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Palladium-Catalyzed Direct C(sp^2)−H Alkoxylation of 2-Aryloxypyridines Using 2-Pyridyloxyl as the Directing Group

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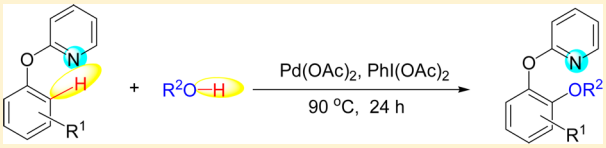
Supporting Information

ABSTRACT: An efficient and highly regioselective palladium-catalyzed *ortho*-C(sp^2)−H bond alkoxylation of 2-aryloxypyridines was developed using 2-pyridyloxyl as the directing group and alcohols as alkoxylation reagents. Under an air atmosphere and in the presence of PhI(OAc)$_2$, the reaction gave the corresponding products in moderate to good yields, and a series of functional groups could be tolerated.



Transition-metal-catalyzed direct C−H bond functionalization has been used in the construction of a variety of carbon−carbon and carbon−heteroatom bonds with features of step-economics and green chemistry primarily.[1] By this strategy, a series of valuable polyfunctional compounds can be synthesized expediently. Among numerous functional groups used as the directing groups in C−H bond functionalization, 2-pyridyl has been thoroughly investigated because of its moderate coordination ability to transition metals and transformation ability. The alkenylation,[2] arylation,[3] acetoxylation,[4] acylation,[5] alkylation,[6] and halogenation[7] on the *ortho*-C(sp^2)−H bond of 2-arylpyridines were intensively studied. Pyridyl-directed C(sp^3)−H bond activations were also developed.[8] To expand the directing function of the pyridyl group is still necessary and valuable. Very recently, a number of C−C bond formation reactions directed by 2-pyridyloxyl were developed, e.g., Pd[9]- or Ru[10]-catalyzed *ortho*-arylation of 2-phenoxypyridines, Pd[11]- or Ru[12]-catalyzed oxidative alkenylation of 2-phenoxypyridines, Pd-catalyzed oxidative C(sp^2)−H acylation,[13] and Pd-catalyzed oxidative alkoxycarbonylation.[14] In these transition-metal-catalyzed C−C bond formation reactions, the six-membered cyclopalladated intermediates were generated by the coordination of the pyridyl group to metals. It is well-known that alkoxyl is an important functional group in organic chemistry; the aryl ethers are also a common motif in pharmaceuticals, functional materials, and many other fine chemicals.[15] Though a few transition-metal-catalyzed direct alkoxylation of arenes to form aryl ethers were developed, compared with the transition-metal-catalyzed direct aromatic C−C bond formation reaction, the alkoxylation of inert C−H is more difficult and still needed to be studied more adequately.[16] On the other hand, 2-phenoxypyridine series compounds have interesting bioactivities and have aroused much attention in the pharmaceutical field.[17] Therefore, to develop the simple and efficient route for the structural modification of these compounds should be significant and valuable. For this purpose, in this note, we describe a Pd-catalyzed *ortho*-alkoxylation of C(sp^2)−H bonds on benzene ring using 2-pyridyloxyl as the directing group and alcohols as alkoxylation reagents.

Optimization studies were performed with 2-(3-methoxyphenoxy)pyridine and methanol in the presence of palladium catalyst and oxidant; the results are summarized in Table 1. The oxidant was very important to the transition-metal-catalyzed alkoxylation reaction.[16] Thus, using Pd(OAc)$_2$ (10 mol %) as the catalyst and methanol as both methoxylation reagent and the solvent, a series of oxidants were first tested for this transformation. Unfortunately, in the presence of AgOAc, BQ (benzoquinone), or O_2, no conversion was observed at 90 °C for 24 h (entries 1−3). We tried other oxidants including $K_2S_2O_8$, $Na_2S_2O_8$, $(NH_4)_2S_2O_8$, and Cu(OAc)$_2$ again, yet only a trace of alkoxylation product was found (entries 4−7). However, to our delight, when 1 equiv of PhI(OAc)$_2$ was added, the desired product was obtained in 44% yield (entry 8). When the amount of PhI(OAc)$_2$ was increased to 2 equiv, a yield of 83% was afforded (entry 9). We then tested the effect of additive. The result showed that the addition of AcOH did not improve the present reaction significantly (entry 11), whereas TFA, TsOH, or $MeSO_3H$ had an evident inhibition to the reaction (entries 12−14). At 90 °C, the reaction gave the highest yield. Raising the reaction temperature to 100 °C could not improve the yield obviously, but reducing it to 70 °C led to the decrease of the reaction activity (entry 9). The appropriate amount of catalyst was 10 mol %. To decrease the amount of Pd(OAc)$_2$ to 5 mol % brought a lower yield of 58% (entry 10). Furthermore, we explored other palladium catalysts, such as $PdCl_2$, $PdCl_2(MeCN)_2$, and $Pd(PPh_3)_4$; the results revealed that they were substantially less effective to the reaction (entries 15−17). Additionally, if mixed solvent MeOH/MeCN (1:1) or

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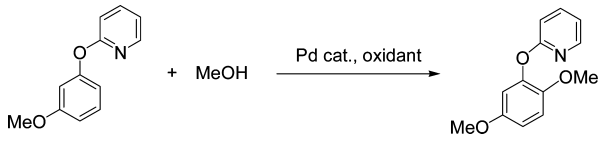
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	oxidant (equiv)	additive (equiv)	yield (%)[b]
1	$Pd(OAc)_2$	AgOAc (1)	none	0
2	$Pd(OAc)_2$	BQ (1)	none	0
3	$Pd(OAc)_2$	O_2 (1 atm)	none	0
4	$Pd(OAc)_2$	$K_2S_2O_8$ (1)	none	<5
5	$Pd(OAc)_2$	$Na_2S_2O_8$ (1)	none	<5
6	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$ (1)	none	<5
7	$Pd(OAc)_2$	$Cu(OAc)_2$ (1)	none	<5
8	$Pd(OAc)_2$	$PhI(OAc)_2$ (1)	none	44
9	$Pd(OAc)_2$	$PhI(OAc)_2$ (2)	none	83 (53, 85)[c]
10[d]	$Pd(OAc)_2$	$PhI(OAc)_2$ (2)	none	58
11	$Pd(OAc)_2$	$PhI(OAc)_2$ (2)	AcOH (5)	81
12	$Pd(OAc)_2$	$PhI(OAc)_2$ (2)	TFA (5)	<10
13	$Pd(OAc)_2$	$PhI(OAc)_2$ (2)	TsOH (5)	0
14	$Pd(OAc)_2$	$PhI(OAc)_2$ (2)	$MeSO_3H$ (5)	0
15	$PdCl_2$	$PhI(OAc)_2$ (2)	none	<5
16	$PdCl_2(CH_3CN)_2$	$PhI(OAc)_2$ (2)	none	16
17	$Pd(PPh_3)_4$	$PhI(OAc)_2$ (2)	none	27
18[e]	$Pd(OAc)_2$	$PhI(OAc)_2$ (2)	none	<10

[a]Unless otherwise specified, the reactions were carried out in a sealed tube in the presence of 2-(3-methoxyphenoxy)pyridine (0.5 mmol), methanol (2 mL), catalyst (10 mol %), and oxidant (1 mmol) under an air atmosphere at 90 °C for 24 h. [b]Isolated yields. [c]At 70 and 100 °C, respectively. [d]$Pd(OAc)_2$ (5 mol %) was used. [e]Mixed solvent MeOH/MeCN (1:1, 2 mL) or MeOH/dioxane (1:1, 2 mL) was used.

MeOH/dioxane (1:1) was used, very low yields were obtained (entry 18).

We then assessed the scope of the reaction between 2-phenoxypyridine derivatives **1**(**a**−**n**) and several alcohols **2**(**a**−**d**) under the optimized reaction conditions (Table 2). Using methanol as the coupling partner, various 2-aryloxypyridines were first examined and the corresponding *ortho*-monomethoxylation products were obtained selectively. The presence of a substituent group on the benzene ring affected the yield of the reaction obviously. It seemed that an electron-rich benzene ring was favorable to this alkoxylation reaction. When the electron-donating group such as methoxyl and methyl substituted on the benzene ring (**1a**−**j**), the higher yields could be obtained. In particular, the reactants with a strong electron-donating group alkoxyl gave the best results (**3ea**, **3fa**, **3ja**). However, when a methyl existed on the *ortho*-position, a low yield of 38% was obtained, which could be attributed to the steric hindrance (**3da**). It is interesting that, when 2-(3-methylphenoxy)pyridine (**1c**) or 2-(3-methoxyphenoxy)pyridine (**1f**) was employed as the reaction substrate, only the product **3ca** or **3fa** was found, but when 2-(benzo[*d*][1,3]dioxol-5-yloxy)pyridine (**1j**) was used, a mixture of **3ja** and **3ja′** was produced with a ratio of 1.2:1, which suggested that the steric hindrance in **1j** was weaker than other 3-substituted reactants. Another reason might be the strong electron-donating property of the substituent group in **1j** bringing about the decrease of the regioselectivity. In contrast, the presence of electron-withdrawing groups, including Cl, Br, and COOMe, led to the lower yields (**3ka**−**3na**).

Some other alcohols, such as ethanol (**2b**), propanol (**2c**), and a secondary alcohol isopropanol (**2d**), were also used as the coupling partners for this Pd-catalyzed alkoxylation reaction, and the desired *ortho*-alkoxylation products were obtained in moderate to good yields (**3ab**−**3fd**). Significantly, an electron-donating group methoxyl substituted on the *meta*-position of the benzene ring increased the reactivity of these transformations similarly as above (**3fb**, **3fc**, **3fd**). It should be pointed out that, in some cases, the presence of 10 equiv of AcOH was helpful to improve the yields.

In summary, we have developed a new palladium-catalyzed direct $C(sp^2)$−H alkoxylation using 2-pyridyloxyl as the directing group and obtained *ortho*-alkoxylation products on the benzene ring selectively in moderate to good yields. This technology was available for both primary and secondary alcohols. The reaction could proceed smoothly in an air atmosphere under mild reaction conditions, making the method highly applicable.

EXPERIMENTAL SECTION

General. All reactions were run in oven-dried flasks under air. Alcohols were dried using a general method; other reagents were commercially available and were used without purification. NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) using TMS as an internal standard. Chemical shifts are given relative to $CDCl_3$ (7.28 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR).. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet. Melting points are uncorrected. For the HRMS measurements, Q-TOF was used.

General Experimental Procedures and Characterizations. 2-Aryloxypyridine (0.5 mmol), $PhI(OAc)_2$ (1 mmol), $Pd(OAc)_2$ (0.05 mmol), and alcohol (2 mL) were added in a 25 mL sealed tube with a Teflon-lined cap. The mixture was heated at 90 °C (oil bath temperature) for 24 h. After cooling to room temperature, the volatiles were removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel using hexane/ethyl acetate (10:1, v/v) as eluent to give the corresponding product. For the solid

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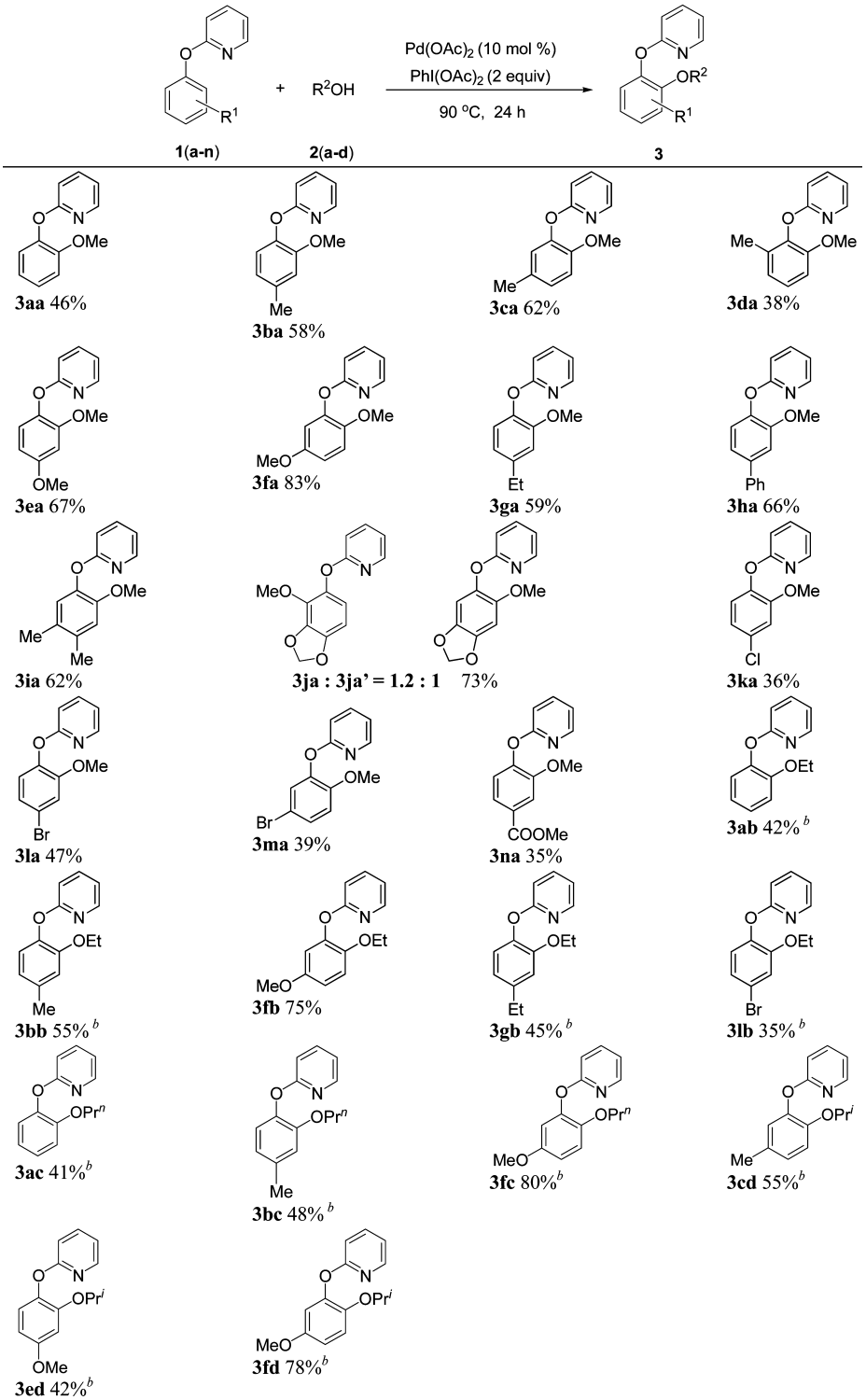
Table 2. *ortho*-Alkoxylation of 2-Phenoxypyridine Derivatives with Alcohols[a,b]



[a]Unless otherwise specified, all reactions were carried out with 2-phenoxypyridine derivatives (**1**, 0.5 mmol), alcohol (**2**, 2 mL), $Pd(OAc)_2$ (10 mol %), and $PhI(OAc)_2$ (1.0 mmol) under air atmosphere at 90 °C for 24 h. All listed yields are isolated ones. [b]10 equiv of AcOH was used as the additive.

products, the melting points were obtained after further recrystallization from this mixed solvent.

*2-(2-Methoxyphenoxy)pyridine (**3aa**).* Yield: 46% (46 mg). R_f 0.46. White solid, mp: 69−71 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18−8.16 (m, 1H), 7.70−7.66 (m, 1H), 7.25−7.21 (m, 1H), 7.16 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.05−6.93 (m, 4H), 3.79 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.7, 151.8, 147.6, 142.6, 139.2, 126.0, 123.1, 121.1, 118.0, 112.9, 110.7, 55.9. HRMS-ESI (m/z): calcd for $C_{12}H_{12}NO_2$ $[M + H]^+$ 202.0863, found 202.0859.

*2-(2-Methoxy-4-methylphenoxy)pyridine (**3ba**).* Yield: 58% (62 mg). R_f 0.42. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17−8.16 (m, 1H), 7.68−7.64 (m, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.97−6.91 (m, 2H), 6.85−6.80 (m, 2H), 3.77 (s, 3H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.9, 151.4, 147.5, 140.2, 139.1, 135.9, 122.8,

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121.5, 117.8, 113.8, 110.6, 55.9, 21.5. HRMS-ESI (m/z): calcd for $C_{13}H_{14}NO_2$ $[M + H]^+$ 216.1019, found 216.1013.

2-(2-Methoxy-5-methylphenoxy)pyridine (**3ca**). Yield: 62% (66 mg). R_f 0.43. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18−8.17 (m, 1H), 7.69−7.65 (m, 1H), 7.02−6.91 (m, 5H), 3.75 (s, 3H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.8, 149.6, 147.6, 142.3, 139.1, 130.8, 126.3, 123.7, 117.9, 113.0, 110.7, 56.1, 20.6. HRMS-ESI (m/z): calcd for $C_{13}H_{14}NO_2$ $[M + H]^+$ 216.1019, found 216.1014.

2-(2-Methoxy-6-methylphenoxy)pyridine (**3da**). Yield: 38% (41 mg). R_f 0.43. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17−8.15 (m, 1H), 7.69−7.64 (m, 1H), 7.13 (t, J = 8.0 Hz, 1H), 6.96−6.86 (m, 4H), 3.75 (s, 3H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.4, 152.1, 147.6, 139.2, 132.5, 130.9, 125.6, 122.9, 117.7, 110.2, 109.9, 56.0, 16.2. HRMS-ESI (m/z): calcd for $C_{13}H_{14}NO_2$ $[M + H]^+$ 216.1019, found 216.1013.

2-(2,4-Dimethoxyphenoxy)pyridine (**3ea**). Yield: 67% (77 mg). R_f 0.40. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17−8.15 (m, 1H), 7.67−7.63 (m, 1H), 7.07 (d, J = 8.8 Hz, 1H), 6.95−6.89 (m, 2H), 6.60 (d, J = 2.8 Hz, 1H), 6.51 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1, 157.8, 152.5, 147.5, 139.1, 136.2, 123.2, 117.8, 110.4, 104.2, 100.7, 55.9, 55.6. HRMS-ESI (m/z): calcd for $C_{13}H_{14}NO_3$ $[M + H]^+$ 232.0968, found 232.0978.

2-(2,5-Dimethoxyphenoxy)pyridine (**3fa**). Yield: 83% (96 mg). R_f 0.38. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (dd, J_1 = 5.2 Hz, J_2 = 1.6 Hz, 1H), 7.69−7.65 (m, 1H), 6.98−6.92 (m, 3H), 6.78−6.73 (m, 2H), 3.77 (s, 3H), 3.72 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.6, 154.1, 147.6, 146.0, 143.3, 139.2, 118.1, 114.2, 110.7, 110.5, 109.6, 56.8, 55.7. HRMS-ESI (m/z): calcd for $C_{13}H_{14}NO_3$ $[M + H]^+$ 232.0968, found 232.0979.

2-(4-Ethyl-2-methoxyphenoxy)pyridine (**3ga**). Yield: 59% (67 mg). R_f 0.45. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (dd, J_1 = 5.2 Hz, J_2 = 1.6 Hz, 1H), 7.68−7.64 (m, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.96−6.91 (m, 2H), 6.87−6.83 (m, 2H), 3.78 (s, 3H), 2.68 (q, J = 7.6 Hz, 2H), 1.29 (t, J = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.9, 151.0, 147.6, 142.1, 140.4, 139.1, 122.7, 120.2, 117.9, 112.7, 110.6, 55.9, 28.8, 15.4. HRMS-ESI (m/z): calcd for $C_{14}H_{16}NO_2$ $[M + H]^+$ 230.1176, found 230.1184.

2-((3-Methoxy-[1,1′-biphenyl]-4-yl)oxy)pyridine (**3ha**). Yield: 66% (91 mg). R_f 0.35. White solid, mp: 115−117 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22−8.20 (m, 1H), 7.73−7.69 (m, 1H), 7.64−7.61 (m, 2H), 7.49−7.45 (m, 2H), 7.40−7.36 (m, 1H), 7.24 (d, J = 0.8 Hz, 3H), 7.01−6.98 (m, 2H), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.7, 151.9, 147.6, 142.1, 141.0, 139.4, 139.3, 128.8, 127.3, 127.2, 123.2, 119.9, 118.1, 112.0, 110.9, 56.0. HRMS-ESI (m/z): calcd for $C_{18}H_{16}NO_2$ $[M + H]^+$ 278.1176, found 278.1178.

2-(2-Methoxy-4,5-dimethylphenoxy)pyridine (**3ia**). Yield: 62% (71 mg). R_f 0.42. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18−8.17 (m, 1H), 7.68−7.64 (m, 1H), 6.96−6.92 (m, 3H), 6.83 (s, 1H), 3.75 (s, 3H), 2.28 (s, 3H), 2.22 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.0, 149.4, 147.6, 140.0, 139.1, 134.0, 129.1, 124.1, 117.8, 114.8, 110.6, 56.2, 19.8, 19.0. HRMS-ESI (m/z): calcd for $C_{14}H_{16}NO_2$ $[M + H]^+$ 230.1176, found 230.1183.

2-((4-Methoxybenzo[d][1,3]dioxol-5-yl)oxy)pyridine (**3ja**). Yield: 40% (49 mg). R_f 0.43. White solid, mp: 103−105 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19−8.17 (m, 1H), 7.70−7.66 (m, 1H), 6.98−6.92 (m, 2H), 6.63 (d, J = 8.8 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 6.00 (s, 2H), 3.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.0, 147.5, 146.4, 139.9, 139.2, 138.1, 137.0, 118.0, 115.1, 110.5, 102.0, 101.6, 59.9. HRMS-ESI (m/z): calcd for $C_{13}H_{12}NO_4$ $[M + H]^+$ 246.0761, found 246.0772.

2-((6-Methoxybenzo[d][1,3]dioxol-5-yl)oxy)pyridine (**3ja′**). Yield: 33% (40 mg). R_f 0.38. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18−8.16 (m, 1H), 7.69−7.65 (m, 1H), 6.98−6.92 (m, 2H), 6.72 (s, 1H), 6.67 (s, 1H), 5.97 (s, 2H), 3.71 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.9, 147.5, 146.6, 144.9, 141.1, 139.2, 136.1, 118.0, 110.6, 104.8, 101.5, 96.7, 57.2. HRMS-ESI (m/z): calcd for $C_{13}H_{12}NO_4$ $[M + H]^+$ 246.0761, found 246.0772.

2-(4-Chloro-2-methoxyphenoxy)pyridine (**3ka**). Yield: 36% (42 mg). R_f 0.37. White solid, mp: 60−62 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16−8.14 (m, 1H), 7.72−7.67 (m, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.01−6.95 (m, 4H), 3.78 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.4, 152.4, 147.5, 141.2, 139.3, 130.9, 123.9, 120.9, 118.3, 113.5, 110.8, 56.1. HRMS-ESI (m/z): calcd for $C_{12}H_{11}NO_2Cl$ $[M + H]^+$ 236.0473, found 236.0484.

2-(4-Bromo-2-methoxyphenoxy)pyridine (**3la**). Yield: 47% (65 mg). R_f 0.40. White solid, mp: 63−65 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16−8.14 (m, 1H), 7.72−7.67 (m, 1H), 7.13 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 2H), 7.03 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.00−6.95 (m, 2H), 3.77 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.3, 152.5, 147.4, 141.8, 139.3, 124.4, 124.0, 118.4, 118.3, 116.4, 110.8, 56.1. HRMS-ESI (m/z): calcd for $C_{12}H_{11}NO_2Br$ $[M + H]^+$ 279.9968, found 279.9980.

2-(5-Bromo-2-methoxyphenoxy)pyridine (**3ma**). Yield: 39% (54 mg). R_f 0.42. White solid, mp: 81−83 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17−8.15 (m, 1H), 7.72−7.67 (m, 1H), 7.31 (dd, J_1 = 9.6 Hz, J_2 = 1.6 Hz, 2H), 7.01−6.95 (m, 2H), 6.89 (d, J = 8.8 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.2, 151.2, 147.5, 143.3, 139.4, 128.7, 126.2, 118.5, 114.1, 112.4, 110.9, 56.1. HRMS-ESI (m/z): calcd for $C_{12}H_{11}NO_2Br$ $[M + H]^+$ 279.9968, found 279.9978.

Methyl 3-Methoxy-4-(pyridin-2-yloxy)benzoate (**3na**). Yield: 35% (45 mg). R_f 0.34. White solid, mp: 95−97 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16−8.14 (m, 1H), 7.74−7.69 (m, 3H), 7.19 (d, J = 8.0 Hz, 1H), 7.02−6.98 (m, 2H), 3.93 (s, 3H), 3.84 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.6, 163.2, 151.5, 147.5, 146.8, 139.4, 127.6, 123.0, 122.6, 118.6, 113.8, 111.2, 56.1, 52.2. HRMS-ESI (m/z): calcd for $C_{14}H_{14}NO_4$ $[M + H]^+$ 260.0917, found 260.0924.

2-(2-Ethoxyphenoxy)pyridine (**3ab**). Yield: 42% (45 mg). R_f 0.45. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (dd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, 1H), 7.69−7.65 (m, 1H), 7.18 (d, J = 7.6 Hz, 2H), 7.02−6.98 (m, 2H), 6.97−6.91 (m, 2H), 4.00 (q, J = 6.8 Hz, 2H), 1.17 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.9, 151.0, 147.4, 139.0, 129.7, 125.9, 123.0, 121.2, 117.9, 114.4, 110.7, 64.4, 14.6. HRMS-ESI (m/z): calcd for $C_{13}H_{14}NO_2$ $[M + H]^+$ 216.1019, found 216.1016.

2-(2-Ethoxy-4-methylphenoxy)pyridine (**3bb**). Yield: 55% (63 mg). R_f 0.43. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (d, J = 4.0 Hz, 1H), 7.68−7.63 (m, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.96−6.92 (m, 2H), 6.83−6.80 (m, 2H), 3.99 (q, J = 7.2 Hz, 2H), 2.37 (s, 3H), 1.17 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1, 150.7, 147.4, 140.7, 139.0, 135.7, 122.7, 121.6, 117.7, 115.3, 110.6, 64.4, 21.4, 14.7. HRMS-ESI (m/z): calcd for $C_{14}H_{16}NO_2$ $[M + H]^+$ 230.1176, found 230.1170.

2-(2-Ethoxy-5-methoxyphenoxy)pyridine (**3fb**). Yield: 75% (92 mg). R_f 0.38. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17−8.15 (m, 1H), 7.67−7.63 (m, 1H), 6.97−6.91 (m, 3H), 6.77 (d, J = 2.8 Hz, 1H), 6.71 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 3.91 (q, J = 7.2 Hz, 2H), 3.76 (s, 3H), 1.10 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.8, 154.3, 147.4, 145.1, 144.0, 139.1, 118.1, 116.1, 110.7, 110.5, 109.4, 65.5, 55.6, 14.8. HRMS-ESI (m/z): calcd for $C_{14}H_{16}NO_3$ $[M + H]^+$ 246.1125, found 246.1134.

2-(2-Ethoxy-4-ethylphenoxy)pyridine (**3gb**). Yield: 45% (54 mg). R_f 0.42. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18−8.16 (m, 1H), 7.67−7.63 (m, 1H), 7.08 (d, J = 7.6 Hz, 1H), 6.96−6.91 (m, 2H), 6.86−6.82 (m, 2H), 4.00 (q, J = 7.2 Hz, 2H), 2.67 (q, J = 7.6 Hz, 2H), 1.28 (t, J = 7.6 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1, 150.7, 147.4, 142.0, 140.9, 139.0, 122.6, 120.4, 117.8, 114.2, 110.6, 64.4, 28.7, 15.5, 14.7. HRMS-ESI (m/z): calcd for $C_{15}H_{18}NO_2$ $[M + H]^+$ 244.1332, found 244.1340.

2-(4-Bromo-2-ethoxyphenoxy)pyridine (**3lb**). Yield: 35% (52 mg). R_f 0.40. White solid, mp: 89−91 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (dd, J_1 = 5.2 Hz, J_2 = 1.2 Hz, 1H), 7.70−7.66 (m, 1H), 7.13−7.11 (m, 2H), 7.05 (d, J = 8.8 Hz, 1H), 6.99−6.94 (m, 2H), 3.97 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.5, 151.8, 147.3, 142.2, 139.2, 124.2, 124.0, 118.2, 117.5, 110.9, 64.7, 14.4. HRMS-ESI (m/z): calcd for $C_{13}H_{13}NO_2Br$ $[M + H]^+$ 294.0124, found 294.0127.

2-(2-Propoxyphenoxy)pyridine (**3ac**). Yield: 41% (47 mg). R_f 0.44. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17−8.15 (m, 1H), 7.68−7.64 (m, 1H), 7.22−7.18 (m, 2H), 7.03−6.98 (m, 2H), 6.96−6.92 (m, 2H), 3.89 (t, J = 6.4 Hz, 2H), 1.61−1.53 (m, 2H), 0.74 (t, J = 7.6 Hz,

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3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.9, 151.2, 147.4, 142.9, 139.0, 125.9, 123.1, 121.0, 117.8, 114.0, 110.6, 70.1, 22.4, 10.2. HRMS-ESI (m/z): calcd for $C_{14}H_{16}NO_2$ $[M + H]^+$ 230.1176, found 230.1169.

*2-(4-Methyl-2-propoxyphenoxy)pyridine (**3bc**).* Yield: 48% (58 mg). R_f 0.42. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17−8.15 (m, 1H), 7.67−7.63 (m, 1H), 7.07 (d, J = 7.6 Hz, 1H), 6.95−6.91 (m, 2H), 6.83−6.79 (m, 2H), 3.88 (t, J = 6.4 Hz, 2H), 2.38 (s, 3H), 1.62−1.53 (m, 2H), 0.74 (t, J = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1, 150.8, 147.4, 140.6, 139.0, 135.8, 122.7, 121.5, 117.7, 114.9, 110.5, 70.1, 22.5, 21.5, 10.2. HRMS-ESI (m/z): calcd for $C_{15}H_{18}NO_2$ $[M + H]^+$ 244.1332, found 244.1339.

*2-(5-Methoxy-2-propoxyphenoxy)pyridine (**3fc**).* Yield: 80% (103 mg). R_f 0.38. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17−8.15 (m, 1H), 7.68−7.64 (m, 1H), 6.97−6.91 (m, 3H), 6.80 (d, J = 2.8 Hz, 1H), 6.72 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 3.82 (t, J = 6.4 Hz, 2H), 3.78 (s, 3H), 1.56−1.48 (m, 2H), 0.72 (t, J = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.8, 154.2, 147.5, 145.3, 143.8, 139.1, 118.0, 115.6, 110.6, 110.5, 109.4, 71.2, 55.7, 22.6, 10.2. HRMS-ESI (m/z): calcd for $C_{15}H_{18}NO_3$ $[M + H]^+$ 260.1281, found 260.1285.

*2-(2-Isopropoxy-5-methylphenoxy)pyridine (**3cd**).* Yield: 55% (67 mg). R_f 0.42. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18−8.17 (m, 1H), 7.68−7.64 (m, 1H), 7.01−6.98 (m, 3H), 6.97−6.89 (m, 2H), 4.45−4.36 (m, 1H), 2.33 (s, 3H), 1.13 (d, J = 6.4 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.0, 147.6, 147.4, 144.0, 139.0, 131.3, 126.2, 123.8, 117.8, 117.1, 110.7, 71.8, 22.0, 20.7. HRMS-ESI (m/z): calcd for $C_{15}H_{18}NO_2$ $[M + H]^+$ 244.1332, found 244.1334.

*2-(2-Isopropoxy-4-methoxyphenoxy)pyridine (**3ed**).* Yield: 42% (54 mg). R_f 0.40. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17−8.15 (m, 1H), 7.67−7.62 (m, 1H), 7.09 (d, J = 8.4 Hz, 1H), 6.95−6.92 (m, 1H), 6.88 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 6.59 (d, J = 2.8 Hz, 1H), 6.52 (dd, J_1 = 8.8 Hz, J_2 = 3.2 Hz, 1H), 4.49−4.40 (m, 1H), 3.82 (s, 3H), 1.15 (d, J = 6.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.2, 157.5, 150.6, 147.4, 138.9, 137.7, 123.3, 117.7, 110.5, 104.8, 103.6, 71.5, 55.6, 21.9. HRMS-ESI (m/z): calcd for $C_{15}H_{18}NO_3$ $[M + H]^+$ 260.1281, found 260.1282.

*2-(2-Isopropoxy-5-methoxyphenoxy)pyridine (**3fd**).* Yield: 78% (101 mg). R_f 0.39. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18−8.16 (m, 1H), 7.67−7.62 (m, 1H), 6.96−6.93 (m, 2H), 6.88 (dd, J_1 = 8.4 Hz, J_2 = 0.8 Hz, 1H), 6.77 (d, J = 3.2 Hz, 1H), 6.70 (dd, J_1 = 8.8 Hz, J_2 = 3.2 Hz, 1H), 4.34−4.28 (m, 1H), 3.76 (s, 3H), 1.11 (d, J = 6.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.7, 154.7, 147.5, 145.3, 143.8, 139.1, 119.1, 118.1, 110.7, 110.6, 109.3, 72.8, 55.6, 22.1. HRMS-ESI (m/z): calcd for $C_{15}H_{18}NO_3$ $[M + H]^+$ 260.1281, found 260.1287.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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