JOC The Journal of Organic Chemistry

Article

Visible-Light-Induced C2 Alkylation of Pyridine N-oxides

Wen-Man Zhang, Jian-Jun Dai, Jun Xu, and Hua-Jian Xu

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b02891 • Publication Date (Web): 19 Jan 2017

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

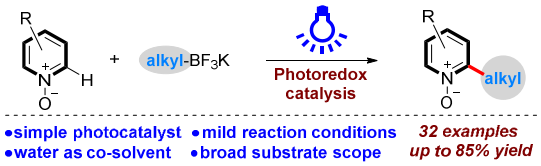
Visible-Light-Induced C2 Alkylation of Pyridine *N*-oxides

Wen-Man Zhang, Jian-Jun Dai,* Jun Xu, and Hua-Jian Xu*

School of Biological and Medical Engineering, Hefei University of Technology, Hefei 230009, China

E-mail: daijj@hfut.edu.cn; hjxu@hfut.edu.cn

RECEIVED DATE (will be automatically inserted after manuscript is accepted).

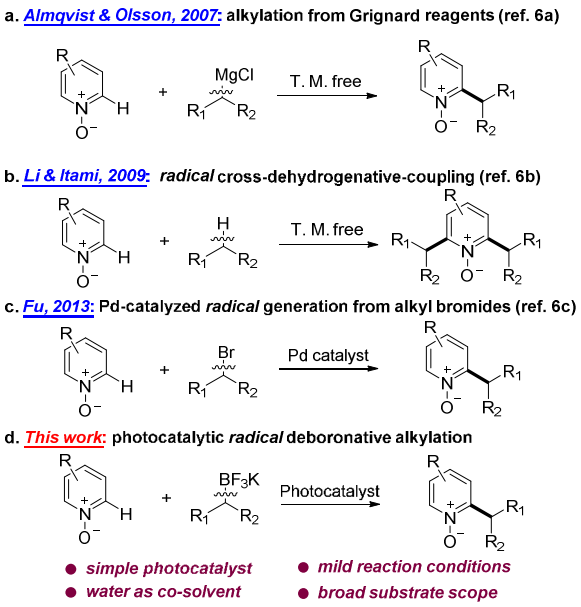


ABSTRACT: A photoredox catalytic method has been developed for the direct C2 alkylation of pyridine *N*-oxides. This reaction is compatible with a range of synthetically relevant functional groups for providing efficient synthesis of a variety of C2-alkylated pyridine *N*-oxides under mild conditions. Mechanistic studies are consistent with the generation of a radical intermediate along the reaction pathway.

INTRODUCTION

Pyridine *N*-oxides and their functionalized derivatives are abundant structural components of biologically active and medicinally important compounds.[1] In recent years, considerable efforts have been devoted to developing new methods for the functionalization of pyridine *N*-oxides.[2–5] However, examples of the direct C2 alkylation of these pyridine *N*-oxides are limited thus far.[6] Almqvist and Olsson achieved 2-substituted pyridine *N*-oxides through the addition of Grignard reagents to pyridine *N*-oxides (Scheme 1a).[6a] In 2009, Li and Itami reported the cross-dehydrogenative-coupling (CDC) of pyridine *N*-oxides and cycloalkanes in the presence of *t*-BuOO-*t*-Bu under transition-metal free conditions.[6b] However, this transformation faces

limitations, such as poor region-selectivity and harsh reaction conditions (Scheme 1b). In 2013, Fu and co-workers described an elegant palladium-catalysed alkylation of pyridine *N*-oxides with non-activated alkyl bromides (Scheme 1c).[6c] The most important and notable feature of the work demonstrated by Li, Itami and Fu is that *both approaches involve the generation of an alkyl radical as the key intermediate*. This implies that the generation methods of alkyl radicals in reactions can significantly influence the outcome.



Scheme 1. C–H Alkylation of Pyridine *N*-oxides

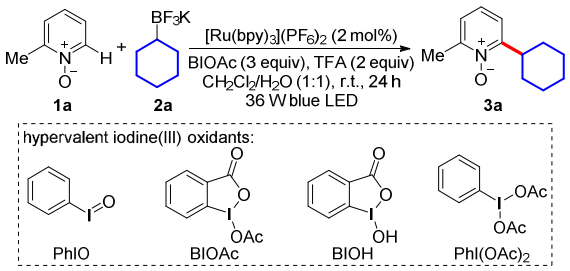
Thanks to the pioneering studies of Akita and Koike,[7] followed by the work of Molander[8] and Chen,[9] photoredox catalysis has emerged as an attractive alternative for the generation of alkyl radicals from potassium alkyltrifluoroborates *via* single-electron transfer (SET) processes.[10] Inspired by these impressive advances and as a continuation of our studies on photocatalytic radical reactions,[11] we now report an unprecedented direct C2 alkylation of pyridine *N*-oxides *via* visible-light photoredox catalysis (Scheme 1d).[12] Our new reaction uses a readily available simple photocatalyst and shows good functional-group compatibility, thus enabling efficient synthesis of

a variety of C2-alkylated pyridine *N*-oxides (32 examples). Moreover, the usefulness of the new method has also been demonstrated by the successful synthesis of the drug molecule ciclopirox.

RESULTS AND DISSCUSION

We initially examined the C2 alkylation reaction of 2-methylpyridine *N*-oxide (**1a**) with potassium cyclohexyltrifluoroborate (**2a**) as a model substrate using $[Ru(bpy)_3](PF_6)_2$ as the photocatalyst. The desired product (**3a**) was obtained in 78% yield with $[Ru(bpy)_3](PF_6)_2$ (2 mol%), 1-acetoxy-1,2-benziodoxol-3-(1H)-one (BIOAc) (3.0 equiv), TFA (2.0 equiv) in CH_2Cl_2/H_2O at room temperature under a nitrogen atmosphere and 36 W blue LEDs irradiation for 24 h (Table 1, entry 1). Replacing BIOAc with a variety of other hypervalent iodine(III) oxidants,[13] including BIOH and PhIO, as well as with a strong oxidant, $K_2S_2O_8$, leads to significantly lower yields (Table 1, entries 2–5). When oxygen (1 atm) was employed in place of BIOAc, the reaction was completely shut down (Table 1, entry 6). Interestingly, the effect of TFA as an acidic additive was dramatic, because other acids (e.g., TsOH, TfOH, HOAc and H_3PO_4) or basic additives (e.g., Na_2CO_3 and DBU) only resulted in moderate to low yields (Table 1, entries 7–13). Use of other solvents such as dioxane, CH_3CN, HFIP, acetone, NMP and toluene can also cause the reaction, but the yields were inferior (Table 1, entries 14–19). The control reactions did not furnish the desired product in the absence of $[Ru(bpy)_3](PF_6)_2$ and/or light, thus confirming the role of photoexcited species derived from the photocatalyst in the reaction (Table 1, entries 20–22).

Table 1. Standard and control reactions [a]



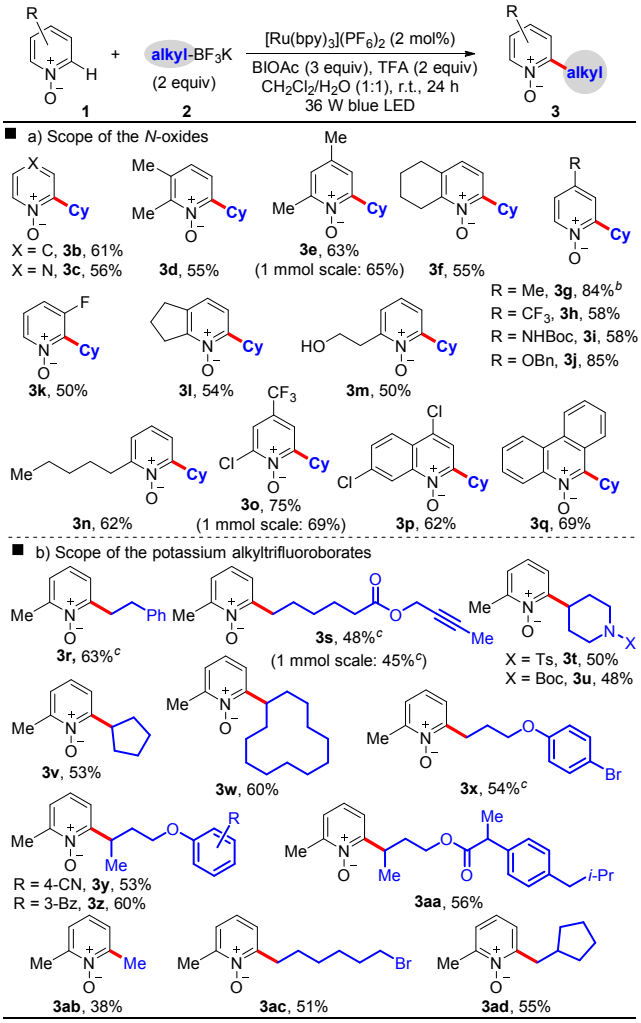
Entry	Variation from the standard conditions	Yield (%)[b]
1	**none**	**78**
2	BIOH instead of BIOAc	41
3	$PhI(OAc)_2$ instead of BIOAc	<5
4	$K_2S_2O_8$ instead of BIOAc	18
5	PhIO instead of BIOAc	trace
6	O_2 (1 atm) instead of BIOAc	0
7	no TFA	34
8	TsOH instead of TFA	50
9	TfOH instead of TFA	38
10	H_3PO_4 instead of TFA	44
11	HOAc instead of TFA	37
12	Na_2CO_3 instead of TFA	21
13	DBU instead of TFA	<2
14	dioxane instead of CH_2Cl_2	33
15	CH_3CN instead of CH_2Cl_2	19
16	HFIP instead of CH_2Cl_2	41
17	acetone instead of CH_2Cl_2	47
18	NMP instead of CH_2Cl_2	8
19	toluene instead of CH_2Cl_2	14
20	no light	<4
21	no $[Ru(bpy)_3](PF_6)_2$	0
22	no light and no $[Ru(bpy)_3](PF_6)_2$	0

[a] Reaction conditions: **1a** (0.2 mmol, 1 equiv), **2a** (0.4 mmol, 2 equiv), $[Ru(bpy)_3](PF_6)_2$ (0.004 mmol, 2 mol%), oxidant (0.6 mmol, 3 equiv), additive (2 equiv), CH_2Cl_2/H_2O (2 mL, v : v = 1 : 1), under a N_2 atmosphere, 24 h at room temperature with 2 × 36 W blue LEDs irradiation, unless otherwise stated. [b] GC yields with 1,1'-biphenyl as an internal standard added after the reaction (averages of two runs).

With an optimized set of reaction conditions, we next investigated the scope of the photocatalytic C2 alkylation process (Table 2a) and found that a variety of pyridine *N*-oxides can be successfully transformed to the desired product in modest to good yields (up to 85%). The reaction can well tolerate many synthetically important functional groups, including ether (**3j**), amide (**3i**), trifluoromethyl (**3o**, **3h**), and even unprotected aliphatic alcohol (**3m**).

Moreover, arene rings carrying fluoro (**3k**), chloro (**3o**–**p**), and *ortho*-methyl (**3d**–**e**) substituents are compatible with the reaction, thus providing additional handles for further functionalization at the halogenated and C(sp^3)–H positions using cross-coupling techniques. It is notable that other *N*-containing heterocyclic substrates (**3c**, **3p**–**q**) could also be used in the reaction. With regard to the scope of potassium alkyltrifluoroborate (Table 2b), both acyclic (**3r**–**s**, **3x**–**z**, **3aa**–**ad**) and cyclic (**3t**–**w**) alkyltrifluoroborates are good substrates. Boc- and Ts-protected piperidine-containing compounds (**3t**–**u**) could be used in the C2 alkylation reaction. Moreover, functional groups such as ester (**3s**, **3aa**), alkyne (**3s**), aryl and alkyl bromides (**3x**, **3ac**), ether (**3x**–**z**), cyano (**3y**), and ketone (**3z**) can be tolerated in the transformation. To further demonstrate the synthetic utility of the current reaction, we conducted reactions on a 1 mmol scale with **1e**, **1o** and **1s** the corresponding product **3e**, **3o** and **3s** were isolated in 65%, 69% and 45% yields, respectively.

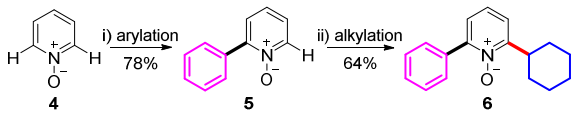
Table 2. Substrate Scope [a]



[a] The reactions were carried out for 24 h on a 0.2 mmol scale, isolated yields based on pyridine *N*-oxides. For details, please see the Supporting Information. [b] 2,6-disubstitued product was obtained in 55% yield with 4 equiv of **2a**. [c] 3 equiv of potassium alkyltrifluoroborates, 48 h.

Moreover, the current photocatalytic system can be applied to sequential C–H arylation/alkylation of pyridine *N*-oxide, as exemplified by the reaction in Scheme 2. According to the pioneering investigation by Fagnou and co-workers,[2a] the palladium-catalysed C–H arylation of pyridine *N*-oxide (**4**) with bromobenzene was achieved in 78% yield, and subsequent treatment of the resulting *N*-oxide (**5**) under our present standard conditions delivered the final alkylated product **6** in 64% yield.

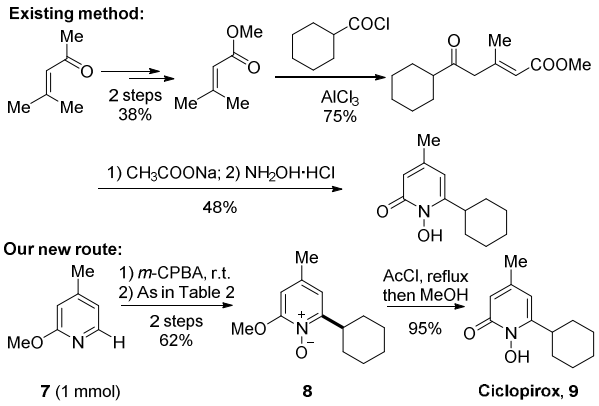
Scheme 2. Sequential C(sp^2)–H Arylation/Alkylation of Pyridine *N*-oxide



Reagents and conditions: (i) Arylation, PhBr, $Pd(OAc)_2$ (10 mol%), $P(tBu)_3 \cdot HBF_4$ (20 mol%), K_2CO_3 (2 equiv), toluene, 110 °C; 78%; (ii) Alkylation, $CyBF_3K$, $[Ru(bpy)_3(PF_6)_2]$ (2 mol%), BIOAc (3 equiv), TFA (2 equiv), CH_2Cl_2/H_2O (1:1), r.t., 36 W blue LED; 64%.

To demonstrate further the synthetic utility with this newly developed protocol, we examined a new route for the preparation of ciclopirox (**9**), a disease-modifying antifungal drug that can be used to treat superficial mycoses such as tinea versicolor and tinea pedis.[14] As shown in Scheme 3, we successfully prepared **9** on a laboratory-scale in three steps with more than 59% overall yield starting from commercially available 2-methoxy-4-methylpyridine (**7**), compared with the existing method, which resulted in less than 14% overall yield after five steps.[15]

Scheme 3. Synthetic Application to the Drug Molecule Ciclopirox

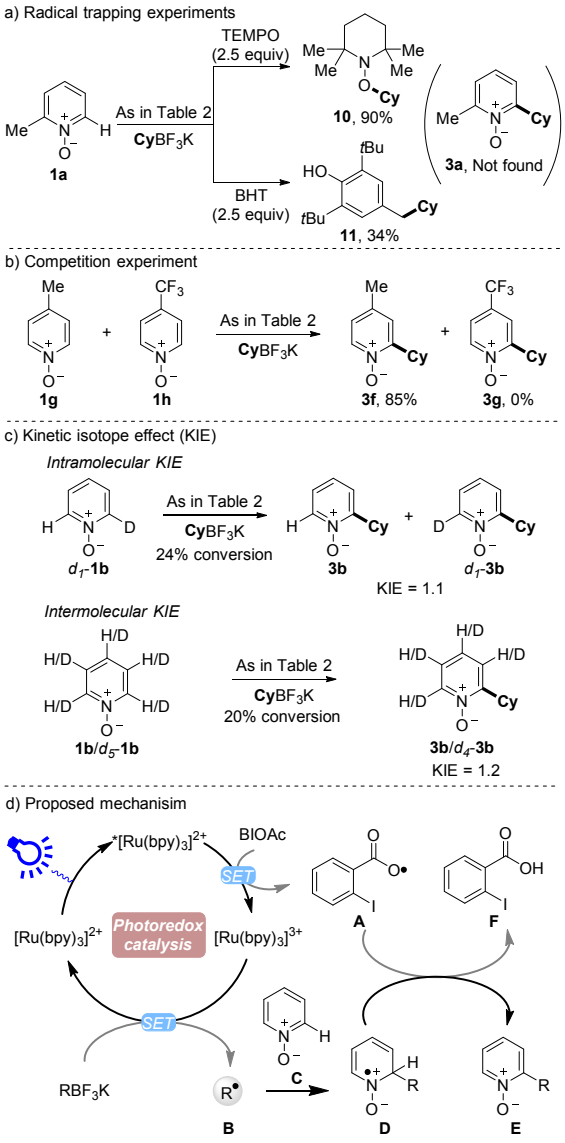


To obtain more insight into the mechanism of this photocatalytic reaction, we conducted radical-trapping experiments using 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) as radical scavengers. In both cases, no C2-alkylated product **3a** was detected. Meanwhile, the alkyl–TEMPO adduct **10** as well as the alkyl–BHT adduct **11** could be isolated in 90% and 34% yield, respectively (Scheme 4a). These above observations suggested that the intermediate of an alkyl radical may be generated in the photocatalytic reaction. Furthermore, potassium cyclohexyltrifluoroborate (**2a**) was reacted in the

presence of both electron-rich 4-methylpyridine *N*-oxide (**1g**) and electron-deficient 4-trifluoromethylpyridine *N*-oxide (**1h**) under the standard conditions (Scheme 4b). In this case, the only product detected using GC analysis of the reaction mixture was **3f**, arising from reaction of the more electron-rich pyridine *N*-oxide, thus indicating that the reaction is compatible with an S_EAr mechanism.[1a] We also determined the intramolecular (k_H/k_D = 1.1) and intermolecular (k_H/k_D = 1.2) kinetic isotopic effect by ^{1}H NMR analysis (Scheme 4c). These results suggest that the C−H bond cleavage might not be the rate determining step in the photocatalytic process.[16] In addition, the reaction's quantum yield Φ was measured to be 3.7 (please see the Supporting Information), indicating a mechanism involving a chain reaction.[17]

Based on the above experiments and previous reports,[8, 9] we propose the possible mechanism depicted in Scheme 4d. Initially, the photocatalyst $[Ru(bpy)_3]^{2+}$ is activated by visible-light irradiation to give the reducing excited-state catalyst $*[Ru(bpy)_3]^{2+}$, which is oxidatively quenched by BIOAc to provide the oxidized catalyst $[Ru(bpy)_3]^{3+}$ and a radical species **A**. Then SET from the alkyltrifluoroborate to $[Ru(bpy)_3]^{3+}$ to form the alkyl radical **B** and regenerating the $[Ru(bpy)_3]^{2+}$ catalyst.. Sequentially, addition of this alkyl radical **B** to pyridine *N*-oxide **C** produces radical cation **D**, which is reoxidized by radical **A**, delivering the desired product **E** and 2-iodobenzoic acid **F**.

Scheme 4. Mechanism Investigations



CONCLUSIONS

In summary, we have reported the first example of a photocatalytic C2 alkylation reaction of pyridine *N*-oxides. This reaction affords the desired C2-alkylated pyridine *N*-oxides under mild conditions. The present reaction has broad substrate scope, including ester, amide, ether, cyano, ketone, alkyne, and halides. A series of mechanistic studies is consistent with this C–H alkylation reaction proceeding through the proposed radical pathway. We are currently investigating of new transformations of alkyl boron reagents *via* photoredox catalysis.

EXPERIMENT SECTION

General Information

Chemicals and solvents were used as received. ^{1}H NMR, ^{13}C NMR, ^{19}F NMR spectra were recorded on a 600 MHz spectrometer at the ambient temperature, using TMS as an internal standard (chemical shifts in δ). Data are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, etc.), coupling constant (Hz), and integration. Gas chromatographic (GC) analyses were performed on a GC equipped with a flame-ionization detector and an Rtx@-65 (30 m × 0.32 mm ID × 0.25 μm df) column using biphenyl as an internal standard, added during reaction workup. GC-MS analyses were performed on a GC-MS with an EI mode. High resolution mass spectra were obtained on a HRMS-TOF spectrometer. Analytical thin layer chromatography (TLC) performed on pre-coated silica gel plates. After elution, plate was visualized under UV illumination at 254 nm for UV active materials. Organic solutions were concentrated under reduced pressure on a rotary evaporator. Column chromatography was performed on silica gel (200−300 mesh) by standard techniques eluting with solvents as indicated.

General Procedure for the Preparation of Pyridine *N*-oxides 1c-q

To a stirred solution of pyridine (10 mmol) in $CHCl_3$ (20 mL) was added 70% *m*-CPBA (10 mmol), portion wise at 0 °C. The mixture was stirred at room temperature for 12 h, at which time complete consumption of starting material was observed by TLC. The reaction mixture was diluted with $CHCl_3$, and solid K_2CO_3 (4.0 equiv) was added. The resulting mixture was stirred for an additional 10 min. The mixture was washed with water for three times. The organic layer was separated and dried with $MgSO_4$,

filtered and concentrated. The crude product was purified by flash chromatography to afford the pyridine *N*-oxides.[18]

Procedure for the Preparation of Alkyltrifluoroborates

Procedure A (2v–w and 2ac): Alkene (10.0 mmol) in THF (2.0 mL) was added dropwise to a solution of BH_3•THF (20 mL, 20 mmol, 1 M solution in THF) at 0 °C. The mixture was stirred for 2 h at room temperature and H_2O (2.0 mL) was slowly added. After stirring for additional 3 h at room temperature, the reaction mixture was concentrated in vacuo, diluted with ethyl acetate (30 mL), and washed with saturated aqueous bicarbonate (20 mL) and brine (20 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated to approximately 5 mL. Petroleum ether was then added. The resultant precipitate was washed with petroleum ether and dried under vacuum to afford the alkylboronic acid as white solid or thick oil. A 100 mL round-bottomed flask equipped with a stir bar was charged with the alkylboronic acid and MeOH (20 mL). To the flask was added KHF_2 (15 mL, 3.91 g, 50 mmol), and the resulting suspension was stirred for 2 h and then concentrated to dryness. The residue, a white solid, was extracted with hot acetone (3 × 30 mL), and the combined filtered extracts were concentrated to approximately 5 mL. Ether was added and the resultant precipitate was collected and dried to afford the potassium trifluoroborate as a white solid.[9a]

Procedure B (2r, **2t–u**, **2x–z**, **2aa** and **2ad):** CuI (190 mg, 1.0 mmol), PPh_3 (341 mg, 1.3 mmol), LiOMe (760 mg, 20 mmol), and bis(pinacolato)diboron (3.8 g, 15.0 mmol) were added to a 100 mL round-bottomed flask equipped with a stir bar. The vessel was evacuated and filled with nitrogen gas three times. DMF (40 mL) and the alkyl bromide (10 mmol) were added by syringe under a nitrogen atmosphere. The resulting reaction mixture was stirred vigorously at 25 ºC for 18 h. The reaction mixture was diluted with EtOAc and filtered through silica gel. Then the mixture was washed with

saturated aqueous brine (3 × 100 mL). The organic layer was dried over sodium sulfate, filtered, concentrated and purified by column chromatography to afford the pinacol ester. To the solution of alkylboronic acids or esters in methanol was added saturated aqueous KHF_2 (5.0 equiv). The resulting suspension was stirred for 2 h and then concentrated to dryness. The residue, a white solid, was extracted with hot acetone (3 × 30 mL), and the combined filtered extracts were concentrated to approximately 5 mL. Diethyl ether was added and the resultant precipitate was collected and dried to afford the potassium trifluoroborate as a white solid.[19]

Procedure C (2s): To a stirred solution of but-2-yn-1-ol (0.54 mL, 7.2 mmol), 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexanoic acid (1.15 g, 4.8 mmol) and DMAP (33.6 mg, 0.276 mmol) in anhydrous DCM (10 mL) was added DCC (1.09 g, 5.2 mmol) separately at room temperature. After stirring for 12 h, the mixture was filtered and washed with 1 M HCl, saturated $NaHCO_3$ aqueous and brine, respectively. After dried over Na_2SO_4, the crude product was concentrated and purified by flash column chromatography to afford pinacol ester as yellow oil. To the solution of alkylboronic acids or esters in methanol was added saturated aqueous KHF_2 (5.0 equiv). The resulting suspension was stirred for 2 h and then concentrated to dryness. The residue, a white solid, was extracted with hot acetone (3 × 30 mL), and the combined filtered extracts were concentrated to approximately 5 mL. Diethyl ether was added and the resultant precipitate was collected and dried to afford the potassium trifluoroborate as a white solid.[20]

General Procedure for Visible-Light-Induced C2 Alkylation of Pyridine *N*-oxides

Method A: To a 10 mL Schlenk tube was sequentially added alkyltrifluoroborates (0.4 mmol), $[Ru(bpy)_3](PF_6)_2$ (3.8 mg, 2 mol%), BIOAc (183.6 mg, 0.6 mmol). The tube was evacuated and backfilled with N_2 for three times. Then, pyridine *N*-oxides (0.2 mmol), CH_2Cl_2 (1 mL), H_2O (1 mL)

and TFA (30 μL, 0.4 mmol) were added. The reaction mixture was stirred for 24 h at room temperature with blue LEDs (2 × 36 W) irradiation. Upon completion, the reaction mixture was diluted with CH_2Cl_2, and solid K_2CO_3 (138.2 mg, 5.0 equiv) was added. The resulting mixture was stirred for an additional 5 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). Then organic layer was combined, dried over sodium sulfate, filtered, concentrated and purified by column chromatography (silica gel) yielded the desired product.

Method B: To a 10 mL Schlenk tube was sequentially added alkyltrifluoroborates (0.6 mmol), $[Ru(bpy)_3](PF_6)_2$ (3.8 mg, 2 mol%), BIOAc (183.6 mg, 0.6 mmol). The tube was evacuated and backfilled with N_2 for three times. Then pyridine *N*-oxides (0.2 mmol), CH_2Cl_2 (1 mL), H_2O (1 mL) and TFA (30 μL, 0.4 mmol) were added. The reaction mixture was stirred for 24 h at room temperature with blue LEDs (2 × 36 W) irradiation. Upon completion, the reaction mixture was diluted with CH_2Cl_2, and solid K_2CO_3 (138.2 mg, 5.0 equiv) was added. The resulting mixture was stirred for an additional 5 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). Then organic layer was combined, dried over sodium sulfate, filtered, concentrated and purified by column chromatography (silica gel) yielded the desired product.

2-cyclohexyl-6-methylpyridine *N*-oxide (3a): Following the Method A, the resulting mixture was purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a colorless oil (0.2 mmol scale: 28.3 mg, 74% yield). Compound **3a** has been previously reported.[21] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.05 (dt, J = 6.6, 5.2 Hz, 3H), 3.56 – 3.45 (m, 1H), 2.46 (s, 3H), 1.99 (d, J = 11.9 Hz, 2H), 1.79 (d, J = 13.0 Hz, 2H), 1.72 (d, J = 13.2 Hz, 1H), 1.45 (ddd, J = 16.2, 11.5, 3.2 Hz, 2H), 1.24 – 1.18 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.6, 149.0, 125.0, 123.4, 120.5, 37.5, 33.6, 31.0, 26.4, 18.6. **Elemental analysis** calcd (%) $C_{12}H_{17}NO$: C 75.35, H 8.96, N 7.32. Found: C 75.21, H 9.07, N 7.18.

2-cyclohexylpyridine *N*-oxide (3b): Following the Method A, the resulting mixture was purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a colorless oil (0.2 mmol scale: 21.6 mg, 61% yield). Compound **3b** has been previously reported.[6f] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.32 (d, *J* = 6.4 Hz, 1H), 7.27 (dt, *J* = 18.0, 7.6 Hz, 2H), 7.13 (dd, *J* = 9.3, 4.2 Hz, 1H), 3.54 (t, *J* = 12.0 Hz, 1H), 2.10 – 2.03 (m, 2H), 1.86 (d, *J* = 13.3 Hz, 2H), 1.80 (d, *J* = 13.2 Hz, 1H), 1.52 (q, *J* = 13.0 Hz, 2H), 1.28 (ddd, *J* = 13.2, 10.6, 4.5 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.1, 139.9, 126.9, 123.3, 123.0, 37.2, 30.9, 26.4, 26.3.

2-cyclohexylpyrazine *N*-oxide (3c): Following the Method A, the resulting mixture was purified by flash chromatography (PE : EA = 2 : 1 to PE : EA = 1 : 1) to give the desired product as a colorless oil (0.2 mmol scale: 20.0 mg, 56% yield). Compound **3c** has been previously reported.[21] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.29 (s, 1H), 8.10 (d, *J* = 3.8 Hz, 1H), 3.34 (t, *J* = 12.0 Hz, 1H), 2.04 (d, *J* = 12.0 Hz, 2H), 1.87 (d, *J* = 13.3 Hz, 2H), 1.80 (d, *J* = 13.2 Hz, 1H), 1.49 (dt, *J* = 25.9, 8.0 Hz, 2H), 1.33 (dddd, *J* = 20.0, 13.0, 9.8, 3.3 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ151.8, 145.7, 144.6, 133.9, 35.7, 30.1, 26.3, 26.1.

6-cyclohexyl-2,3-dimethylpyridine *N*-oxide (3d): Following the Method A, the resulting mixture was purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a colorless oil (0.2 mmol scale: 22.6 mg, 55% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.1 Hz, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 3.51 (t, *J* = 12.0 Hz, 1H), 2.50 (s, 3H), 2.29 (s, 3H), 2.02 (d, *J* = 11.8 Hz, 2H), 1.83 (d, *J* = 13.4 Hz, 2H), 1.77 (d, *J* = 13.0 Hz, 1H), 1.49 (dt, *J* = 16.1, 11.5 Hz, 2H), 1.25 (d, *J* = 13.6 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 154.2, 148.4, 131.5, 127.2, 119.3, 37.7, 31.2, 26.6, 26.4, 19.5, 14.5. **HRMS** (ESI) m/z calcd for $C_{13}H_{20}NO$ $[M+H]^+$: 206.1539; found: 206.1540.

2-cyclohexyl-4,6-dimethylpyridine *N*-oxide (3e): Following the Method A, the resulting mixture was

purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a colorless oil (0.2 mmol scale: 25.9 mg, 63% yield, 1 mmol scale: 133.5 mg, 65% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.88 (s, 1H), 3.55 (t, *J* = 12.0 Hz, 1H), 2.49 (s, 3H), 2.28 (s, 3H), 2.02 (d, *J* = 12.2 Hz, 2H), 1.83 (d, *J* = 13.4 Hz, 2H), 1.77 (d, *J* = 13.1 Hz, 1H), 1.54 – 1.45 (m, 2H), 1.30 – 1.22 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 155.9, 148.3, 140.1, 124.3, 121.5, 37.5, 31.3, 26.5, 26.4, 20.6, 18.6. **HRMS** (ESI) m/z calcd for $C_{13}H_{20}NO$ $[M+H]^+$: 206.1539; found: 206.1542.

2-cyclohexyl-5,6,7,8-tetrahydroquinoline *N*-oxide (3f): Following the Method A, the resulting mixture was purified by flash chromatography (PE : EA = 1:1 to EA) to give the desired product as a colorless oil (0.2 mmol scale: 25.5 mg, 55% yield). Compound **3f** has been previously reported.[21] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.98 (dd, *J* = 18.6, 8.1 Hz, 2H), 3.54 (t, *J* = 12.0 Hz, 1H), 2.95 (t, *J* = 6.6 Hz, 2H), 2.73 (t, *J* = 6.2 Hz, 2H), 2.03 (d, *J* = 12.2 Hz, 2H), 1.91 – 1.83 (m, 3H), 1.83 – 1.72 (m, 3H), 1.51 (qd, *J* = 13.1, 3.1 Hz, 2H), 1.31 – 1.25 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 153.9, 148.6, 132.9, 125.9, 119.2, 37.5, 31.1, 28.6, 26.6, 26.4, 25.3, 22.2, 21.8.

2-cyclohexyl-4-methylpyridine *N*-oxide (3g): Following the Method A, the resulting mixture was purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a colorless oil (0.2 mmol scale: 32.1 mg, 84% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.15 (d, *J* = 6.6 Hz, 1H), 7.01 (s, 1H), 6.90 (d, *J* = 6.5 Hz, 1H), 3.56 – 3.47 (m, 1H), 2.32 (s, 3H), 2.03 (d, *J* = 12.3 Hz, 2H), 1.84 (d, *J* = 13.4 Hz, 2H), 1.78 (d, *J* = 13.1 Hz, 1H), 1.55 – 1.46 (m, 2H), 1.27 (dd, *J* = 12.7, 3.3 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.1, 139.1, 123.9, 123.7, 37.0, 31.0, 26.4, 26.3, 20.7. **HRMS** (ESI) m/z calcd for $C_{12}H_{18}NO$ $[M+H]^+$: 192.1383; found: 192.1383.

2-cyclohexyl-4-(trifluoromethyl)pyridine *N*-oxide (3h): Following the Method A, the resulting mixture was purified by flash chromatography (PE : EA = 2 : 1 to PE : EA = 1 : 1) to give the desired

product as a colorless oil (0.2 mmol scale: 28.4 mg, 58% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.31 (d, *J* = 6.7 Hz, 1H), 7.42 (s, 1H), 7.33 (d, *J* = 6.3 Hz, 1H), 3.47 (t, *J* = 11.7 Hz, 1H), 2.06 (d, *J* = 11.8 Hz, 2H), 1.85 (dd, *J* = 26.6, 13.1 Hz, 3H), 1.52 (dd, *J* = 25.8, 12.8 Hz, 2H), 1.29 (dd, *J* = 23.4, 11.2 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.7, 140.0, 126.5 (q, *J* = 34.9 Hz), 122.6 (q, *J* = 273.7 Hz), 119.9 (q, *J* = 3.7 Hz), 119.5 (q, *J* = 3.6 Hz), 37.2, 30.4, 26.1, 26.0. **HRMS** (ESI) m/z calcd for $C_{12}H_{15}F_3NO$ $[M+H]^+$: 246.1100; found: 246.1102.

4-((*tert*-butoxycarbonyl)amino)-2-cyclohexylpyridine *N*-oxide (3i): Following the Method A, the resulting mixture was purified by flash chromatography (EA to EA : MeOH = 10 : 1) to give the desired product as a colorless oil (0.2 mmol scale: 33.9 mg, 58% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.17 (d, *J* = 7.1 Hz, 1H), 7.47 (s, 1H), 7.32 (s, 1H), 3.49 (t, *J* = 12.0 Hz, 1H), 2.03 (d, *J* = 11.8 Hz, 2H), 1.79 (dd, *J* = 41.0, 13.0 Hz, 3H), 1.51 – 1.40 (m, 10H), 1.32 – 1.18 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.9, 152.4, 139.7, 112.2, 111.8, 81.6, 37.5, 31.0, 28.3, 26.4, 26.1. **HRMS** (ESI) m/z calcd for $C_{16}H_{25}N_2O_3$ $[M+H]^+$: 293.1860; found: 293.1860.

4-(benzyloxy)-2-cyclohexylpyridine *N*-oxide (3j): Following the Method A, the resulting mixture was purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a yellow solid (0.2 mmol scale: 48.2 mg, 85% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.2 Hz, 1H), 7.61 – 7.27 (m, 5H), 6.80 (d, *J* = 3.2 Hz, 1H), 6.70 (dd, *J* = 7.1, 3.3 Hz, 1H), 5.07 (s, 2H), 3.51 (t, *J* = 12.0 Hz, 1H), 2.04 (d, *J* = 12.2 Hz, 2H), 1.83 (d, *J* = 13.3 Hz, 2H), 1.78 (d, *J* = 13.1 Hz, 1H), 1.49 (q, *J* = 13.0 Hz, 2H), 1.26 – 1.17 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.9, 157.5, 140.6, 135.1, 128.9, 128.7, 127.7, 109.9, 109.4, 70.8, 37.5, 31.0, 26.3, 26.2. **HRMS** (ESI) m/z calcd for $C_{18}H_{22}NO_2$ $[M+H]^+$: 284.1645; found: 284.1645.

2-cyclohexyl-3-fluoropyridine *N*-oxide (3k): Following the Method A, the resulting mixture was

purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a colorless oil (0.2 mmol scale: 19.5 mg, 50% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.10 (d, *J* = 6.4 Hz, 1H), 7.02 (dt, *J* = 13.4, 6.7 Hz, 1H), 6.97 (t, *J* = 8.7 Hz, 1H), 3.81 (t, *J* = 11.1 Hz, 1H), 1.79 (dt, *J* = 28.1, 16.4 Hz, 6H), 1.42 (dd, *J* = 25.7, 12.7 Hz, 2H), 1.34 – 1.22 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 160.0 (d, *J* = 248.9 Hz), 136.5, 121.9 (d, *J* = 9.5 Hz), 113.9 (d, *J* = 25.4 Hz), 107.5, 35.8, 28.4, 26.6, 25.9. **HRMS** (ESI) m/z calcd for $C_{11}H_{15}FNO$ $[M+H]^+$: 196.1132; found: 196.1132. **Elemental analysis** calcd (%) $C_{11}H_{14}FNO$: C 67.67, H 7.23, N 7.17. Found: C 67.73, H 7.45, N 7.09.

2-cyclohexyl-6,7-dihydro-5H-cyclopenta[b]pyridine *N*-oxide H (3l): Following the Method A, the resulting mixture was purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a colorless oil (0.2 mmol scale: 23.5 mg, 54% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.06 (d, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 3.52 (t, *J* = 12.0 Hz, 1H), 3.16 (t, *J* = 7.6 Hz, 2H), 2.97 (t, *J* = 7.6 Hz, 2H), 2.15 (p, *J* = 7.7 Hz, 2H), 2.02 (d, *J* = 11.9 Hz, 2H), 1.83 (d, *J* = 13.3 Hz, 2H), 1.77 (d, *J* = 13.1 Hz, 1H), 1.49 (dtt, *J* = 13.0, 6.4, 3.2 Hz, 2H), 1.29 – 1.21 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 154.7, 153.0, 138.5, 122.4, 120.9, 36.9, 31.5, 31.4, 30.2, 26.5, 26.4, 22.4. **HRMS** (ESI) m/z calcd for $C_{14}H_{20}NO$ $[M+H]^+$: 218.1539; found: 218.1538.

2-cyclohexyl-6-(2-hydroxyethyl)pyridine *N*-oxide (3m): Following the Method A, the resulting mixture was purified by flash chromatography (EA : MeOH = 10 : 1) to give the desired product as a colorless oil (0.2 mmol scale: 22.1 mg, 50% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 1H), 7.15 (dd, *J* = 12.8, 7.9 Hz, 2H), 5.64 (s, 1H), 4.06 – 3.95 (m, 2H), 3.51 (t, *J* = 11.8 Hz, 1H), 3.33 – 3.21 (m, 2H), 2.05 (d, *J* = 12.3 Hz, 2H), 1.85 (d, *J* = 12.8 Hz, 2H), 1.79 (d, *J* = 13.0 Hz, 1H), 1.49 (dd, *J* = 25.9, 13.0 Hz, 2H), 1.32 – 1.24 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.3, 151.6, 127.3, 124.1, 121.6, 63.4, 37.8, 35.4, 31.0, 26.4, 26.3. **HRMS** (ESI) m/z calcd for $C_{13}H_{20}NO_2$ $[M+H]^+$: 222.1489;

found: 222.1492.

2-cyclohexyl-6-pentylpyridine *N*-oxide (3n): Following the Method A, the resulting mixture was purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a colorless oil (0.2 mmol scale: 30.7 mg, 62% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.14 (d, *J* = 6.8 Hz, 1H), 7.08 (s, 2H), 3.56 (t, *J* = 11.1 Hz, 1H), 2.91 (d, *J* = 6.7 Hz, 2H), 2.05 (d, *J* = 11.9 Hz, 2H), 1.84 (d, *J* = 12.9 Hz, 2H), 1.78 (d, *J* = 13.0 Hz, 1H), 1.75 – 1.67 (m, 2H), 1.50 (d, *J* = 12.9 Hz, 2H), 1.41 – 1.35 (m, 3H), 1.32 – 1.19 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.9, 152.8, 125.1, 122.3, 120.4, 37.7, 31.8, 31.1, 29.8, 26.5, 26.4, 26.1, 22.6, 14.1. **HRMS** (ESI) m/z calcd for $C_{16}H_{26}NO$ $[M+H]^+$: 248.2009; found: 248.2012.

2-chloro-6-cyclohexyl-4-(trifluoromethyl)pyridine *N*-oxide (3o): Following the Method A, the resulting mixture was purified by flash chromatography (PE : EA = 5 : 1 to PE : EA = 2 : 1) to give the desired product as a colorless oil (0.2 mmol scale: 42.0 mg, 75% yield, 1 mmol scale: 193 mg, 69% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 1.8 Hz, 1H), 7.32 (d, *J* = 1.6 Hz, 1H), 3.50 – 3.42 (m, 1H), 2.06 (d, *J* = 12.1 Hz, 2H), 1.87 (d, *J* = 13.5 Hz, 2H), 1.80 (d, *J* = 13.1 Hz, 1H), 1.54 – 1.45 (m, 2H), 1.27 (ddd, *J* = 24.3, 12.1, 8.2 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.5, 143.1, 125.8 (q, *J* = 35.3 Hz), 122.3 (q, *J* = 272.4 Hz), 120.7 (q, *J* = 3.9 Hz), 117.4 (q, *J* = 3.6 Hz), 38.5, 30.5, 26.2, 26.1. **HRMS** (ESI) m/z calcd for $C_{12}H_{14}ClF_3NO$ $[M+H]^+$: 280.0711; found: 280.0709.

4,7-dichloro-2-cyclohexylquinoline *N*-oxide (3p): Following the Method A, the resulting mixture was purified by flash chromatography (PE : EA = 5 : 1) to give the desired product as a colorless oil (0.2 mmol scale: 36.7 mg, 62% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.8 Hz, 1H), 8.05 (s, 1H), 7.50 (d, *J* = 8.9 Hz, 1H), 7.39 (s, 1H), 2.85 (tt, *J* = 12.0, 2.9 Hz, 1H), 2.00 (d, *J* = 12.8 Hz, 2H), 1.89 (d, *J* = 13.1 Hz, 2H), 1.78 (d, *J* = 13.0 Hz, 1H), 1.59 (qd, *J* = 12.6, 3.0 Hz, 2H), 1.50 – 1.41 (m, 2H), 1.36 –

1.27 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 168.2, 149.2, 142.6, 136.3, 128.4, 127.6, 125.4, 123.7, 120.2, 47.4, 32.7, 26.5, 26.1. **HRMS** (ESI) m/z calcd for $C_{15}H_{16}Cl_2NO$ $[M+H]^+$: 296.0603; found: 296.0602.

6-cyclohexylphenanthridine *N*-oxide (3q): Following the Method A, the resulting mixture was purified by flash chromatography (PE : EA = 5 : 1) to give the desired product as a yellow solid (0.2 mmol scale: 38.3 mg, 69% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.65 (d, *J* = 8.2 Hz, 1H), 8.54 (d, *J* = 8.1 Hz, 1H), 8.32 (d, *J* = 8.2 Hz, 1H), 8.14 (s, 1H), 7.82 (t, *J* = 7.5 Hz, 1H), 7.69 (q, *J* = 6.9 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 3.62 (t, *J* = 11.2 Hz, 1H), 2.07 (t, *J* = 12.3 Hz, 2H), 1.97 (dd, *J* = 19.0, 8.3 Hz, 3H), 1.85 (d, *J* = 12.6 Hz, 1H), 1.67 – 1.53 (m, 3H), 1.44 (dd, *J* = 24.9, 11.9 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.4, 133.1, 130.0, 128.5, 127.2, 126.2, 125.7, 124.8, 123.4, 122.7, 121.9, 42.1, 32.4, 27.0, 26.4. **HRMS** (ESI) m/z calcd for $C_{19}H_{20}NO$ $[M+H]^+$: 278.1539; found: 278.1541.

2-methyl-6-phenethylpyridine *N*-oxide (3r): Following the Method B, the resulting mixture was purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a colorless oil (0.2 mmol scale: 26.8 mg, 63% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 2H), 7.25 – 7.11 (m, 4H), 7.08 – 6.96 (m, 2H), 3.25 (t, *J* = 7.7 Hz, 2H), 3.11 – 3.03 (m, 2H), 2.57 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 151.6, 149.4, 141.1, 128.6, 128.5, 126.2, 124.9, 124.2, 123.5, 33.3, 32.3, 18.4. **HRMS** (ESI) m/z calcd for $C_{14}H_{16}NO$ $[M+H]^+$: 214.1226; found: 214.1225.

2-(6-(but-2-yn-1-yloxy)-6-oxohexyl)-6-methylpyridine *N*-oxide (3s): Following the Method B, the resulting mixture was purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a colorless oil (0.2 mmol scale: 26.4 mg, 48% yield, 1 mmol scale: 123.9 mg, 45% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.14 (d, *J* = 4.6 Hz, 1H), 7.11 (s, 2H), 4.62 (q, *J* = 2.3 Hz, 2H), 2.93 (s, 2H), 2.53 (s, 3H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.84 (t, *J* = 2.4 Hz, 3H), 1.72 (dtd, *J* = 22.9, 15.3, 7.6 Hz, 4H), 1.45 (dt, *J* = 15.4, 7.7 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.0, 152.5, 149.5, 125.1, 124.0, 123.0, 83.2, 73.4, 52.7, 34.0, 30.9, 29.0, 26.0, 24.7, 18.4, 3.7. **HRMS** (ESI) m/z calcd for $C_{16}H_{22}NO_3$

[M+H]+: 276.1594; found: 276.1594.

2-methyl-6-(1-tosylpiperidin-4-yl)pyridine *N*-oxide (3t): Following the Method A, the resulting mixture was purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a yellow solid (0.2 mmol scale: 34.6 mg, 50% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.16 (d, *J* = 4.3 Hz, 2H), 7.09 – 7.05 (m, 1H), 3.94 (d, *J* = 11.7 Hz, 2H), 3.45 (t, *J* = 12.1 Hz, 1H), 2.50 (s, 3H), 2.44 (s, 3H), 2.41 (d, *J* = 11.9 Hz, 2H), 2.11 (d, *J* = 12.5 Hz, 2H), 1.67 (qd, *J* = 12.5, 3.8 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 154.1, 149.5, 143.7, 133.0, 129.8, 127.8, 125.4, 124.3, 120.6, 46.7, 35.4, 29.3, 21.6, 18.5. **HRMS** (ESI) m/z calcd for $C_{18}H_{23}SN_2O_3$ $[M+H]^+$: 347.1424; found: 347.1424. **Elemental analysis** calcd (%) $C_{18}H_{22}SN_2O_3$: C 62.40, H 6.40, N 8.09, S 9.25. Found: C 62.27, H 6.55, N 8.13, S 9.21.

2-(1-(tert-butoxycarbonyl)piperidin-4-yl)-6-methylpyridine *N*-oxide (3u): Following the Method A, the resulting mixture was purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a colorless oil (0.2 mmol scale: 28.1 mg, 48% yield). Compound **3u** has been previously reported.[21] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.16 (d, *J* = 4.7 Hz, 2H), 7.11 – 7.02 (m, 1H), 4.25 (dd, *J* = 56.5, 5.9 Hz, 2H), 3.70 (t, *J* = 12.1 Hz, 1H), 2.90 (s, 2H), 2.53 (s, 3H), 2.03 (d, *J* = 10.8 Hz, 2H), 1.46 (s, 9H), 1.24 (s, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 154.9, 154.8, 149.4, 125.4, 124.1, 120.6, 79.6, 43.8, 36.2, 29.8, 28.5, 18.6.

2-cyclopentyl-6-methylpyridine *N*-oxide (3v): Following the Method A, the resulting mixture was purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a colorless oil (0.2 mmol scale: 18.8 mg, 53% yield). Compound **3v** has been previously reported.[21] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.15 (d, *J* = 4.0 Hz, 1H), 7.11 (s, 2H), 3.86 – 3.77 (m, 1H), 2.54 (s, 3H), 2.25 – 2.18 (m,

2H), 1.89 – 1.67 (m, 4H), 1.61 – 1.52 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.4, 149.4, 125.0, 123.6, 120.6, 39.7, 31.2, 25.4, 18.6.

2-cyclododecyl-6-methylpyridine *N*-oxide (3w): Following the Method A, the resulting mixture was purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a colorless oil (0.2 mmol scale: 33.1 mg, 60% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.13 – 7.09 (m, 3H), 3.56 (ddd, *J* = 12.0, 7.4, 2.8 Hz, 1H), 2.52 (s, 3H), 2.04 (d, *J* = 12.1 Hz, 3H), 1.97 – 1.81 (m, 4H), 1.78 (d, *J* = 13.1 Hz, 3H), 1.50 (qd, *J* = 13.0, 9.8 Hz, 4H), 1.41 – 1.15 (m, 8H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.9, 149.2, 124.9, 123.5, 120.7, 37.7, 31.2, 26.6, 26.4, 18.6. **HRMS** (ESI) m/z calcd for $C_{18}H_{30}NO$ $[M+H]^+$: 276.2322; found: 276.2324.

2-(3-(4-bromophenoxy)propyl)-6-methylpyridine *N*-oxide (3x): Following the Method B, the resulting mixture was purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a colorless oil (0.2 mmol scale: 34.8 mg, 54% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 2H), 7.16 (dd, *J* = 7.4, 2.1 Hz, 1H), 7.14 – 7.06 (m, 2H), 6.78 – 6.72 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.16 – 3.10 (m, 2H), 2.54 (s, 3H), 2.24 (dd, *J* = 8.1, 6.8 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 158.1, 151.5, 149.5, 132.3, 125.0, 124.3, 123.5, 116.4, 112.9, 67.5, 28.2, 25.9, 18.4. **HRMS** (ESI) m/z calcd for $C_{15}H_{17}BrNO_2$ $[M+H]^+$: 322.0437; found: 322.0436.

2-(4-(4-cyanophenoxy)butan-2-yl)-6-methylpyridine *N*-oxide (3y): Following the Method A, the resulting mixture was purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a colorless oil (0.2 mmol scale: 29.9 mg, 53% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.7 Hz, 2H), 7.16 (s, 3H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.12 – 4.04 (m, 2H), 3.95 (dd, *J* = 13.7, 6.8 Hz, 1H), 2.52 (s, 3H), 2.29 (dd, *J* = 13.7, 6.7 Hz, 1H), 2.08 (dd, *J* = 13.7, 6.8 Hz, 1H), 1.38 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.2, 155.8, 149. 6, 134.0, 125.3, 124.1, 121.1, 119.3, 115.2,

103.9, 66.9, 34.0, 30.9, 29.8, 18.6. **HRMS** (ESI) m/z calcd for $C_{17}H_{19}N_2O_2$ $[M+H]^+$: 283.1441; found: 283.1441.

2-(4-(3-benzoylphenoxy)butan-2-yl)-6-methylpyridine *N*-oxide (3z): Following the Method A, the resulting mixture was purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a yellow solid (0.2 mmol scale: 43.4 mg, 60% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.6 Hz, 2H), 7.73 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.17 (s, 3H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.16 – 4.07 (m, 2H), 3.97 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.53 (s, 3H), 2.31 (td, *J* = 13.3, 6.6 Hz, 1H), 2.12 (td, *J* = 13.4, 6.6 Hz, 1H), 1.40 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 195.6, 162.6, 156.1, 149.6, 138.4, 132.6, 131.9, 130.1, 129.8, 128.2, 125.1, 124.0, 121.2, 114.1, 107.4, 66.7, 34.0, 31.0, 18.6, 14.3. **HRMS** (ESI) m/z calcd for $C_{23}H_{24}NO_3$ $[M+H]^+$: 362.1751; found: 362.1750.

2-(4-((2-(4-isobutylphenyl)propanoyl)oxy)butan-2-yl)-6-methylpyridine *N*-oxide (3aa): Following the Method A, the resulting mixture was purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a yellow solid (0.2 mmol scale: 37.7 mg, 56% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.20 – 7.15 (m, 2H), 7.14 – 7.04 (m, 4H), 7.00 (t, J = 7.9 Hz, 1H), 4.14 – 4.08 (m, 1H), 4.07 – 4.00 (m, 1H), 3.78 – 3.69 (m, 1H), 3.66 – 3.60 (m, 1H), 2.51 (s, 3H), 2.43 (d, J = 7.0 Hz, 2H), 2.14 – 2.04 (m, 1H), 1.84 (ddd, J = 19.7, 13.3, 6.7 Hz, 2H), 1.45 (dd, J = 7.1, 2.4 Hz, 3H), 1.24 (dd, J = 17.8, 7.0 Hz, 3H), 0.88 (d, J = 6.6 Hz, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.7, 155.7, 149.5, 140.5, 137.8, 129.3, 127.2, 125.2, 124.0, 121.3, 63.2, 45.1, 32.9, 31.1, 30.8, 30.2, 22.4, 18.5, 18.2. **HRMS** (ESI) m/z calcd for $C_{23}H_{32}NO_3$ $[M+H]^+$: 370.2377.; found: 370.2377.

2,6-dimethylpyridine *N*-oxide (3ab): Following the Method B (5.0 equiv BIOAc), the resulting mixture was purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a

colorless oil (0.2 mmol scale: 9.4 mg, 38% yield). Compound **3ab** has been previously reported.[18] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.11 (d, *J* = 7.8 Hz, 2H), 7.08 – 7.03 (m, 1H), 2.49 (s, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 149.2, 125.3, 124.1, 18.3. **Elemental analysis** calcd (%) C_7H_9NO: C 68.27, H 7.37, N 11.37. Found: C 68.18, H 7.66, N 11.32.

2-(6-bromohexyl)-6-methylpyridine *N*-oxide (3ac): Following the Method B, the resulting mixture was purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a colorless oil (0.2 mmol scale: 27.8 mg, 51% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.21 – 7.07 (m, 3H), 3.41 (t, J = 6.8 Hz, 2H), 3.01 – 2.90 (m, 2H), 2.54 (s, 3H), 1.88 (dd, J = 14.5, 6.9 Hz, 2H), 1.80 – 1.72 (m, 2H), 1.55 – 1.43 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 152.4, 149.3, 124.9, 124.0, 122.9, 34.0, 32.7, 31.0, 28.7, 28.0, 26.1, 18.5. **HRMS** (ESI) m/z calcd for $C_{12}H_{19}BrNO$ $[M+H]^+$: 272.0645.; found: 272.0645.

2-(cyclopentylmethyl)-6-methylpyridine *N*-oxide (3ad): Following the Method B, the resulting mixture was purified by flash chromatography (PE : EA = 1 : 1 to EA) to give the desired product as a colorless oil (0.2 mmol scale: 21.0 mg, 55% yield). Compound **3ad** has been previously reported.[21] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.21 – 6.95 (m, 3H), 2.93 (d, *J* = 7.3 Hz, 2H), 2.53 (s, 3H), 2.43 (dt, *J* = 15.3, 7.7 Hz, 1H), 1.78 (dd, *J* = 11.6, 7.0 Hz, 2H), 1.72 (s, 1H), 1.66 (dd, *J* = 14.7, 6.6 Hz, 2H), 1.60 – 1.47 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 152.4, 149.3, 125. 6, 123.9, 123.5, 37.3, 36.5, 32.8, 25.1, 18.5.

Sequential C(sp^2)–H Arylation/Alkylation of Pyridine *N*-oxide

C–H arylation step: To a 10 mL Schlenk tube was sequentially added K_2CO_3 (276 mg, 2.0 mmol), P^tBu_3-HBF_4 (43.5 mg, 0.15 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol). The tube was evacuated and backfilled with N_2 for three times. Then pyridine *N*-oxide (380 mg, 4.0 mmol), bromobenzene (157 mg, 1.0 mmol) and toluene (3.5 mL) were added. The mixture was then heated to 110 ºC overnight. The

reaction mixture was purified by flash chromatography (PE : EA = 1 : 1 to EA) to give **5** as a white solid (133.5 mg, 78% yield).

C–H alkylation step: To a 15 mL Schlenk tube was sequentially added 2-phenylpyridine *N*-oxide (133.5 mg, 0.78 mmol), potassium cyclohexyltrifluoroborate (297 mg, 1.56 mmol), $[Ru(bpy)_3](PF_6)_2$ (14.8 mg, 2 mol%), BIOAc (716 mg, 2.34 mmol). The tube was evacuated and backfilled with N_2 for three times. Then, CH_2Cl_2 (3 mL), H_2O (3 mL) and TFA (117 μL, 1.56 mmol) were added. The reaction mixture was stirred for 24 h at room temperature with blue LEDs (2 × 36 W) irradiation. The reaction mixture was purified by flash chromatography (EA to EA : MeOH = 10 : 1) to give **6** as a pale yellow solid (85.5 mg, 64% yield).

2-phenylpyridine *N*-oxide (5): Compound **5** has been previously reported.[2a] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.33 (d, *J* = 4.8 Hz, 1H), 7.80 (dd, *J* = 7.2, 1.0 Hz, 2H), 7.51 – 7.36 (m, 4H), 7.29 (ddd, *J* = 7.8, 5.3, 1.2 Hz, 1H), 7.24 – 7.17 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 149.3, 140.5, 132.6, 129.6, 129.3, 128.3, 127.4, 125.9, 124.6.

2-cyclohexyl-6-phenylpyridine *N*-oxide (6): Compound **6** has been previously reported.[21] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.1 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.43 – 7.38 (m, 1H), 7.28 – 7.24 (m, 2H), 7.20 (dd, *J* = 6.9, 3.0 Hz, 1H), 3.61 – 3.53 (m, 1H), 2.12 (d, *J* = 12.2 Hz, 2H), 1.86 (d, *J* = 13.4 Hz, 2H), 1.79 (d, *J* = 13.1 Hz, 1H), 1.55 – 1.46 (m, 2H), 1.34 – 1.26 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.4, 149.5, 133.8, 129.6, 129.2, 128.1, 125.2, 124.5, 121.8, 37.9, 31.0, 26.6, 26.4.

Synthetic Application to the Drug Molecule Ciclopirox

Step 1: To a stirred solution of 2-methoxy-4-methylpyridine (**7**) (123.2 mg, 1.0 mmol) in $CHCl_3$ (2 mL) was added 70% *m*-CPBA (172.6 mg, 1.0 mmol), portion wise at 0 °C. The mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with $CHCl_3$, and solid K_2CO_3 (552.8 mg, 4

mmol) was added. The resulting mixture was stirred for an additional 10 min. The crude product was purified by flash chromatography to give the 2-methoxy-4-methylpyridine *N*-oxide as a colorless oil (128.0 mg, 92% yield).[18]

Step 2: To a 15 mL Schlenk tube was sequentially added potassium cyclohexyltrifluoroborate (349.6 mg, 1.84 mmol), $[Ru(bpy)_3](PF_6)_2$ (17.5 mg, 2 mol%), BIOAc (844.6 mg, 2.76 mmol). The tube was evacuated and backfilled with N_2 for three times. Then, 2-methoxy-4-methylpyridine *N*-oxide (128.0 mg, 0.92 mmol), CH_2Cl_2 (3 mL), H_2O (3 mL) and TFA (138 μL, 1.84 mmol) were added. The reaction mixture was stirred for 24 h at room temperature with blue LEDs (2 × 36 W) irradiation. The reaction mixture was purified by flash chromatography (EA to EA : MeOH = 10 : 1) to give 2-cyclohexyl-6-methoxy-4-methylpyridine *N*-oxide (**8**) as a colorless oil (138.4 mg, 68% yield).

Step 3: The 2-cyclohexyl-6-methoxy-4-methylpyridine *N*-oxide (**8**) (138.4 mg, 0.62 mmol) was dissolved in AcCl (3.0 mL) and refluxed for 1 h. The solvent was removed under reduced pressure. The residue was dissolved in MeOH (3.0 mL) and stirred overnight at room temperature. MeOH was removed under reduced pressure and the residue was washed with Et_2O to afford ciclopirox (**9**) as an off-white powder (123.2 mg, 95% yield).[22]

2-cyclohexyl-6-methoxy-4-methylpyridine *N*-oxide (8): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.66 (s, 1H), 6.53 (s, 1H), 4.00 (d, *J* = 8.6 Hz, 3H), 3.54 (t, *J* = 12.0 Hz, 1H), 2.32 (s, 3H), 2.04 (d, *J* = 12.4 Hz, 2H), 1.81 (d, *J* = 13.3 Hz, 2H), 1.76 (d, *J* = 13.8 Hz, 1H), 1.49 (dd, *J* = 26.1, 13.0 Hz, 2H), 1.28 – 1.22 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 158.0, 156.8, 138.6, 115.6, 105.6, 57.1, 37.2, 31.0, 26.4, 26.4, 21.3. **HRMS** (ESI) m/z calcd for $C_{13}H_{20}NO_2$ $[M+H]^+$: 222.1489; found: 222.1489.

6-cyclohexyl-1-hydroxy-4-methylpyridin-2(1H)-one (9): ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.39 (s, 1H), 6.01 (d, *J* = 1.4 Hz, 1H), 3.12 (t, *J* = 11.9 Hz, 1H), 2.17 (s, 3H), 2.00 (d, *J* = 10.8 Hz, 2H), 1.82 (d, *J* =

13.3 Hz, 2H), 1.75 (d, *J* = 13.0 Hz, 1H), 1.47 – 1.38 (m, 2H), 1.25 (dddd, *J* = 16.6, 13.2, 9.9, 3.2 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 158.5, 149.9, 147.1, 112.1, 106.0, 38.0, 31.4, 26.4, 26.2, 21.5.

ASSOCIATED CONTENT

Supporting Information.

Optimization data, ^{1}H and ^{13}C NMR spectra and HPLC analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

***Email: daijj@hfut.edu.cn; hjxu@hfut.edu.cn**

ORCID

Jian-Jun Dai: 0000-0001-7918-0080

Hua-Jian Xu: 0000-0002-0789-3484

Notes

We declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21402036, 21472033, 21502038 and 21272050) and the China Postdoctoral Science Foundation (2014M551793 and 2015T80645) for financial support.

REFERENCES

(1) (a) Youssif, S. *ARKIVOC*, **2001**, 242. (b) Albini, A.; Pietra, S. *Heterocyclic N-oxides*, CRC Press, Boca Raton, **1991**. (c) Albini, A. *Synthesis* **1993**, 263. (d) Balzarini, J.; Keyaerts, E.; Vijgen, L.; Vandermeer, F.; Stevens, M.; De Clercq, E.; Egberink, H.; Van Ranst, M. *J.*

Antimicrob. Chemother. **2006**, *57*, 472. (e) Mfuh, A. M.; Larionov, O. V. *Curr. Med. Chem.* **2015**, *22*, 2819.

(2) For selected C–H arylation of pyridine *N*-oxides, see: (a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (b) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (c) Gong, X.; Song, G.; Zhang, H.; Li, X. *Org. Lett.* **2011**, *13*, 1766. (d) Tan, Y.; Barrios-Landeros, F.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 3683. (e) Duric, S.; Sypaseuth, F. D.; Hoof, S.; Svensson, E.; Tzschucke, C. C. *Chem. Eur. J.* **2013**, *19*, 17456. (f) Liu, W.; Li, Y.; Wang, Y.; Kuang, C. *Org. Lett.* **2013**, *15*, 4682. (g) Bering, L.; Antonchick, A. P. *Org. Lett.* **2015**, *17*, 3134. (h) Kianmehr, E.; Faghih, N.; Khan, K. M. *Org. Lett.* **2015**, *17*, 414.

(3) For selected C–H alkenylation of pyridine *N*-oxides, see: (a) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 8872. (b) Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y. *J. Am. Chem. Soc.* **2009**, *131*, 13888. (c) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (d) Ryu, J.; Cho, S. H.; Chang, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3677. (e) Huckins, J. R.; Bercot, E. A.; Thiel, O. R.; Hwang, T.-L.; Bio, M. M. *J. Am. Chem. Soc.* **2013**, *135*, 14492. (f) Neufeldt, S. R.; Jiménez-Osés, G.; Huckins, J. R.; Thiel, O. R.; Houk, K. N. *J. Am. Chem. Soc.* **2015**, *137*, 9843. (g) Crisenza, G. E. M.; Dauncey, E. M.; Bower, J. F. *Org. Biomol. Chem.* **2016**, *14*, 5820. (h) Xia, H.; Liu, Y.; Zhao, P.; Gou, S.; Wang, J. *Org. Lett.* **2016**, *18*, 1796.

(4) For recent C–H amination of pyridine *N*-oxides, see: (a) Farrell, R. P.; Elipe, M. V. S.; Bartberger, M. D.; Tedrow, J. S.; Vounatsos, F. *Org. Lett.* **2013**, *15*, 168. (b) Li, G.; Jia, C.; Sun, K. *Org. Lett.* **2013**, *15*, 5198. (c) Zhu, C.; Yi, M.; Wei, D.; Chen, X.; Wu, Y.; Cui, X. *Org. Lett.*

2014, *16*, 1840. (d) Chen, X.; Li, X.; Qu, Z.; Ke, D.; Qu, L.; Duan, L.; Mai, W.; Yuan, J.; Chen, J.; Zhao, Y. *Adv. Synth. Catal.* **2014**, *356*, 1979. (e) Xiong, H.; Hoye, A. T.; Fan, K.-H.; Li, X.; Clemens, J.; Horchler, C. L.; Lim, N. C.; Attardo, G. *Org. Lett.* **2015**, *17*, 3726.

(5) For the C–H sulfonylation of pyridine *N*-oxides, see: (a) Wu, Z.; Song, H.; Cui, X.; Pi, C.; Du, W.; Wu, Y. *Org. Lett.* **2013**, *15*, 1270. (b) Su, Y.; Zhou, X.; He, C.; Zhang, W.; Ling, X.; Xiao, X. *J. Org. Chem.* **2016**, *81*, 4981. (c) Sun, K.; Chen, X.-L.; Li, X.; Qu, L.-B.; Bi, W.-Z.; Chen, X.; Ma, H.-L.; Zhang, S.-T.; Han, B.-W.; Zhao, Y.-F.; Li, C.-J. *Chem. Commun.* **2015**, *51*, 12111. (d) Wang, R.; Zeng, Z.; Chen, C.; Yi, N.; Jiang, J.; Cao, Z.; Deng, W.; Xiang, J. *Org. Biomol. Chem.* **2016**, *14*, 5317.

(6) Representative examples for the C–H alkylation of pyridine *N*-oxides: (a) Andersson, H.; Almqvist, F.; Olsson, R. *Org. Lett.* **2007**, *9*, 1335. (b) Deng, G.; Ueda, K.; Yanagisawa, S.; Itami, K.; Li, C.-J. *Chem. Eur. J.* **2009**, *15*, 333. (c) Xiao, B.; Liu, Z.-J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 616. (d) Larionov, O. V.; Stephens, D.; Mfuh, A.; Chavez, G. *Org. Lett.* **2014**, *16*, 864. (e) Zhang, F.; Duan, X.-F. *Org. Lett.* **2011**, *13*, 6102. (f) Jha, A. K.; Jain, N. *Chem. Commun.* **2016**, *52*, 1831. (g) Sun, W.; Xie, Z.; Liu, J.; Wang, L. *Org. Biomol. Chem.* **2015**, *13*, 4596. (h) Jo, W.; Kim, J.; Choi, S.; Cho, S. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 9690.

(7) (a) Yasu, Y.; Koike, T.; Akita, M. *Adv. Synth. Catal.* **2012**, *354*, 3414. (b) Miyazawa, K.; Yasu, Y.; Koike, T.; Akita, M. *Chem. Commun.* **2013**, *49*, 7249. (c) Miyazawa, K.; Koike, T.; Akita, M. *Adv. Synth. Catal.* **2014**, *356*, 2749. (d) Li, Y.; Miyazawa, K.; Koike, T.; Akita, M. *Org. Chem. Front.* **2015**, *2*, 319. (e) Chinzei, T.; Miyazawa, K.; Yasu, Y.; Koike, T.; Akita, M. *RSC Adv.* **2015**, *5*, 21297.

(8) (a) Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science* **2014**, *345*, 433. (b) Primer, D. N.; Karakaya, I.; Tellis, J. C.; Molander, G. A. *J. Am. Chem. Soc.* **2015**, *137*, 2195. (c) Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2015**, *137*, 4896. (d) Yamashita, Y.; Tellis, J. C.; Molander, G. A. *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112*, 12026. (e) Karakaya, I.; Primer, D. N.; Molander, G. A. *Org. Lett.* **2015**, *17*, 3294. (f) Ryu, D.; Primer, D. N.; Tellis, J. C.; Molander, G. A. *Chem. Eur. J.* **2016**, *22*, 120. (g) El Khatib, M.; Serafim, R. A. M.; Molander, G. A. *Angew. Chem., Int. Ed.* **2016**, *55*, 254. (h) Amani, J.; Sodagar, E.; Molander, G. A. *Org. Lett.* **2016**, *18,* 732.

(9) (a) Huang, H.; Zhang, G.; Gong, L.; Zhang, S.; Chen, Y. *J. Am. Chem. Soc.* **2014**, *136*, 2280. (b) Huang, H.; Jia, K.; Chen, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 1881.

(10) Recent reviews on photoredox reactions: (a) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, 40, 102. (b) Xuan, J.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6828. (c) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (d) Duret, G.; Quinlan, R.; Bisseret, P.; Blanchard, N. *Chem. Sci.* **2015**, *6*, 5366. (e) Chen, J.-R.; Hu, X.-Q.; Lu, L.-Q.; Xiao, W.-J. *Chem. Soc. Rev.* **2016**, *45,* 2044. (f) Ravelli, D.; Protti, S.; Fagnoni, M. *Chem. Rev.* **2016**, *116*, 9850.

(11) (a) Dai, J.-J.; Zhang, W.-M.; Shu, Y.-J.; Sun, Y.-Y.; Xu, J.; Feng, Y.-S.; Xu, H.-J. *Chem. Commun.* **2016**, *52*, 6793. (b) Xu, W.-T.; Huang, B.; Dai, J.-J.; Xu, J.; Xu, H.-J. *Org. Lett.* **2016**, *18*, 3114.

(12) For related photoredox-catalyzed alkylation of *N*-heteroarenes, see: (a) DiRocco, D. A.; Dykstra, K.; Krska, S.; Vachal, P.; Conway, D. V.; Tudge, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 4802. (b) Jin, J.; MacMillan, D. W. C. *Nature* **2015**, *525*, 87. (c) Jin, J.; MacMillan, D. W. C.

Angew. Chem., Int. Ed. **2015**, *54*, 1565. (d) McCallum, T.; Barriault, L. *Chem. Sci.* **2016**, *7*, 4754. (e) Li, G.-X.; Morales-Rivera, C. A.; Wang, Y.; Gao, F.; He, G.; Liu, P.; Chen, G. *Chem. Sci.* **2016**, *7*, 6407.

(13) The examples of using hypervalent iodine(III) reagents in visible light-driven photoredox reactions: (a) Xie, J.; Xu, P.; Li, H.; Xue, Q.; Jin, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2013**, *49*, 5672. (b) Moteki, S. A.; Usui, A.; Selvakumar, S.; Zhang, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2014**, *53*, 11060. (c) Zhou, Q.-Q.; Guo, W.; Ding, W.; Wu, X.; Chen, X.; Lu, L.-Q.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2015**, *54*, 11196. (d) Huang, H.; Zhang, G.; Chen, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 7872. (e) Tan, H.; Li, H.; Ji, W.; Wang, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 8374. (f) Ji, W.; Tan, H.; Wang, M.; Li, P.; Wang, L. *Chem. Commun.* **2016**, *52*, 1462. (g) Jia, K.; Zhang, F.; Huang, H.; Chen, Y. *J. Am. Chem. Soc.* **2016**, *128*, 1514. (h) Wang, L.; Liu, J. *Eur. J. Org. Chem.* **2016**, 1813.

(14) (a) Gupta, A. K.; Skinner, A. R. *Int. J. Dermatol.* **2003**, *42*, 3. (b) Subissi, A.; Monti, D.; Togni, G.; Mailland, F. *Drugs*, **2010**, *70*, 2133.

(15) (a) Kern, J. W.; Shriner, R. L.; Adams, R. *J. Am. Chem. Soc.* **1925**, *47*, 1147. (b) Auwers, K. v.; König, F. *Liebigs Ann. Chem.* **1932**, *496*, 269. (c) Lohaus, G.; Friedrich, W.; Jeschke, J. P. *Chem. Ber.* **1967**, *100*, 658. (d) Lohaus, G.; Dittmar, W. DE 2214608, **1973**.

(16) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066.

(17) (a) Majek, M.; Filace, F.; von Wangelin, A. J. *Beilstein J. Org. Chem.* **2014**, *10*, 981. (b) Cismesia, M. A.; Yoon, T. P. *Chem. Sci.* **2015**, *6*, 5426. (c) Kärkäs, M. D.; Matsuura, B. S.; Stephenson, C. R. J. *Science* **2015**, *349*, 1285. (d) Candish, L.; Pitzer, L.; Gomez-Suarez, A.;

Glorius, F. *Chem. Eur. J.* **2016**, *22*, 4753. (e) Studer, A.; Curran, D. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 58. (f) Studer, A.; Curran, D. P. *Nature Chem.* **2014**, *6*, 765.

(18) Kokatla, H. P.; Thomson, P. F.; Bae, S.; Doddi, V. R.; Lakshman, M. K. *J. Org. Chem.* **2011**, *76*, 7842.

(19) Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. *Angew. Chem.; Int. Ed.* **2012**, *51*, 528.

(20) Mun, S.; Lee, J.-E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887.

(21) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781.

(22) Deng, L.; Sundriyal, S.; Rubio, V.; Shi, Z.; Song, Y. *J. Med. Chem.* **2009**, *52*, 6539.