

**Palladium-Catalyzed Direct C–H Arylation of Pyridine N-oxides with Potassium Aryl- and Heteroaryltrifluoroborates**

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## Palladium-Catalyzed Direct C–H Arylation of Pyridine *N*-oxides with Potassium Aryl- and Heteroaryltrifluoroborates

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An efficient ligand-free Pd(OAc)<sub>2</sub>-catalyzed selective arylation of pyridine *N*-oxides using potassium (hetero)aryltrifluoroborates as coupling partners via C–H bond activation was achieved in the presence of TBAI. This approach has the broad substrate scope and shows moderate to high yields.

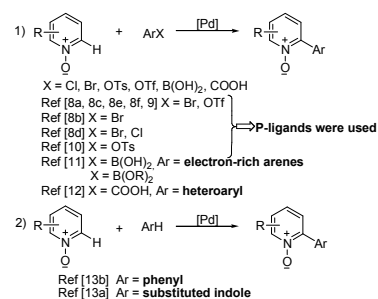
### Introduction

The heterocycle-aryl structural motif containing 2-arylpyridyl moiety represents an important class of molecule and is frequently encountered in pharmacophores, natural products, functional materials and ligands, and its corresponding derivatives also serve as valuable synthetic building blocks.<sup>1</sup> Consequently, the significance of this class of compounds has inspired chemists to develop efficient synthetic methods. Traditional cross-couplings through two alternative paths have proven to be important methods. One path is the cross-coupling of 2-pyridyl boronic acid/ester or borate with aryl halides<sup>2</sup> and the other uses 2-halogenated pyridines as one of the coupling partners.<sup>3</sup> However, the former is limited in terms of the accessibility and/or the stability of the boron-containing reagents and the latter requires preinstallation of reactive carbon–halogen bonds precisely at the bond forming sites. To avoid the prefunctionalization such as metalation and halogenation, *N*-activated pyridine species have emerged as a promising alternative to synthesize 2-arylpyridines via the direct C–H functionalization of pyridine rings.<sup>4</sup>

Recently, the development of selective functionalization of C–H bonds catalyzed by transition metals has witnessed tremendous progress and attracted intensive attention because of its economic advantages.<sup>5</sup> Pioneered by Fagnou,<sup>6</sup> *N*-Oxides have been introduced for direct arylation of inert C–H bonds.<sup>7</sup> Subsequently, several protocols demonstrated the palladium-catalyzed direct arylation of pyridine *N*-oxides for constructing 2-arylpyridines with some commonly used coupling partners such as aryl halides,<sup>8</sup> aryl triflates,<sup>9</sup> aryl tosylates,<sup>10</sup> arylboronic acids or esters<sup>11</sup> and aromatic carboxylic acids<sup>12</sup> (Scheme 1, eq 2). Moreover, the elegant C–H

activation-based couplings of arenes and heteroarenes have been described (Scheme 1, eq 2).<sup>13</sup> Despite significant progress in this area, the development of novel, efficient methods using other partners with broader substrate scope still remain highly desirable. Interestingly, potassium aryltrifluoroborates as coupling partners for synthesis of biaryls have provided an attractive alternative over the past decade.<sup>14</sup> However, to the best of our knowledge there is no example employing the use of them to form 2-arylpyridines via functionalization of the C–H bond. Considering their broad application, potassium aryltrifluoroborates have the potential to serve as the ideal aryl sources for C–C bond-forming reactions via C–H bond activation. Herein, we report a novel approach to 2-arylpyridines from pyridine *N*-oxides and potassium aryltrifluoroborates via Pd-catalyzed selective oxidative C–H bond activation of pyridine *N*-oxides in the presence of Ag<sub>2</sub>O (Scheme 1, eq 3).

Previous work



**Scheme 1** Direct C–H arylation of pyridine *N*-oxides using different coupling partners.

### Results and Discussion

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We initiated our investigations by selecting the pyridine *N*-oxide **1a** as substrate model and potassium phenyltrifluoroborate **2a** as a coupling partner to optimize various reaction parameters. First, various catalysts were investigated for this transformation (See Supporting Information), and Pd(OAc)<sub>2</sub> proved to be a superior catalyst, providing the highest yield (Table 1, entry 2). No reaction was detected in the absence of a catalyst (Table 1, entry 1). The examination of oxidants demonstrated Ag<sub>2</sub>O was essential for the formation of the desired product **3a** in the presence of Pd(OAc)<sub>2</sub> in 1,4-dioxane as a solvent (Table 1, entry 2). In contrast, a trace amount of product was detected when Ag<sub>2</sub>O was omitted (Table 1, entry 3). 14% yield was obtained with Ag<sub>2</sub>CO<sub>3</sub> (Table 1, entry 4). In sharp contrast, Ag<sub>2</sub>SO<sub>4</sub> gave a trace amount of the product and the reactions almost did not take place using AgNO<sub>3</sub> and AgBF<sub>4</sub> as oxidants (Table 1, entries 5–7). To improve the yield further, tetrabutylammonium salts as additives were screened.<sup>13a</sup> While all five tetrabutylammonium salts improved the yields, the effect was most pronounced with addition of 20 mol% TBAI, and the yield was improved to 88% (Table 1, entry 11). However, the addition of tetraethylammonium hydroxide decreased the yield to 49% (Table 1, entry 13). Instead of TBAI, when 20 mol % KI, I<sub>2</sub> and AgI were examined as additives, 66%, 62% and 66% yields were obtained, respectively. These results also suggested that not the iodide anion but the tetrabutylammonium cation (which might solubilise the silver oxide) is playing a key role. Finally, the reaction was successfully carried out with 3.3 equiv. of pyridine *N*-oxide when 10 mol% of Pd(OAc)<sub>2</sub> was used in combination with Ag<sub>2</sub>O (2 equiv), and TBAI (20 mol%) in 1,4-dioxane at 90 °C for 17 h (Table 1, entry 11). This transformation is high in regioselectivity and chemoselectivity, and C–H functionalization occurs at the 2-position of pyridine *N*-oxide.

**Table 1** Optimization of reaction conditions<sup>a</sup>

Entry	Catalyst	Oxidant	Additive	Yield (%) <sup>b</sup>
1	-	Ag <sub>2</sub> O	-	n.r. <sup>c</sup>
2	Pd(OAc) <sub>2</sub>	Ag <sub>2</sub> O	-	60
3	Pd(OAc) <sub>2</sub>	-	-	trace
4	Pd(OAc) <sub>2</sub>	Ag <sub>2</sub> CO <sub>3</sub>	-	14
5	Pd(OAc) <sub>2</sub>	Ag <sub>2</sub> SO <sub>4</sub>	-	trace
6	Pd(OAc) <sub>2</sub>	AgNO <sub>3</sub>	-	n.r.
7	Pd(OAc) <sub>2</sub>	AgBF <sub>4</sub>	-	n.r.
8	Pd(OAc) <sub>2</sub>	Ag <sub>2</sub> O	TBAF	81
9	Pd(OAc) <sub>2</sub>	Ag <sub>2</sub> O	TBAC	79
10	Pd(OAc) <sub>2</sub>	Ag <sub>2</sub> O	TBAB	78

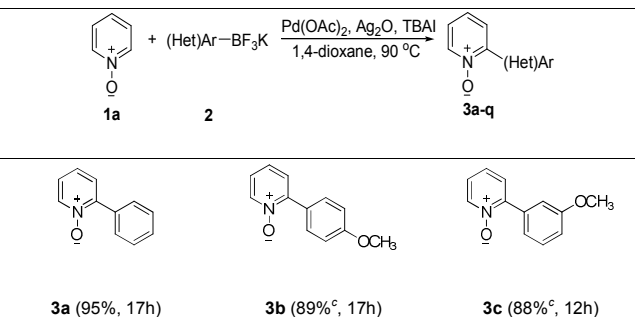
11	Pd(OAc) <sub>2</sub>	Ag <sub>2</sub> O	TBAI	88(95 <sup>d</sup> )
12	Pd(OAc) <sub>2</sub>	Ag <sub>2</sub> O	TBAOH	80
13	Pd(OAc) <sub>2</sub>	Ag <sub>2</sub> O	TEAOH	49
14	Pd(OAc) <sub>2</sub>	Ag <sub>2</sub> O	KI	66
15	Pd(OAc) <sub>2</sub>	Ag <sub>2</sub> O	I <sub>2</sub>	62
16	Pd(OAc) <sub>2</sub>	Ag <sub>2</sub> O	AgI	66

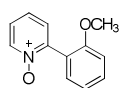
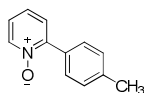
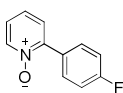
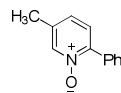
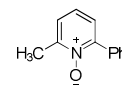
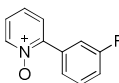
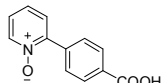
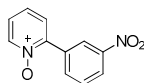
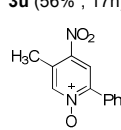
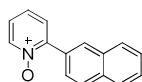
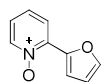
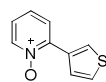
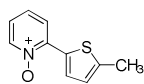
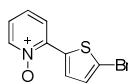
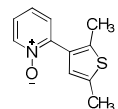
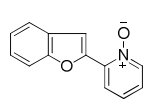
<sup>a</sup> Reactions were carried out with pyridine *N*-oxide **1a** (0.45 mmol), potassium phenyltrifluoroborate **2a** (0.15 mmol), oxidant (2.0 equiv), Pd(OAc)<sub>2</sub> (10 mol%) and additive (20 mol%) in 1,4-dioxane (0.5 mL) at 90 °C for 17 h. <sup>b</sup> Isolated yield. <sup>c</sup> n.r. = no reaction. <sup>d</sup> 3.3 equiv of pyridine *N*-oxide **1a** was used.

With the optimal reaction conditions in hand, we turned our attention to explore the reactions of various potassium aryltrifluoroborates **2** with **1a** (Table 2). It was found that the reactions could proceed well with a series of substituents on the benzene ring of **2**, affording the corresponding products **3a–i** in moderate to good yields. Potassium phenyltrifluoroborate with electron-donating groups, such as methyl or MeO groups substituted in the aromatic rings, proceeded smoothly and provided the desired products in 68–98% yields (Table 2, **3b–e**). Electron-withdrawing groups, such as F, afforded the desired products in 92% and 91% yields, respectively (Table 2, **3f** and **3g**). Potassium 4-formylphenyltrifluoroborate might give 65% yield (Table 2, **3h**). Unfortunately, only 47% yield was obtained with a NO<sub>2</sub> group (Table 2, **3i**). The product **3j** could be offered with 71% yield when this reaction system was applied to potassium 2-naphthyltrifluoroborate.

To expand the substrate scope, we applied this catalytic system to potassium heteroaryltrifluoroborates of a number of oxygen- or sulphur-containing heterocycles such as furan and thiophene. It was found that they could be employed as suitable substrates, giving the corresponding products **3k–q** in moderate to good yields. Disubstituted potassium 3-thienyltrifluoroborate can also be utilized as a coupling partner and provided 57% yield (Table 2, **3p**). In addition, 91% yield was obtained with potassium benzofuran-2-trifluoroborate (Table 2, **3q**).

**Table 2** Reactions of the pyridine *N*-oxide **1a** with various potassium (hetero)aryltrifluoroborates<sup>a, b</sup>

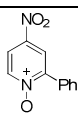
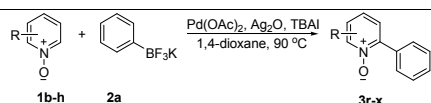
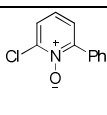
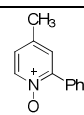


**3d** (68%<sup>c</sup>, 17h)**3e** (98%<sup>c</sup>, 12h)**3f** (92%, 17h)**3u** (56%<sup>c</sup>, 17h)**3v** (62%<sup>c</sup>, 21h)**3w** (87%<sup>d</sup>, 27h)**3g** (91%<sup>d</sup>, 17h)**3h** (65%, 17h)**3i** (47%, 20h)**3x** (84%<sup>e</sup>, 21h)**3j** (71%, 17h)**3k** (83%<sup>d</sup>, 12h)**3l** (59%<sup>c</sup>, 17h)**3m** (68%<sup>e</sup>, 17h)**3n** (72%<sup>f</sup>, 12h)**3o** (51%<sup>d</sup>, 17h)**3p** (57%, 17h)**3q** (91%<sup>f</sup>, 20h)

<sup>a</sup> Reactions were performed using pyridine *N*-oxide **1a** (0.5 mmol), potassium aryltrifluoroborate **2a** (0.15 mmol), Ag<sub>2</sub>O (0.3 mmol, 2 equiv.), Pd(OAc)<sub>2</sub> (10 mol%) and TBAI (20 mol%) in 1,4-dioxane (0.5 mL) at 90 °C for specified time. <sup>b</sup> Isolated yield. <sup>c</sup> 80 °C. <sup>d</sup> 120 °C. <sup>e</sup> 110 °C. <sup>f</sup> 100 °C.

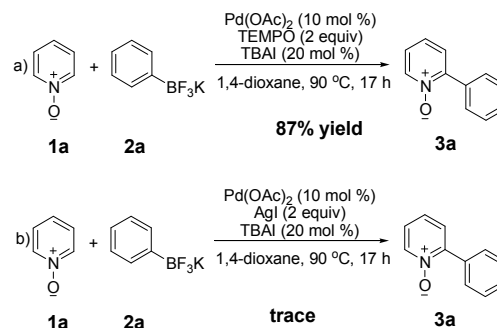
Encouraged by the results obtained, a range of pyridine *N*-oxide derivatives were next examined with **2a** under the optimized conditions. Pyridine *N*-oxides having electron-withdrawing 4-nitro and 2-chloro groups underwent the reactions, affording the desired products in 98% and 75% yields, respectively (Table 3, **3r** and **3s**). Pyridine *N*-oxides substituted with 4-methyl, 3-methyl, 2-methyl and 4-methoxy groups reacted smoothly with **2a** and provided the desired products in moderate to good yields (Table 3, **3t-w**). Notably, 84% yield could be obtained when 4-nitro-3-methyl pyridine *N*-oxide was employed (Table 3, **3x**).

**Table 3** Reactions of the potassium penyltrifluoroborate **2a** with various pyridine *N*-oxides<sup>a,b</sup>

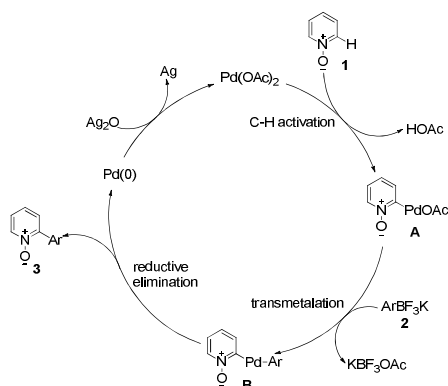
**3r** (98%, 17h)**3s** (75%<sup>c</sup>, 21h)**3t** (88%<sup>d</sup>, 27h)

<sup>a</sup> Reactions were performed using pyridine *N*-oxide **1** (0.5 mmol), potassium aryltrifluoroborate **2a** (0.15 mmol), Ag<sub>2</sub>O (0.3 mmol, 2 equiv.), Pd(OAc)<sub>2</sub> (10 mol%) and TBAI (20 mol%) in 1,4-dioxane (0.5 mL) at 90 °C for specified time. <sup>b</sup> Isolated yield. <sup>c</sup> 120 °C. <sup>d</sup> 100 °C. <sup>e</sup> 80 °C.

To probe the reaction mechanism, the coupling of pyridine *N*-oxide with PhBF<sub>3</sub>K was carried out in the presence of a typical radical inhibitor TEMPO (2 equiv). The fact that the yield of product **3a** was only slightly affected by the reagent (87%) suggested the irrelevancy of organic radical species (Scheme 2a).<sup>15</sup> In addition, Ag(0) was detected using XPS in the reaction system that utilized Ag<sub>2</sub>O as a oxidant (Table 1, entry 11). However, only trace amount of product **3a** was provided when AgI was adopted as a oxidant and Ag(0) was not detected (Scheme 2b). On the basis of the observations and related precedents,<sup>16</sup> a plausible catalytic cycle is proposed in Scheme 3. The process begins with the electrophilic palladation at the preferential C-2 position of pyridine *N*-oxide to lead to the key heterocoupling intermediate **A**, which undergoes transmetalation to form the arylpalladium intermediate **B**, followed by reductive elimination to produce the desired product with the generation of Pd(0). The active Pd(II) catalyst is regenerated when the Pd(0) is reoxidized by Ag(I).



**Scheme 2** Mechanistic studies.



Scheme 3 Proposed mechanism.

## Conclusions

In summary, we present the first example of Pd-catalyzed direct arylation of pyridine *N*-oxide compounds with potassium aryl- and heteroaryltrifluoroborates without requiring the addition of any ligand, thus leading to the highly site-selective synthesis of 2-arylpiperidine *N*-oxides. This method proves to be a very general method, applicable to both potassium (hetero)aryltrifluoroborates and pyridine *N*-oxides. Importantly, this method provides moderate to high yields of desired biaryl products, good functional group tolerability, and high regioselectivity.

## Experimental section

### General information

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Deuterated solvents were purchased from Aldrich. Refinement of the mixed system through column chromatography was performed on silica gel (200-300 mesh) with ethyl acetate (solvent A)/alcohol (solvent B) gradients as elution. In addition, all yields were referred to isolated yields (average of two runs) of compounds unless otherwise specified. On the one hand, the known compounds were partly characterized by melting points (for solid samples),  $^1\text{H}$  NMR, and compared to authentic samples or the literature data. Melting points were determined with a RD-II digital melting point apparatus and were uncorrected.  $^1\text{H}$  NMR data were obtained at 300 K on a Bruker AMX-600 spectrometer. The  $^1\text{H}$  NMR (600 MHz) chemical shifts were measured relative to  $\text{CDCl}_3$  as the internal reference ( $\text{CDCl}_3$ :  $\delta = 7.26$  ppm). Spectra are reported as follows: chemical shift ( $\delta = \text{ppm}$ ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration, and assignment. On the other hand, the unknown compounds were partly characterized by  $^{13}\text{C}$  NMR and HR-MS as well. The  $^{13}\text{C}$  NMR (100 MHz) chemical shifts were given using  $\text{CDCl}_3$  as the internal standard ( $\text{CDCl}_3$ :  $\delta = 77.16$  ppm). High-resolution mass spectra (HR-MS) were obtained with a Waters-Q-TOF-Premier (ESI).

### General procedure for direct arylation of pyridine *N*-oxides with potassium phenyltrifluoroborate

To a tube equipped with a magnetic stir bar were added the catalyst  $\text{Pd}(\text{OAc})_2$  (10 mol%),  $\text{Ag}_2\text{O}$  (2 equiv.), TBAI (20 mol%), potassium phenyltrifluoroborate (**2a**, 0.15 mmol) and pyridine *N*-oxide (**1a**, 3.3 equiv.) in turn. Subsequently, the solvent (1,4-dioxane, 0.5 mL) was added under air atmosphere. The reaction system was then stirred at 90 °C until potassium phenyltrifluoroborate was completely consumed as determined by TLC. At last, the reaction mixture was purified by silica gel column chromatography to afford the desired pure coupling product **3a**.

**2-phenylpyridine *N*-oxide (3a).**  $R_f = 0.5$  (AcOEt/Alcohol = 10/1 v/v); light yellow solid; M.p. = 141-142 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.20$ -7.24 (m, 1H), 7.28 (td,  $J = 7.6, 1.1$  Hz, 1H), 7.41 (dd,  $J = 8.0, 2.2$  Hz, 1H), 7.44-7.47 (m, 1H), 7.46-7.50 (m, 2H), 7.80-7.83 (m, 2H), 8.32 (dd,  $J = 6.6, 0.7$  Hz, 1H) ppm. IR ( $\text{cm}^{-1}$ , KBr): 3063, 3044, 1477, 1418, 1240, 841, 759, 724, 697.

**2-(4-methoxyphenyl)-pyridine *N*-oxide (3b).**  $R_f = 0.6$  (AcOEt/Alcohol = 6/1 v/v); Yellowish solid; M.p. = 121-123 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta = 3.87$  (s, 3H), 6.99 (dt,  $J = 8.9, 2.9$  Hz, 2H), 7.17-7.21 (m, 1H), 7.27 (td,  $J = 7.7, 1.2$  Hz, 1H), 7.41 (dd,  $J = 7.9, 2.0$  Hz, 1H), 7.81 (dt,  $J = 8.9, 2.9$  Hz, 2H), 8.31 (dd,  $J = 6.6, 0.5$  Hz, 1H) ppm. IR ( $\text{cm}^{-1}$ , KBr): 3064, 2984, 1584, 1497, 1446, 1332, 1251, 1204, 1179, 833, 766.

**2-(3-methoxyphenyl)-pyridine *N*-oxide (3c).**  $R_f = 0.6$  (AcOEt/Alcohol = 6/1 v/v); White solid; M.p. = 120-122 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta = 3.85$  (s, 3H), 6.99 (ddd,  $J = 8.2, 2.6, 1.0$  Hz, 1H), 7.22-7.26 (m, 1H), 7.29-7.34 (m, 2H), 7.38 (t,  $J = 7.7$  Hz, 1H), 7.42-7.44 (m, 2H), 8.32 (dd,  $J = 6.5, 0.8$  Hz, 1H) ppm. IR ( $\text{cm}^{-1}$ , KBr): 3102, 3057, 2935, 2841, 1608, 1531, 1435, 1243, 830, 761.

**2-(2-methoxyphenyl)-pyridine *N*-oxide (3d).**  $R_f = 0.5$  (AcOEt/Alcohol = 6/1 v/v); White solid; M.p. = 169-171 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta = 3.82$  (s, 3H), 7.01 (d,  $J = 8.3$  Hz, 1H), 7.05 (td,  $J = 7.5, 1.0$  Hz, 1H), 7.23-7.27 (m, 1H), 7.27 (dd,  $J = 7.6, 1.4$  Hz, 1H), 7.34-7.37 (m, 1H), 7.38 (dd,  $J = 7.5, 1.7$  Hz, 1H), 7.43-7.46 (m, 1H), 8.33-8.35 (m, 1H) ppm. IR ( $\text{cm}^{-1}$ , KBr): 3094, 3044, 2961, 2843, 1598, 1487, 1435, 1367, 1243, 961, 827, 733.

**2-(4-methylphenyl)-pyridine *N*-oxide (3e).**  $R_f = 0.6$  (Petroleum ether/AcOEt = 6/1 v/v); Yellowish solid; M.p. = 129-131 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta = 2.41$  (s, 3H), 7.19-7.23 (m, 1H), 7.28-7.32 (m, 3H), 7.60-7.64 (m, 3H), 7.4 (dd,  $J = 7.9, 2.3$  Hz, 1H), 7.71 (dt,  $J = 8.1, 2.0$  Hz, 2H), 8.32 (dt,  $J = 6.1, 1.0$  Hz, 1H) ppm. IR ( $\text{cm}^{-1}$ , KBr): 3066, 3043, 2915, 1614, 1430, 1240, 1010, 816, 760.

**2-(4-fluorophenyl)-pyridine *N*-oxide (3f).**  $R_f = 0.6$  (AcOEt/Alcohol = 10/1 v/v); Yellowish solid; M.p. = 161-163 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.15$ -7.20 (m, 2H), 7.23-7.26 (m, 1H), 7.30 (td,  $J = 7.8, 1.2$  Hz, 1H), 7.41 (dd,  $J = 7.8, 2.0$  Hz, 1H), 7.83-7.86 (m, 2H), 8.33 (dd,  $J = 6.4, 0.9$  Hz, 1H) ppm. IR ( $\text{cm}^{-1}$ , KBr): 3062, 3040, 2463, 1916, 1597, 1246, 1018, 760, 572.

**2-(3-fluorophenyl)-pyridine *N*-oxide (3g).**  $R_f = 0.6$  (AcOEt/Alcohol = 6/1 v/v); Yellowish solid; M.p. = 106-107 °C;  $^1\text{H}$  NMR (600

MHz, CDCl<sub>3</sub>):  $\delta$  = 7.14-7.18 (m, 1H), 7.25-7.29 (m, 1H), 7.31 (td,  $J$  = 7.7, 1.2 Hz, 1H), 7.43-7.48 (m, 2H), 7.55-7.58 (m, 1H), 7.61 (dt,  $J$  = 9.9, 1.7 Hz, 1H), 8.34 (dd,  $J$  = 6.4, 0.7 Hz, 1H) ppm; <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$  = 119.4, 119.5, 119.7, 127.9, 128.8, 130.2, 132.7 (d,  $J$  = 8.6 Hz), 132.8, 143.5, 164.5 (d,  $J$  = 244.2 Hz) ppm; HRMS (ESI,  $m/z$ ): Calcd for C<sub>11</sub>H<sub>8</sub>FNO [M + H]<sup>+</sup> 190.0668, found 190.0662. IR (cm<sup>-1</sup>, KBr): 3074, 3051, 2421, 1603, 1497, 1332, 1263, 1007, 801, 596.

**4-(*N*-Oxopyridin-2-yl)benzoic acid (3h).** R<sub>f</sub> = 0.2 (AcOEt); Yellow solid; M.p. = 162-164 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.28-7.33 (m, 1H), 7.33 (td,  $J$  = 7.6, 1.3 Hz, 1H), 7.46 (dd,  $J$  = 7.8, 2.0 Hz, 1H), 8.00 (s, 4H), 8.35 (dd,  $J$  = 6.2, 0.8 Hz, 1H), 10.8 (s, 1H) ppm. IR (cm<sup>-1</sup>, KBr): 3632, 3103, 3051, 2443, 1597, 1497, 1348, 1203, 819, 796.

**2-(3-nitrophenyl)-pyridine *N*-oxide (3i).** R<sub>f</sub> = 0.4 (AcOEt/Alcohol = 10/1 v/v); pale yellow solid; M.p. = 175-177 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.31 (td,  $J$  = 6.4, 2.2 Hz, 1H), 7.36 (td,  $J$  = 7.6, 1.4 Hz, 1H), 7.50 (dd,  $J$  = 7.8, 2.2 Hz, 1H), 7.66 (t,  $J$  = 8.0 Hz, 1H), 8.25 (dt,  $J$  = 8.1, 1.3 Hz, 1H), 8.31 (dq,  $J$  = 8.3, 1.0 Hz, 1H), 8.36 (dd,  $J$  = 6.2, 0.9 Hz, 1H), 8.66 (t,  $J$  = 1.9 Hz, 1H) ppm. IR (cm<sup>-1</sup>, KBr): 3076, 3041, 1580, 1440, 1368, 1237, 1108, 928, 743.

**2-(2-naphthalenyl)-pyridine *N*-oxide (3j).** R<sub>f</sub> = 0.4 (AcOEt/Alcohol = 6/1 v/v); pale solid; M.p. = 139-141 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.25-7.28 (m, 1H), 7.33 (td,  $J$  = 7.6, 1.1 Hz, 1H), 7.50-7.53 (m, 1H), 7.52-7.57 (m, 2H), 7.87 (d,  $J$  = 7.9 Hz, 1H), 7.91 (t,  $J$  = 5.9 Hz, 1H), 7.93-7.97 (m, 2H), 8.26 (s, 1H), 8.37-8.39 (m, 1H) ppm. IR (cm<sup>-1</sup>, KBr): 3097, 3056, 1607, 1529, 1430, 1368, 1137, 892, 698.

**2-(2-furanyl)-pyridine *N*-oxide (3k).** R<sub>f</sub> = 0.4 (AcOEt); pale yellow solid; M.p. = 94-96 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 6.61 (q,  $J$  = 1.7 Hz, 1H), 7.11 (td,  $J$  = 7.1, 1.9 Hz, 1H), 7.29-7.33 (m, 1H), 7.59 (d,  $J$  = 1.1 Hz, 1H), 7.93 (dd,  $J$  = 8.2, 1.9 Hz, 1H), 8.02 (d,  $J$  = 3.4 Hz, 1H), 8.27 (d,  $J$  = 6.4 Hz, 1H) ppm. IR (cm<sup>-1</sup>, KBr): 3075, 1594, 1498, 1423, 1276, 1258, 898, 841, 591.

**2-(3-thienyl)-pyridine *N*-oxide (3l).** R<sub>f</sub> = 0.4 (AcOEt); pale yellow solid; M.p. = 118-119 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.15-7.18 (m, 1H), 7.28-7.32 (m, 1H), 7.40 (dd,  $J$  = 5.2, 3.1 Hz, 1H), 7.64 (dd,  $J$  = 5.2, 1.3 Hz, 1H), 7.68 (dd,  $J$  = 8.1, 1.9 Hz, 1H), 8.33 (dd,  $J$  = 6.2, 0.8 Hz, 1H), 8.86 (dd,  $J$  = 3.2, 1.3 Hz, 1H) ppm. IR (cm<sup>-1</sup>, KBr): 3044, 1563, 1477, 1450, 1291, 1197, 898, 872, 633.

**2-(2-thienyl)-pyridine *N*-oxide (3m).** R<sub>f</sub> = 0.4 (AcOEt); Pale solid; M.p. = 143-146 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.11 (td,  $J$  = 6.9, 1.9 Hz, 1H), 7.21-7.23 (m, 1H), 7.30-7.34 (m, 1H), 7.57 (dd,  $J$  = 5.2, 1.1 Hz, 1H), 7.86 (dd,  $J$  = 4.0, 1.1 Hz, 1H), 7.93 (td,  $J$  = 8.3, 1.8 Hz, 1H), 8.31 (dd,  $J$  = 6.8, 0.8 Hz, 1H) ppm. IR (cm<sup>-1</sup>, KBr): 3059, 1544, 1498, 1423, 1276, 1258, 898, 841, 591.

**2-(5-methyl-2-thienyl)-pyridine *N*-oxide (3n).** R<sub>f</sub> = 0.4 (AcOEt); Yellow solid; M.p. = 140-142 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.55 (s, 3H), 6.88 (dd,  $J$  = 4.0, 1.0 Hz, 1H), 7.06 (td,  $J$  = 7.1, 1.9 Hz, 1H), 7.28 (dd,  $J$  = 7.6, 1.3 Hz, 1H), 7.67 (d,  $J$  = 4.0 Hz, 1H), 7.85 (dd,  $J$  = 8.3, 1.7 Hz, 1H), 8.27-8.30 (m, 1H) ppm. IR (cm<sup>-1</sup>, KBr): 3034, 3017, 2986, 1599, 1509, 1479, 1329, 1276, 1128, 935, 698.

**2-(5-bromo-2-thienyl)-pyridine *N*-oxide (3o).** R<sub>f</sub> = 0.4 (AcOEt); pale yellow solid; M.p. = 164-166 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.14 (dd,  $J$  = 7.2, 1.8 Hz, 1H), 7.18 (d,  $J$  = 4.3 Hz, 1H), 7.33-7.36 (m, 1H), 7.59 (d,  $J$  = 4.3 Hz, 1H), 7.87 (dd,  $J$  = 8.3, 1.7 Hz, 1H), 8.30 (d,  $J$  = 6.9 Hz, 1H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 119.9, 121.3, 122.3, 126.1, 126.5, 128.8, 132.4, 139.1, 142.5 ppm; HRMS (ESI,  $m/z$ ): Calcd for C<sub>9</sub>H<sub>6</sub>BrNOS [M + H]<sup>+</sup> 255.9432, found 255.9442. IR (cm<sup>-1</sup>, KBr): 3071, 1603, 1508, 1329, 1307, 1258, 1124, 1085, 876, 691.

**2-(2,5-dimethyl-3-thienyl)-pyridine *N*-oxide (3p).** R<sub>f</sub> = 0.4 (AcOEt/Alcohol = 6/1 v/v); pale yellow liquid; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.38 (s, 3H), 2.42 (s, 3H), 6.89 (d,  $J$  = 0.6 Hz, 1H), 7.18 (td,  $J$  = 6.7, 2.5 Hz, 1H), 7.23 (d,  $J$  = 8.1 Hz, 1H), 7.26-7.29 (m, 1H), 8.31 (d,  $J$  = 6.4 Hz, 1H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 14.4, 15.2, 124.2, 124.9, 126.4, 128.0, 129.1, 136.1, 138.0, 140.5, 146.0 ppm; HRMS (ESI,  $m/z$ ): Calcd for C<sub>11</sub>H<sub>12</sub>NOS [M + H]<sup>+</sup> 206.0640, found 206.0643. IR (cm<sup>-1</sup>, KBr): 3077, 3049, 2989, 2908, 1583, 1494, 1371, 1267, 1209, 1107, 877, 806.

**2-(2-benzofuranyl)-pyridine *N*-oxide (3q).** R<sub>f</sub> = 0.5 (AcOEt); Pale yellow solid; M.p. = 139-141 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.19-7.22 (m, 1H), 7.28-7.31 (m, 1H), 7.35 (dd,  $J$  = 8.2, 0.9 Hz, 1H), 7.37-7.42 (m, 1H), 7.52 (dd,  $J$  = 8.3, 0.7 Hz, 1H), 7.71-7.74 (m, 1H), 8.15 (dd,  $J$  = 8.2, 2.0 Hz, 1H), 8.34-8.36 (m, 1H), 8.46 (d,  $J$  = 0.9 Hz, 1H) ppm. IR (cm<sup>-1</sup>, KBr): 3098, 3059, 1558, 1494, 1307, 1298, 1109, 1047, 897, 791.

**4-nitro-2-phenylpyridine *N*-oxide (3r).** R<sub>f</sub> = 0.5 (AcOEt); Pale yellow solid; M.p. = 135-136 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.52-7.54 (m, 3H), 7.80-7.82 (m, 2H), 8.02 (dd,  $J$  = 7.1, 3.2 Hz, 1H), 8.28 (d,  $J$  = 3.2 Hz, 1H), 8.36 (d,  $J$  = 7.2 Hz, 1H) ppm. IR (cm<sup>-1</sup>, KBr): 3041, 1597, 1508, 1339, 1284, 1231, 1114, 895, 724.

**2-chloro-6-phenylpyridine *N*-oxide (3s).** R<sub>f</sub> = 0.3 (Petroleum ether/AcOEt = 3/1 v/v); Pale yellow solid; M.p. = 141-142 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.20 (t,  $J$  = 8.0 Hz, 1H), 7.35 (dd,  $J$  = 7.9, 2.0 Hz, 1H), 7.45-7.50 (m, 4H), 7.78-7.81 (m, 2H) ppm. IR (cm<sup>-1</sup>, KBr): 3048, 1610, 1508, 1497, 1328, 1263, 1209, 1095, 747, 678.

**4-methyl-2-phenylpyridine *N*-oxide (3t).** R<sub>f</sub> = 0.2 (AcOEt /Alcohol = 6/1 v/v); Pale yellow liquid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.39 (s, 3H), 7.04 (dd,  $J$  = 6.5, 2.3 Hz, 1H), 7.31 (t,  $J$  = 8.1 Hz, 1H), 7.45-7.50 (m, 3H), 7.78-7.84 (m, 2H), 8.27 (d,  $J$  = 6.7 Hz, 1H) ppm. IR (cm<sup>-1</sup>, KBr): 3072, 2978, 1598, 1541, 1469, 1382, 1294, 1098, 814, 716.

**5-methyl-2-phenylpyridine *N*-oxide (3u).** R<sub>f</sub> = 0.3 (AcOEt /Alcohol = 10/1 v/v); Pale solid; M.p. = 168-169 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.33 (s, 3H), 7.12-7.15 (m, 1H), 7.30 (d,  $J$  = 8.0 Hz, 1H), 7.42-7.50 (m, 3H), 7.78 (dd,  $J$  = 8.3, 1.7 Hz, 2H), 8.20 (s, 1H) ppm. IR (cm<sup>-1</sup>, KBr): 3048, 2967, 1603, 1523, 1481, 1378, 1321, 1245, 1103, 829, 732, 699.

**6-methyl-2-phenylpyridine *N*-oxide (3v).** R<sub>f</sub> = 0.5 (Petroleum ether/AcOEt = 2/1 v/v); Pale solid; M.p. = 118-119 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.58 (s, 3H), 7.18 (t,  $J$  = 7.7 Hz, 1H), 7.24 (d,  $J$  = 2.2 Hz, 1H), 7.30 (dd,  $J$  = 8.0, 2.2 Hz, 1H), 7.42-7.48 (m, 3H), 7.77 (dd,  $J$  = 8.3, 1.6 Hz, 2H) ppm. IR (cm<sup>-1</sup>, KBr): 3059, 3015, 2946, 2889, 1597, 1523, 1470, 1369, 1315, 1287, 1103, 799, 693.

**4-methoxy-2-phenylpyridine N-oxide (3w).**  $R_f$  = 0.5 (AcOEt/Alcohol = 4/1 v/v); Pale yellow liquid;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 3.87 (s, 3H), 6.78 (q,  $J$  = 3.5 Hz, 1H), 6.92 (d,  $J$  = 3.5 Hz, 1H), 7.44–7.50 (m, 3H), 7.80 (dd,  $J$  = 9.7, 1.9 Hz, 2H), 8.23 (d,  $J$  = 7.3 Hz, 1H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 56.1, 110.9, 112.4, 128.3, 129.3, 129.7, 132.8, 141.2, 149.8, 157.6 ppm; HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{12}\text{H}_{11}\text{NO}_2[\text{M} + \text{H}]^+$  202.0868, found 202.0867. IR ( $\text{cm}^{-1}$ , KBr): 3074, 2954, 2883, 1590, 1514, 1473, 1382, 1342, 1291, 1249, 1073, 832, 719.

**3-methyl-4-nitro-6-phenylpyridine N-oxide (3x).**  $R_f$  = 0.3 (Petroleum ether/AcOEt = 3/1 v/v); Yellow solid; M.p. = 169–170 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.63 (d,  $J$  = 0.5 Hz, 3H), 7.50–7.53 (m, 3H), 7.78–7.81 (m, 2H), 8.20 (s, 1H), 8.26 (s, 1H) ppm. IR ( $\text{cm}^{-1}$ , KBr): 3082, 1590, 1514, 1346, 1295, 1249, 1073, 827, 743.

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