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Palladium-Catalyzed *ortho*-Sulfonylation of 2-Aryloxypyridines and Subsequent Formation of *ortho*-Sulfonylated Phenols

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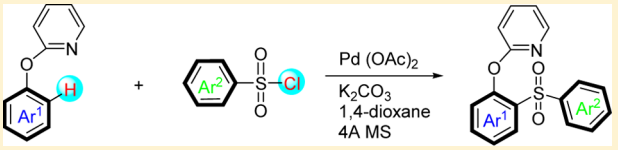
Supporting Information

ABSTRACT: A palladium-catalyzed direct sulfonylation of 2-aryloxypyridines on the *ortho*-position of the benzene ring was developed using 2-pyridyloxyl as the directing group and sulfonyl chlorides as sulfonylation reagents. The protocol was available for both electron-rich and electron-deficient substrates. The *ortho*-sulfonylated phenol was synthesized expediently from the sulfonylation product by the removal of the pyridyl group.



Sulfones have been extensively used as the key compounds applied in numerous total syntheses.[1] Molecules containing this motif also have evident bioactivity, for example, anticancer, anti-HIV, and antibacterial, and, therefore, have attracted considerable attention in the medicinal chemistry.[2] Sulfones can be generally synthesized by the oxidation of sulfides.[1a,b] Friedel−Crafts sulfonylation has provided the alternative method for the preparation of aromatic sulfones,[3] but it is limited by the electronic effect of the electron-withdrawing groups and the steric effect of the *ortho* groups on the benzene ring. Several transition-metal-catalyzed direct sulfonylations exhibited a new vision for the preparation of sulfones in recent years.[4] The increasing applications of sulfones have stimulated investigations on new methodologies for the synthesis of these compounds.

As a straightforward and atom economic method for the construction of C−C and C−heteroatom bonds, transition-metal-catalyzed C−H functionalization reactions have been used in the synthesis of many multifunctional molecules.[5] Among these approaches, 2-pyridyl was proved to be a versatile directing group to obtain the high regioselectivity, and a range of C−C,[6] C−O,[7] and C−halogen[8] bond formation reactions on the *ortho*-C(sp^2)−H bond of 2-arylpyridines or the C(sp^3)−H bond were reported. Pyridyl is also a removable group in 2-phenoxypyridine to produce phenols. Thus, several transition-metal-catalyzed C−C bond formation reactions directed by 2-pyridyloxyl were also developed in recent years.[9] Very recently, we used 2-pyridyloxyl as the directing group to carry out the palladium-catalyzed *ortho*-C(sp^2)−H bond alkoxylation of 2-aryloxypyridines.[10] This group is expected to play a more important role in organic synthesis. We herein present palladium(II)-catalyzed direct *ortho*-C−S formation reaction on the benzene ring of 2-aryloxypyridines with sulfonyl chlorides and demonstrate that the pyridyl group can be further removed to produce *ortho*-sulfonylated phenols.

At the outset of our study, we examined the reaction between 2-phenoxypyridine (**1a**) and 4-methylbenzenesulfonyl chloride (**2a**) (Table 1). Without catalyst, the reaction could not take place at all. Thus, $PdCl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(CH_3CN)_2Cl_2$, and $Pd(OAc)_2$ were tested to catalyze this transformation, in which $Pd(OAc)_2$ gave the best result. In the presence of $Pd(OAc)_2$ (8 mol %) and K_2CO_3 (2 equiv), the desired product 2-(2-tosylphenoxy)pyridine (**3aa**) was obtained in 62% yield (entries 1−4). A 10 mol % catalyst loading did not bring the evidently better result (entry 5); however, the presence of 5 mol % $Pd(OAc)_2$ led to a lower yield of 48% (entry 6). In the absence of base, the reaction nearly could not take place (entry 7). Thus, the addition of base was essential for the reaction. Among the general bases, such as K_2CO_3, Na_2CO_3, Cs_2CO_3, and K_3PO_4, K_2CO_3 was proved to be the most effective (entries 4, 8−10). The experiments demonstrated that the choice of solvent is also crucial. In 1,4-dioxane, the reaction proceeded smoothly and gave the best result; but when DCE, toluene, DMF, or CH_3CN was employed as the solvent, respectively, the very low yield was obtained (entries 11−14). Another factor was the reaction temperature. The appropriate temperature was found to be 120 °C. Raising the temperature to 140 °C failed to further improve the yield (entry 15), but reducing it to 100 °C brought the decrease of the reaction performance (entry 16). Furthermore, the excess of sulfuryl chloride was essential, and the stoichiometric ratio of **1a** and **2a** (1:1) led to a very low yield (entry 17). In addition, the presence of molecular sieves (MS) was favorable for the reaction.

Having established the optimum reaction conditions, the substrate scope was next examined (Table 2). 4-Methylbenzenesulfonyl chloride (**2a**) was first selected as the coupling partner for the sulfonylation of various 2-aryloxypyridines (**1a**−**k**). For most of the reactants, the reaction gave the desired

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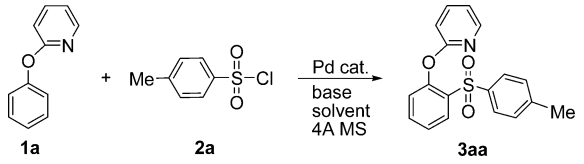
Table 1. Optimization of Reaction Conditions[a]



1a 2a 3aa

entry	catalyst	base	solvent	conversion (%)[b]	yield
1	$PdCl_2$	K_2CO_3	1,4-dioxane	trace	trace
2	$Pd(PPh_3)_2Cl_2$	K_2CO_3	1,4-dioxane	trace	trace
3	$Pd(CH_3CN)_2Cl_2$	K_2CO_3	1,4-dioxane	27	18
4	$Pd(OAc)_2$	K_2CO_3	1,4-dioxane	69	62
5	$Pd(OAc)_2$	K_2CO_3	1,4-dioxane	72	63[c]
6	$Pd(OAc)_2$	K_2CO_3	1,4-dioxane	55	48[d]
7	$Pd(OAc)_2$		1,4-dioxane	trace	trace
8	$Pd(OAc)_2$	Na_2CO_3	1,4-dioxane	59	52
9	$Pd(OAc)_2$	Cs_2CO_3	1,4-dioxane	56	47
10	$Pd(OAc)_2$	K_3PO_4	1,4-dioxane	16	<10
11	$Pd(OAc)_2$	K_2CO_3	DCE	27	20
12	$Pd(OAc)_2$	K_2CO_3	toluene	15	<10
13	$Pd(OAc)_2$	K_2CO_3	DMF	16	<10
14	$Pd(OAc)_2$	K_2CO_3	CH_3CN	14	<10
15	$Pd(OAc)_2$	K_2CO_3	1,4-dioxane	70	60[e]
16	$Pd(OAc)_2$	K_2CO_3	1,4-dioxane	59	51[f]
17	$Pd(OAc)_2$	K_2CO_3	1,4-dioxane	28	21[g]

[a]Unless otherwise specified, the reactions were carried out in a sealed tube in the presence of **1a** (0.5 mmol), **2a** (1.5 mmol), catalyst (8 mol %), base (1.0 mmol), 4A MS (100 mg), and solvent (2 mL) at 120 °C for 24 h. [b]Based on **1a**. [c]$Pd(OAc)_2$ 10 mol %. [d]$Pd(OAc)_2$ 5 mol %. [e]At 140 °C. [f]At 100 °C. [g]0.5 mmol of **2a** was used.

ortho-sulfonylated products (**3**) in moderate yields. In general, the reactivity of the substrates with an electron-donating group (e.g., OMe, Me) (**3ba**, **3ca**, **3fa**) on the benzene ring was higher than that with an electron-withdrawing group (e.g., F, Cl, MeCO) (**3ga**, **3ha**, **3ia**), but when a methyl was substituted on the *ortho*-position, only a low yield of 33% was obtained, which could obviously be attributed to the steric hindrance (**3ea**). 2-(4-Phenylphenoxy)pyridine also gave a 58% yield (**3ja**). It was interesting that, for the reaction of 2-(naphthalen-2-yloxy)-pyridine (**1k**), only a α-sulfonylation product (**3ka**) was obtained with a 57% yield. A variety of arylsulfonyl chlorides were then employed for this sulfonylation reaction. For an electron-donating or electron-withdrawing group on the arylsulfonyl chlorides, the corresponding products were obtained with high selectivity.

The structures of **3ka** and **3cd** have been further confirmed by single-crystal X-ray diffraction analysis (see the Supporting Information).[11]

A large-scale reaction to demonstrate the practical utility of the method is necessary, especially for industry. We then attempted to use 8 mmol (1.37 g) of 2-phenoxypyridine (**1a**) and 24 mmol of (4.56 g) 4-methylbenzenesulfonyl chloride (**2a**) as the reactants to carry out the reaction. Under the established reaction conditions, 1.45 g (yield 56%) of 2-(2-tosylphenoxy)pyridine (**3aa**) was obtained, which revealed that the decrease of the yield was less than 10% when the reaction took place in the gram scale.

The six-membered metallacycles were believed to be generated as the intermediates in the transition-metal-catalyzed 2-pyridyloxyl group directed C−H functionalization.[9] A Pd(IV) intermediate (**B**) via oxidative addition of sulfonyl chloride to the cyclopalladated intermediate (**A**) was proposed in this palladium(II)-catalyzed sulfonylation of 2-aryloxypyridines according to the related reports.[5a,12] The reductive elimination of (**B**) gave the final product (**3aa**). Thus, the possible mechanism is postulated as illustrated in Scheme 1.

In the 2-phenoxypyridine motifs, pyridyl can be removed through a simple operation to generate phenols.[9] According to this concept, we treated the sulfonylation product 2-(5-methoxy-2-tosylphenoxy)pyridine (**3ba**) with methyl trifluoromethanesulfonate (MeOTf) in toluene, and then added the generated pyridinium into a refluxing Na/MeOH solution to produce 5-methoxy-2-tosylphenol (**4ba**) in 56% yield by two steps (Scheme 2).

In summary, we have developed a new palladium-catalyzed direct C(sp^2)−H sulfonation using 2-pyridyloxyl as the directing group. The reaction exhibits a good tolerance for a broad range of general functional groups. The present work demonstrated the utility of pyridine as a removable directing group through the direct C−H bond activation/functionalization and deprotecting group to form *ortho*-sulfonylated phenols.

EXPERIMENTAL SECTION

General. All reactions were run in oven-dried flasks under air. 2-Aryloxypyridines were prepared according to the literature.[13] 1,4-Dioxane was dried using the general method; other reagents were commercially available and were used without further purification. NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) using TMS as an internal standard. ^{13}C NMR spectra are proton-decoupled $^{13}C\{^1H\}$ NMR acquisitions. 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, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet. Melting points are uncorrected. For the HRMS measurements, Q-TOF was used.

General Experimental Procedures and Characterizations. *Palladium-Catalyzed Sulfonation of 2-Aryloxypyridines.* 2-Arylox-

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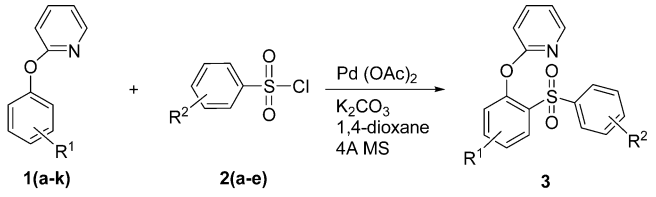
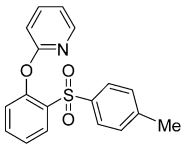
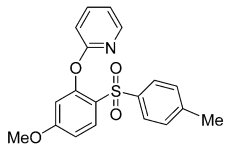
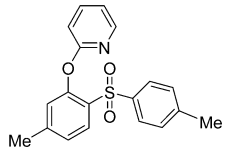
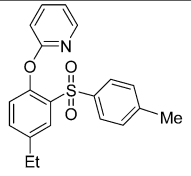
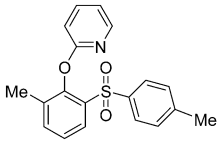
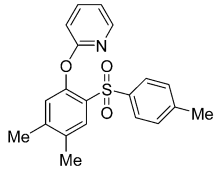
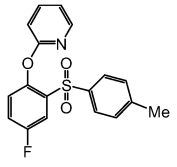
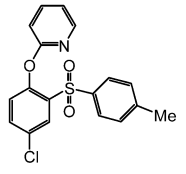
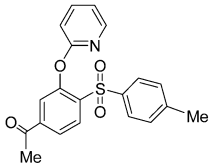
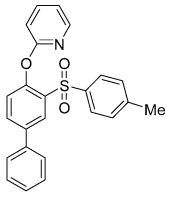
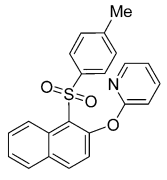
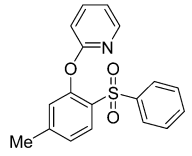
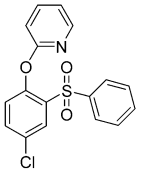
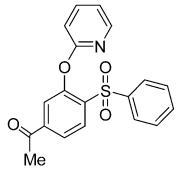
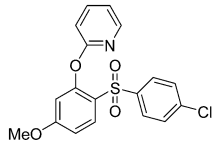
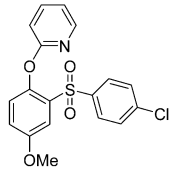
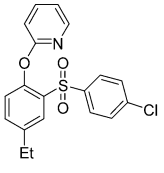
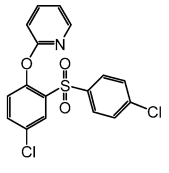
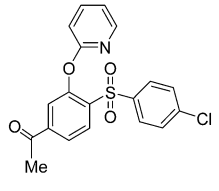
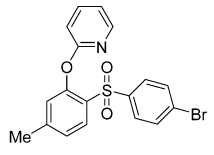
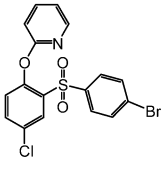
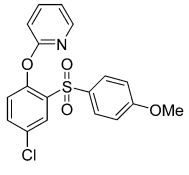
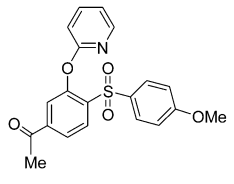
Table 2. *ortho*-Sulfonylation of 2-Aryloxypyridines with Arylsulfonyl Chlorides[a]



1(a-k) 2(a-e) 3

 **3aa**, 62%	 **3ba**, 64%	 **3ca**, 62%	 **3da**, 46%
 **3ea**, 33%	 **3fa**, 67%	 **3ga**, 40%	 **3ha**, 43%
 **3ia**, 47%	 **3ja**, 58%	 **3ka**, 57%	 **3cb**, 52%
 **3hb**, 48%.	 **3ib**, 47%	 **3bc**, 61%	 **3lc**, 57%
 **3dc**, 56%	 **3hc**, 46%	 **3ic**, 36%	 **3cd**, 44%
 **3hd**, 31%	 **3he**, 53%	 **3ie**, 29%	

[a]The reactions were carried out with **1** (0.5 mmol), **2** (1.5 mmol), $Pd(OAc)_2$ (8 mol %), K_2CO_3 (2 equiv), 4A MS (100 mg), and 1,4-dioxane (2 mL) at 120 °C for 24 h.

ypyridine (0.5 mmol), arylsulfonyl chloride (1.5 mmol), K_2CO_3 (1.0 mmol, 138 mg), $Pd(OAc)_2$ (0.04 mmol, 9 mg), and 4A molecular sieves (100 mg) were added in 1,4-dioxane (2 mL) in a 25 mL sealed tube with a Teflon lined cap. The mixture was heated at 120 °C (oil bath temperature) for 24 h. After the reaction finished, the mixture was cooled to room temperature and diluted with dichloromethane and

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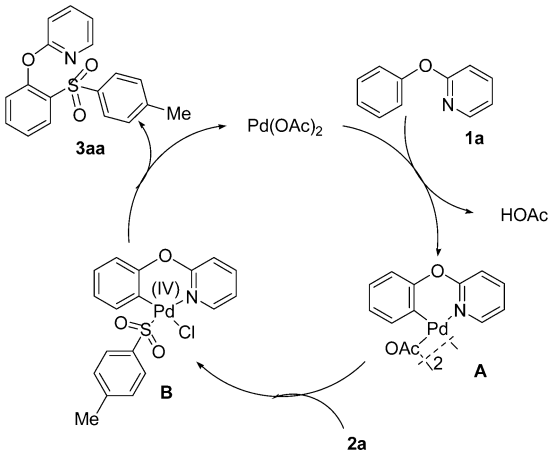
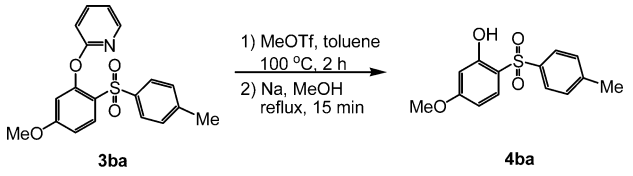
Scheme 1. Plausible Reaction Mechanism



Scheme 2. Removal of Directing Group



then washed with water and dried. The solution was concentrated by vacuum and separated on a silica gel column using hexane/EtOAc (5:1, v/v) as eluent to give the corresponding pure *ortho*-sulfonation products. For the solid products, the melting points were obtained after further recrystallization from hexane.

Preparation of 5-Methoxy-2-tosylphenol from Sulfonation Product 2-(5-Methoxy-2-tosylphenoxy)pyridine. To a solution of 2-(5-methoxy-2-tosylphenoxy)pyridine (**3ba**) (177 mg, 0.5 mmol) in dry toluene (15 mL), MeOTf (144 mg, 0.88 mmol) was added. The solution was stirred at 100 °C under a N_2 atmosphere for 2 h. The reaction mixture was cooled to ambient temperature, and the solvent was evaporated under vacuum. The crude product was dissolved in dry methanol (5.0 mL) and then added to a solution of Na (276 mg, 12 mmol) in dry methanol (15 mL) under a N_2 atmosphere. The reaction mixture was heated to reflux for 15 min and then cooled to room temperature. After evaporating the solvent under vacuum, water (70 mL) was added, and the aqueous solution was extracted with EtOAc (50 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4. The solution was concentrated by vacuum, and the residue was purified by column chromatography on silica gel (hexane/EtOAc: 10/1) to give the corresponding product **4ba**.

*2-(2-Tosylphenoxy)pyridine (**3aa**).* Yield: 62% (101 mg). Yellow solid, mp: 134−136 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (dd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, 1H), 7.69−7.63 (m, 3H), 7.36 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.31 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 7.23−7.17 (m, 4H), 6.99−6.96 (m, 1H), 6.72 (d, J = 8.0 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.5, 147.2, 145.7, 145.1, 141.4, 139.2, 132.9, 129.5, 128.5, 127.8, 125.5, 124.5, 123.7, 118.6, 111.2, 21.7. HRMS-ESI (m/z): calcd for $C_{18}H_{15}NO_3SK$ $[M + K]^+$ 364.0404, found 364.0403.

*2-(5-Methoxy-2-tosylphenoxy)pyridine (**3ba**).* Yield: 64% (113 mg). Yellow solid, mp: 117−118 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19 (d, J = 8.8 Hz, 1H), 8.00 (dd, J_1 = 4.8 Hz, J_2 = 1.2 Hz, 1H), 7.76 (d, J = 8.0, 2H), 7.74−7.67 (m, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.00−6.97 (m, 1H), 6.91−6.87 (m, 2H), 6.63 (d, J = 2.4 Hz, 1H), 3.81 (s, 3H), 2.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.6, 162.3, 153.0, 147.3, 143.5, 139.5, 138.6, 131.1, 129.2, 128.1, 125.9, 119.0, 111.9, 110.5, 109.2, 55.8, 21.5. HRMS-ESI (m/z): calcd for $C_{19}H_{18}NO_4S$ $[M + H]^+$ 356.0951, found 356.0953.

*2-(5-Methyl-2-tosylphenoxy)pyridine (**3ca**).* Yield: 62% (105 mg). Yellow solid, mp: 129−131 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15 (d, J = 8.0 Hz, 1H), 7.98 (dd, J_1 = 4.4 Hz, J_2 = 1.6 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.70−7.66 (m, 1H), 7.19 (dd, J_1 = 8.0 Hz, J_2 = 0.4 Hz, 1H), 7.12 (d, J = 8.0 Hz, 2H), 6.99−6.95 (m, 1H), 6.92 (d, J = 0.8 Hz, 1H), 6.89 (d, J = 8.4 Hz, 2H), 2.38 (s, 3H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.5, 151.3, 147.3, 146.2, 143.6, 139.4, 138.3, 131.0, 129.5, 129.2, 128.2, 125.8, 124.2, 118.8, 111.8, 21.6, 21.5. HRMS-ESI (m/z): calcd for $C_{19}H_{18}NO_3S$ $[M + H]^+$ 340.1002, found 340.1005.

*2-(4-Ethyl-2-tosylphenoxy)pyridine (**3da**).* Yield: 46% (82 mg). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (d, J = 1.6 Hz, 1H), 7.96 (dd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.68−7.64 (m, 1H), 7.42 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.4 Hz, 1H), 6.96−6.93 (m, 1H), 6.86 (d, J = 8.4 Hz, 1H), 2.76 (q, J = 7.6 Hz, 2H), 2.31 (s, 3H), 1.32 (t, J = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.6, 149.1, 147.2, 143.7, 141.3, 139.3, 138.1, 134.3, 133.4, 129.2, 128.5, 128.3, 123.9, 118.7, 111.6, 28.2, 21.5, 15.2. HRMS-ESI (m/z): calcd for $C_{20}H_{20}NO_3S$ $[M + H]^+$ 354.1158, found 354.1158.

*2-(2-Methyl-6-tosylphenoxy)pyridine (**3ea**).* Yield: 33% (56 mg). Yellow solid, mp: 121−123 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16−8.14 (m, 1H), 7.89−7.88 (m, 1H), 7.72 (dd, J_1 = 6.4 Hz, J_2 = 1.6 Hz, 2H), 7.69−7.64 (m, 1H), 7.51−7.48 (m, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.11 (dd, J_1 = 8.4 Hz, J_2 = 0.4 Hz, 2H), 6.93−6.89 (m, 1H), 6.87 (d, J = 8.4 Hz, 1H), 2.33 (s, 3H), 1.99 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.2, 149.1, 147.3, 143.7, 139.3, 138.0, 136.9, 134.8, 134.1, 129.2, 128.3, 127.5, 125.5, 118.1, 110.4, 21.5, 16.7. HRMS-ESI (m/z): calcd for $C_{19}H_{18}NO_3S$ $[M + H]^+$ 340.1002, found 340.1005.

*2-(4,5-Dimethyl-2-tosylphenoxy)pyridine (**3fa**).* Yield: 67% (118 mg). Yellow solid, mp: 110−112 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (s, 1H), 7.95−7.94 (m, 1H), 7.75 (d, J = 7.6 Hz, 2H), 7.68−7.63 (m, 1H), 7.10 (d, J = 8.0 Hz, 2H), 6.95−6.92 (m, 1H), 6.89 (s, 1H), 6.87 (d, J = 8.4 Hz, 1H), 2.35 (s, 3H), 2.30 (s, 3H), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.8, 148.9, 147.2, 144.7, 143.5, 139.3, 138.3, 134.0, 130.9, 130.0, 129.2, 128.2, 125.0, 118.5, 111.6, 21.5, 20.2, 19.3. HRMS-ESI (m/z): calcd for $C_{20}H_{20}NO_3S$ $[M + H]^+$ 354.1158, found 354.1159.

*2-(4-Fluoro-2-tosylphenoxy)pyridine (**3ga**).* Yield: 40% (69 mg). Yellow solid, mp: 93−94 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05−8.03 (m, 1H), 7.69−7.64 (m, 3H), 7.24 (d, J = 8.0 Hz, 2H), 7.17−7.11 (m, 2H), 7.05−6.96 (m, 2H), 6.73 (d, J = 8.4 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.5, 160.2, 147.1, 145.4, 139.4, 132.6, 129.6, 128.5, 124.5 (d, J = 9.3 Hz), 118.7, 114.7, 114.5, 112.2, 111.9, 111.1, 21.7. HRMS-ESI (m/z): calcd for $C_{18}H_{15}FNO_3S$ $[M + H]^+$ 344.0751, found 344.0767.

*2-(4-Chloro-2-tosylphenoxy)pyridine (**3ha**).* Yield: 43% (77 mg). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05−8.03 (m, 1H), 7.69−7.64 (m, 3H), 7.37 (d, J = 2.4 Hz, 1H), 7.29−7.23 (m, 3H), 7.13 (d, J = 8.8 Hz, 1H), 7.00−6.97 (m, 1H), 6.73 (d, J = 8.0 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.2, 147.2, 145.4, 144.4, 141.6, 139.4, 132.5, 130.1, 129.6, 128.5, 127.9, 124.8, 124.6, 118.8, 111.2, 21.7. HRMS-ESI (m/z): calcd for $C_{18}H_{14}ClNO_3SNa$ $[M + Na]^+$ 382.0275, found 382.0301.

*1-(3-(Pyridin-2-yloxy)-4-tosylphenyl)ethan-1-one (**3ia**).* Yield: 47% (86 mg). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04−8.02 (m, 1H), 7.80 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.78 (d, J = 1.6 Hz, 1H), 7.67 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 3H), 7.46 (d, J = 8.4 Hz, 1H), 7.23 (d, J = 8.2 Hz, 2H), 7.02−6.98 (m, 1H), 6.75 (dd, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 2.58 (s, 3H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.2, 162.2, 147.2, 145.8, 145.5, 145.0, 139.5, 136.4, 132.6, 129.7, 128.4, 125.6, 124.4, 123.8, 119.0, 111.3, 26.6, 21.7. HRMS-ESI (m/z): calcd for $C_{20}H_{18}NO_4S$ $[M + H]^+$ 368.0951, found 368.0969.

*2-((3-Tosyl-[1,1′-biphenyl]-4-yl)oxy)pyridine (**3ja**).* Yield: 58% (116 mg). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.51 (d, J = 2.4 Hz, 1H), 8.01−8.00 (m, 1H), 7.83−7.79 (m, 3H), 7.73−7.69 (m, 1H), 7.66 (dd, J_1 = 7.2 Hz, J_2 = 2.0 Hz, 2H), 7.52−7.48 (m, 2H), 7.45−7.40 (m, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 8.4 Hz, 2H), 7.01−6.98 (m, 1H), 6.95 (d, J = 8.0 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.4, 150.5, 147.3, 143.9, 139.5, 139.0, 138.3, 137.9, 134.1, 133.1, 129.3, 129.0, 128.4, 128.0, 127.9, 127.2, 124.3,

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119.0, 111.8, 21.5. HRMS-ESI (m/z): calcd for $C_{24}H_{19}NO_3S$ $[M]^+$ 401.1080, found 401.1057.

*2-((1-Tosylnaphthalen-2-yl)oxy)pyridine (**3ka**).* Yield: 57% (107 mg). Orange solid, mp: 166−168 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.51 (dd, J_1 = 8.8 Hz, J_2 = 0.4 Hz, 1H), 8.05−8.02 (m, 2H), 7.88 (d, J = 8.4 Hz, 3H), 7.73−7.68 (m, 2H), 7.59−7.55 (m, 1H), 7.18 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.02−6.99 (m, 1H), 6.94 (d, J = 8.4 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.6, 152.2, 147.3, 143.5, 140.5, 139.4, 135.6, 131.6, 130.9, 129.3, 129.1, 128.8, 128.6, 127.3, 126.0, 124.8, 122.4, 119.0, 111.9, 21.5. HRMS-ESI (m/z): calcd for $C_{22}H_{18}NO_3S$ $[M + H]^+$ 376.1002, found 376.1006.

*2-(5-Methyl-2-(phenylsulfonyl)phenoxy)pyridine (**3cb**).* Yiled: 52% (85 mg). Brown solid, mp: 148−150 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (d, J = 8.0 Hz, 1H), 7.98 (dd, J_1 = 5.2 Hz, J_2 = 1.6 Hz, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.70−7.66 (m, 1H), 7.45−7.41 (m, 1H), 7.33 (t, J = 7.6 Hz, 2H), 7.20 (d, J = 8.4 Hz, 1H), 6.98−6.95 (m, 1H), 6.93 (s, 1H), 6.88 (d, J = 8.0 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.3, 151.4, 147.3, 146.4, 141.2, 139.5, 132.7, 130.6, 129.6, 128.5, 128.2, 125.8, 124.1, 119.0, 111.8, 21.6. HRMS-ESI (m/z): calcd for $C_{18}H_{16}NO_3S$ $[M + H]^+$ 326.0845, found 326.0849.

*2-(4-Chloro-2-(phenylsulfonyl)phenoxy)pyridine (**3hb**).* Yield: 48% (83 mg). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (dd, J_1 = 4.8 Hz, J_2 = 1.2 Hz, 1H), 7.82 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 2H), 7.67−7.62 (m, 2H), 7.48 (t, J = 7.8 Hz, 2H), 7.37 (d, J = 2.4 Hz, 1H), 7.30−7.27 (m, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.00−6.97 (m, 1H), 6.69 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.2, 147.2, 144.4, 141.6, 139.5, 135.6, 134.2, 130.2, 129.0, 128.4, 128.1, 124.8, 124.6, 118.9, 111.2. HRMS-ESI (m/z): calcd for $C_{17}H_{12}ClNO_3SK$ $[M + K]^+$ 383.9858, found 383.9859.

*1-(4-(Phenylsulfonyl)-3-(pyridin-2-yloxy)phenyl)ethan-1-one (**3ib**).* Yield: 47% (83 mg). Yellow solid, mp: 79−81 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.40 (d, J = 8.4 Hz, 1H), 7.95−7.90 (m, 4H), 7.74−7.72 (m, 1H), 7.70 (d, J = 1.6 Hz, 1H), 7.48−7.44 (m, 1H), 7.36 (t, J = 7.2 Hz, 2H), 7.02−6.99 (m, 1H), 6.95 (d, J = 8.4 Hz, 1H), 2.60 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.2, 161.9, 151.8, 147.3, 142.2, 140.3, 139.7, 137.2, 133.3, 130.1, 128.7, 128.4, 124.3, 123.4, 119.5, 111.9, 26.9. HRMS-ESI (m/z): calcd for $C_{19}H_{15}NO_4SNa$ $[M + Na]^+$ 376.0614, found 376.0626.

*2-(2-((4-Chlorophenyl)sulfonyl)-5-methoxyphenoxy)pyridine (**3bc**).* Yield: 61% (114 mg). Brown solid, mp: 122−124 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (d, J = 9.2 Hz, 1H), 8.01−8.00 (m, 1H), 7.80 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 2H), 7.73−7.69 (m, 1H), 7.29 (dd, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 2H), 7.04−7.00 (m, 1H), 6.91−6.88 (m, 2H), 6.62 (d, J = 2.4 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.0, 162.1, 153.2, 147.4, 140.0, 139.7, 139.3, 131.2, 129.6, 128.8, 125.1, 119.3, 111.8, 110.7, 109.2, 55.9. HRMS-ESI (m/z): calcd for $C_{18}H_{15}ClNO_4S$ $[M + H]^+$ 376.0405, found 376.0409.

*2-(2-((4-Chlorophenyl)sulfonyl)-4-methoxyphenoxy)pyridine (**3lc**).* Yield: 57% (107 mg). Brown solid, mp: 117−119 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96−7.94 (m, 1H), 7.81 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 2H), 7.76 (d, J = 3.2 Hz, 1H), 7.70−7.65 (m, 1H), 7.30 (s, 1H), 7.29 (dd, J_1 = 8.8 Hz, J_2 = 4.4 Hz, 1H), 7.16 (dd, J_1 = 8.8 Hz, J_2 = 3.2 Hz, 1H), 7.07 (d, J = 8.8 Hz, 1H), 6.99−6.96 (m, 1H), 6.85 (d, J = 8.4 Hz,1H), 3.93 (s,3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.7, 156.5, 147.3, 144.5, 139.7, 139.4, 139.2, 133.8, 129.8, 128.9, 125.6, 121.7, 118.8, 113.0, 111.2, 56.1. HRMS-ESI (m/z): calcd for $C_{18}H_{15}ClNO_4S$ $[M + H]^+$ 376.0405, found 376.0408.

*2-(2-((4-Chlorophenyl)sulfonyl)-4-ethylphenoxy)pyridine (**3dc**).* Yield: 56% (104 mg). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (d, J = 2.4 Hz, 1H), 7.98−7.96 (m, 1H), 7.82 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 2H), 7.71−7.67 (m, 1H), 7.46 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.30 (d, J = 3.2 Hz, 1H), 7.05 (d, J = 8.4 Hz, 2H), 7.00−6.97 (m, 1H), 6.87 (d, J = 8.0 Hz, 1H), 2.78 (q, J = 7.6 Hz, 2H), 1.33 (t, J = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.4, 149.2, 147.4, 147.1, 141.5, 139.5, 134.7, 132.8, 129.8, 128.8, 128.5, 123.9, 120.6, 119.0, 111.5, 28.2, 15.2. HRMS-ESI (m/z): calcd for $C_{19}H_{17}ClNO_3S$ $[M + H]^+$ 374.0612, found 374.0621.

*2-(4-Chloro-2-((4-chlorophenyl)sulfonyl)phenoxy)pyridine (**3hc**).* Yelid: 46% (87 mg). Yellow solid, mp: 143−145 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (d, J = 2.8 Hz, 1H), 7.97−7.95 (m, 1H), 7.82 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 2H), 7.75−7.71 (m, 1H), 7.57 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 7.32 (dd, J_1 = 7.2 Hz, J_2 = 2.0 Hz, 2H), 7.11 (d, J = 8.8 Hz, 1H), 7.05−7.01 (m, 1H), 6.92 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.9, 150.0, 147.3, 140.0, 139.8, 138.7, 135.0, 134.5, 130.6, 129.9, 129.3, 129.0, 125.5, 119.5, 111.6. HRMS-ESI (m/z): calcd for $C_{17}H_{12}Cl_2NO_3S$ $[M + H]^+$ 379.9909, found 379.9916.

*1-(4-((4-Chlorophenyl)sulfonyl)-3-(pyridin-2-yloxy)phenyl)ethan-1-one (**3ic**).* Yield: 36% (70 mg). Orange solid, mp: 135−137 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.38 (d, J = 8.0 Hz, 1H), 7.96−7.91 (m, 2H), 7.82 (J_1 = 6.8 Hz, J_2 = 1.6 Hz, 2H), 7.77−7.72 (m, 1H), 7.68 (d, J = 1.6 Hz, 1H), 7.31 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 2H), 7.06−7.03 (m, 1H), 6.95 (d, J = 8.0 Hz, 1H), 2.60 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.1, 161.8, 151.9, 147.4, 142.4, 140.1, 139.9, 138.7, 136.9, 130.0, 129.9, 129.0, 124.4, 123.5, 119.7, 111.8, 26.9. HRMS-ESI (m/z): calcd for $C_{19}H_{15}ClNO_4S$ $[M + H]^+$ 388.0405, found 388.0405.

*2-(2-((4-Bromophenyl)sulfonyl)-5-methylphenoxy)pyridine (**3cd**).* Yield: 44% (89 mg). Yellow solid, mp: 168−170 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (d, J = 8.4 Hz, 1H), 7.99−7.97 (m, 1H), 7.74−7.71 (m, 3H), 7.45 (dd, J_1 = 7.2 Hz, J_2 = 2.0 Hz, 2H), 7.21 (dd, J_1 = 8.0 Hz, J_2 = 0.4 Hz, 1H), 7.03−7.00 (m, 1H), 6.93 (d, J = 0.4 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.3, 151.4, 147.4, 146.8, 140.2, 139.6, 131.8, 130.3, 129.8, 129.5, 128.0, 126.0, 124.2, 119.2, 111.7, 21.7. HRMS-ESI (m/z): calcd for $C_{18}H_{15}BrNO_3S$ $[M + H]^+$ 405.9931, found 405.9941.

*2-(2-((4-Bromophenyl)sulfonyl)-4-chlorophenoxy)pyridine (**3hd**).* Yield: 31% (66 mg). Yellow solid, mp: 149−150 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.26 (d, J = 2.8 Hz, 1H), 7.96−7.95 (m, 1H), 7.76−7.72 (m, 3H), 7.57 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 7.48 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 2H), 7.10 (d, J = 8.4 Hz, 1H), 7.05−7.02 (m, 1H), 6.92 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.9, 150.0, 147.4, 139.8, 139.2, 135.0, 134.5, 132.0, 130.6, 130.0, 129.3, 128.6, 125.5, 119.5, 111.6. HRMS-ESI (m/z): calcd for $C_{17}H_{12}BrClNO_3S$ $[M + H]^+$ 425.9382, found 425.9390.

*2-(4-Chloro-2-((4-methoxyphenyl)sulfonyl)phenoxy)pyridine (**3he**).* Yelid: 53% (99 mg). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (dd, J_1 = 4.8 Hz, J_2 = 1.2 Hz, 1H), 7.72 (dd, J_1 = 7.2 Hz, J_2 = 2.0 Hz, 2H), 7.70−7.64 (m, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.27 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 7.00−6.97 (m, 1H), 6.89 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 2H), 6.75 (d, J = 8.0 Hz,1H), 3.86 (s. 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.2, 162.2, 147.1, 144.4, 141.7, 139.5, 130.7, 130.2, 127.9, 126.7, 124.8, 124.6, 118.9, 114.2, 111.2, 55.7. HRMS-ESI (m/z): calcd for $C_{18}H_{15}ClNO_4S$ $[M + H]^+$ 376.0405, found 376.0424.

*1-(4-((4-Methoxyphenyl)sulfonyl)-3-(pyridin-2-yloxy)phenyl)-ethan-1-one (**3ie**).* Yield: 29% (56 mg). Brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05−8.03 (m, 1H), 7.81 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.72−7.66 (m, 3H), 7.47 (d, J = 8.4 Hz, 1H), 7.02−6.98 (m, 1H), 6.88 (dd, J_1 = 7.2 Hz, J_2 = 2.4 Hz, 2H), 6.78 (dd, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 3.86 (s, 3H), 2.58 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.2, 164.2, 162.2, 147.2, 145.9, 145.1, 139.5, 136.4, 130.7, 126.9, 125.6, 124.5, 123.8, 119.0, 114.2, 111.3, 55.7, 26.6. HRMS-ESI (m/z): calcd for $C_{20}H_{18}NO_5S$ $[M + H]^+$ 384.0900, found 384.0912.

*5-Methoxy-2-tosylphenol (**4ba**).* Yield: 56% (78 mg). Yellow solid, mp: 77−78 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.34 (s, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 6.52 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 1H), 6.47 (d, J = 2.4 Hz, 1H), 3.81 (s, 3H), 2.42 (s, 3H). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 165.7, 157.8, 144.4, 139.4, 130.5, 130.0, 126.6, 115.8, 108.8, 102.3, 55.7, 21.6. HRMS-ESI (m/z): calcd for $C_{14}H_{14}O_4SNa$ $[M + Na]^+$ 301.0505, found 301.0510.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra for all products, and the crystal structures of **3ka** and **3cd**. 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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