9H_{10}ClN_2$ $[M+H]^+$: 181.0533, found: 181.0529.

3-chloro-4-isopropyl-pyridine-2-carbonitrile (**10b**). Synthesized using Procedure 2, 21% yield (9.5 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.52 (d, *J* = 5.0 Hz, 1H), 7.43 (d, *J* = 5.0 Hz, 1H), 3.42 (hept, *J* = 6.9 Hz, 1H), 1.29 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.7, 148.9, 135.3, 133.8, 124.8, 115.4, 30.6, 21.8 (2C). HRMS (ESI), m/z: calculated for $C_9H_{10}ClN_2$ $[M+H]^+$: 181.0533, found: 181.0529.

Methyl 5-isopropylpyrimidine-2-carboxylate (**11a**). Synthesized using Procedure 2, 40% yield (18.0 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.98 – 8.63 (m, 1H), 7.42 – 7.29 (m, 1H), 4.04 (s, 3H), 3.16 (hept, *J* = 6.9 Hz, 1H), 1.33 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 177.5, 164.4, 157.7, 156.3, 119.9, 53.6, 36.3, 21.9 (2C). HRMS (ESI), m/z: calculated for $C_9H_{13}N_2O_2$ $[M+H]^+$: 181.0977, found: 181.0974.

Methyl 4-isopropylpyrimidine-2-carboxylate (**11b**). Synthesized using procedure 2, 15% yield (6.8 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.78 (s, 2H), 4.06 (s, 3H), 3.04 (hept, *J* = 7.0 Hz, 1H), 1.35 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.6, 156.2 (2C), 154.1, 143.5, 53.6, 30.0, 23.5 (2C). HRMS (ESI), m/z: calculated for $C_9H_{13}N_2O_2$ $[M+H]^+$: 181.0977, found: 181.0975.

Methyl 4-chloro-5-isopropyl-pyrimidine-2-carboxylate and methyl 4-chloro-6-isopropyl-pyrimidine-2-carboxylate (**12a-b**). Synthesized using procedure 2, Inseparable by column chromatography, 32% yield (17.1 mg), C-5:C-6 (12.3:1). ^{1}H NMR (400 MHz, Chloroform-*d*) Major: δ 8.72 (s, 1H), 4.03 (s, 3H), 3.35 (hept, *J* = 6.9 Hz, 1H), 1.34 (d, *J* = 7.0 Hz, 6H). Minor: δ 6.69 (s, 1H), 3.99 (s, 3H), 3.05 (hept, *J* = 6.9 Hz, 1H), 1.27 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) Major: δ 162.8, 161.5, 154.2, 142.1, 106.0, 53.8, 29.2, 21.7 (2C). Minor peaks are too similar to noise. HRMS (ESI), m/z: calculated for $C_9H_{12}ClN_2O_2$ $[M+H]^+$: 215.0587, found: 215.0582.

Methyl 4-ethylisoquinoline-3-carboxylate (**13a**). Synthesized using Procedure 6, 19% yield (10.2 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.17 (s, 1H), 8.25 – 8.14 (m, 1H), 8.12 – 7.96 (m, 1H), 7.87 – 7.76 (m, 1H), 7.76 – 7.65 (m, 1H), 4.04 (s, 3H), 3.38 (q, *J* = 7.5 Hz, 2H), 1.40 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.6, 150.6, 140.5, 136.7, 135.2, 131.1, 129.5, 128.7, 128.5, 124.3, 52.9, 21.6, 15.5. HRMS (ESI), m/z: calculated for $C_{13}H_{14}NO_2$ $[M+H]^+$: 216.1019, found: 216.1018.

Methyl 1-ethylisoquinoline-3-carboxylate (**13b**). Synthesized using Procedure 6, 11% yield (5.9 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.45 (s, 1H), 8.28 – 8.19 (m, 1H), 8.00 – 7.92 (m, 1H), 7.82 – 7.67 (m, 2H), 4.05 (s, 3H), 3.42 (q, *J* = 7.6 Hz, 2H), 1.46 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.8, 164.3, 140.7, 136.1, 130.6, 129.4, 129.1, 128.2, 125.7, 123.1, 53.01, 29.2, 14.4. HRMS (ESI), m/z: calculated for $C_{13}H_{14}NO_2$ $[M+H]^+$: 216.1019, found: 216.1019.

4-ethylisoquinoline-3-carbonitrile (**14a**). Synthesized using Procedure 2, 26% yield (23.7 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.14 (s, 1H), 8.18 – 8.10 (m, 1H), 8.08 – 8.03 (m, 1H), 7.92 – 7.85 (m, 1H), 7.82 – 7.72 (m, 1H), 3.34 (q, *J* = 7.6 Hz, 2H), 1.42 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 152.3, 141.6, 133.7, 131.9, 129.9, 129.5, 128.9, 126.3, 123.9, 117.6, 23.3, 15.3. HRMS (ESI), m/z: calculated for $C_{12}H_{11}N_2$ $[M+H]^+$: 183.0917, found: 183.0917.

1-ethylisoquinoline-3-carbonitrile (**14b**). Synthesized using Procedure 2, 9% yield (4.1 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.29 – 8.19 (m, 1H), 8.01 (s, 1H), 7.96 – 7.86 (m, 1H), 7.84 – 7.73 (m, 2H), 3.35 (q, *J* = 7.6 Hz, 2H), 1.45 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.5, 135.1, 131.4, 130.3, 128.1, 127.9, 126.5, 126.2, 125.7, 118.6, 28.6, 13.3. HRMS (ESI), m/z: calculated for $C_{12}H_{11}N_2$ $[M+H]^+$: 183.0917, found: 183.0917.

Methyl 4,6-dichloro-5-isopropyl-pyridine-2-carboxylate (**15a**). Synthesized using Procedure 2, 37% yield (22.9 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 (s, 1H), 3.98 (s, 3H), 3.88 (hept, *J* = 7.2 Hz, 1H), 1.43 (d, *J* = 7.2 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.9, 146.4, 145.4, 143.0, 127.8, 124.7, 53.4, 30.0-31.5 (broad), 19.0 (2C). HRMS (ESI), m/z: calculated for $C_{10}H_{12}Cl_2NO_2$ $[M+H]^+$: 248.0245, found: 248.0239.

Methyl 6-chloro-5-isopropyl-pyridine-2-carboxylate (**15b**). Synthesized using Procedure 4, 39% yield (20.8 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 7.9 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 3.99 (s, 3H), 3.41 (hept., *J* = 6.9 Hz, 1H), 1.29 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.8, 151.0, 146.7, 145.5, 136.2, 124.4, 53.2, 30.6, 22.2 (2C). HRMS (ESI), m/z: calculated for $C_{10}H_{13}ClNO_2$ $[M+H]^+$: 214.0635, found: 214.0627.

6-chloro-5-isopropyl-3-methyl-pyridine-2-carbonitrile (**16a**). Synthesized using procedure 2, 60% yield (29.2 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.55 (s, 1H), 3.35 (hept, *J* = 6.9 Hz, 1H), 2.53 (s, 3H), 1.27 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 149.3, 146.8, 138.1, 137.5, 130.4, 115.6, 30.5, 22.2 (2C), 18.3. HRMS (ESI), m/z: calculated for $C_{10}H_{12}ClN_2$ $[M+H]^+$: 195.0689, found 195.0684.

6-chloro-5-ethyl-3-methylpicolinonitrile and 6-chloro-4-ethyl-3-methylpicolinonitrile (**16b-c**). Synthesized using procedure 2, 42% yield (19.0 mg), C-5:C-4 (7:1). ^{1}H NMR (400 MHz, Chloroform-*d*) Major: δ 7.52 (s, 1H), 2.78 (q, *J* = 7.5, 2H), 2.52 (s, 3H), 1.27 (t, *J* = 7.5 Hz, 3H). Minor: δ 7.33 (s, 1H), 2.68 (q, *J* = 7.5 Hz, 2H), 2.49 (s, 3H), 1.27 (t, *J* = 7.5 Hz, 3H).^{13}C NMR (101 MHz, Chloroform-*d*) Major: δ 149.7, 142.6, 139.7, 138.0, 130.5, 115.6, 26.5, 18.1, 13.1. Minor: δ 156.6, 150.1, 136.4, 133.3 (peak is not visible in ^{13}C however it was seen by 2D NMR (COESY, HMBC, HMQC)), 126.8, 115.9, 26.1, 15.3, 12.8. HRMS (ESI), m/z: calculated for $C_9H_{10}ClN_2$ $[M+H]^+$: 181.0533, found: 181.0529.

Methyl 2-cyano-5-isopropyl-pyridine-4-carboxylate (**17**). Synthesized using Procedure 2, 30% yield (15.3 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.81 (s, 1H), 7.93 (s, 1H), 3.96 (s, 3H), 3.74 (hept, *J* = 7.0 Hz, 1H), 1.33 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.3, 151.2, 147.4, 137.6, 131.6, 127.8, 116.9, 53.2, 28.8, 23.3 (2C). HRMS (ESI), m/z: calculated for $C_{11}H_{13}N_2O_2$ $[M+H]^+$: 205.0977, found 205.0970.

3-isopropyl-1-methyl-indole-2-carbaldehyde (**18a**). Synthesized using procedure 4, 72% yield (36.2 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.23 (s, 1H), 7.95 – 7.84 (m, 1H), 7.48 – 7.31 (m, 2H), 7.18 – 7.04 (m, 1H), 4.05 (s, 3H), 3.75 (hept, *J* = 7.0 Hz, 1H), 1.54 (d, *J* = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 181.9, 140.3, 137.2, 130.2, 127.0, 124.8, 123.3, 120.0, 110.6, 31.8, 25.7, 24.3 (2C). HRMS (ESI), m/z: calculated for $C_{13}H_{16}NO$ $[M+H]^+$: 202.1232, found: 202.1229.

3-tetrahydropyran-4-yl-1-methyl-indole-2-carbaldehyde (**18b**). Synthesized using procedure 4, 50% yield (30.4 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.27 (s, 1H), 8.00 – 7.83 (m, 1H), 7.50 – 7.32 (m, 2H), 7.20 – 7.07 (m, 1H), 4.23 – 4.10 (m, 2H), 4.06 (s, 3H), 3.70 – 3.49 (m, 3H), 2.53 – 2.26 (m, 2H), 1.86 – 1.74 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 181.5, 140.1, 133.6, 130.4, 127.0, 124.9, 123.1, 120.3, 110.7, 68.7 (2C), 33.7 (2C), 33.4, 31.7. HRMS (ESI), m/z: calculated for $C_{15}H_{18}NO_2$ $[M+H]^+$: 244.1334, found: 244.1334.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Additional experiments (reaction optimizations), pictures of the light set-up, kinetic study, ^{1}H and ^{13}C spectra (PDF)

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