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Palladium-catalyzed direct C–H arylation of pyridine *N*-oxides with potassium aryl- and heteroaryltrifluoroborates†

Mengli Li, Xing Li,* Honghong Chang, Wenchao Gao and Wenlong Wei*

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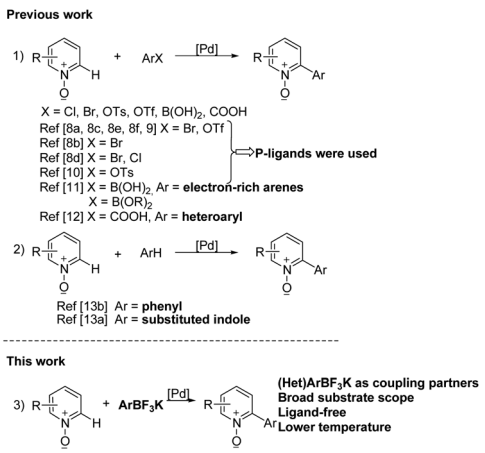
An efficient ligand-free $Pd(OAc)_2$-catalyzed selective arylation of pyridine *N*-oxides using potassium (hetero)aryltrifluoroborates as coupling partners *via* C–H bond activation was achieved in the presence of TBAI. This approach has a broad substrate scope and shows moderate to high yields.

Introduction

The heterocycle-aryl structural motif containing a 2-arylpyridyl moiety represents an important class of molecules and is frequently encountered in pharmacophores, natural products, functional materials and ligands, and its corresponding derivatives also serve as valuable synthetic building blocks.[1] 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[2] and the other uses 2-halogenated pyridines as one of the coupling partners.[3] However, the former is limited in terms of the accessibility and/or stability of the boron-containing reagents and the latter requires preinstallation of reactive carbon–halogen bonds precisely at the bond forming sites. To avoid prefunctionalization such as metalation and halogenation, *N*-activated pyridine species have emerged as a promising alternative to synthesize 2-arylpyridines *via* direct C–H functionalization of pyridine rings.[4]

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.[5] Pioneered by Fagnou,[6] *N*-oxides have been introduced for direct arylation of inert C–H bonds.[7] 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,[8] aryl triflates,[9] aryl tosylates,[10] arylboronic acids or esters[11] and aromatic carboxylic acids[12] (Scheme 1, eqn (2)). Moreover, the elegant C–H activation-based couplings of arenes and heteroarenes have been described (Scheme 1, eqn (2)).[13] Despite significant progress in this area, the development of novel and efficient methods using other partners with a broader substrate scope still remains highly desirable. Interestingly, potassium aryltrifluoroborates as coupling partners for the synthesis of biaryls have provided an attractive alternative over the past decade.[14] 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 applications, 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_2O (Scheme 1, eqn (3)).



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

Taiyuan University of Technology, Department of Chemistry and Chemical Engineering, 79 West Yingze Street, Taiyuan 030024, People's Republic of China. E-mail: lixing@tyut.edu.cn

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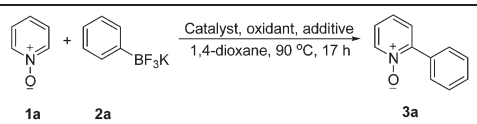
Results and discussion

We initiated our investigations by selecting pyridine *N*-oxide **1a** as a substrate model and potassium phenyltrifluoroborate **2a** as a coupling partner to optimize various reaction parameters. First, various catalysts were investigated for this transformation (ESI†), and $Pd(OAc)_2$ 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 that Ag_2O was essential for the formation of the desired product **3a** in the presence of $Pd(OAc)_2$ in 1,4-dioxane as a solvent (Table 1, entry 2). In contrast, a trace amount of the product was detected when Ag_2O was omitted (Table 1, entry 3). 14% yield was obtained with Ag_2CO_3 (Table 1, entry 4). In sharp contrast, Ag_2SO_4 gave a trace amount of the product and the reactions almost did not take place when $AgNO_3$ and $AgBF_4$ were used as oxidants (Table 1, entries 5–7). To improve the yield further, tetrabutylammonium salts as additives were screened.[13a] 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_2 and AgI were examined as additives, 66%, 62% and 66% yields were obtained, respectively (Table 1, entries 14–16). 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 $Pd(OAc)_2$ was used in combination with Ag_2O (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.

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 phenyltrifluoroborates 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,

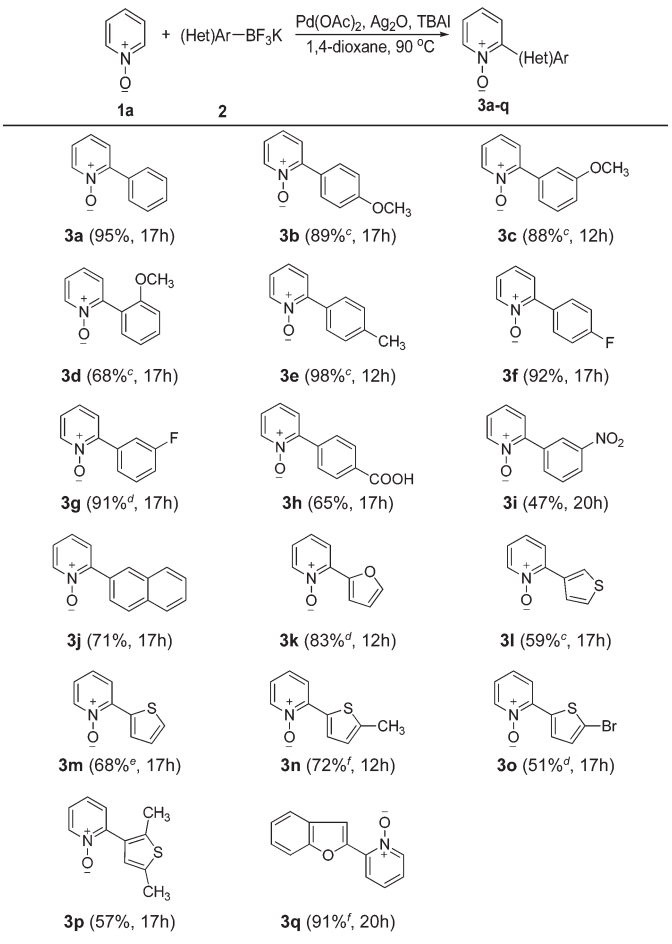
Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Oxidant	Additive	Yield (%)[b]
1	—	Ag_2O	—	n.r.[c]
2	$Pd(OAc)_2$	Ag_2O	—	60
3	$Pd(OAc)_2$	—	—	Trace
4	$Pd(OAc)_2$	Ag_2CO_3	—	14
5	$Pd(OAc)_2$	Ag_2SO_4	—	Trace
6	$Pd(OAc)_2$	$AgNO_3$	—	n.r.
7	$Pd(OAc)_2$	$AgBF_4$	—	n.r.
8	$Pd(OAc)_2$	Ag_2O	TBAF	81
9	$Pd(OAc)_2$	Ag_2O	TBAC	79
10	$Pd(OAc)_2$	Ag_2O	TBAB	78
11	$Pd(OAc)_2$	Ag_2O	TBAI	88(95[d])
12	$Pd(OAc)_2$	Ag_2O	TBAOH	80
13	$Pd(OAc)_2$	Ag_2O	TEAOH	49
14	$Pd(OAc)_2$	Ag_2O	KI	66
15	$Pd(OAc)_2$	Ag_2O	I_2	62
16	$Pd(OAc)_2$	Ag_2O	AgI	66

[a] Reactions were carried out with pyridine *N*-oxide **1a** (0.45 mmol), potassium phenyltrifluoroborate **2a** (0.15 mmol), oxidant (2.0 equiv.), $Pd(OAc)_2$ (10 mol%) and additive (20 mol%) in 1,4-dioxane (0.5 mL) at 90 °C for 17 h. [b] Isolated yield. [c] n.r. = no reaction. [d] 3.3 equiv. of pyridine *N*-oxide **1a** was used.

Table 2 Reactions of the pyridine *N*-oxide **1a** with various potassium (hetero)aryltrifluoroborates[a,b]



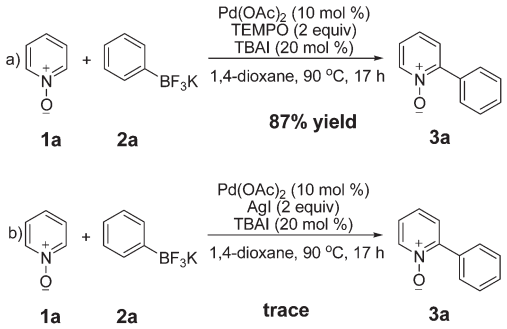
[a] Reactions were performed using pyridine *N*-oxide **1a** (0.5 mmol), potassium aryltrifluoroborate **2** (0.15 mmol), Ag_2O (0.3 mmol, 2 equiv.), $Pd(OAc)_2$ (10 mol%) and TBAI (20 mol%) in 1,4-dioxane (0.5 mL) at 90 °C for a specified time. [b] Isolated yield. [c] 80 °C. [d] 120 °C. [e] 110 °C. [f] 100 °C.

3f and **3g**). Potassium 4-formylphenyltrifluoroborate might give 65% yield (Table 2, **3h**). Unfortunately, only 47% yield was obtained with a NO_2 group (Table 2, **3i**). The product **3j** could be offered with 71% yield when this reaction system was applied to potassium 2-naphthyltrifluoroborate.

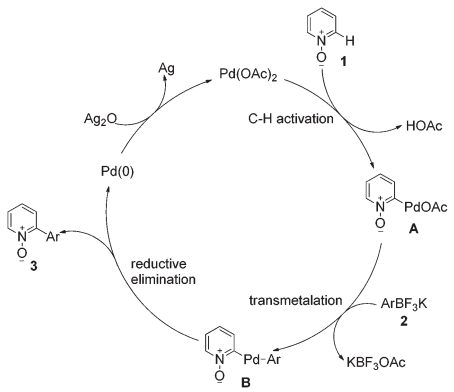
To expand the substrate scope, we applied this catalytic system to potassium heteroaryltrifluoroborates of a number of oxygen- or sulphur-containing heterocycles such as furan and thiophene. It was found that they could be employed as suitable substrates, giving the corresponding products **3k–q** in 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**).

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**).

To probe the reaction mechanism, the coupling of pyridine *N*-oxide with $PhBF_3K$ 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).[15] In addition, Ag(0) was detected by XPS in the reaction system that utilized Ag_2O as a oxidant (Table 1, entry 11). However, only a trace amount of product **3a** was provided when AgI was adopted as an oxidant and Ag(0) was not detected (Scheme 2b). On the basis of the observations and related precedents,[16] 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 leading 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).

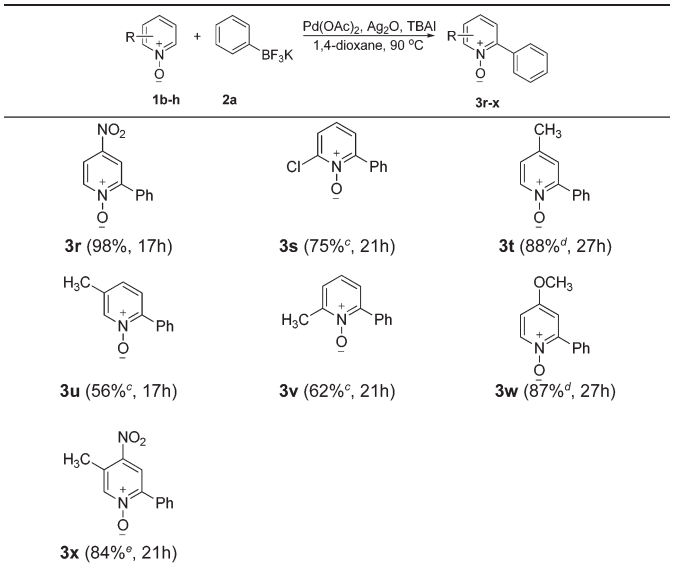


Scheme 2 Mechanistic studies.



Scheme 3 Proposed mechanism.

Table 3 Reactions of the potassium phenyltrifluoroborate **2a** with various pyridine *N*-oxides[a,b]



[a] Reactions were performed using pyridine *N*-oxide 1 (0.5 mmol), potassium aryltrifluoroborate 2a (0.15 mmol), Ag_2O (0.3 mmol, 2 equiv.), $Pd(OAc)_2$ (10 mol%) and TBAI (20 mol%) in 1,4-dioxane (0.5 mL) at 90 °C for a specified time. [b] Isolated yield. [c] 120 °C. [d] 100 °C. [e] 80 °C.

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-arylpyridine *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. Purification of the products was carried out by flash column chromatography on silica gel (200–300 mesh) using an ethyl acetate/alcohol gradient. In addition, all yields were referred to isolated yields (average of two runs) of compounds unless otherwise specified. On one hand, the known compounds were partly characterized by melting points (for solid samples) and ^{1}H NMR, and compared to authentic samples or the literature data. Melting points were determined with RD-II digital melting point apparatus and were uncorrected. ^{1}H NMR data were obtained at 300 K on a Bruker AMX-600 spectrometer. The ^{1}H NMR (600 MHz) chemical shifts were measured relative to $CDCl_3$ as the internal reference ($CDCl_3$: δ = 7.26 ppm). Spectra are reported as follows: chemical shift (δ = 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}C NMR and HR-MS as well. The ^{13}C NMR (100 MHz) chemical shifts were given using $CDCl_3$ as the internal standard ($CDCl_3$: δ = 77.16 ppm). High-resolution mass spectra (HR-MS) were obtained with 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 $Pd(OAc)_2$ (10 mol%), Ag_2O (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 in air. The reaction system was then stirred at 90 °C until potassium phenyltrifluoroborate was completely consumed as determined by TLC. Finally, 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}H NMR (600 MHz, $CDCl_3$): δ = 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 (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}H NMR (600 MHz, $CDCl_3$): δ = 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 (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}H NMR (600 MHz, $CDCl_3$): δ = 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 (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}H NMR (600 MHz, $CDCl_3$): δ = 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 (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}H NMR (600 MHz, $CDCl_3$): δ = 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 (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}H NMR (600 MHz, $CDCl_3$): δ = 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 (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}H NMR (600 MHz, $CDCl_3$): δ = 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; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 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 $C_{11}H_8FNO$ $[M + H]^+$ 190.0668, found 190.0662. IR (cm^{-1}, KBr): 3074, 3051, 2421, 1603, 1497, 1332, 1263, 1007, 801, 596.

4-(*N*-Oxopyridin-2-yl)benzoic acid (3h). R_f = 0.2 (AcOEt); yellow solid; m.p. = 162–164 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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^{-1}, KBr): 3632, 3103, 3051, 2443, 1597, 1497, 1348, 1203, 819, 796.

2-(3-Nitrophenyl)-pyridine *N*-oxide (3i). R_f = 0.4 (AcOEt/alcohol = 10/1 v/v); pale yellow solid; m.p. = 175–177 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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^{-1}, KBr): 3076, 3041, 1580, 1440, 1368, 1237, 1108, 928, 743.

2-(2-Naphthalenyl)-pyridine *N*-oxide (3j). R_f = 0.4 (AcOEt/alcohol = 6/1 v/v); white solid; m.p. = 139–141 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 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^{-1}, KBr): 3097, 3056, 1607, 1529, 1430, 1368, 1137, 892, 698.

2-(2-Furanyl)-pyridine *N*-oxide (3k). R_f = 0.4 (AcOEt); pale yellow solid; m.p. = 94–96 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 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^{-1}, KBr): 3075, 1594, 1498, 1423, 1276, 1258, 898, 841, 591.

2-(3-Thienyl)-pyridine *N*-oxide (3l). R_f = 0.4 (AcOEt); pale yellow solid; m.p. = 118–119 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 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^{-1}, KBr): 3044, 1563, 1477, 1450, 1291, 1197, 898, 872, 633.

2-(2-Thienyl)-pyridine *N*-oxide (3m). R_f = 0.4 (AcOEt); pale yellow solid; m.p. = 143–146 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 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^{-1}, KBr): 3059, 1544, 1498, 1423, 1276, 1258, 898, 841, 591.

2-(5-Methyl-2-thienyl)-pyridine *N*-oxide (3n). R_f = 0.4 (AcOEt); yellow solid; m.p. = 140–142 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 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^{-1}, KBr): 3034, 3017, 2986, 1599, 1509, 1479, 1329, 1276, 1128, 935, 698.

2-(5-Bromo-2-thienyl)-pyridine *N*-oxide (3o). R_f = 0.4 (AcOEt); pale yellow solid; m.p. = 164–166 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 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; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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_9H_6BrNOS $[M + H]^+$ 255.9432, found 255.9442. IR (cm^{-1}, KBr): 3071, 1603, 1508, 1329, 1307, 1258, 1124, 1085, 876, 691.

2-(2,5-Dimethyl-3-thienyl)-pyridine *N*-oxide (3p). R_f = 0.4 (AcOEt/alcohol = 6/1 v/v); pale yellow liquid; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 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; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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 $C_{11}H_{12}NOS$ $[M + H]^+$ 206.0640, found 206.0643. IR (cm^{-1}, KBr): 3077, 3049, 2989, 2908, 1583, 1494, 1371, 1267, 1209, 1107, 877, 806.

2-(2-Benzofuranyl)-pyridine *N*-oxide (3q). R_f = 0.5 (AcOEt); pale yellow solid; m.p. = 139–141 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 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^{-1}, KBr): 3098, 3059, 1558, 1494, 1307, 1298, 1109, 1047, 897, 791.

4-Nitro-2-phenylpyridine *N*-oxide (3r). R_f = 0.5 (AcOEt); pale yellow solid; m.p. = 135–136 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 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^{-1}, KBr): 3041, 1597, 1508, 1339, 1284, 1231, 1114, 895, 724.

2-Chloro-6-phenylpyridine *N*-oxide (3s). R_f = 0.3 (petroleum ether/AcOEt = 3/1 v/v); pale yellow solid; m.p. = 141–142 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 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^{-1}, KBr): 3048, 1610, 1508, 1497, 1328, 1263, 1209, 1095, 747, 678.

4-Methyl-2-phenylpyridine *N*-oxide (3t). R_f = 0.2 (AcOEt/alcohol = 6/1 v/v); pale yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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^{-1}, KBr): 3072, 2978, 1598, 1541, 1469, 1382, 1294, 1098, 814, 716.

5-Methyl-2-phenylpyridine *N*-oxide (3u). R_f = 0.3 (AcOEt/alcohol = 10/1 v/v); pale yellow solid; m.p. = 168–169 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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^{-1}, KBr): 3048, 2967, 1603, 1523, 1481, 1378, 1321, 1245, 1103, 829, 732, 699.

6-Methyl-2-phenylpyridine *N*-oxide (3v). R_f = 0.5 (petroleum ether/AcOEt = 2/1 v/v); pale yellow solid; m.p. = 118–119 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 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^{-1}, 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}H NMR (400 MHz, $CDCl_3$): δ = 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}C NMR (100 MHz, $CDCl_3$): δ = 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 $C_{12}H_{11}NO_2$[M + H]$^+$ 202.0868, found 202.0867. IR (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}H NMR (400 MHz, $CDCl_3$): δ = 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 (cm^{-1}, KBr): 3082, 1590, 1514, 1346, 1295, 1249, 1073, 827, 743.

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Notes and references

1 For selected examples, see: (*a*) A. G. Fang, J. V. Mello and N. S. Finney, *Org. Lett.*, 2003, **5**, 967; (*b*) Y. Liu, K. Ye, Y. Fan, W. Song, Y. Wang and Z. Hou, *Chem. Commun.*, 2009, 3699; (*c*) S. W. Thomas, K. Venkatesan, P. Müller and T. M. Swager, *J. Am. Chem. Soc.*, 2006, **128**, 16641; (*d*) A. S. Tsai, M. E. Tauchert, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2011, **133**, 1248.

2 For recent selected examples, see: (*a*) K. L. Billingsley and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2008, **47**, 4695; (*b*) D. X. Yang, S. L. Colletti, K. Wu, M. Song, G. Y. Li and H. C. Shen, *Org. Lett.*, 2009, **11**, 381; (*c*) S. Sakashita, M. Takizawa, J. Sugai, H. Ito and Y. Yamamoto, *Org. Lett.*, 2013, **15**, 4308; (*d*) J. Z. Deng, D. V. Paone, A. T. Ginnetti, H. Kurihara, S. D. Dreher, S. A. Weissman, S. R. Stauffer and C. S. Burgey, *Org. Lett.*, 2009, **11**, 345; (*e*) I. A. I. Mkhalid, D. N. Coventry, D. Albesa-Jove, A. S. Batsanov, J. A. K. Howard, R. N. Perutz and T. B. Marder, *Angew. Chem., Int. Ed.*, 2006, **45**, 489.

3 For recent selected examples, see: (*a*) M. Pal, V. R. Batchu, I. Dager, N. K. Swamy and S. Padakanti, *J. Org. Chem.*, 2005, **70**, 2376; (*b*) C. A. Fleckenstein and H. Plenio, *J. Org. Chem.*, 2008, **73**, 3236; (*c*) C. Liu and W. Yang, *Chem. Commun.*, 2009, 6267; (*d*) Y. Zou, G. Yue, J. Xu and J. Zhou, *Eur. J. Org. Chem.*, 2014, 5901; (*e*) C. Senter, A. Rumple, W. Medina-Ramos, D. Houle, Z. Cheng, C. Gelbaum, J. Fisk, B. Holden, P. Pollet, C. A. Eckerta and C. L. Liotta, *Org. Biomol. Chem.*, 2014, **12**, 7598.

4 (*a*) A. Larivée, J. J. Mousseau and A. B. Charette, *J. Am. Chem. Soc.*, 2007, **130**, 52; (*b*) J. Xu, G. Cheng, D. Su, Y. Liu, X. Wang and Y. Hu, *Chem. – Eur. J.*, 2009, **15**, 13105; (*c*) J. A. Bull, J. J. Mousseau, G. Pelletier and A. B. Charette, *Chem. Rev.*, 2012, **112**, 2642; (*d*) I. B. Seiple, S. Su, R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel and P. S. Baran, *J. Am. Chem. Soc.*, 2010, **132**, 13194.

5 (*a*) G. P. McGlacken and L. M. Bateman, *Chem. Soc. Rev.*, 2009, **38**, 2447; (*b*) F. Bellina and R. Rossi, *Tetrahedron*, 2009, **65**, 10269; (*c*) J. J. Mousseau and A. B. Charette, *Acc. Chem. Res.*, 2013, **46**, 412; (*d*) A. M. Berman, J. C. Lewis, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2008, **130**, 14926; (*e*) D. J. Schipper, L.-C. Campeau and K. Fagnou, *Tetrahedron*, 2009, **65**, 3155; (*f*) H. Zhao, R. Wang, P. Chen, B. T. Gregg, M. M. Hsia and W. Zhang, *Org. Lett.*, 2012, **14**, 1872; (*g*) C., S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (*h*) C. Liu, J. Yuan, M. Gao, S. Tang, W. Li, R. Shi and A. Lei, *Chem. Rev.*, 2015, **115**, 12138.

6 L.-C. Campeau, S. Rousseaux and K. Fagnou, *J. Am. Chem. Soc.*, 2005, **127**, 18020.

7 (*a*) J.-P. Leclerc and K. Fagnou, *Angew. Chem., Int. Ed.*, 2006, **45**, 7781; (*b*) L.-C. Campeau, M. Bertrand-Laperle, J.-P. Leclerc, E. Villemure, S. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2008, **130**, 3276; (*c*) M. P. Huestis and K. Fagnou, *Org. Lett.*, 2009, **11**, 1357; (*d*) D. Lapointe, T. Markiewicz, C. J. Whipp, A. Toderian and K. Fagnou, *J. Org. Chem.*, 2011, **76**, 749; (*e*) W. Liu, Y. Li, Y. Wang and C. Kuang, *Org. Lett.*, 2013, **15**, 4682; (*f*) G. Yan, A. J. Borah and M. Yang, *Adv. Synth. Catal.*, 2014, **356**, 2375.

8 (*a*) See ref. 6; (*b*) H.-Y. Sun, S. I. Gorelsky, D. R. Stuart, L.-C. Campeau and K. Fagnou, *J. Org. Chem.*, 2010, **75**, 8180; (*c*) F. Gosselin, S. J. Savage, N. Blaquiere and S. T. Staben, *Org. Lett.*, 2012, **14**, 862; (*d*) L.-C. Campeau, D. R. Stuart, J.-P. Leclerc, M. Bertrand-Laperle, E. Villemure, H.-Y. Sun, S. Lasserre, N. Guimond, M. Lecavallier and K. Fagnou, *J. Am. Chem. Soc.*, 2009, **131**, 3291; (*e*) S. Duric and C. C. Tzschucke, *Org. Lett.*, 2011, **13**, 2310; (*f*) M. P. Huestis and K. Fagnou, *Org. Lett.*, 2009, **11**, 1357.

9 D. J. Schipper, M. El-Salfiti, C. J. Whipp and K. Fagnou, *Tetrahedron*, 2009, **65**, 4977.

10 L. Ackermann and S. Fenner, *Chem. Commun.*, 2011, **47**, 430.

11 (*a*) P. Mai, J. Yuan, Z. Li, G. Sun and L. Qu, *Synlett*, 2012, 145; (*b*) Y. Shen, J. Chen, M. Liu, J. Ding, W. Gao, X. Huang and H. Wu, *Chem. Commun.*, 2014, **50**, 4292.

12 R. Suresh, S. Muthusubramanian, R. S. Kumaran and G. Manickam, *Asian J. Org. Chem.*, 2014, **3**, 604.

13 (*a*) X. Gong, G. Song, H. Zhang and X. Li, *Org. Lett.*, 2011, **13**, 1766; (*b*) S. H. Cho, S. J. Hwang and S. Chang, *J. Am. Chem. Soc.*, 2008, **130**, 9254.

14 For recent reviews and selected examples on the coupling reactions with R-BF_3K salts, see: (*a*) S. Darses and J.-P. Genet, *Chem. Rev.*, 2008, **108**, 288; (*b*) G. A. Molander, C.-S. Yun, M. Ribagorda and B. Biolatto, *J. Org. Chem.*, 2003, **68**, 5534; (*c*) E. Alacid and C. Nájera, *Org. Lett.*, 2008, **10**, 5011; (*d*) V. Colombel, M. Presset, D. Oehlrich, F. Rombouts and G. A. Molander, *Org. Lett.*, 2012, **14**, 1680; (*e*) A. Joliton and E. M. Carreira, *Org. Lett.*, 2013, **15**, 5147; (*f*) J.-J. Tan, Y.-G. Chen, H.-M. Li and N. Yasuda, *J. Org. Chem.*, 2014, **79**, 8871; (*g*) H. Huang, K. Jia and Y. Chen, *Angew. Chem., Int. Ed.*, 2015, **54**, 1881.

15 H. Wang, S. Yu, Z. Qi and X. Li, *Org. Lett.*, 2015, **17**, 2812.

16 (*a*) K. M. Engle, P. S. Thuy-Boun, M. Dang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 18183; (*b*) W.-H. Rao and B.-F. Shi, *Org. Lett.*, 2015, **17**, 2784; (*c*) Y. Tan, F. Barrios-Lan deros and J. F. Hartwig, *J. Am. Chem. Soc.*, 2012, **134**, 3683.

