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Pyridine *N*-Oxides

# Visible-Light-Promoted Copper-Catalyzed Regioselective Benzylation of Pyridine *N*-Oxides versus Thermal Acylation Reaction with Toluene Derivatives

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**Abstract:** Copper-catalyzed visible light mediated direct C–H bond benzylation of pyridine *N*-oxides with toluene derivatives was accomplished by recent developments in photochemical carbon–carbon bond formation through a photo-induced bond-dissociation strategy. This visible light driven protocol has been successfully applied to a broad scope of pyridine *N*-oxides and toluene derivatives. Furthermore, preliminary research indicates that the acylation reaction can be carried out under thermal reaction conditions. This protocol provides easy access to 2-benzyl and 2-acyl pyridine *N*-oxide derivatives in the presence of a copper catalyst.

## Introduction

Transition metal catalyzed cross-coupling reactions of two readily accessible reagents has emerged as a straightforward and economical strategies for new C–C bond construction.[1] Over the past decades, the functionalization of C–H bonds through a transition metal catalyzed approach has received much attention. This strategy is more appealing when it comes to choosing starting materials without any requirements of pre-functionalization. Cross-dehydrogenative coupling (CDC) reactions are highly beneficial and avoid the need to prepare pre-functionalized molecules and make synthetic routes shorter, more efficient and easier.[2] Oxidative coupling reactions have been successfully applied to construct C–C bonds between Csp–H and Csp–H,[3] Csp–H and $Csp^2$–H,[4] Csp–H and $Csp^3$–H,[5] $Csp^2$–H and $Csp^2$–H,[6] $Csp^3$–H and $Csp^2$–H bonds.[7] Despite the significant progress made in this area, the more challenging $Csp^3$–H and $Csp^2$–H couplings through CDC reactions remain scarce.

2-Benzylpyridine unit is a significant building block found in biologically active molecules, pharmaceuticals, and organic functional materials,[8] for example α-(2-pyridine) benzyl aryl ketones, compound **1**, are potential hypocholesteremic agents.[9] In particular, 2-benzylpridine compound **2** is used for rat-selective induction of the mitochondrial permeability transition[10] (Figure 1).

Most C–H bond functionalization processes generally rely on the strategies of directing group-assisted C–H bond activation, which provides a unique approach to target molecules.[11] Pyridine *N*-oxides often serve as important intermediates for the activation and functionalization of the pyridine ring. Palladium and copper catalysts have been shown to be very effective for functionalization of pyridine *N*-oxides.[12]

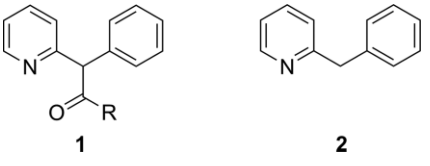


Figure 1. Examples of bioactive 2-benzylpyridines.

Synthesis of 2-benzylpyridines by direct arylation of benzylic $Csp^3$–H bond of 2-methylpyridine *N*-oxides was reported by Fagnou in 2008 (Scheme 1).[13] In 2010, Liu and co-workers reported cross-coupling of 2-(2-pyridyl)acetates with aryl halides for the synthesis of 2-benzylpyridine derivatives.[14] Palladium-catalyzed arylation of 2-methylpyridine with aryl halides was reported by Knochel in 2011 for the synthesis of 2-benzylpyridines.[15] In 2012, Pd-catalyzed benzylic cross-coupling reactions of pyridine *N*-oxides with benzyl chloride in the presence of $tBu_3P$–$HBF_4$ and $K_2CO_3$ for the synthesis of the corresponding 2-benzyl pyridine *N*-oxides was developed by Mai (Scheme 1).[16] A copper-catalyzed regioselective cross-coupling of *N*-tosylhydrazones with azine *N*-oxides to yield *ortho*-alkylated products was developed by Jain in 2016 (Scheme 1).[17] In all of the above-mentioned methods, pre-functionalization of the coupling partner of pyridine *N*-oxides is necessary. A palladium-catalyzed benzylation of pyridine *N*-oxides was reported by us recently (Scheme 1).[18] Visible-light provides a new approach for C–C,[19] C–N,[20] C–P,[21] C–S,[22] and C–Se[23] bond formation through the generated radicals from visible light promoted cleavage of weak bonds. Recently, light-promoted procedures in the present of various photocatalysts emerged as one of the most powerful C–H activation processes. In particular, the visible light catalyzed CDC reaction has received much attention because of its mild, clean, and eco-friendly properties.

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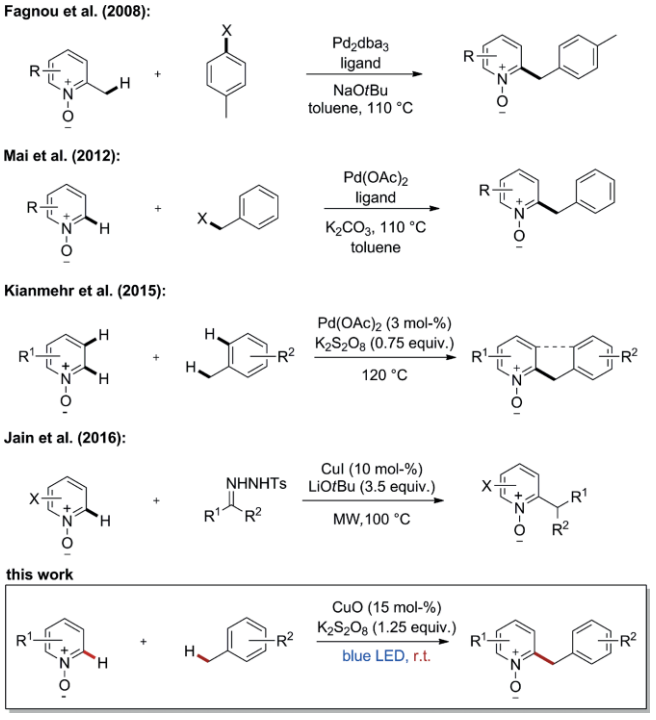



Scheme 1. Different routes for benzylation of pyridine *N*-oxides.

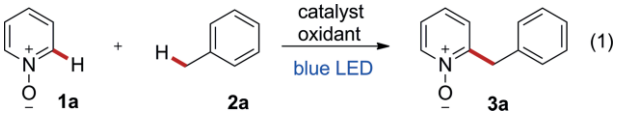
As part of our ongoing interest to explore C–C bond formations through CDC reactions[24] herein we report an efficient and highly regioselective procedure for the direct benzylation of pyridine *N*-oxides with toluenes at room temperature induced by visible light in the presence of a copper catalyst, which is less expensive and more environmentally benign relative to palladium or rhodium complexes. The reaction represents a regioselective route towards synthesis of 2-benzylpyridine *N*-oxide derivatives.

## Results and Discussion

Our initial effort began with the reaction of pyridine *N*-oxide (**1a**) with toluene (**2a**) in the presence of $Cu(OAC)_2$ (15 mol-%) and $K_2S_2O_8$ under 8 W blue LED irradiation in acetonitrile. Product formation was seen after 12 h. However, by increasing the reaction time to 24 h, desired product 2-benzylpyridine-1-oxide (**3a**) was obtained in 25 % yield (Table 1, Entry 1).

Optimization of the reaction conditions with respect to solvent, catalyst, oxidant, and time was carried out. The use of copper-based catalysts, such as CuCl and CuO, improved the yield of the product up to 70 and 81 %, respectively (Table 1, Entries 3 and 5). By changing the copper catalyst to $Pd(OAc)_2$ and $PdCl_2$ dropped the yield of **3a** to 24 and 28 %, respectively (Table 1, Entries 6 and 7). Furthermore, an increase in catalyst loading to 20 mol-% did not improve the reaction efficiency (Table 1, Entry 8). A variety of solvents were examined. As a result, $CH_3CN$, which gave the product in 81 % yield, was selected as the best solvent among chlorobenzene, 1,2-dichloroethane (DCE), dimethyl sulfoxide (DMSO) and dimethylformamide (DMF). Notably, the desired product was not observed in

Table 1. Optimization of the reaction conditions.[a]




| Entry | Catalyst [mol-%] | Oxidant (equiv.) | Solvent | Yield [%] |
|---|---|---|---|---|
| 1 | $Cu(OAc)_2$ (15) | $K_2S_2O_8$ (1.25) | $CH_3CN$ | 25 |
| 2 | CuBr (15) | $K_2S_2O_8$ (1.25) | $CH_3CN$ | 31 |
| 3 | CuCl (15) | $K_2S_2O_8$ (1.25) | $CH_3CN$ | 70 |
| 4 | $CuBr_2$ (15) | $K_2S_2O_8$ (1.25) | $CH_3CN$ | 41 |
| **5** | **CuO (15)** | **$K_2S_2O_8$ (1.25)** | **$CH_3CN$** | **81** |
| 6 | $Pd(OAc)_2$ (15) | $K_2S_2O_8$ (1.25) | $CH_3CN$ | 24 |
| 7 | $PdCl_2$ (15) | $K_2S_2O_8$ (1.25) | $CH_3CN$ | 28 |
| 8 | CuO (20) | $K_2S_2O_8$ (1.25) | $CH_3CN$ | 79 |
| 9 | CuO (15) | $K_2S_2O_8$ (1.25) | toluene | 0 |
| 10 | CuO (15) | $K_2S_2O_8$ (1.25) | DCE | 11 |
| 11 | CuO (15) | $K_2S_2O_8$ (1.25) | PhCl | 25 |
| 12 | CuO (15) | $K_2S_2O_8$ (1.25) | DMSO | 0 |
| 13 | CuO (15) | $K_2S_2O_8$ (1.25) | DMF | 0 |
| 14 | CuO (15) | TBHP (2.0) | $CH_3CN$ | 0 |
| 15 | CuO (15) | DTBP (2.0) | $CH_3CN$ | 0 |
| 16 | CuO (15) | $(NH_4)_2S_2O_8$ (1.25) | $CH_3CN$ | 68 |
| 17 | CuO (15) | $Na_2S_2O_8$ (1.25) | $CH_3CN$ | 53 |
| 18 | CuO (15) | $K_2S_2O_8$ (0.75) | $CH_3CN$ | 33 |
| 19 | CuO (15) | $K_2S_2O_8$ (2.0) | $CH_3CN$ | 80 |
| 20 | CuO (15) | $K_2S_2O_8$ (1.25) | $CH_3CN$ | 79[b] |
| 21 | CuO (15) | $K_2S_2O_8$ (1.25) | $CH_3CN$ | 80[c] |
| 22 | CuO (15) | $K_2S_2O_8$ (1.25) | $CH_3CN$ | 78[d] |
| 23 | CuO (15) | $K_2S_2O_8$ (1.25) | $CH_3CN$ | 0[e] |

[a] General reaction conditions: All reactions were irradiated for 24 h under 8 W blue LED strips by using **1a** (1 equiv., 1 mmol), **2a** (3 equiv., 3 mmol). [b] Reaction time: 48 h. [c] Methylene blue (5 mol-%) was added. [d] Eosin Y (5 mol-%) was added. [e] Reaction was performed in the dark.

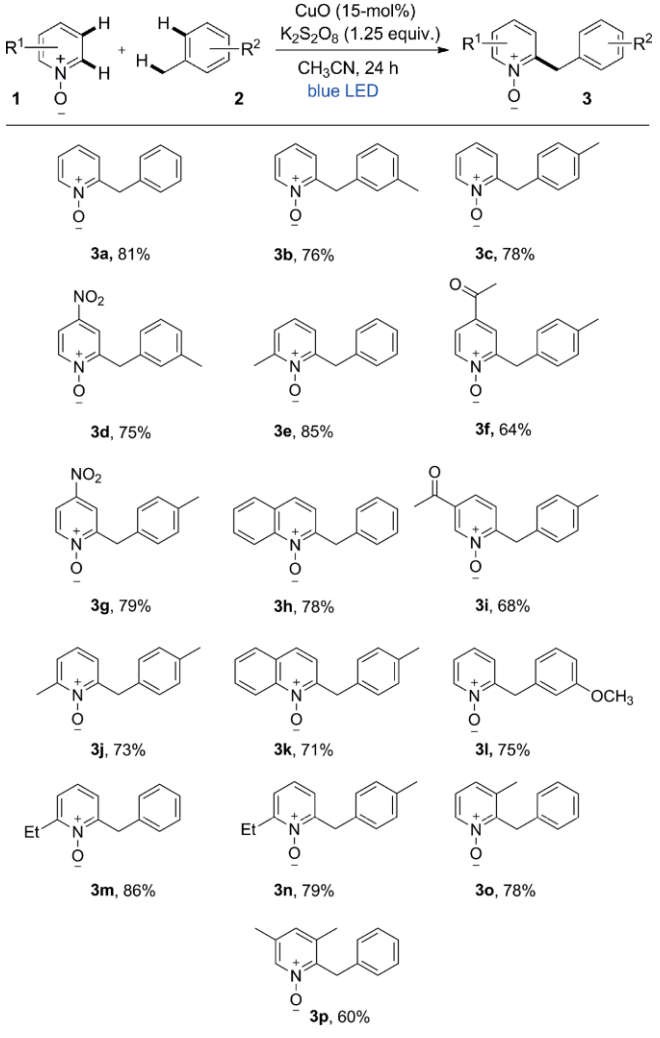
toluene, which acted as both reactant and reaction medium (Table 1, Entry 9). As shown in Table 1, a variety of oxidants, such as *tert*-butyl hydroperoxide (TBHP) and di-*tert*-butyl peroxide (DTBP) were totally insufficient (Table 1, Entries 14 and 15). To our delight oxidants such as $K_2S_2O_8$, $Na_2S_2O_8$, and $(NH_4)_2S_2O_8$, were effective in this reaction and the best result was obtained with potassium persulfate (Table 1, Entries 5, 16 and 17).

The optimum amount of oxidant for the reaction was $K_2S_2O_8$ (1.25 equiv.). The reaction did not go to completion with less than 1.25 equiv. of $K_2S_2O_8$, and an increased amount of oxidant did not result in higher yields (Table 1, Entries 18 and 19). The yield of the reaction was not improved by increasing the reaction time beyond 24 h. (Table 1, Entry 20). Control experiments revealed that light illumination in the presence of a photocatalyst, such as methylene blue and eosin Y, didn't affect the reaction efficiency (Table 1, Entries 21 and 22). The reaction didn't afford the desired product in the absence of light, which confirms the role of light in the reaction mechanism (Table 1, Entry 23). Thus, the optimum reaction conditions involved irradiating the substrates under 8 W blue LED strips for 24 hours with $K_2S_2O_8$ (1.25 equiv.) and CuO (15 mol-%) in acetonitrile.

Once the optimized conditions for the desired benzylation reaction were established, the scope of the reaction was investi-

gated. A variety of combinations of substrates were examined, and the results are summarized in Table 2. Pyridine *N*-oxides with both electron-donating and electron-withdrawing groups reacted smoothly and resulted in the corresponding 2-benzyl pyridine *N*-oxides in moderate to good yields. Pyridine *N*-oxides with electron-donating groups gave higher yields (**3e** and **3m**).

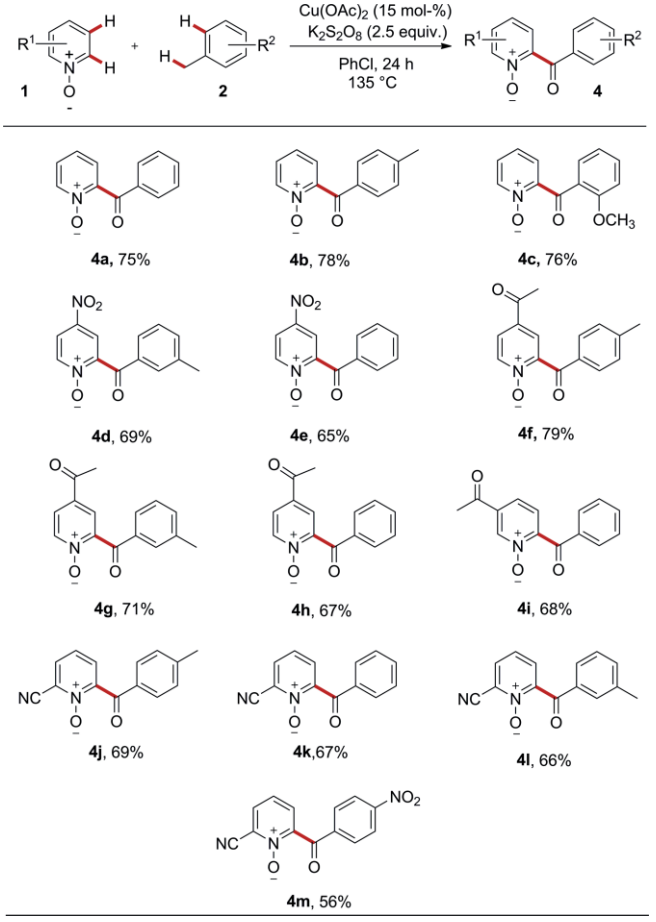
Table 2. Copper-catalyzed direct benzylation reactions of pyridine *N*-oxides by toluene derivatives.[a]




[a] Reaction conditions: Pyridine *N*-oxides (1 equiv., 1 mmol), toluene derivatives (3 equiv., 3 mmol), CuO (15 mol-%), and $K_2S_2O_8$ (1.25 equiv., 1.25 mmol) in acetonitrile (2 mL) irradiated by 8 W blue LED strips for 24 h.

In the optimization study, we found that the visible light irradiation was crucial for the benzylation reaction and, when the reaction was performed under thermal conditions, the acylated product was obtained exclusively instead. A series of 2-acylated pyridine *N*-oxides, prepared by this procedure, are shown in Table 3. 2-Acyl pyridine *N*-oxide derivatives are known to be important synthetic precursors for the preparation of agrochemical[25] and pharmaceutical[26] products. A silver-catalyzed decarboxylative acylation of pyridine *N*-oxides by α-oxo-carboxylic acids, which leads to the formation of both C2- and C4-acylated products, has been reported recently.[27]

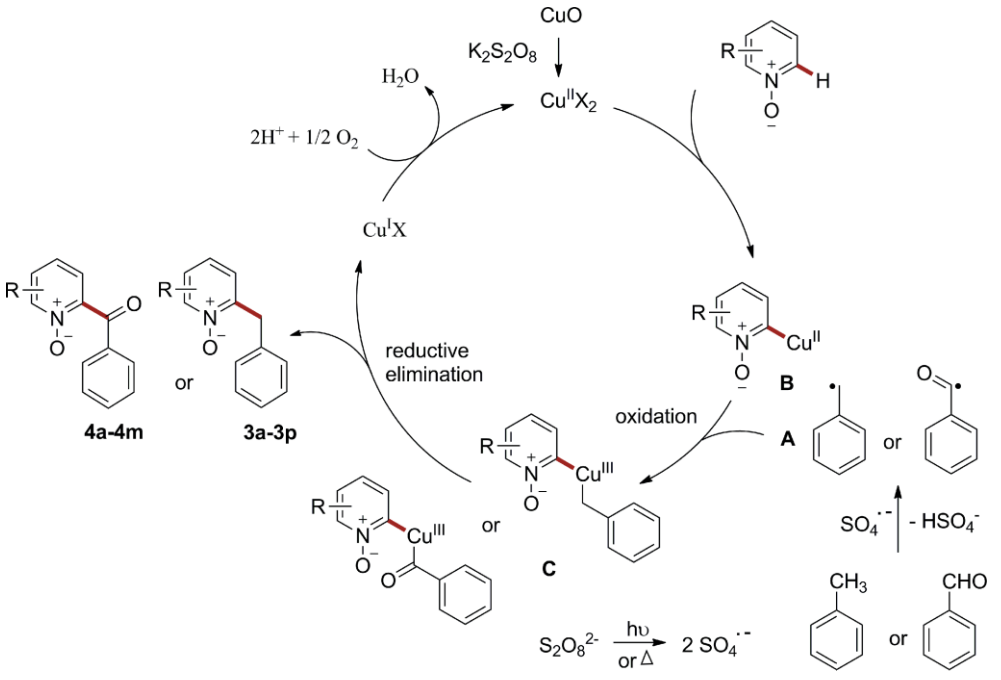
Table 3. Copper-catalyzed direct acylation reaction of pyridine *N*-oxides by toluene derivatives.[a]




[a] Reaction conditions: Pyridine *N*-oxides (1 equiv., 0.5 mmol), toluene derivatives (3 equiv., 1.5 mmol), $Cu(OAc)_2$ (15 mol-%), and $K_2S_2O_8$ (2.5 equiv., 1.25 mmol) in chlorobenzene (2.0 mL) at 135 °C for 24 h.

Based upon the above experimental results and previous reports, a plausible mechanism is proposed and described in Scheme 2.

Initially, a metallation reaction occurs preferentially at the C2-position of the pyridine *N*-oxide derivatives that leads to the formation of intermediate **B**. Radical intermediate **A** is generated in situ by hydrogen-atom abstraction from toluene or benzaldehyde produced by toluene oxidation under the reaction conditions[28] facilitated by the sulfate radical anion that is produced from $K_2S_2O_8$.[29] Next, coordination of copper complex **B** with radical **A** gives intermediate **C**, which undergoes reductive elimination to afford final product **3** or **4**. To prove the radical mechanism, a control reaction that involves the use of 2,6-di-*tert*-butyl-4-methylphenol as a radical scavenger was performed. When **1a** was treated in the presence of butylated hydroxytoluene (1 equiv.) no desired product **3a** (or **4a**) was observed.[30]




Scheme 2. Plausible mechanism.

## Conclusions

In conclusion, an efficient method for ortho C–H bond benzylation and acylation of pyridine *N*-oxides with methyl arenes has been disclosed, that allows for synthesis of a broad range of 2-benzyl and 2-acyl pyridine *N*-oxides. We have established a straightforward and versatile protocol that employed abundantly available methyl arenes as a coupling partner and avoids unproductive steps for pre-functionalization of starting materials.

## Experimental Section

**General Information:** Solvents, copper catalyst, toluene and pyridine derivatives were purchased from Merck and Sigma. Other reagents were purchased from commercial distributors and used without further purification. Pyridine *N*-oxides derivatives was synthesized in accordance with the literature. Analytical thin layer chromatography (TLC) was performed with pre-coated silica gel 60 F254 plates. The products were purified by preparative column chromatography on silica gel (0.063–0.200 mm; Merck). $^1$H and $^{13}$C NMR Spectra: were recorded with a Bruker 500 and 400 Advance instrument in $CDCl_3$. Mass spectrometry was obtained with an Agilent 5975C VL MSD (Ion source: EI+, 70 eV, 230 °C).

**General Procedure for the Synthesis of 2-Acylated Pyridine *N*-Oxides by Using Toluene as an Acylating Agent:** A 10 mL microwave vial was charged with pyridine *N*-oxide derivatives (1 equiv., 0.5 mmol), toluene derivatives (3 equiv., 1.5 mmol), $K_2S_2O_8$ (2.5 equiv., 1.25 mmol), Cu catalyst (15 mol-%), and chlorobenzene (2 mL). The vial was then sealed and immersed in an oil bath at 135 °C for 24 h. After this time the reaction mixture was cooled to room temperature and then diluted with methanol and filtered. The residue was purified by using column chromatography (*n*-hexane/EtOAc/methanol, 1:1:0.1) to yield the desired products.

**General Procedure for the Synthesis of 2-Benzyl pyridine *N*-Oxides by Using Toluene as a Benzylation Agent:** A 10 mL microwave vial was charged with pyridine *N*-oxide derivatives (1 equiv., 1 mmol), toluene derivatives (3 equiv., 3 mmol), $K_2S_2O_8$ (1.25 equiv., 1.25 mmol), Cu catalyst (15 mol-%), and acetonitrile (2 mL). The vial was irradiated with 8 W blue LED strips for 24 h. After this time the reaction mixture was diluted with methanol and filtered. The residue was purified by using column chromatography (*n*-hexane/EtOAc/methanol, 1:1:0.1) to yield the desired products.

**2-Benzylpyridine 1-Oxide (3a):** The general procedure was followed by using pyridine *N*-oxide (1 mmol, 95 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), CuO (12 mg, 15 mol-%), toluene (3 mmol, 0.32 mL), and acetonitrile (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **3a** (150 mg, 81 % yield) as a pale brown oil. $^1$H NMR (400 MHz, CDCl3): $\delta$ = 8.33–8.31 (m, 1 H), 7.85 (d, $J$ = 7.4 Hz, 1 H), 7.50 (t, $J$ = 7.7 Hz, 1 H), 7.37 (d, $J$ = 7.5 Hz, 2 H), 7.33–7.29 (m, 2 H), 7.19–7.16 (m, 1 H), 6.97 (d, $J$ = 6.7 Hz, 1 H), 4.28 (s, 2 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 152.0, 139.4, 136.2, 129.7, 129.3, 128.9, 127.1, 125.9, 123.6, 36.6 ppm. MS (EI): $m/z$ (%) = 185 (26) $[M]^+$, 168 (100), 154 (6), 139 (7), 106 (14), 91 (7), 78 (50), 65 (15), 51 (29). $C_{12}H_{11}NO$ (185.22): calcd. C 77.81, H 5.99, N 7.56; found C 77.98, H 5.96, N 7.58.

**2-(3-Methylbenzyl) pyridine 1-Oxide (3b):** The general procedure was followed by using pyridine *N*-oxide (1 mmol, 95 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), CuO (12 mg, 15 mol-%), *m*-xylene (3 mmol, 0.37 mL) and acetonitrile (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **3b** (151 mg, 76 % yield) as a pale brown oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.35–8.33 (m, 1 H), 7.19–7.16 (m, 2 H), 7.14–7.07 (m, 4 H), 6.99–6.96 (m, 1 H), 4.26 (s, 2 H), 2.37 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 152.2, 139.4, 138.6, 136.1, 130.5, 128.8, 127.8, 126.7, 125.9, 123.5, 36.4, 21.4 ppm. MS (EI): $m/z$ (%) = 199 (33) $[M]^+$, 182 (96), 167 (100), 152 (7), 136 (6), 119 (14), 106 (14), 91 (35), 78

(37), 65 (28), 51 (33), 43 (33). $C_{13}H_{13}NO$ (199.25): calcd. C 78.36, H 6.58, N 7.03; found C 78.58.74, H 6.60, N 7.00.

**2-(4-Methylbenzyl) pyridine 1-Oxide (3c):** The general procedure was followed by using pyridine *N*-oxide (1 mmol, 95 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), CuO (12 mg, 15 mol-%), *p*-Xylene (3 mmol, 0.37 mL), and acetonitrile (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **3c** (155 mg, 78 % yield) as a dark brown oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.32–8.30 (m, 1 H), 7.20–7.12 (m, 6 H), 7.97–6.95 (m, 1 H), 4.23 (s, 2 H), 2.37 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 152.2, 139.4, 136.7, 133.1, 129.6, 129.5, 125.7, 123.5, 36.1, 22.7 ppm. MS (EI): *m/z* (%) = 199 (30) $[M]^+$, 182 (100), 167 (96), 152 (7), 139 (7), 119 (8), 106 (30), 91 (21), 78 (74), 65 (20), 51 (25). $C_{13}H_{13}NO$ (199.25): calcd. C 78.36, H 6.58, N 7.03; found C 78.51, H 6.56, N 7.01.

**2-(3-Methylbenzyl)-4-nitropyridine 1-Oxide (3d):** The general procedure was followed by using 4-nitropyridine *N*-oxide (1 mmol, 140 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), CuO (12 mg, 15 mol-%), *m*-Xylene (3 mmol, 0.37 mL), and acetonitrile (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **3d** (183 mg, 75 % yield) as a pale yellow solid. M.p. 143–145 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.36 (d, *J* = 7.1 Hz, 1 H), 8.02 (dd, *J* = 7.1,& *J* = 3.2 Hz, 1 H), 7.83 (d, *J* = 3.1 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 1 H), 7.32 (d, *J* = 7.6 Hz, 1 H), 7.18 (d, *J* = 7.6 Hz, 1 H), 7.11 (s, 1 H), 4.21 (s, 2 H), 2.40 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 153.8, 140.1, 139.0, 134.4, 130.3, 129.6, 129.1, 128.6, 126.6, 120.1, 118.1, 36.6, 21.4 ppm. MS (EI): *m/z* (%) = 244 (23) $[M]^+$, 227 (48), 197 (11), 181 (100), 166 (15), 154 (18), 139 (16), 128 (11), 115 (12), 105 (12), 91 (18), 77 (20), 63 (13), 51 (21), 41 (12). $C_{13}H_{12}N_2O_3$ (244.25): calcd. C 63.93, H 4.95, N 11.47; found C 63.78, H 4.96, N 11.51.

**2-Benzyl-6-methylpyridine 1-Oxide (3e):** The general procedure was followed by using 2-methylpyridine *N*-oxide (1 mmol, 109 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), CuO (12 mg, 15 mol-%), toluene (3 mmol, 0.32 mL), and acetonitrile (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **3e** (169 mg, 85 % yield) as a light brown solid. M.p. 168–170 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.42–7.34 (m, 2 H), 7.33–7.25 (m, 3 H), 7.17 (d, *J* = 7.6 Hz, 1 H), 7.07 (t, *J* = 7.8 Hz, 1 H), 6.84 (d, *J* = 6.8 Hz, 1 H), 4.30 (s, 2 H), 2.58 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 151.9, 149.0, 136.8, 129.8, 128.8, 126.9, 124.7, 124.0, 123.4, 37.1, 18.4 ppm. MS (EI): *m/z* (%) = 199 (33) $[M]^+$, 182 (100), 167 (48), 154 (7), 139 (7), 128 (6), 115 (7), 106 (7), 91 (10), 77 (15), 65 (16), 51 (15), 41 (7). $C_{13}H_{13}NO$ (199.25): calcd. C 78.36, H 6.58, N 7.03; found C 78.11, H 6.60, N 7.05.

**4-Acetyl-2-(4-methylbenzyl) pyridine 1-Oxide (3f):** The general procedure was followed by using 4-acetylpyridine *N*-oxide (1 mmol, 137 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), CuO (12 mg, 15 mol-%), *p*-Xylene (3 mmol, 0.37 mL), and acetonitrile (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **3f** (154 mg, 64 % yield) as a pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.34 (d, *J* = 6.6 Hz, 1 H), 7.68 (dd, *J* = 6.5 & *J* = 2.3 Hz, 1 H), 7.55 (d, *J* = 2.3 Hz, 1 H), 7.22 (d, *J* = 7.9 Hz, 2 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 4.23 (s, 2 H), 2.51 (s, 3 H), 2.38 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 194.3, 152.6, 139.7, 137.0, 132.4, 129.7, 129.4, 127.9, 124.6, 122.3, 36.1, 26.3, 21.2 ppm. MS (EI): *m/z* (%) = 241 (22) $[M]^+$, 224 (100), 209 (29), 194 (7), 181 (15), 166 (14), 152 (7), 139 (7), 120 (14), 105 (13), 91 (15), 77 (13), 65 (9), 53 (9), 43 (28). $C_{15}H_{15}NO_2$ (241.29): calcd. C 74.67, H 6.27, N 5.81; found C 74.39, H 6.25, N 5.78.

**2-(4-Methylbenzyl)-4-nitropyridine 1-Oxide (3g):** The general procedure was followed by using 4-nitropyridine *N*-oxide (1 mmol, 140 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), CuO (12 mg, 15 mol-%), *p*-Xylene (3 mmol, 0.37 mL), and acetonitrile (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **3g** (192 mg, 79 % yield) as a pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.37 (d, *J* = 7.1 Hz, 1 H), 8.00 (dd, *J* = 7.0 & *J* = 3.1 Hz, 1 H), 7.82 (d, *J* = 3.1 Hz, 1 H), 7.24 (d, *J* = 8.1 Hz, 2 H), 7.19 (d, *J* = 8.1 Hz, 2 H), 4.21 (s, 2 H), 2.41 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 152.2, 139.4, 138.6, 136.2, 130.5, 128.8, 127.8, 123.5, 119.12, 32.0, 22.7 ppm. MS (EI): *m/z* (%) = 244 (44) $[M]^+$, 227 (66), 211 (7), 197 (14), 181 (70), 169 (13), 154 (14), 136 (40), 127 (17), 119 (25), 110 (18), 97 (30), 85 (48), 71 (73), 57 (100), 43 (46). $C_{13}H_{12}N_2O_3$ (244.25): calcd. C 63.93, H 4.95, N 11.47; found C 63.67, H 4.95, N 11.49.

**2-Benzylquinoline 1-Oxide (3h):** The general procedure was followed by using quinoline *N*-oxide (1 mmol, 145 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), CuO (12 mg, 15 mol-%), toluene (3 mmol, 0.32 mL), and acetonitrile (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **3h** (183 mg, 78 % yield) as a pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.85 (d, *J* = 8.2 Hz, 1 H), 7.60 (d, *J* = 7.9 Hz, 1 H), 7.55 (td, *J* = 8.2 Hz & *j* = 1.8 Hz, 2 H), 7.47–7.32 (m, 4 H), 7.26 (t, *J* = 7.7 Hz, 2 H), 6.75 (d, *J* = 8.1 Hz, 1 H), 4.47 (s, 2 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 152.0, 140.1, 139.4, 136.2, 135.0, 134.3, 129.7, 129.3, 128.9, 127.1, 125.9, 125.7, 123.6, 36.6 ppm. MS (EI): *m/z* (%) = 235 (15) $[M]^+$, 145 (100), 128 (10), 117 (70), 105 (7), 90 (40), 77 (14), 63 (21), 51 (15), 41 (7). $C_{16}H_{13}NO$ (235.28): calcd. C 81.68, H 5.57, N 5.95; found C 81.42, H 5.59, N 5.92.

**5-Acetyl-2-(4-methylbenzyl) pyridine 1-Oxide (3i):** The general procedure was followed by using 3-acetylpyridine *N*-oxide (1 mmol, 137 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), CuO (12 mg, 15 mol-%), *p*-Xylene (3 mmol, 0.37 mL), and acetonitrile (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **3i** (164 mg, 68 % yield) as a pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.84 (d, *J* = 1.6 Hz, 1 H), 7.66 (dd, *J* = 8.0 & *J* = 1.7 Hz, 1 H), 7.21 (d, *J* = 8.1 Hz, 2 H), 7.19 (d, *J* = 7.8 Hz, 2 H), 7.07 (d, *J* = 7.9 Hz, 1 H) 4.27 (s, 2 H), 2.60 (s, 3 H), 2.39 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 193.9, 156.3, 139.7, 137.1, 132.3, 129.7, 129.6, 127.9, 125.6, 124.3, 36.4, 26.7, 21.1 ppm. MS (EI): *m/z* (%) = 241 (25) $[M]^+$, 224 (100), 209 (45), 194 (7), 180 (21), 166 (23), 152 (5), 139 (5), 120 (5), 105 (7), 91 (8), 77 (9), 63 (7), 43 (45). $C_{15}H_{15}NO_2$ (241.29): calcd. C 74.67, H 6.27, N 5.81; found C 74.83, H 6.24, N 5.83.

**2-Methyl-6-(4-methylbenzyl) pyridine 1-Oxide (3j):** The general procedure was followed by using 2-methylpyridine *N*-oxide (1 mmol, 109 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), CuO (12 mg, 15 mol-%), *p*-Xylene (3 mmol, 0.37 mL), and acetonitrile (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **3j** (155 mg, 73 % yield) as a pale yellow oil. $^1$H NMR (400 MHz, CDCl3): $\delta$ = 7.21–7.12 (m, 5 H), 7.06 (t, *J* = 7.7 Hz, 1 H), 6.84 (d, *J* = 7.7 Hz, 1 H), 4.25 (s, 2 H), 2.58 (s, 3 H), 2.36 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 152.1, 148.9, 137.3, 135.2, 129.7, 129.5, 127.9, 123.9, 123.3, 43.6, 21.1, 18.4 ppm. MS (EI): *m/z* (%) = 213 (25) $[M]^+$, 196 (100), 181 (95), 163 (30), 120 (25), 105 (45), 91 (27), 77 (25), 65 (20), 51 (8), 43 (35). $C_{14}H_{15}NO$ (213.27): calcd. C 78.84, H 7.09, N 6.57; found C 78.18, H 7.11, N 6.54.

**2-(4-Methylbenzyl) quinoline 1-Oxide (3k):** The general procedure was followed by using quinoline *N*-oxide (1 mmol, 145 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), CuO (12 mg, 15 mol-%), *p*-Xylene (3 mmol, 0.37 mL), and acetonitrile (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **3k** (177 mg, 71 % yield) as a brown solid. M.p. 81–

84 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.83 (d, *J* = 8.1 Hz, 1 H), 7.59 (d, *J* = 7.8 Hz, 1 H), 7.53 (t, *J* = 7.9 Hz, 1 H), 7.43–7.31 (m, 3 H), 7.20 (d, *J* = 8.1 Hz, 2 H), 7.16 (d, *J* = 8.2 Hz, 2 H), 4.40 (s, 2 H), 2.36 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 141.1, 138.4, 138.3, 137.3, 135.2, 130.7, 129.4, 128.8, 128.7, 127.9, 122.7, 111.9, 116.1, 43.5, 23.3 ppm. MS (EI): *m/z* (%) = 249 (10) $[M]^+$, 219 (15), 163 (59), 149 (23), 120 (35), 106 (100), 91 (29), 77 (25), 65 (14), 51 (14), 43 (59). $C_{17}H_{15}NO$ (249.31): calcd. C 81.90, H 6.06, N 5.62; found C 81.65, H 6.04, N 5.63.

**2-(3-Methoxybenzyl) pyridine 1-Oxide (3l):** The general procedure was followed by using pyridine *N*-oxide (1 mmol, 95 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), CuO (12 mg, 15 mol-%), 3-methylanisol (3 mmol, 0.38 mL), and acetonitrile (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **3l** (161 mg, 75 % yield) as a brown oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.33 (d, *J* = 7.7 Hz, 1 H), 7.35–7.29 (m, 2 H), 7.18 (t, *J* = 5.2 Hz, 2 H), 6.98 (t, *J* = 5.6 Hz, 1 H), 6.90–6.88 (m, 1 H), 6.86 (s, 1 H), 4.27 (s, 2 H), 3.83 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 151.9,139.4, 137.8, 129.9, 125.8, 125.6, 123.6, 122.1, 115.5, 112.4, 55.2, 36.6 ppm. MS (EI): *m/z* (%) = 215 (28) $[M]^+$, 198 (100), 183 (63), 167 (15), 154 (28), 117 (9), 92 (9), 78 (21), 65 (10), 51 (13), 41 (7). $C_{13}H_{13}NO_2$ (215.25): calcd. C 72.54, H 6.09, N 6.51; found C 72.27, H 6.08, N 6.53.

**2-Benzyl-6-ethylpyridine 1-Oxide (3m):** The general procedure was followed by using 2-ethylpyridine *N*-oxide (1 mmol, 123 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), CuO (12 mg, 15 mol-%), toluene (3 mmol, 0.32 mL), and acetonitrile (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **3m** (183 mg, 86 % yield) as a pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.41–7.31 (m,4 H), $\delta$ = 7.18–7.10 (m,3 H), 6.83 (dd, *J* = 7.6,& *J* = 2.0 Hz, 1 H), 4.30 (s, 2 H), 3.02 (q, *J* = 7.5 Hz, 2 H), 1.35 (t, *J* = 7.5 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 153.6, 151.8, 136.8, 129.8, 128.8, 127.9, 126.9, 124.8, 123.1, 37.1, 24.1, 10.7 ppm. MS (EI): *m/z* (%) = 213 (30) $[M]^+$, 196 (100), 181 (42), 167 (21), 149 (15), 106 (25), 91 (21), 77 (20), 65 (15), 43 (16). $C_{14}H_{15}NO$ (213.27): calcd. C 78.84, H 7.09, N 6.57; found C 78.94, H 7.12, N 6.54.

**2-Ethyl-6-(4-methylbenzyl) pyridine 1-Oxide (3n):** The general procedure was followed by using 2-ethylpyridine *N*-oxide (1 mmol, 123 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), CuO (12 mg, 15 mol-%), *p*-Xylene (3 mmol, 0.37 mL), and acetonitrile (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **3n** (179 mg, 79 % yield) as a dark brown solid. M.p. 43–44 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.19 (d, *J* = 7.7 Hz, 2 H), 7.16–7.10 (m, 4 H), 6.83 (dd, *J* = 7.3, 2.4 Hz, 1 H), 4.23 (s, 2 H), 3.00 (q, *J* = 7.4 Hz, 2 H), 2.38 (s, 3 H), 1.34 (t, *J* = 7.5 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 153.6, 152.1, 136.5, 133.6, 129.5, 129.4, 127.9, 125.1, 123.0, 43.5, 23.3, 21.1, 10.7 ppm. MS (EI): *m/z* (%) = 228 (33) [M + 1$^+$], 227 (18) $[M]^+$, 210 (51), 195 (20), 180 (10), 163 (74), 148 (15), 120 (51), 106 (100), 91 (33), 77 (19), 65 (15), 43 (53). $C_{15}H_{17}NO$ (227.30): calcd. C 79.26, H 7.54, N 6.16; found C 79.09, H 7.56, N 6.18.

**2-Benzyl-3-methylpyridine 1-Oxide (3o):** The general procedure was followed by using 3-methylpyridine *N*-oxide (1 mmol, 109 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), CuO (12 mg, 15 mol-%), toluene (3 mmol, 0.32 mL), and acetonitrile (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **3o** (155 mg, 78 % yield) as a brown oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.22 (d, *J* = 7.2 Hz, 1 H), 7.33–7.20 (m, 5 H), 7.10 (d, *J* = 7.4 Hz, 2 H), 4.44 (s, 2 H), 2.36 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 150.3, 137.5, 136.7, 135.9, 129.6, 128.6, 128.3, 127.8, 126.6, 32.7, 19.3 ppm. MS (EI): *m/z* (%) = 199 (28) $[M]^+$, 182 (100), 167 (42), 152 (7), 106 (9), 91 (10), 77 (15), 65 (16), 51 (15), 41 (7). $C_{13}H_{13}NO$ (199.25): calcd. C 78.36, H 6.58, N 7.03; found C 78.53, H 6.55, N 7.01.

**2-Benzyl-3,5-dimethylpyridine 1-Oxide (3p):** The general procedure was followed by using 3,5-dimethylpyridine *N*-oxide (1 mmol, 123 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), CuO (12 mg, 15 mol-%), toluene (3 mmol, 0.32 mL), and acetonitrile (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **3p** (127 mg, 60 % yield) as a brown oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.04 (s, 1 H), 7.28–7.16 (m, 5 H), 6.92 (s, 1 H), 4.36 (s, 2 H), 2.27 (s, 3 H), 2.23 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 147.2, 137.3, 137.0, 135.2, 133.4, 129.7, 128.5, 128.2, 126.5, 32.3, 19.1, 17.9 ppm. MS (EI): *m/z* (%) = 213 (29) $[M]^+$, 196 (100), 181 (40), 162 (7), 152 (7), 120 (10), 106 (10), 91 (9), 77 (14), 59 (13), 51 (9), 43 (15). $C_{14}H_{15}NO$ (213.27): calcd. C 78.84, H 7.09, N 6.57; found C 78.71, H 7.07, N 6.60.

**2-Benzoylpyridine 1-Oxide (4a):**[31] The general procedure was followed by using pyridine *N*-oxide (0.5 mmol, 47 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), $Cu(OAc)_2$ (14 mg, 15 mol-%), toluene (1.5 mmol, 0.16 mL), and chlorobenzene (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **4a** (74 mg, 75 % yield) as a yellow solid. M.p. 85–87 °C. $^1$H NMR (500 MHz, CDCl3): $\delta$ = 8.31 (d, *J* = 5.26 Hz, 1 H), 7.89 (d, *J* = 7.26 Hz, 2 H), 7.87 (t, *J* = 7.36 Hz, 1 H), 7.65 (t, *J* = 7.64 Hz, 2 H), 7.52–7.45 (m, 3 H) ppm. $^{13}$C NMR (125 MHz, CDCl3): $\delta$ = 189.2, 147.2, 140.1, 134.3, 129.3, 128.9, 128.4, 127.0, 126.04, 125.8 ppm. HRMS (EI): *m/z* calcd. for $C_{12}H_9NO_2$ $[M]^+$ 199.0624; found 199.0633.

**2-(4-Methylbenzoyl) pyridine 1-Oxide (4b):**[31] The general procedure was followed by using pyridine *N*-oxide (0.5 mmol, 47 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), $Cu(OAc)_2$ (14 mg, 15 mol-%), *p*-Xylene (1.5 mmol, 0.18 mL), and chlorobenzene (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **4b** (83 mg, 78 % yield) as an off-white solid. M.p. 142–144 °C. $^1$H NMR (400 MHz, CDCl3): $\delta$ = 8.09 (br. s, 1 H), 7.79 (d, *J* = 6.3 Hz, 2 H), 7.63–7.46 (m, 3 H), 7.32 (d, *J* = 6.7 Hz, 2 H), 2.45 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, CDCl3): $\delta$ = 188.2, 155.1, 145.6, 140.1, 135.1, 132.4, 129.7, 129.6, 128.5, 122.1, 21.5 ppm. MS (EI): *m/z* (%) = 213 (17) $[M]^+$, 196 (11), 169 (46), 106 (92), 91 (40), 78 (100), 65 (31), 51 (31). $C_{13}H_{11}NO_2$ (213.23): calcd. C 73.23, H 5.20, N 6.57; found C 73.46, H 5.21, N 6.54.

**2-(2-Methoxybenzoyl) pyridine 1-Oxide (4c):** The general procedure was followed by using pyridine *N*-oxide (0.5 mmol, 47 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), $Cu(OAc)_2$ (14 mg, 15 mol-%), 2-methylanisole (1.5 mmol, 0.19 mL), and chlorobenzene (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **4c** (87 mg, 76 % yield) as a brown solid. M.p. 267–269 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.97 (d, *J* = 7.5 Hz, 1 H), 7.70–7.33 (m, 5 H), 7.12 (t, *J* = 7.5 Hz, 1 H), 6.94 (d, *J* = 8.3 Hz, 1 H), 3.67 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 186.2, 159.7, 151.1, 138.4, 135.9, 135.2, 130.8, 128.1, 127.5, 125.2, 121.4, 111.7, 56.4 ppm. MS (EI): *m/z* (%) = 229 (10) $[M]^+$, 198 (88), 170 (18), 135 (14), 106 (66), 78 (100), 51 (29). $C_{13}H_{11}NO_3$ (229.23): calcd. C 68.11, H 4.84, N 6.11; found C 68.27, H 4.83, N 6.13.

**2-(3-Methylbenzoyl)-4-nitropyridine 1-Oxide (4d):** The general procedure was followed by using 4-nitropyridine *N*-oxide (0.5 mmol, 70 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), $Cu(OAc)_2$ (14 mg, 15 mol-%), *m*-Xylene (1.5 mmol, 0.18 mL), and chlorobenzene (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **4d** (89 mg, 69 % yield) as an orange solid. M.p. 144–146 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.40 (d, *J* =

7.2 Hz, 1 H), 8.31 (d, *J* = 3.2 Hz, 1 H), 8.07 (dd, *J* = 7.2, 3.2 Hz, 1 H), 7.61 (s, 1 H), 7.46 (t, *J* = 7.6 Hz, 1 H), 7.43–7.33 (m, 2 H), 2.48 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 184.2, 150.6, 141.4, 138.5, 136.0, 131.6, 129.6, 128.6, 126.2, 121.7, 118.5, 29.7 ppm. MS (EI): *m/z* (%) = 258 (7) $[M]^+$, 241 (10), 230 (33), 214 (9), 201 (21), 181 (28), 154 (45), 139 (28), 123 (46), 105 (13), 91 (65), 77 (66), 57 (63), 43 (100). $C_{13}H_{10}N_2O_4$ (258.23): calcd. C 60.47, H 3.90, N 10.85; found C 60.63, H 3.92, N 10.88.

**2-Benzoyl-4-nitropyridine 1-Oxide (4e):**[31] The general procedure was followed by using 4-nitropyridine *N*-oxide (0.5 mmol, 70 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), $Cu(OAc)_2$ (14 mg, 15 mol-%), toluene (1.5 mmol, 0.16 mL), and chlorobenzene (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **4e** (79 mg, 65 % yield) as a white solid. M.p. 187–189 °C. $^1$H NMR (500 MHz, CDCl3): $\delta$ = 8.36 (d, *J* = 7.5 Hz, 1 H), 8.27 (d, *J* = 3.0 Hz, 1 H), 8.02 (dd, *J* = 7.0 & *J* = 3.0 Hz, 1 H), 7.79 (dd, *J* = 7.1 & *J* = 2.0 Hz, 2 H), 7.80–7.51 (m, 3 H) ppm. $^{13}$C NMR (125 MHz, CDCl3): $\delta$ = 185.8, 141.4, 133.6, 130.8, 130.6, 129.1, 128.9, 128.7, 121.6, 118.5 ppm. MS (EI): *m/z* (%) = 244 (15) $[M]^+$, 215 (7), 168 (8), 139 (8), 122 (18), 115 (22), 105 (44), 77 (96), 69 (8), 63 (22), 57 (23), 51 (100), 45 (44). $C_{12}H_8N_2O_4$ (244.20): calcd. C 59.02, H 3.30, N 11.47; found C 59.26, H 3.32, N 11.43.

**4-Acetyl-2-(4-methylbenzoyl) pyridine 1-Oxide (4f):**[31] The general procedure was followed by using 4-acetylpyridine *N*-oxide (0.5 mmol, 68 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), $Cu(OAc)_2$ (14 mg, 15 mol-%), *p*-Xylene (1.5 mmol, 0.18 mL), and chlorobenzene (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **4f** (100 mg, 79 % yield) as a light brown solid. M.p. 125–127 °C. $^1$H NMR (400 MHz, CDCl3): $\delta$ = 8.24 (d, *J* = 7.2 Hz, 1 H), 7.92 (d, *J* = 7.1 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz,2 H), 7.24 (d, *J* = 8.2 Hz,2 H), 7.18 (s, 1 H), 2.66 (s, 3 H), 2.4 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, CDCl3): $\delta$ = 193.2, 189.8, 163.0, 139.5, 129.9, 129.5, 128.8, 128.7, 127.9, 126.5, 126.4, 29.7, 21.3 ppm. MS (EI): *m/z* (%) = 257 (9) $[M + 2]^+$, 256 (7) $[M + 1]^+$, 255 (9) $[M]^+$, 243 (39), 208 (3), 149 (36), 105 (100), 77 (18), 43 (22). $C_{15}H_{13}NO_3$ (255.27): calcd. C 70.58, H 5.13, N 5.49; found C 70.39, H 5.11, N 5.51.

**4-Acetyl-2-(3-methylbenzoyl)pyridine 1-Oxide (4g):** The general procedure was followed by using 4-acetylpyridine *N*-oxide (0.5 mmol, 68 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), $Cu(OAc)_2$ (14 mg, 15 mol-%), *m*-Xylene (1.5 mmol, 0.18 mL), and chlorobenzene (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **4g** (90 mg, 71 % yield) as a pale yellow solid. M.p. 121–123 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.32 (d, *J* = 7.2 Hz, 1 H), 7.95 (d, *J* = 7.2 Hz, 1 H), 7.88 (s, 1 H), 7.56 (d, *J* = 7.9 Hz, 1 H), 7.49 (d, *J* = 8.2 Hz, 1 H), 7.44 (s, 1 H), 7.37 (t, *J* = 7.8 Hz, 1 H), 2.52 (s, 3 H), 2.44 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 190.2, 185.6, 147.1, 139.6, 138.9, 135.5, 133.8, 132.2, 129.3, 129.1, 126.1, 125.3, 119.5, 29.72, 21.35 ppm. MS (EI): *m/z* (%) = 256 (9) $[M + 1]^+$, 255 (7) $[M]^+$, 241 (33), 224 (100), 209 (32), 194 (15), 180 (33), 167 (16), 149 (16), 115 (33), 105 (16), 91 (33), 71 (32), 57 (45), 43 (78). $C_{15}H_{13}NO_3$ (255.27): calcd. C 70.58, H 5.13, N 5.49; found C 70.76, H 5.14, N 5.48.

**4-Acetyl-2-benzoylpyridine 1-Oxide (4h):**[31] The general procedure was followed by using 4-acetylpyridine *N*-oxide (0.5 mmol, 68 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), $Cu(OAc)_2$ (14 mg, 15 mol-%), toluene (1.5 mmol, 0.16 mL), and chlorobenzene (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **4h** (80 mg, 67 % yield) as a light brown solid. M.p. 120–122 °C; $^1$H NMR (400 MHz, CDCl3): $\delta$ = 8.33 (d, *J* = 7.9 Hz, 1 H), 7.95 (d, *J* = 7.8 Hz, 2 H), 7.91 (s, 1 H), 7.69 (dd, *J* = 8.0 & *J* = 2.2 Hz, 1 H), 7.50–7.45 (m, 3 H), 2.65 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, CDCl3): $\delta$ = 194.0, 186.2, 146.8, 143.8, 139.7, 134.4, 131.3, 129.2, 128.7, 125.3, 119.7, 29.4 ppm. MS (EI): *m/z* (%) = 242 (14) $[M + 1]^+$, 241 (3) $[M]^+$, 224 (100), 180 (8), 141 (9), 122 (49), 103 (44), 77 (70), 51 (40). $C_{14}H_{11}NO_3$ (241.24): calcd. C 69.70, H 4.60, N 5.81; found C 69.48, H 4.62, N 5.83.

**5-Acetyl-2-benzoylpyridine 1-Oxide (4i):**[31] The general procedure was followed by using 3-acetylpyridine *N*-oxide (0.5 mmol, 68 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), $Cu(OAc)_2$ (14 mg, 15 mol-%), toluene (1.5 mmol, 0.16 mL), and chlorobenzene (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **4i** (82 mg, 68 % yield) as a pale yellow solid. M.p. 95–97 °C. $^1$H NMR (400 MHz, CDCl3): $\delta$ = 8.80 (s, 1 H), 8.38 (d, *J* = 7.9 Hz, 1 H), 7.89 (t, *J* = 7.4 Hz, 1 H), 7.68 (dd, *J* = 8.0 & *J* = 2.4 Hz, 1 H), 7.48 (d, *J* = 7.4 Hz, 2 H), 7.37 (t, *J* = 7.3 Hz, 2 H), 2.62 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, CDCl3): $\delta$ = 191.0, 186.0, 163.2, 147.9, 134.1, 131.5, 129.2, 128.8, 128.5, 127.1, 125.9, 29.7 ppm. MS (EI): *m/z* (%) = 242 (26) $[M + 1]^+$, 241 (6) $[M]^+$, 225 (100), 180 (18), 153 (77), 131 (65), 103 (65), 77 (55), 51 (29). $C_{14}H_{11}NO_3$ (241.24): calcd. C 69.70, H 4.60, N 5.81; found C 69.94, H 4.63, N 5.84.

**2-Cyano-6-(4-methylbenzoyl) pyridine 1-Oxide (4j):**[31] The general procedure was followed by using 2-cyanopyridine *N*-oxide (0.5 mmol, 60 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), $Cu(OAc)_2$ (14 mg, 15 mol-%), *p*-Xylene (1.5 mmol, 0.18 mL), and chlorobenzene (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **4j** (82 mg, 69 % yield) as an off-white solid. M.p. 98–100 °C. $^1$H NMR (500 MHz, CDCl3): $\delta$ = 8.47 (dd, *J* = 7.8 &, *J* = 1.9 Hz, 1 H), 8.26 (d, *J* = 7.4 Hz, 1 H), 7.46 (t, *J* = 7.7 Hz, 1 H), 7.27 (d, *J* = 7.2 Hz, 2 H), 7.1 5 (d, *J* = 7.6 Hz, 2 H), 2.33 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, CDCl3): $\delta$ = 188.2, 159.8, 140.6, 137.1, 134.8, 129.4, 129.0, 127.7, 127.3, 127.2, 116.0, 21.1 ppm. MS (EI): *m/z* (%) = 239 (27) $[M + 1]^+$, 238 (6) $[M]^+$, 225 (91), 167 (7), 149 (10), 135 (20), 119 (18), 106 (74), 91 (27), 78 (100), 65 (11), 57 (14), 43 (14). $C_{14}H_{10}N_2O_2$ (238.24): calcd. C 70.58, H 4.23, N 11.76; found C 70.77, H 4.21, N 11.81.

**2-Benzoyl-6-cyanopyridine 1-Oxide (4k):**[31] The general procedure was followed by using 2-cyanopyridine *N*-oxide (0.5 mmol, 60 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), $Cu(OAc)_2$ (14 mg, 15 mol-%), toluene (1.5 mmol, 0.16 mL), and chlorobenzene (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **4k** (75 mg, 67 % yield) as a white solid. M.p. 100–102 °C. $^1$H NMR (500 MHz, CDCl3): $\delta$ = 7.79 (d, *J* = 7.0 Hz, 2 H), 7.96–7.59 (m, 1 H), 7.50–7.35 (m, 2 H), 7.46–7.42 (m, 3 H) ppm. $^{13}$C NMR (125 MHz, CDCl3): $\delta$ = 188.7, 156.7, 133.5, 132.1, 130.6, 130.1, 128.9, 128.7, 128.4, 127.4; 114.7 ppm. MS (EI): *m/z* (%) = 226 (15) $[M + 2]^+$, 211 (14), 196 (25), 183 (37), 121 (51), 105 (80), 77 (100), 51 (74). $C_{13}H_8N_2O_2$ (224.22): calcd. C 69.64, H 3.60, N 12.49; found C 69.39, H 3.58, N 12.46.

**2-Cyano-6-(3-methylbenzoyl) pyridine 1-Oxide (4l):** The general procedure was followed by using 2-cyanopyridine *N*-oxide (0.5 mmol, 60 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), $Cu(OAc)_2$ (14 mg, 15 mol-%), *m*-Xylene (1.5 mmol, 0.18 mL), and chlorobenzene (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **4l** (78 mg, 66 % yield) as a light brown solid. M.p. 74–76 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.61 (d, *J* = 7.3 Hz, 1 H), 8.23 (d, *J* = 7.9 Hz, 1 H), 7.89 (td, *J* = 7.7, 1.6 Hz, 1 H), 7.75–7.51 (m, 2 H), 7.51–7.42 (m, 1 H), 7.29 (s, 1 H), 2.42 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 189.6, 169.9, 148.4, 138.5, 137.3, 133.4, 132.7, 128.5, 128.1, 126.5, 124.3, 122.5, 21.4 ppm. MS (EI): *m/z* (%) = 238 (6) $[M]^+$, 135 (70), 119 (100), 106 (10), 91 (90), 79 (48), 65 (33), 44 (30). $C_{14}H_{10}N_2O_2$ (238.24): calcd. C 70.58, H 4.23, N 11.67; found C 70.44, H 4.25, N 11.70.

**2-Cyano-6-(4-nitrobenzoyl) pyridine 1-Oxide (4m):**[31] The general procedure was followed by using 2-cyanopyridine *N*-oxide

(0.5 mmol, 60 mg), $K_2S_2O_8$ (1.25 mmol, 338 mg), $Cu(OAc)_2$ (14 mg, 15 mol-%), 4–nitrotoluene (1.5 mmol, 0.19 mL), and chlorobenzene (2 mL). Purification by column chromatography (silica gel, *n*-hexane/EtOAc/methanol, 1:1:0.1) gave final product **4m** (75 mg, 56 % yield) as a brown solid. M.p. 110–112 °C. $^1$H NMR (500 MHz, CDCl3): $\delta$ = 8.46 (d, $J$ = 7.6 Hz, 1 H), 8.24 (d, $J$ = 7.2 Hz, 1 H), 7.44 (t, $J$ = 7.1 Hz, 1 H), 7.31 (d, $J$ = 7.1 Hz, 2 H), 6.87 (d, $J$ = 6.9 Hz, 2 H) ppm. $^{13}$C NMR (100 MHz, CDCl3): $\delta$ = 190.1, 166.8, 162.6, 149.5, 148.3, 137.3, 129.3, 126.52, 122.5, 114.5, 113.8 ppm. MS (EI): *m/z* (%) = 271 (22) $[M + 2]^+$, 269 (5) $[M]^+$, 256 (5), 241 (11), 151 (74), 135 (100), 121 (35), 107 (18), 92 (25), 77 (35), 69 (11), 57 (14), 43 (14). $C_{13}H_7N_3O_4$ (269.21): calcd. C 58.00, H 2.62, N 15.61; found C 58.13, H 2.61, N 15.65.

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