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C–H Activation

Palladium-Catalysed Chemo- and Regioselective C–H Bond Acylation of Pyridine *N*-Oxides with Benzyl Halides and Alcohols

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Abstract: A palladium-catalysed method for the acylation of *ortho* C–H bonds of pyridine *N*-oxides using readily available benzyl halides and benzyl alcohols as the active acylating agents is described. This procedure provides a new approach to 2-acylpyridine *N*-oxides, which may be used as precursors for the synthesis of pharmaceuticals and agrochemicals.

Introduction

Pyridine *N*-oxides have found applications in a large number of areas. They have been used to control the chirality in asymmetric synthesis,[1] and they have also been found to act as inhibitors of human severe acute respiratory syndrome (SARS), human immunodeficiency virus (HIV), and feline infectious peritonitis corona virus.[2] 2-Acylpyridine *N*-oxides are used as prochiral ketones in the asymmetric Henry reaction[3] to give tertiary nitro aldols,[4] which are building blocks for the synthesis of pharmaceuticals and agrochemicals[5] (Figure 1, compound **A**). They show excellent chelating properties in several asymmetric metal-catalysed reactions,[6] and they have also been used as precursors for the synthesis of norbormide (NRB; Figure 1, compound **B**), which acts as a rat-selective toxicant,[7] vasoconstrictor, and calcium-channel blocker.[8]

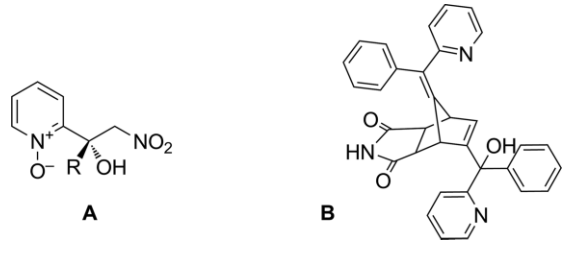
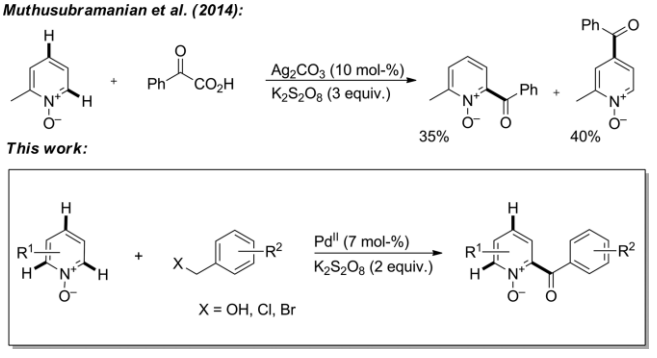


Figure 1. Examples of applications of 2-acylpyridine.

The direct functionalization of pyridine *N*-oxides has been investigated, and it has been found to take place with complete selectivity for the 2-position.[9] In 2005, the palladium-catalysed arylation of pyridine *N*-oxides was reported by Fagnou.[10] Subsequently, coupling reactions of pyridine *N*-oxides with aryl halides,[11] triflates,[12] and alkyl bromides[13] were developed using various transition-metal catalysts and reaction conditions. Oxidative cross-coupling reactions of pyridine *N*-oxides with indoles,[14] thiophenes, furans,[15] and toluene derivatives[16] have also been reported.

The acylation of pyridine *N*-oxide derivatives has rarely been reported. In 2014, the acylation of pyridine *N*-oxides using α-oxo carboxylic acids in the presence of a silver catalyst through a decarboxylative process was described.[17] The reaction is not regioselective, and acylation takes place at both the C-2 and C-4 positions (Scheme 1). With this in mind, and in a continuation of our interest in this area,[18] we report the palladium-catalysed regioselective C–H bond acylation of pyridine *N*-oxides using benzyl halides and alcohols as the acylating agents (Scheme 1).



Scheme 1. Literature precedent for the acylation of pyridine *N*-oxides.

Results and Discussion

Our initial investigation began with the coupling of pyridine *N*-oxide (**1a**) with benzyl alcohol (**2a**) or benzyl chloride (**2b**) as model reactions. Various conditions were screened to optimize the reaction conditions (Table 1). A screening of catalysts revealed that $PdCl_2$ gave the best result when benzyl alcohol was

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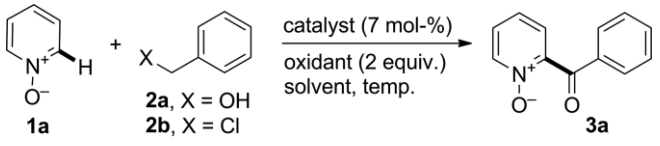
used as the acylating agent; $PdCl_2(COD)$ (COD = 1,5-cyclooctadiene) gave the best result when benzyl chloride was used (Table 1, Entries 1 and 2). Copper-based catalysts such as $CuBr_2$ and $Cu(OAc)_2$ were found to be inferior (Table 1, Entries 4–6). The reaction was also tested with different catalyst loadings, and the results showed that 7 mol-% of the Pd catalyst was the best choice for completing the reaction (Table 1, Entries 1, 2, and 7). Commonly used organic solvents were screened. Chlorobenzene gave the best yields for both acylating agents **2a** and **2b**; solvents such as DMF, DMSO, and DCE (1,2-dichloroethane) gave moderate yields of the product, and CH_3CN gave poor results (Table 1, Entries 8–11). No reaction took place when H_2O or AcOH were used as the solvent (Table 1, Entries 12 and 13). The effectiveness of various oxidants was also examined. $K_2S_2O_8$ was found to be more effective than other oxidants such as $(NH_4)_2S_2O_8$, TBHP (*tert*-butyl hydroperoxide), and DTBP (di-*tert*-butyl peroxide) (Table 1, Entries 14–16). The reaction temperature was also varied, and we found that the best results were obtained at 130 °C (Table 1, Entries 1, 2, and 17). No reaction occurred in the absence of catalyst or in the absence of oxidant (Table 1, Entries 18 and 19).

Once the optimized conditions for the desired acylation reaction were established, the scope of the reaction with regard to different benzyl alcohols and halides as the acylating agents was investigated. We found that a variety of benzyl alcohols and halides with both electron-donating and electron-withdrawing substituents on the aromatic ring were tolerated, and moderate to good yields were obtained in most cases.

The presence of alkyl groups at the *para* position of the benzyl alcohols and halides resulted in better yields of the desired products (Table 2; **3b** and **3g**). Benzyl alcohols and halides bearing electron-withdrawing groups such as CF_3 or NO_2 gave the acylated products in poor to moderate yields. (Table 2; **3i**, **3j**, and **3q**). Pyridine *N*-oxides bearing electron-withdrawing groups such as nitro or methyl ketone groups reacted smoothly to give the corresponding 2-acylpyridine *N*-oxides in good yields. Halogen groups on either the pyridine *N*-oxide or the acylating agent – the benzyl alcohol or halide – remained intact during the reactions; thus, they could be further transformed to give other important structures.

On the basis of the above results and previous reports, a plausible catalytic mechanism is shown in Scheme 2. Metallation of the pyridine *N*-oxide derivative with Pd^{II} generates intermediate **A**. The benzyl alcohol or halide is oxidized with $K_2S_2O_8$ to give the corresponding aldehyde.[19] Radical intermediate **B** is generated in situ through hydrogen atom abstraction from the aldehyde in the presence of a sulfate radical anion, which is produced from $K_2S_2O_8$ under the reaction conditions (Scheme 2). Pd^{II} intermediate **A** reacts with acyl radical **B** to give Pd^{IV} intermediate **C**. This then undergoes reductive elimination to produce the desired product and regenerate the Pd^{II} species.[20] To prove the role of $K_2S_2O_8$ as a radical agent, a control reaction was carried out using 2,6-di-*tert*-butyl-4-methylphenol (butylated hydroxytoluene, BHT) as a radical scavenger. When the reaction of **1a** was carried out in the presence of BHT, none of the desired product **3a** was observed.

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



Entry	Catalyst	Oxidant	Solvent	Temp. [°C]	Yield[b] with **2a** [%]	Yield[b] with **2b** [%]
1	$PdCl_2(COD)$	$K_2S_2O_8$	PhCl	130	63	65
2	$PdCl_2$	$K_2S_2O_8$	PhCl	130	72	57
3	$Pd(OAc)_2$	$K_2S_2O_8$	PhCl	130	18	21
4	CuCl	$K_2S_2O_8$	PhCl	130	11	trace
5	$Cu(OAc)_2$	$K_2S_2O_8$	PhCl	130	69	28
6	$CuBr_2$	$K_2S_2O_8$	PhCl	130	32	24
7	Pd^{II}[c,d]	$K_2S_2O_8$	PhCl	130	70	62
8	Pd^{II}[c]	$K_2S_2O_8$	DCE	130	10	55
9	Pd^{II}[c]	$K_2S_2O_8$	DMF	130	23	19
10	Pd^{II}[c]	$K_2S_2O_8$	DMSO	130	31	28
11	Pd^{II}[c]	$K_2S_2O_8$	CH_3CN	130	2	9
12	Pd^{II}[c]	$K_2S_2O_8$	H_2O	130	0	0
13	Pd^{II}[c]	$K_2S_2O_8$	AcOH	130	0	0
14	Pd^{II}[c]	$(NH_4)S_2O_8$	PhCl	130	30	0
15	Pd^{II}[c]	TBHP	PhCl	130	0	0
16	Pd^{II}[c]	DTBP	PhCl	130	0	0
17	Pd^{II}[c]	$K_2S_2O_8$	PhCl	100	51	13
18	–	$K_2S_2O_8$	PhCl	130	0	0
19	Pd^{II}[c]	–	PhCl	130	0	0

[a] **1a** (0.5 mmol), **2a** (1.5 mmol), and solvent (2.0 mL) were stirred at 130 °C for 20 h. [b] Isolated yields of **3a**. [c] $PdCl_2$ was used with **2a**, and $PdCl_2(COD)$ was used with **2b**. [d] 10 mol-% of catalyst was used.

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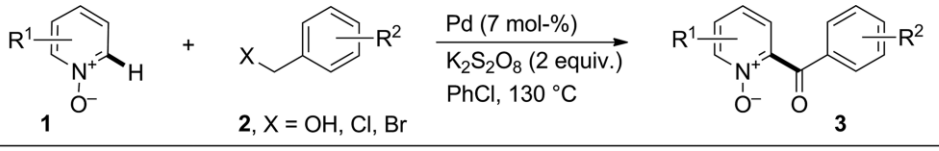
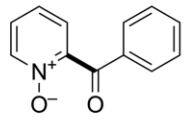
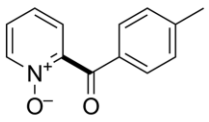
Table 2. Substrate scope.[a]

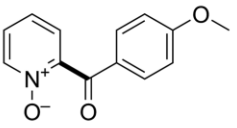




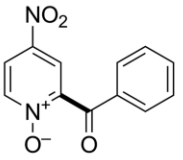
3a, X = OH, 72%
X = Cl, 65%



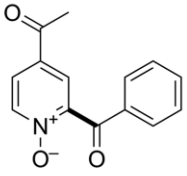
3b, X = OH, 78%
X = Cl, 71%



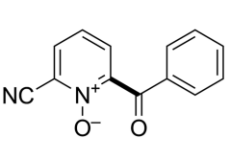
3c, X = OH, 76%
X = Cl, 70%



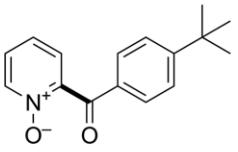
3d, X = OH, 65%
X =Cl, 61%



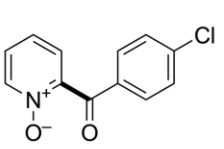
3e, X = OH, 81%
X = Cl, 79%



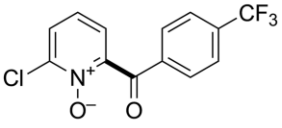
3f, X = OH, 68%
X =Cl, 61%



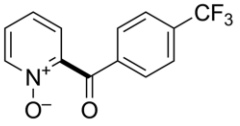
3g, X = OH, 85%



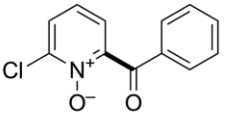
3h, X = OH, 66%
X = Cl, 59%
X =Br, 62%



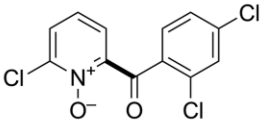
3i, X = OH, 45%



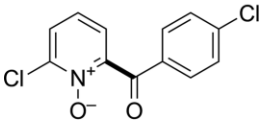
3j, X = OH, 38%



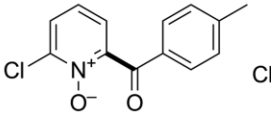
3k, X = OH, 68%
X = Cl, 66%



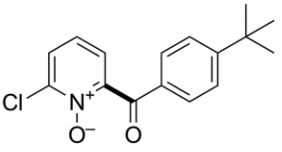
3l, X = OH, 53%



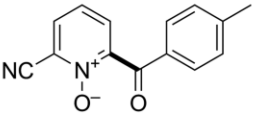
3m, X = OH, 60%
X = Cl, 57%
X = Br, 59%



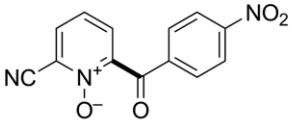
3n, X = OH, 71%
X = Cl, 70%



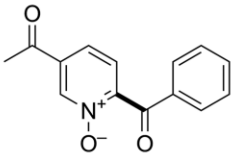
3o, X = OH, 73%



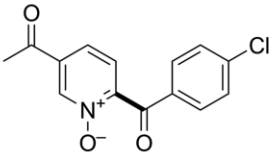
3p, X = OH, 68%
X = Cl, 63%



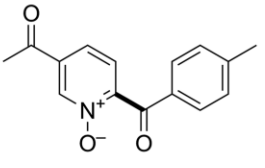
3q, X = OH, 48%
X = Cl, 43%



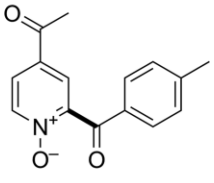
3r, X = OH, 88%
X = Cl, 81%



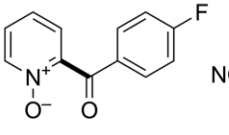
3s, X = OH, 77%
X = Cl, 73%
X = Br, 74%



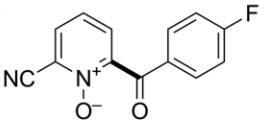
3t, X = OH, 80%
X = Cl, 77%



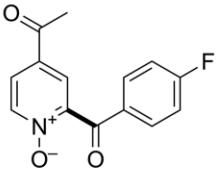
3u, X = OH, 83%
X = Cl, 80%



3v, X = Cl, 52%
X = Br, 55%



3w, X = Cl, 32%
X = Br, 35%



3x, X = Cl, 46%
X = Br, 48%

[a] **1a** (0.5 mmol), **2a** (1.5 mmol), Pd catalyst (7 mol-%), $K_2S_2O_8$ (2.0 equiv.), chlorobenzene (2.0 mL), 130 °C, 20 h.

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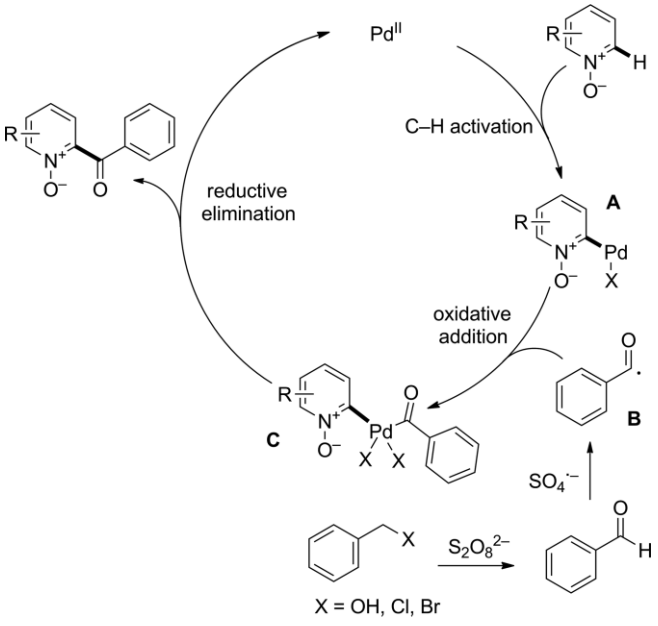

Scheme 2. Plausible mechanism.

Conclusions

We have explored an efficient method for the *ortho* C–H bond acylation of pyridine *N*-oxides with benzyl alcohols and halides as aroyl surrogates. The reaction is applicable to numerous substrates with good tolerance of various functional groups, and it provides a straightforward route to 2-acylpyridine *N*-oxides from accessible starting materials. The reaction products are interesting compounds for research into pharmaceuticals and agrochemicals.

Experimental Section

General Remarks: Solvents, benzyl alcohols, benzyl halides, and pyridine derivatives were purchased from Merck and Sigma. Other reagents were purchased from commercial distributors and were used without further purification. Pyridine *N*-oxide derivatives and palladium catalysts were synthesized according to literature procedures. Analytical thin-layer chromatography (TLC) was carried out on precoated silica gel 60 F_{254} plates. 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 Bruker DRX 600, 500, and 400 Avance instruments in $CDCl_3$; chemical shifts are reported on the δ scale in ppm; coupling constants (J) are reported in Hz. Mass spectrometry was carried out with an Agilent 5975C VL MSD instrument (ion source: EI$^+$, 70 eV, 230 °C). High-resolution mass spectra were recorded with a Kratos Concept IIH mass spectrometer.

General Procedure for the Synthesis of 2-Acylated Pyridine *N*-Oxides Using Benzyl Alcohols and Halides as Acylating Agents: A microwave vial (10 mL) was loaded with pyridine *N*-oxide derivative (1 equiv., 0.5 mmol), acylating agent [procedure A: benzyl alcohol (3 equiv., 1.5 mmol); procedure B: benzyl chloride (3 equiv., 1.5 mmol); procedure C: benzyl bromide (3 equiv., 1.5 mmol)], $K_2S_2O_8$ (2 equiv., 1 mmol), Pd catalyst (7 mol-%), and chlorobenzene (2 mL). The vial was then sealed and immersed in an oil bath, which was preheated at 130 °C, for 20 h. After this time, the reaction mixture was cooled to room temperature. The mixture was diluted with methanol and filtered, and the solvent was removed in vacuo. The resulting residue was purified by column chromatography (*n*-hexane/EtOAc/methanol, 1:1:0.1) to give the desired product.

2-Benzoylpyridine 1-Oxide (3a):[3] General procedure A was applied, using pyridine *N*-oxide (0.5 mmol, 47 mg), benzyl alcohol (1.5 mmol, 0.15 mL), $PdCl_2$ (6 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure B was applied, using pyridine *N*-oxide (0.5 mmol, 47 mg), benzyl chloride (1.5 mmol, 0.17 mL), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3a** (procedure A: 71 mg, 72 %; procedure B: 64 mg, 65 %) as a yellow solid. M.p. 85–87 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 189.2, 147.2, 140.1, 134.3, 129.3, 128.9, 128.4, 127.0, 126.04, 125.8 ppm. HRMS (EI): calcd. for $C_{12}H_9NO_2$ [M]$^+$ 199.0624; found 199.0633.

2-(4-Methylbenzoyl)pyridine 1-Oxide (3b): General procedure A was applied, using pyridine *N*-oxide (0.5 mmol, 47 mg), 4-methylbenzyl alcohol (2 mmol, 183 mg), $PdCl_2$ (6 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure B was applied, using pyridine *N*-oxide (0.5 mmol, 47 mg), 4-methylbenzyl chloride (1.5 mmol, 0.20 mL), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3b** (procedure A: 83 mg, 78 %; procedure B: 75 mg, 71 %) as an off-white solid. M.p. 142–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 73.43, H 5.24, N 6.54.

2-(4-Methoxybenzoyl)pyridine 1-Oxide (3c):[3] General procedure A was applied, using pyridine *N*-oxide (0.5 mmol, 47 mg), 4-methoxybenzyl alcohol (1.5 mmol, 200 mg), $PdCl_2$ (6 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure B was applied, using pyridine *N*-oxide (0.5 mmol, 47 mg), 4-methoxybenzyl chloride (1.5 mmol, 0.20 mL), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3c** (procedure A: 86 mg, 76 %; procedure B: 79 mg, 70 %) as an off-white solid. M.p. 256–258 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (br. s, 1 H), 7. 85 (d, J = 8.8 Hz, 2 H), 7.50–7.36 (m, 3 H), 6.98 (d, J = 8.8 Hz, 2 H), 3.91 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.2, 164.7, 140.1, 134.4, 132.1, 128.0, 126.9, 126.8, 125.7, 114.4, 55.8 ppm. MS (EI): m/z (%) = 229 (22) [M]$^+$, 212 (11), 185 (17), 135 (12), 126 (17), 106 (50), 92 (19), 78 (100), 69 (12), 63 (20), 51 (25), 43 (30). $C_{13}H_{11}NO_3$ (229.23): calcd. C 68.11, H 4.84, N 6.11; found C 68.35, H 4.81, N 6.14.

2-Benzoyl-4-nitropyridine 1-Oxide (3d): General procedure A was applied, using 4-nitropyridine *N*-oxide (0.5 mmol, 70 mg), benzyl alcohol (1.5 mmol, 0.15 mL), $PdCl_2$ (6 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure B was applied, using 4-nitropyridine *N*-oxide (0.5 mmol, 70 mg), benzyl chloride (1.5 mmol, 0.17 mL), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3d** (procedure A: 79 mg, 65 %; proce-

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dure B: 74 mg, 61 %) as a white solid. M.p. 187–19 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 59.17, H 3.32, N 11.51.

4-Acetyl-2-benzoylpyridine 1-Oxide (3e): General procedure A was applied, using 4-acetylpyridine *N*-oxide (0.5 mmol, 68 mg), benzyl alcohol (1.5 mmol, 0.15 mL), $PdCl_2$ (6 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure B was applied, using 4-acetylpyridine *N*-oxide (0.5 mmol, 68 mg), benzyl chloride (1.5 mmol, 0.17 mL), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3e** (procedure A: 97 mg, 81 %; procedure B: 95 mg, 79 %) as a pale brown solid. M.p. 120–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 69.56, H 4.65, N 5.85.

2-Benzoyl-6-cyanopyridine 1-Oxide (3f): General procedure A was applied, using 2-cyanopyridine *N*-oxide (0.5 mmol, 60 mg), benzyl alcohol (1.5 mmol, 0.15 mL), $PdCl_2$ (6 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure B was applied, using 2-cyanopyridine *N*-oxide (0.5 mmol, 60 mg), benzyl chloride (1.5 mmol, 0.17 mL), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3f** (procedure A: 76 mg, 68 %; procedure B: 68 mg, 61 %) as a white solid. M.p. 100–102 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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). $C_{13}H_8N_2O_2$ (224.21): calcd. C 69.64, H 3.60, N 12.49; found C 69.87, H 3.63, N 72.45.

2-[4-(*tert*-Butyl)benzoyl]pyridine 1-Oxide (3 g): General procedure A was applied, using pyridine *N*-oxide (0.5 mmol, 47 mg), 4-*tert*-Butylbenzyl alcohol (1.5 mmol, 0.26 mL), $PdCl_2$ (6 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3g** (108 mg, 85 %) as a pale yellow solid. M.p. 130–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, J = 4.9 Hz, 1 H), 7.81 (d, J = 8.6 Hz, 2 H), 7.52 (d, J = 8.6 Hz, 2 H), 7.46–7.42 (m, 3 H), 1.35 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.7, 158.1, 147.6, 140.0, 132.4, 129.4, 126.9, 125.9, 125.7 125.6, 34.6, 30.7 ppm. MS (EI): m/z (%) = 255 (17) $[M]^+$, 240 (45), 224 (11), 211 (17), 196 (31), 182 (17), 163 (26), 106 (77), 78 (100), 51 (14), 41 (11). $C_{16}H_{17}NO_2$ (255.31): calcd. C 75.27, H 6.71, N 5.49; found C 75.07, H 6.66, N 5.44.

2-(4-Chlorobenzoyl)pyridine 1-Oxide (3h):[3] General procedure A was applied, using pyridine *N*-oxide (0.5 mmol, 47 mg), 4-chlorobenzyl alcohol (1.5 mmol, 214 mg), $PdCl_2$ (6 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure B was applied, using pyridine *N*-oxide (0.5 mmol, 47 mg), 4-chlorobenzyl chloride (1.5 mmol, 240 mg), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure C was applied, using pyridine *N*-oxide (0.5 mmol, 47 mg), 4-chlorobenzyl bromide (1.5 mmol, 308 mg), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3h** (procedure A: 77 mg, 66 %; procedure B: 68 mg, 59 %; procedure C: 72 mg, 62 %) as a white solid. M.p. 117–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, J = 6.8 Hz, 1 H), 7.81 (d, J = 8.7 Hz, 2 H), 7.49–7.46 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.0, 140.6, 140.1, 133.5, 130.9, 130.6, 129.3, 127.3, 126.0, 125.9, 255 ppm. MS (EI): m/z (%) = 235 $[M + 2]^+$, 233 (16) $[M]^+$, 216 (17), 167 (25), 149 (44), 139 (11), 113 (17), 106 (74), 78 (100), 71 (18), 57 (29), 43 (22). $C_{12}H_8ClNO_2$ (233.65): calcd. C 61.69, H 3.45, N 5.99; found C 61.88, H 3.48, N 6.03.

2-Chloro-6-[4-(trifluoromethyl)benzoyl]pyridine 1-Oxide (3i): General procedure A was applied, using 2-chloropyridine *N*-oxide (0.5 mmol, 64 mg), 4-(trifluoromethyl) benzyl alcohol (1.5 mmol, 0.20 mL), $PdCl_2$ (6 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3i** (67 mg, 45 %) as a black solid. M.p. 78–80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, J = 8.1 Hz, 2 H), 7.43 (d, J = 8.0 Hz, 2 H), 7.41–7.35 (m, 1 H), 6.66 (d, J = 7.2 Hz, 1 H), 6.23 (td, J = 6.7, J = 1.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.3, 162.5, 144.5, 140.1, 139.7, 137.1, 132.4, 129.1, 127.8, 126.8, 125.90, 125.87, 125.83, 125.80, 123.3, 121.6, 106.5 ppm. MS (EI): m/z (%) = 302 (13) $[M + 1]^+$, 301 (7) $[M]^+$, 252 (49), 253 (51), 254 (14), 234 (7), 189 (3), 159 (100), 140 (7), 109 (37), 79 (25), 43 (7). $C_{13}H_7ClF3NO_2$ (301.65): calcd. C 51.76, H 2.34, N 4.64; found C 51.52, H 2.36, N 4.68.

2-[4-(Trifluoromethyl)benzoyl]pyridine 1-Oxide (3j): General procedure A was applied, using pyridine *N*-oxide (0.5 mmol, 47 mg), 4-(trifluoromethyl)benzyl alcohol (1.5 mmol, 0.20 mL), $PdCl_2$ (6 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3j** (45 mg, 38 %) as an off-white solid. M.p. 111–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, J = 6.1 Hz, 1 H), 8.22 (d, J = 8.2 Hz, 2 H), 7.98 (d, J = 8.1 Hz, 2 H), 7.80–7.73 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.2, 152.3, 137.9, 135.7, 134.88, 133.6, 131.1, 130.8, 130.5, 130.1, 128.8, 125.59, 125.55, 125.52, 125.48, 125.35, 124.79 ppm. MS (EI): m/z (%) = 267 (13) $[M]^+$, 238 (35), 223 (14), 190 (100), 173 (88), 145 (47), 125 (14), 95 (14), 75 (15), 50 (14). $C_{13}H_8F_3NO_2$ (267.20): calcd. C 58.43, H 3.02, N 5.24; found C 58.22, H 3.05, N 5.21.

2-Benzoyl-6-chloropyridine 1-Oxide (3k): General procedure A was applied, using 2-chloropyridine *N*-oxide (0.5 mmol, 64 mg), benzyl alcohol (1.5 mmol, 0.15 mL), $PdCl_2$ (6 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure B was applied, using 2-chloropyridine *N*-oxide (0.5 mmol, 64 mg), benzyl chloride (2 mmol, 0.17 mL), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3k** (procedure A: 79 mg, 68 %; procedure B: 76 mg, 66 %) as a black solid. M.p. 55–57 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.29 (m, 6 H), 6.63 (d, J = 7.4 Hz, 1 H), 6.14 (td, J = 6.9, J = 1.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.1, 162.8, 139.3, 137.3, 136.4, 128.7, 128.1, 128.0, 120.9, 107.0 ppm. MS (EI): m/z (%) = 235 (6) $[M + 2]^+$, 233 (18) $[M]^+$, 218 (10), 184 (80), 185 (85), 186 (20), 156 (3), 128 (3), 91 (100), 65 (22), 41 (3). $C_{12}H_8ClNO_2$ (233.65): calcd. C 61.69, H 3.45, N 5.99; found C 61.51, H 3.42, N 6.03.

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2-Chloro-6-(2,4-dichlorobenzoyl)pyridine 1-Oxide (3l): General procedure A was applied, using 2-chloropyridine *N*-oxide (0.5 mmol, 64 mg), 2,6-dichlorobenzyl alcohol (1.5 mmol, 260 mg), $PdCl_2$ (6 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3l** (80 mg, 53 %) as a black solid. M.p. 64–66 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 6.4 Hz, 1 H), 7.37–7.26 (m, 2 H), 7.23 (d, *J* = 6.7 Hz, 1 H), 6.63 (d, *J* = 7.1 Hz, 1 H), 6.19 (t, *J* = 6.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.5, 162.4, 145.0, 139.8, 137.5, 134.5, 134.1, 132.4, 131.2, 129.4, 121.4, 107.0 ppm. MS (EI): *m/z* (%) = 302 (21) $[M]^+$, 253 (7), 218 (100), 219 (35), 220 (80), 183 (11), 159 (88), 123 (55), 109 (11), 89 (18), 79 (11), 63 (11), 51 (11). $C_{12}H_6Cl_3NO_2$ (302.54): calcd. C 47.64, H 2.00, N 4.63; found C 47.46, H 2.03, N 4.67.

2-Chloro-6-(4-chlorobenzoyl)pyridine 1-Oxide (3m): General procedure A was applied, using 2-chloropyridine *N*-oxide (0.5 mmol, 64 mg), 4-chlorobenzyl alcohol (1.5 mmol, 214 mg), $PdCl_2$ (6 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure B was applied, using 2-chloropyridine *N*-oxide (0.5 mmol, 64 mg), 4-chlorobenzyl chloride (1.5 mmol, 240 mg), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure C was applied, using 2-chloropyridine *N*-oxide (0.5 mmol, 64 mg), 4-chlorobenzyl bromide (1.5 mmol, 308 mg), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3m** (procedure A: 80 mg, 60 %; procedure B: 76 mg, 57 %; procedure C: 79 mg, 59 %) as a black solid. M.p. 76–78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.25 (m, 3 H), 7.37–7.32 (m, 2 H), 6.64 (d, *J* = 7.4 Hz, 1 H), 6.20–6.17 (td, *J* = 6.8, *J* = 1.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.4, 162.8, 139.6, 137.1, 134.9, 134.0, 129.5, 129.1, 121.4, 106.0 ppm. MS (EI): *m/z* (%) = 270 (6) $[M + 2]^+$, 268 (18) $[M]^+$, 253 (2), 218 (20), 219 (61), 220 (20), 183 (2), 149 (3), 125 (100), 99 (22), 79 (29), 57 (44). $C_{12}H_7Cl_2NO_2$ (268.09): calcd. C 53.76, H 2.63, N 5.22; found C 53.59, H 2.65, N 5.19.

2-Chloro-6-(4-methylbenzoyl)pyridine 1-Oxide (3n): General procedure A was applied, using 2-chloropyridine *N*-oxide (0.5 mmol, 64 mg), 4-methylbenzyl alcohol (1.5 mmol, 183 mg), $PdCl_2$ (6 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure B was applied, using 2-chloropyridine *N*-oxide (0.5 mmol, 64 mg), 4-methylbenzyl chloride (1.5 mmol, 0.20 mL), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3n** (procedure A: 87 mg, 71 %; procedure B: 86 mg, 70 %) as a black solid. M.p. 33–35 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.26 (m, 1 H), 7. 23 (d, *J* = 8.1 Hz, 2 H), 7.17 (d, *J* = 8.0 Hz, 2 H), 6.63 (d, *J* = 7.3 Hz, 1 H), 6.17–6.13 (td, *J* = 6.7, *J* = 1.0 Hz, 1 H), 2.35 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.6, 163.0, 139.5, 137.9, 137.1, 133.2, 129.4, 128.1, 121.1, 106.2, 21.3 ppm. MS (EI): *m/z* (%) = 247 (19) $[M]^+$, 198 (24), 199 (81), 200 (10), 167 (7), 149 (11), 119 (11), 105 (100), 98 (7), 91 (11), 79 (25), 65 (7), 57 (7), 51 (11), 43 (7). $C_{13}H_{10}ClNO_2$ (247.68): calcd. C 63.04, H 4.07, N 5.66; found C 63.28, H 4.11, N 5.62.

2-[4-(*tert*-Butyl)benzoyl]-6-chloropyridine 1-Oxide (3o): General procedure A was applied, using 2-chloropyridine *N*-oxide (0.5 mmol, 64 mg), 4-*tert*-butylbenzyl alcohol (1.5 mmol, 0.26 mL), $PdCl_2$ (6 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3o** (105 mg, 73 %) as a black solid. M.p. 122–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 8.4 Hz, 2 H), 7.33–7.29 (m, 1 H), 7.26 (d, *J* = 8.2 Hz, 2 H), 6.63 (d, *J* = 7.5 Hz, 1 H), 6.18–6.14 (td, *J* = 6.8, *J* = 1.2 Hz, 1 H), 1.32 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.6, 162.2, 145.05, 139.4, 137.2, 133.2, 128.0, 125.8, 121.2, 106.1, 34.2, 31.6 ppm. MS (EI): *m/z* (%) = 292 (11) $[M + 2]^+$, 290 (21) $[M]^+$, 240 (22), 241 (85), 242 (15), 196 (3), 168 (3), 147 (100), 117 (40), 91 (22), 65 (3), 41 (7). $C_{16}H_{16}ClNO_2$ (289.76): calcd. C 66.32, H 5.57, N 4.83; found C 66.49, H 5.61, N 4.86.

2-Cyano-6-(4-methylbenzoyl)pyridine 1-Oxide (3p): General procedure A was applied, using 2-cyanopyridine *N*-oxide (0.5 mmol, 60 mg), 4-methylbenzyl alcohol (1.5 mmol, 183 mg), $PdCl_2$ (6 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure B was applied, using 2-cyanopyridine *N*-oxide (0.5 mmol, 60 mg), 4-methylbenzyl chloride (1.5 mmol, 0.20 mL), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3p** (procedure A: 81 mg, 68 %; procedure B: 75 mg, 63 %) as an off-white solid. M.p. 98–100 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 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), 7.15 (d, *J* = 7.6 Hz, 2 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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 70.41, H 4.25, N 11.73.

2-Cyano-6-(4-nitrobenzoyl)pyridine 1-Oxide (3q): General procedure A was applied, using 2-cyanopyridine *N*-oxide (0.5 mmol, 60 mg), 4-nitrobenzyl alcohol (1.5 mmol, 230 mg), $PdCl_2$ (6 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure B was applied, using 2-cyanopyridine *N*-oxide (0.5 mmol, 60 mg), 4-nitrolbenzyl chloride (1.5 mmol, 260 mg), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3q** (procedure A: 64 mg, 48 %; procedure B: 57 mg, 43 %) as a brown solid. M.p. 110–112 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 58.18, H 2.60, N 15.64.

5-Acetyl-2-benzoylpyridine 1-Oxide (3r): General procedure A was applied, using 3-acetylpyridine *N*-oxide (0.5 mmol, 68 mg), benzyl alcohol (1.5 mmol, 0.15 mL), $PdCl_2$ (6 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure B was applied, using 3-acetylpyridine *N*-oxide (0.5 mmol, 68 mg), benzyl chloride (1.5 mmol, 0.17 mL), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3r** (procedure A: 106 mg, 88 %; procedure B: 97 mg, 81 %) as a pale yellow solid. M.p. 95–97 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 69.83, H 4.63, N 5.77.

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5-Acetyl-2-(4-chlorobenzoyl)pyridine 1-Oxide (3s): General procedure A was applied, using 3-acetylpyridine *N*-oxide (0.5 mmol, 68 mg), 4-chlorobenzyl alcohol (2 mmol, 214 mg), $PdCl_2$ (6 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure B was applied, using 3-acetylpyridine *N*-oxide (0.5 mmol, 68 mg), 4-chlorobenzyl chloride (1.5 mmol, 241 mg), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure C was applied, using 3-acetylpyridine *N*-oxide (0.5 mmol, 68 mg), 4-chlorobenzyl bromide (2 mmol, 308 mg), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3s** (procedure A: 105 mg, 77 %; procedure B: 100 mg, 73 %; procedure C: 101 mg, 74 %) as an off-white solid. M.p. 119–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.81 (s, 1 H), 7.91 (d, J = 8.3 Hz, 1 H), 7.63 (d, J = 8.1 Hz, 1 H), 7.46 (d, J = 8.4 Hz, 2 H), 7.40 (d, J = 8.0 Hz, 2 H), 2.48 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.3, 186.0, 175.1, 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* (%) = 277 (6) $[M + 2]^+$, 275 (18) $[M]^+$, 259 (22), 242 (7), 224 (14), 165 (62), 153 (29), 137 (51), 125 (62), 111 (22), 101 (98), 89 (22), 75 (80), 63 (100), 51 (85), 43 (40). $C_{14}H_{10}ClNO_3$ (275.69): calcd. C 60.99, H 3.66, N 5.08; found C 60.70, H 3.68, N 5.11.

5-Acetyl-2-(4-methylbenzoyl)pyridine 1-Oxide (3t): General procedure A was applied, using 3-acetylpyridine *N*-oxide (0.5 mmol, 68 mg), 4-methylbenzyl alcohol (1.5 mmol, 183 mg), $PdCl_2$ (6 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure B was applied, using 3-acetylpyridine *N*-oxide (0.5 mmol, 68 mg), 4-methybenzyl chloride (1.5 mmol, 0.20 mL), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3t** (procedure A: 102 mg, 80 %; procedure B: 98 mg, 77 %) as a brown solid. M.p. 185–187 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8. 81 (s, 1 H), 8.38 (d, J = 8.5 Hz, 1 H), 7.90 (d, J = 8.0 Hz, 1 H), 7.34 (d, J = 8.0 Hz, 2 H), 7.19 (d, J = 7.8 Hz, 2 H), 2.54 (s, 3 H), 2.37 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.6, 189.7, 163.2, 147.8, 142.7, 140.3, 130.0, 129.5, 129.2, 128.7, 127.1, 29.7, 21.1 ppm. MS (EI): *m/z* (%) = 256 (35) $[M + 1]^+$, 255 (10) $[M]^+$, 243 (74), 222 (37), 208 (11), 194 (12), 153 (77), 122 (33), 105 (100), 91 (22), 77 (22), 63 (21), 53 (21), 43 (22). $C_{15}H_{13}NO_3$ (255.27): calcd. C 70.58, H 5.13, N 5.49; found C 70.77, H 5.09, N 5.43.

4-Acetyl-2-(4-methylbenzoyl)pyridine 1-Oxide (3u): General procedure A was applied, using 4-acetylpyridine *N*-oxide (0.5 mmol, 68 mg), 4-methylbenzyl alcohol (1.5 mmol, 183 mg), $PdCl_2$ (6 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure B was applied, using 4-acetylpyridine *N*-oxide (0.5 mmol, 68 mg), 4-methybenzyl chloride (1.5 mmol, 0.20 mL), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3u** (procedure A: 105 mg, 83 %; procedure B: 102 mg, 80 %) as a pale brown solid. M.p. 125–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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) $[M + 1]^+$, 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 70.76, H 5.16, N 5.50.

2-(4-Fluorobenzoyl)pyridine 1-Oxide (3v): General procedure B was applied, using pyridine *N*-oxide (0.5 mmol, 47 mg), 4-fluorobenzyl chloride (1.5 mmol, 0.18 mL), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure C was applied, using pyridine *N*-oxide (0.5 mmol, 47 mg), 4-fluorobenzyl bromide (1.5 mmol, 0.19 mL), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3v** (procedure B: 56 mg, 52 %; procedure C: 59 mg, 55 %) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.25 (d, J = 5.21 Hz, 1 H), 7.86 (dd, J = 7.3, J = 5.2 Hz, 2 H), 7.45–7.39 (m, 3 H), 7.26–7.12 (m, 2 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 187.1, 167.4, 165.5, 140.3, 132.8, 132.3, 132.2, 127.3, 126.0, 116.4, 116.2 ppm. HRMS (EI): calcd. for $C_{12}H_8FNO_2$ $[M]^+$ 217.0535; found 217.0539.

2-Cyano-6-(4-fluorobenzoyl)pyridine 1-Oxide (3w): General procedure B was applied, using 2-cyanopyridine *N*-oxide (0.5 mmol, 60 mg), 4-fluorobenzyl chloride (1.5 mmol, 0.18 mL), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure C was applied, using 2-cyanopyridine *N*-oxide (0.5 mmol, 60 mg), 4-fluorobenzyl bromide (1.5 mmol, 0.19 mL), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3w** (procedure B: 38 mg, 32 %; procedure C: 42 mg, 35 %) as a white solid. M.p. 140–142 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.81 (dd, J = 8.4, J = 5.4 Hz, 2 H), 7.20–7.17 (m, 2 H), 7.13–7.10 (m, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 188.9, 168.4, 165.9, 133.34, 133.3, 132.73, 132.7, 129.8, 129.75, 115.8, 115.7, 115.5 ppm. MS (EI): *m/z* (%) = 242 (13) $[M]^+$, 139 (77), 123 (100), 95 (77), 75 (66), 69 (11), 57 (7), 50 (10), 44 (13). $C_{13}H_7FN_2O_2$ (242.20): calcd. C 64.47, H 2.91, N 11.57; found C 64.63, H 2.93, N 11.53.

4-Acetyl-2-(4-fluorobenzoyl)pyridine 1-Oxide (3x): General procedure B was applied, using 4-acetylpyridine *N*-oxide (0.5 mmol, 68 mg), 4-fluorobenzyl chloride (1.5 mmol, 0.18 mL), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Also, general procedure C was applied, using 4-acetylpyridine *N*-oxide (0.5 mmol, 68 mg), 4-fluorobenzyl bromide (1.5 mmol, 0.19 mL), $PdCl_2$(COD) (8 mg, 7 mol-%), $K_2S_2O_8$ (1 mmol, 270 mg), and chlorobenzene (2 mL). Purification by column chromatography (silica gel; *n*-hexane/EtOAc/methanol, 1:1:0.1) gave the desired product **3x** (procedure B: 60 mg, 46 %; procedure C: 62 mg, 48 %) as a white solid. M.p. 108–110 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.28 (d, J = 6.0 Hz, 1 H), 8.07 (dd, J = 8.7, J = 5.3 Hz, 1 H), 7.90 (d, J = 6.24 Hz, 2 H), 7.85 (s, 1 H), 7.62 (dd, J = 8.6, J = 5.5 Hz, 2 H), 2.6 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 190.2, 185.3, 166.9, 165.3, 163.7, 145.6, 139.8, 132.8, 132.7, 130.8, 130.7, 125.2, 29.7 ppm. MS (EI): *m/z* (%) = 261 (16) $[M + 2]^+$, 259 (6) $[M]^+$, 227 (92), 198 (9), 170 (7), 149 (100), 121 (59), 101 (77), 78 (48), 51 (77). $C_{14}H_{10}FNO_3$ (259.23): calcd. C 64.86, H 3.89, N 5.40; found C 64.68, H 3.86, N 5.43.

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