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Note

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.5b00167 • Publication Date (Web): 09 Feb 2015

Just Accepted

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Palladium-Catalyzed Aryl C(sp^2)–H Bond Hydroxylation of 2-Arylpyridine Using TBHP as Oxidant

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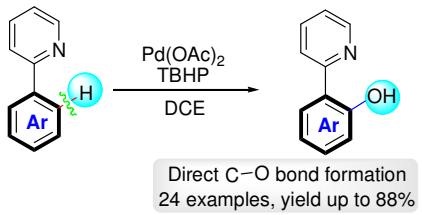


ABSTRACT: An efficient synthesis of phenols via Pd-catalyzed, pyridyl-directed homogeneous hydroxylation of aryl C–H bond was developed, in which *tert*-butyl hydroperoxide (TBHP) was used as the sole oxidant. The method had a broad group tolerance and was available for both electron-rich and electron-deficient substrates. The reaction of a series of 2-arylpyridine derivatives gave the *ortho*-hydroxylation products in moderate to good yields.

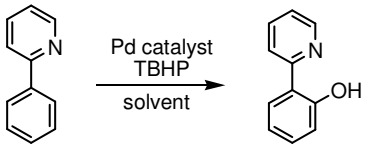
As a class of important compounds, phenols are naturally abundant. Besides of their application in organic synthesis, phenols are major constituents of many biological and natural compounds and almost ubiquitously exist in the structural organization of plants and animals.[1] Phenolic compounds were generally industrially synthesized by multi-step procedures as represented by the cumene process.[1b] In view of green and sustainable chemistry as well as in economic terms, a direct C(sp^2)–H bond hydroxylation for phenol synthesis with an inexpensive oxidant and without any sacrificial reactant is desired. Transition metal-catalyzed C(sp^2)–H bond functionalization

provided the possibility for this transformation.[1a,2] Though the transition metal-catalyzed C–O bond formation is considered to be more difficult compared with C–C and some other C–heteroatom bonds,[3] there have been many successful examples in this regard. A range of palladium-catalyzed alkoxylation of C(sp^2)–H bond were developed.[4] Moreover, a series of encouraging progresses on the direct oxidation of aryl C(sp^2)–H bond catalyzed by transition metals to form phenols also have been achieved in recent years. These hydroxylation regioselectively took place at the *ortho*-position of aromatic rings directed by the carbonyl,[5] ester,[6] carbamyl,[7] carbamate,[8] carboxyl,[9] acylamino,[10] phosphate[11] and some azacyclic groups.[12] After the *ortho*-hydroxylation of aryl moiety of 2-arylpyridines using $Pd(OAc)_2$/oxone in PEG-3400/*t*-BuOH reported by Kim et al,[12a] Jiao et al[12b] developed a novel $PdCl_2$ and NHPI (N-hydroxyphthalimide) cocatalyzed aromatic C(sp^2)–H bond hydroxylation of 2-phenylpyridines recently, in which molecular oxygen was used as a heterogeneous oxidant for this transformation. Patel et al[12e] also obtained a hydroxylation product of 2-phenylpyridine by using *tert*-butyl hydroperoxide (TBHP) as the oxidant in their study on the palladium-catalyzed acylation of 2-phenylpyridines, but the further study was not done. In our continuous study on the palladium-catalyzed oxidative coupling reaction, we found that the peroxide could be as an effective homogeneous oxidant for the C–H bond functionalization.[13] We herein present an efficient method for the synthesis of phenols via Pd−catalyzed, pyridyl-directed homogeneous hydroxylation of aryl C−H bond using TBHP as the sole oxidant.

We initiated our study by employing 2-phenylpyridine (**1a**) as the reactant in the presence of catalyst and TBHP (Table 1). Without palladium catalyst, the reaction could not take place at all (entry 1). Thus, $Pd(OAc)_2$, $PdCl_2$, $Pd(PPh_3)_2Cl_2$, and $Pd(CH_3CN)_2Cl_2$ were tested for this transformation, in which $Pd(OAc)_2$ was proved to be most effective (entries 5, 14−16). The oxidation reaction could be catalyzed by 5 mol % $Pd(OAc)_2$ to give the hydroxylation product 2-(pyridin-2-yl)phenol (**2a**) in 58% yield using 4.0 equiv TBHP as the oxidant in DCE (1,2-dichloroethane) (entry 3). The amount of the oxidant had an evident effect to this oxidation. In the absence of TBHP, no desired product was detected (entry 2). Increasing TBHP to 6.0 equiv led to a higher yield of 82% (entry 5); further raising it to 7.0 equiv did not improve the yield evidently (entry 6). Another influence factor to this reaction was the solvent. In DCE, the reaction

proceeded smoothly and gave a highest yield; in TCE (1,1,2,2-tetrachloroethane), the hydroxylation product with a lower yield of 79% was obtained (entry 8). In CH_3CN, dioxane or DMF, however, only trace desired product was found (entries 9−11). The reaction temperature was also crucial. The appropriate temperature was proved to be 115 °C. Raising the temperature to 125 ℃ failed to further increase the yield (entry 13), but at 100 ℃, only 43% yield was obtained (entry 12). It is noticeable that when the reaction proceeded in nitrogen atmosphere, the similar result was obtained as that in air (entry 17).

Table 1. Optimization of Reaction Conditions[a]



1a **2a**

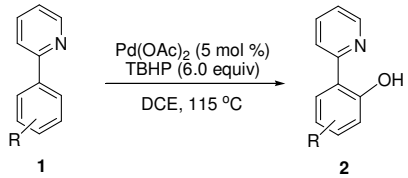
entry	catalyst (mol %)	TBHP (equiv)	solvent	yield (%)
1	-	6.0	DCE	0
2	$Pd(OAc)_2$ (5)	-	DCE	0
3	$Pd(OAc)_2$ (5)	4.0	DCE	58
4	$Pd(OAc)_2$ (5)	5.0	DCE	77
5	$Pd(OAc)_2$ (5)	6.0	DCE	82
6	$Pd(OAc)_2$ (5)	7.0	DCE	83
7	$Pd(OAc)_2$ (10)	6.0	DCE	86
8	$Pd(OAc)_2$ (5)	6.0	TCE	79
9	$Pd(OAc)_2$ (5)	6.0	CH_3CN	trace
10	$Pd(OAc)_2$ (5)	6.0	dioxane	trace
11	$Pd(OAc)_2$ (5)	6.0	DMF	trace
12[b]	$Pd(OAc)_2$ (5)	6.0	DCE	43
13[c]	$Pd(OAc)_2$ (5)	6.0	DCE	80
14	$PdCl_2$ (5)	6.0	DCE	62
15	$Pd(PPh_3)_2Cl_2$ (5)	6.0	DCE	45

16	$Pd(CH_3CN)_2Cl_2$ (5)	6.0	DCE	53
17[d]	$Pd(OAc)_2$ (5)	6.0	DCE	85

[a]Unless otherwise specified, the reactions were carried out in a sealed tube in the presence of 2-phenypyridine (**1a**, 0.3 mmol), solvent (1 mL), catalyst, and TBHP under air atmosphere at 115 °C for 20 h. [b]At 100 °C. [c]At 125 °C. [d]In N_2 atmosphere.

With the optimal conditions in hand, a series of 2-arylpyridines were tested and the results are summarized in Table 2. The *meta*- or *para*-halogenated substrates were well-compatible with the process and afforded corresponding hydroxylated products in good yields (**2c**–**2h**). However, 2-(2-fluorophenyl)pyridine gave the desire product in a relatively lower yield of 55% (**2b**), which might be because of the steric effect. Arenes containing other electron-withdrawing groups also afforded the expected product with good yields, except the case of carbonyl or ester-containing compounds which only gave moderate yields (**2n**, **2o**). Interestingly, the reaction of 2-(naphthalen-2-yl)pyridine exactly gave a β-hydroxylation product (**2w**), which might also be attributed to the less steric hindrance of its β-position. The large conjugated reactant benzo[*h*]quinolone also gave a 10-hydroxylated product in 79% yield (**2x**). Some substrates with electron-donating groups seemed to be disadvantageous to the reaction. For example, the moderate yields were obtained from methoxy-, ethyl- or *n*-pentyl substituted 2-phenylpyridines (**2p**, **2s**, **2t**), and the exact reason is not clear. In general, formation of the dihydroxylation product was not observed, and for *meta*-substituted substrates the hydroxylation proceeded at the less steric hindered position with high regioselectivity. It must be pointed out that when 7 mmol (1.09 g) **1a** was used, the product **2a** was still achieved with a yield of 79%, which demonstrated the practical utility of the present method.

Table 2. Palladium-Catalyzed Hydroxylation of 2-Arylpyridines with TBHP[a]



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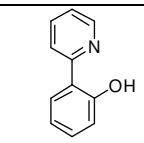
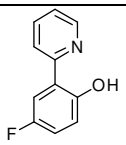
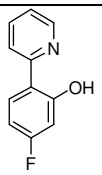


2a, 82%, (79%)[b]

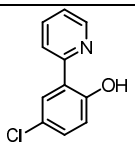
2b, 55%



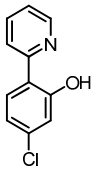
2c, 72%



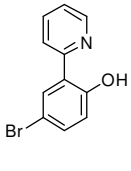
2d, 70%



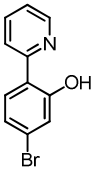
2e, 68%



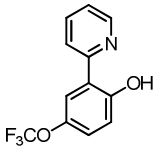
2f, 84%



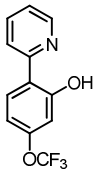
2g, 76%



2h, 73%

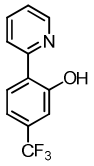


2i, 84%

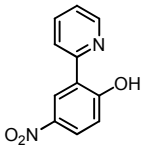


2j, 88%

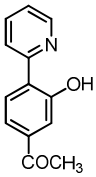
2k, 85%



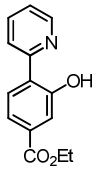
2l, 85%



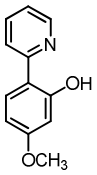
2m, 87%



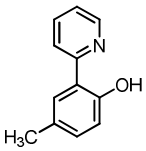
2n, 64%



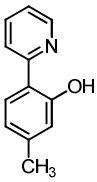
2o, 69%



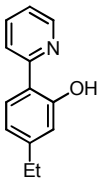
2p, 51%



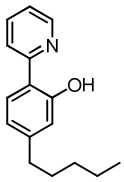
2q, 80%



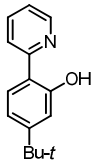
2r, 73%



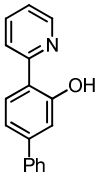
2s, 59%



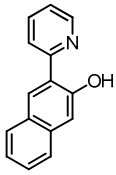
2t, 62%



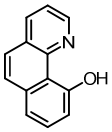
2u, 83%



2v, 65%



2w, 61%



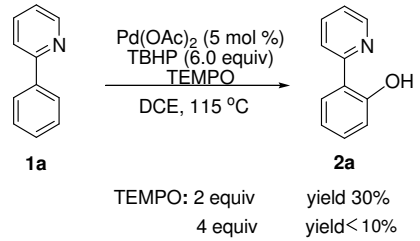
2x, 79%

[a]Reaction conditions: 2-arylpyridine (**1**, 0.3 mmol), $Pd(OAc)_2$ (5 mol %) and TBHP (6.0 equiv) in DCE (1 mL) under air atmosphere at 115 °C for 20 h. [b]The reaction of **1a** (7 mmol, 1.09 g) under the standard reaction conditions.

A control experiment was also carried out (Scheme 1). A radical-trapping reagent 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added in the reaction mixture of **1a** under the established reaction conditions. The results showed that in the presence of 2 equiv TEMPO, the yield of **2a** was reduced to 30%, while the amount of TEMPO was increased to 4 equiv, a yield

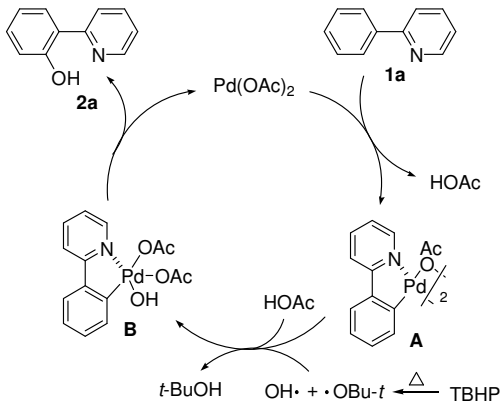
lower than 10% was obtained (Scheme 1). The obvious inhibitory effect of TEMPO indicated that the radicals maybe existed in this transformation.

Scheme 1. Effect of TEMPO to Reaction



As that mentioned in our optimization to reaction conditions, when the reaction proceeded in nitrogen atmosphere, the similar result was obtained as that in air (Table 1, entry 17), which revealed that TBHP was the sole hydroxyl source. Based on our experimental results and related reports,[14] we proposed a possible mechanism for this direct hydroxylation of aryl C–H bond (Scheme 2). Initially, the chelation-assisted C–H activation at the *ortho*-position of directing group with $Pd(OAc)_2$ to form a Pd(II) intermediate **A**. Homolysis of TBHP gave the HO• and *t*-BuO•,[13] which could abstract a hydrogen radical from HOAc, then released AcO•, followed by oxidative addition of HO• and AcO• to form Pd(IV) intermediate **B**. Finally, reductive elimination of **B** gave the product **2a** and regenerated the Pd(II) species.

Scheme 2. Plausible Reaction Mechanism



In summary, a simple method for the synthesis of phenols by $Pd(OAc)_2$ catalyzed, pyridyl-directed aryl sp^2 C–H bond activation using TBHP as the solo oxidant and without any ligand has been explored. Various substituents on the aryl ring, including some coupling reaction sensitive group (Cl, Br) tolerated the reaction and gave the hydroxylation products in moderate to good yields.

Experimental Section

General

All reactions were run in air. All reagents were commercially available and were used without further purification. NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz ($^{13}C\{^1H\}$) 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 $^{13}C\{^1H\}$ NMR). The following abbreviations were used to describe peak splitting patterns when appropriate: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, td = triplet of doublets, brs = broad singlet. Melting points are uncorrected. For the HRMS measurements, Q-TOF analyzer was used.

General Experimental Procedures for Palladium-catalyzed *ortho*-Hydroxylation of 2-Arylpyridines and Characterizations

A mixture of 2-arylpyridines **1** (0.3 mmol), $Pd(OAc)_2$ (3.4 mg, 5 mol %) and TBHP (0.25 mL, 6.0 equiv, 70% aqueous solution) combined in 1,2-dichloroethane (DCE, 1 mL) was sealed in a 25 mL tube with a Teflon lined cap. The tube was then placed in an oil bath, stirred and heated at 115 °C for 20 h. After cooling to room temperature, the reaction mixture was quenched with brine and extracted with dichloromethane (30 mL × 3). The combined organic layer was dried with anhydrous Na_2SO_4 and the solvent was removed under vacuum. The crude product was purified over a column of silica gel (eluant: hexane/ethyl acetate) to afford the desired product **2**.

2-(Pyridin-2-yl)phenol (**2a**)[12b] Yellow oil (42.1 mg, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.34 (brs, 1H), 8.52 (d, *J* = 4.5 Hz, 1H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.89–7.76 (m, 2H), 7.35–7.28 (m, 1H), 7.28–7.23 (m, 1H), 7.04 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.95–6.87 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.0, 157.8, 145.8, 137.8, 131.5, 126.2, 121.5, 119.1, 118.8, 118.6.

3-Fluoro-2-(pyridin-2-yl)phenol (**2b**) Yellow solid (31.2 mg, 55% yield). Mp: 55-57 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.86 (brs, 1H), 8.61–8.53 (m, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.93–7.85 (m, 1H), 7.32 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H), 7.24 (td, *J* = 8.3, 6.4 Hz, 1H), 6.86 (dt, *J* = 8.3, 1.0 Hz, 1H), 6.67 (ddd, *J* = 12.7, 8.2, 1.2 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.0 (d, *J* = 251.2 Hz), 161.3 (d, *J* = 5.6 Hz), 154.5, 145.4, 138.1, 130.9 (d, *J* = 12.7 Hz), 124.7 (d, *J* = 21.1 Hz), 122.0, 114.2 (d, *J* = 2.8 Hz), 108.7 (d, *J* = 11.4 Hz), 106.2 (d, *J* = 25.0 Hz); HRMS-ESI (m/z): calcd for $C_{11}H_8FNONa$ $[M + Na]^+$ 212.0482, found 212.0484.

4-Fluoro-2-(pyridin-2-yl)phenol (**2c**)[12b] Yellow solid (40.9 mg, 72% yield). Mp: 76-77 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.98 (brs, 1H), 8.61–8.50 (m, 1H), 7.87 (ddd, *J* = 13.4, 10.0, 4.9 Hz, 2H), 7.47 (dd, *J* = 9.9, 2.9 Hz, 1H), 7.30 (ddd, *J* = 6.7, 5.0, 1.5 Hz, 1H), 7.11–6.93 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.7 (d, *J* = 2.8 Hz), 156.0 (d, *J* = 1.6 Hz), 155.7 (d, *J* = 236.3 Hz), 146.0, 138.1, 122.1, 119.5 (d, *J* = 7.9 Hz), 119.3, 118.8 (d, *J* = 7.2 Hz), 118.4 (d, *J* = 23.2 Hz), 111.8 (d, *J* = 24.3 Hz).

5-Fluoro-2-(pyridin-2-yl)phenol (**2d**)[12b] Yellow solid (39.7 mg, 70% yield). Mp: 109-111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.81 (brs, 1H), 8.56–8.44 (m, 1H), 7.89–7.81 (m, 2H), 7.77 (dd, *J* = 8.9, 6.5 Hz, 1H), 7.32–7.20 (m, 1H), 6.74 (dd, *J* = 10.6, 2.6 Hz, 1H), 6.64 (ddd, *J* = 8.9, 8.0, 2.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.6 (d, *J* = 250.3 Hz), 162.0 (d, *J* = 12.9 Hz), 157.2, 145.6, 137.9, 127.5 (d, *J* = 10.8 Hz), 121.5, 118.8, 115.4 (d, *J* = 2.8 Hz), 106.3 (d, *J* = 22.4 Hz), 105.2 (d, *J* = 23.3 Hz).

4-Chloro-2-(pyridin-2-yl)phenol (**2e**) Yellow solid (41.9 mg, 68% yield). Mp: 95-96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.34 (brs, 1H), 8.54 (dt, *J* = 5.0, 1.5 Hz, 1H), 7.92–7.81 (m, 2H), 7.77 (d, *J* = 2.5 Hz, 1H), 7.34–7.18 (m, 2H), 6.99 (d, *J* = 8.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.6, 156.6, 146.0, 138.1, 131.2, 125.7, 123.5, 122.1, 120.0, 119.8, 119.2; HRMS-ESI (m/z): calcd for $C_{11}H_9ClNO$ $[M + H]^+$ 206.0367, found 206.0365.

5-Chloro-2-(pyridin-2-yl)phenol (**2f**)[12b] Yellow solid (51.8 mg, 84% yield). Mp: 82-83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.70 (brs, 1H), 8.52 (dt, *J* = 5.0, 1.4 Hz, 1H), 7.91–7.80 (m, 2H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.33–7.21 (m, 1H), 7.05 (d, *J* = 2.2 Hz, 1H), 6.90 (dd, *J* = 8.6, 2.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.8, 157.0, 145.8, 138.0, 136.7, 127.0, 121.8, 119.1, 119.0, 118.6, 117.4.

4-Bromo-2-(pyridin-2-yl)phenol (**2g**) Yellow solid (57.0 mg, 76% yield). Mp: 111-114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.22 (brs, 1H), 8.54 (dt, *J* = 5.0, 1.4 Hz, 1H), 7.92–7.86 (m, 3H), 7.39 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.34–7.29 (m, 1H), 6.94 (d, *J* = 8.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.0, 156.4, 145.9, 138.1, 134.1, 128.7, 122.2, 120.5, 120.4, 119.2, 110.6; HRMS-ESI (m/z): calcd for $C_{11}H_8BrNONa$ $[M + Na]^+$ 271.9681, found 271.9694.

5-Bromo-2-(pyridin-2-yl)phenol (**2h**) Yellow solid (54.8 mg, 73% yield). Mp: 67-68 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.64 (brs, 1H), 8.51 (dt, *J* = 5.0, 1.4 Hz, 1H), 7.91–7.81 (m, 2H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.32–7.25 (m, 1H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.04 (dd, *J* = 8.5, 2.1 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.8, 157.0, 145.8, 138.0, 127.1, 124.9, 122.0, 121.9, 121.6, 119.0, 117.7; HRMS-ESI (m/z): calcd for $C_{11}H_8BrNONa$ $[M + Na]^+$ 271.9681, found 271.9691.

2-(Pyridin-2-yl)-4-(trifluoromethoxy)phenol (**2i**) Yellow solid (64.3 mg, 84% yield). Mp: 62-64 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.26 (brs, 1H), 8.55 (dt, *J* = 5.0, 1.4 Hz, 1H), 7.94–7.82 (m, 2H), 7.65 (d, *J* = 2.7 Hz, 1H), 7.35–7.29 (m, 1H), 7.22–7.17 (m, 1H), 7.04 (d, *J* = 9.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.6, 156.5, 145.9, 141.0 (d, *J* = 2.0 Hz), 138.1, 122.3, 120.7 (q, *J* = 257.0 Hz), 119.6, 119.3, 119.0, 119.0; HRMS-ESI (m/z): calcd for $C_{12}H_9F_3NO_2$ $[M + H]^+$ 256.0580, found 256.0584.

2-(Pyridin-2-yl)-5-(trifluoromethoxy)phenol (**2j**) Yellow solid (67.4 mg, 88% yield). Mp: 68-70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.69 (brs, 1H), 8.51 (dt, *J* = 5.1, 1.4 Hz, 1H), 7.89–7.83 (m, 2H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.32–7.25 (m, 1H), 6.90 (dd, *J* = 2.4, 1.1 Hz, 1H), 6.77 (ddd, *J* = 8.8, 2.4, 1.1 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.4, 156.8, 151.2 (d, *J* = 1.7 Hz), 145.8, 138.0, 127.2, 121.9, 120.4 (q, *J* = 257.7 Hz), 119.1, 117.3, 110.8, 110.4; HRMS-ESI (m/z): calcd for $C_{12}H_9F_3NO_2$ $[M + H]^+$ 256.0580, found 256.0584.

2-(Pyridin-2-yl)-4-(trifluoromethyl)phenol (**2k**) Yellow solid (60.1 mg, 85% yield). Mp: 88-89 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.77 (brs, 1H), 8.56 (d, *J* = 4.7 Hz, 1H), 8.07 (d, *J* = 1.4 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.95–7.88 (m, 1H), 7.56 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.35 (ddd, *J* = 7.2, 5.1, 0.9 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.7, 156.5, 145.8, 138.3, 128.2 (q, *J* = 3.5 Hz), 124.5 (q, *J* = 272.1 Hz), 123.6 (q, *J* = 3.9 Hz), 122.4, 120.9 (q, J = 32.7 Hz), 119.3, 119.1, 118.4; HRMS-ESI (m/z): calcd for $C_{12}H_9F_3NO$ $[M + H]^+$ 240.0631, found 240.0627.

2-(Pyridin-2-yl)-5-(trifluoromethyl)phenol (**2l**)[12b] Yellow solid (60.1 mg, 85% yield). Mp: 107-108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.51 (brs, 1H), 8.57 (d, *J* = 4.8 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.94–7.87 (m, 2H), 7.39–7.32 (m, 1H), 7.29 (s, 1H), 7.17–7.09 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.1, 156.5, 146.0, 138.2, 132.9 (q, *J* = 32.6 Hz), 126.6, 123.8 (q, *J* = 272.4 Hz), 122.6, 121.5, 119.6, 115.8 (q, *J* = 3.9 Hz), 115.0 (q, *J* = 3.8 Hz).

4-Nitro-2-(pyridin-2-yl)phenol (**2m**) Yellow solid (56.4 mg, 87% yield). Mp: 212-213 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.65 (brs, 1H), 8.82 (d, *J* = 2.7 Hz, 1H), 8.59 (ddd, *J* = 5.0, 1.7, 0.9 Hz, 1H), 8.22 (dd, *J* = 9.1, 2.7 Hz, 1H), 8.09 (d, *J* = 8.3 Hz, 1H), 8.00 (ddd, *J* = 8.3, 7.6, 1.8 Hz, 1H), 7.42 (ddd, *J* = 7.5, 5.1, 1.1 Hz, 1H), 7.10 (d, *J* = 9.1 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.1, 155.8, 145.7, 139.8, 138.7, 126.9, 123.0, 122.7, 119.5, 119.3, 118.1; HRMS-ESI (m/z): calcd for $C_{11}H_8N_2O_3Na$ $[M + Na]^+$ 239.0427, found 239.0429.

1-(3-Hydroxy-4-(pyridin-2-yl)phenyl)ethanone (**2n**) Yellow solid (40.9 mg, 64% yield). Mp: 116-117 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.48 (brs, 1H), 8.56 (ddd, *J* = 5.0, 1.7, 0.9 Hz, 1H), 7.98 (d, *J* = 8.3 Hz, 1H), 7.94–7.84 (m, 2H), 7.58 (d, *J* = 1.8 Hz, 1H), 7.50 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.34 (ddd, *J* = 7.4, 5.0, 1.1 Hz, 1H), 2.62 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.8, 160.0, 156.7, 146.1, 139.2, 138.1, 126.3, 122.6, 122.5, 119.8, 119.0, 118.0, 26.8; HRMS-ESI (m/z): calcd for $C_{13}H_{11}NO_2Na$ $[M + Na]^+$ 236.0682, found 236.0687.

Ethyl 3-hydroxy-4-(pyridin-2-yl)benzoate (**2o**) Yellow solid (50.4 mg, 69% yield). Mp: 94-95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.41 (brs, 1H), 8.55 (d, *J* = 4.9 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.92–7.83 (m, 2H), 7.70 (d, *J* = 1.7 Hz, 1H), 7.57 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.32 (ddd, *J* = 7.4, 5.0, 0.9 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.2, 159.7, 156.9, 146.0, 138.0, 132.9, 126.1, 122.4, 119.8, 119.8, 119.5, 61.1, 14.3; HRMS-ESI (m/z): calcd for $C_{14}H_{13}NO_3Na$ $[M + Na]^+$ 266.0788, found 266.0793.

5-Methoxy-2-(pyridin-2-yl)phenol (**2p**) Yellow oil (30.8 mg, 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.66 (brs, 1H), 8.45 (d, *J* = 5.0 Hz, 1H), 7.83–7.76 (m, 2H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.21–7.13 (m, 1H), 6.56 (d, *J* = 2.6 Hz, 1H), 6.49 (dd, *J* = 8.8, 2.6 Hz, 1H), 3.84 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.4, 161.9, 157.8, 145.5, 137.6, 127.2, 120.5, 118.3, 112.1, 106.6, 102.2, 55.3; HRMS-ESI (m/z): calcd for $C_{12}H_{12}NO_2$ $[M + H]^+$ 202.0863, found 202.0860.

4-Methyl-2-(pyridin-2-yl)phenol (**2q**) Yellow oil (44.4 mg, 80% yield). ^{1}H NMR (400 MHz,

$CDCl_3$) δ 14.01 (brs, 1H), 8.55–8.48 (m, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.88–7.79 (m, 1H), 7.61 (d, *J* = 1.7 Hz, 1H), 7.25 (ddd, *J* = 7.4, 5.0, 1.0 Hz, 1H), 7.14 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.9, 157.7, 145.9, 137.7, 132.4, 127.7, 126.3, 121.4, 119.0, 118.4, 20.8; HRMS-ESI (m/z): calcd for $C_{12}H_{11}NONa$ $[M + Na]^+$ 208.0733, found 208.0735.

5-Methyl-2-(pyridin-2-yl)phenol (**2r**)[12b] Yellow oil (40.6 mg, 73% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 14.19 (brs, 1H), 8.50 (d, *J* = 4.8 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.86–7.79 (m, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.25–7.19 (m, 1H), 6.87 (s, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.9, 158.0, 145.8, 142.1, 137.7, 125.9, 121.1, 119.9, 118.9, 118.7, 116.2, 21.4.

5-Ethyl-2-(pyridin-2-yl)phenol (**2s**) Yellow oil (35.3 mg, 59% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 14.24 (brs, 1H), 8.52 (ddd, *J* = 5.1, 1.8, 0.9 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.84 (ddd, *J* = 8.3, 7.4, 1.8 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.24 (ddd, *J* = 7.3, 5.1, 1.1 Hz, 1H), 6.95–6.88 (m, 1H), 6.78 (dd, *J* = 8.1, 1.8 Hz, 1H), 2.66 (q, *J* = 7.6 Hz, 2H), 1.28 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.0, 157.9, 148.5, 145.7, 137.8, 126.1, 121.1, 118.9, 118.8, 117.6, 116.4, 28.8, 15.1; HRMS-ESI (m/z): calcd for $C_{13}H_{14}NO$ $[M + H]^+$ 200.1070, found 200.1068.

5-Pentyl-2-(pyridin-2-yl)phenol (**2t**) Yellow oil (44.9 mg, 62% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 14.36 (brs, 1H), 8.51 (ddd, *J* = 5.0, 1.8, 1.0 Hz, 1H), 7.93–7.86 (m, 1H), 7.82 (ddd, *J* = 8.4, 7.4, 1.8 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.22 (ddd, *J* = 7.4, 5.0, 1.1 Hz, 1H), 6.89 (d, *J* = 1.6 Hz, 1H), 6.76 (dd, *J* = 8.1, 1.7 Hz, 1H), 2.67–2.52 (m, 2H), 1.74–1.61 (m, 2H), 1.41–1.32 (m, 4H), 0.92 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.9, 158.0, 147.2, 145.8, 137.7, 125.9, 121.1, 119.3, 118.8, 118.2, 116.4, 35.8, 31.5, 30.7, 22.6, 14.0; HRMS-ESI (m/z): calcd for $C_{16}H_{20}NO$ $[M + H]^+$ 242.1539, found 242.1535.

5-(tert-Butyl)-2-(pyridin-2-yl)phenol (**2u**) Yellow oil (56.6 mg, 83% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 14.30 (brs, 1H), 8.51 (ddd, *J* = 5.0, 1.8, 0.9 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.82 (ddd, *J* = 8.3, 7.4, 1.8 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.22 (ddd, *J* = 7.3, 5.0, 1.1 Hz, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 6.98 (dd, *J* = 8.4, 2.0 Hz, 1H), 1.36 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.7, 157.8, 155.4, 145.8, 137.7, 125.8, 121.1, 118.8, 116.3, 116.2, 115.5, 34.8, 31.1; HRMS-ESI (m/z): calcd for $C_{15}H_{17}NONa$ $[M + Na]^+$ 250.1202, found 250.1202.

4-(Pyridin-2-yl)-[1,1'-biphenyl]-3-ol (**2v**)[12b] Yellow solid (48.2 mg, 65% yield). Mp: 156-157 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.45 (brs, 1H), 8.54 (ddd, *J* = 5.0, 1.8, 0.9 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.91–7.80 (m, 2H), 7.70 (dq, *J* = 2.8, 1.7 Hz, 2H), 7.52–7.44 (m, 2H), 7.43–7.37 (m, 1H), 7.34 (d, *J* = 1.9 Hz, 1H), 7.29–7.23 (m, 1H), 7.20 (dd, *J* = 8.3, 1.9 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.3, 157.6, 145.9, 144.2, 140.2, 137.8, 128.8, 127.8, 127.0, 126.6, 121.5, 119.1, 117.8, 117.7, 116.8.

3-(Pyridin-2-yl)naphthalen-2-ol (**2w**) Yellow solid (40.5 mg, 61% yield). Mp: 150-151 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.05 (brs, 1H), 8.59 (d, *J* = 4.4 Hz, 1H), 8.35 (s, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.94 (t, *J* = 7.4 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.40 (s, 1H), 7.37–7.29 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.3, 156.6, 145.8, 138.4, 135.9, 128.4, 127.5, 127.4, 127.2, 126.0, 123.3, 122.2, 121.3, 120.6, 112.3; HRMS-ESI (m/z): calcd for $C_{15}H_{11}NONa$ $[M + Na]^+$ 244.0733, found 244.0735.

Benzo[h]quinolin-10-ol (**2x**)[4a] Yellow solid (46.3 mg, 79% yield). Mp: 102-104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.96 (s, 1H), 8.85 (dd, *J* = 4.7, 1.7 Hz, 1H), 8.27 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.83 (d, *J* = 8.9 Hz, 1H), 7.67–7.61 (m, 2H), 7.58 (dd, *J* = 8.0, 4.7 Hz, 1H), 7.44 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.30–7.26 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.4, 148.3, 145.0, 136.3, 135.0, 129.9, 129.2, 126.3, 124.6, 120.8, 118.1, 115.9, 114.0.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (Project 21272117) and the Priority Academic Program Development of Jiangsu Higher Education Institutions. The authors also thank Mr. Zilie Liu for the determination of HRMS.

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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