Synthesis X.-H. Li et al. Paper

# Substituent Effects of 2-Pyridones on Selective O-Arylation with Diaryliodonium Salts: Synthesis of 2-Aryloxypyridines under Transition-Metal-Free Conditions

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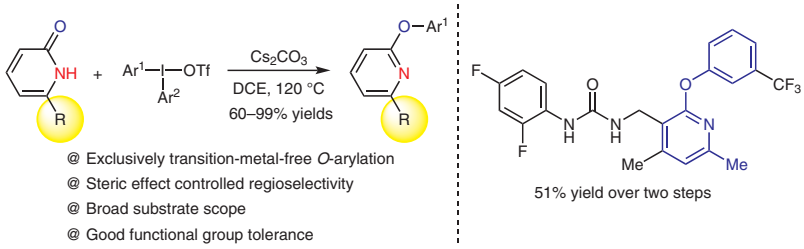



Received: 03.12.2017
Accepted after revision: 08.12.2017
Published online: 24.01.2018
DOI: 10.1055/s-0036-1591884; Art ID: ss-2017-h0647-op

**Abstract** An efficient transition-metal-free strategy to synthesize 2-aryloxypyridine derivatives has been developed by a selective O-arylation of 2-pyridones with diaryliodonium salts. The reaction was compatible with a series of functional groups for 2-pyridones and diaryliodonium salts such as halides, nitro, cyano, and ester groups. The substituents at the C6-position of 2-pyridones favored O-arylation products because of steric hindrance. The reaction was easily performed on a gram-scale and 6-chloro-2-pyridone was a good precursor to access various unsubstituted 2-aryloxypyridines by dehalogenation. A $P2Y_1$ lead compound analogue could be prepared in good yield over two steps.

**Key words** aryloxypyridine, diaryliodonium salt, O-arylation, 2-pyridone, substituent effects

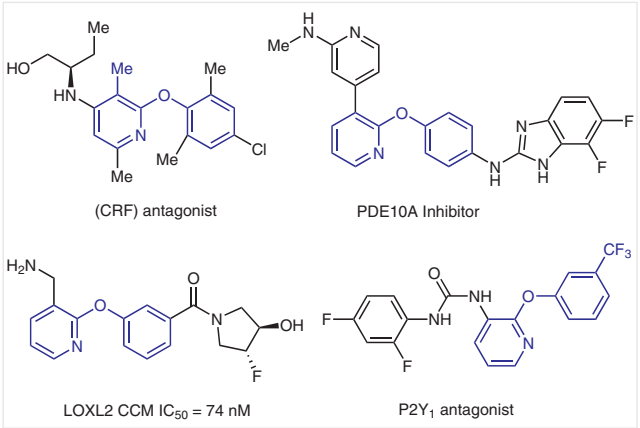
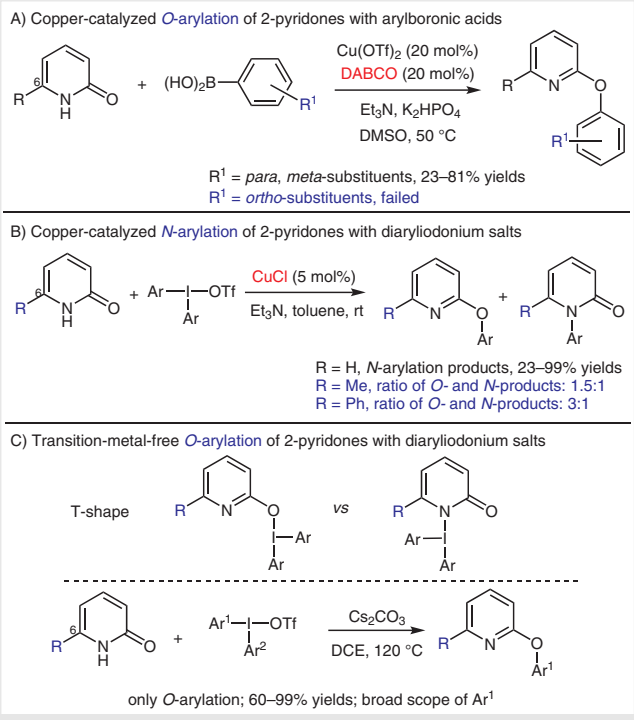



**Figure 1** Biologically active molecules containing a 2-aryloxypyridine scaffold

2-Aryloxypyridine is an important class of pyridine derivatives, and is an ubiquitous scaffold existing in many biologically active molecules and pharmaceutical drugs, such as corticotropin-releasing factor (CRF) antagonist, PDE 10A inhibitors, lysyl oxidase-like 2 (LOXL2) inhibitors, or $P2Y_1$ antagonist (Figure 1).[1]

Due to their intriguing biological activity, many studies were focused on the preparation or modification of 2-aryloxypyridines up to now.[2,3] 2-Pyridones serving as ambident nucleophiles (N- or O-atoms as nucleophilic sites) have attracted many chemists' interest to control the reaction selectivity. In most cases, transition-metal-catalyzed arylation of 2-pyridones dominantly afforded N-arylation products while only few examples of O-arylation products were reported.[4,5] However, selective O-arylation of 2-pyridones is a direct strategy to synthesize 2-aryloxypyridines. In 2012, Luo and co-workers developed a copper-mediated selective O-arylation of 2-pyridones with arylboronic acids to provide 2-aryloxypyridines in moderate to good yields (Scheme 1, A).[5a] DABCO as a ligand played an important role in the selective O-arylation of 2-pyridones under copper-mediated conditions. This method controlled the O-arylation by using C6-position of 2-pyridones, but the reaction scope was limited and not tolerated with *ortho*-substituted arylboronic acids owing to the sensitive steric effects on the coupling reaction. In recent years, diaryliodonium salts serving as useful arylation reagents have been applied extensively in organic synthesis because of their easy preparation, high selectivity and reactivity, as well as nontoxicity.[6] Arylation of heteroatom nucleophiles was successfully utilized to construct C–N and C–O bonds in the past decade.[7] In 2016, Kim and co-workers reported an efficient copper-catalyzed coupling of 2-pyridones with diaryliodonium salts under mild conditions, but N-arylation products were obtained as major products for most of the substituted 2-pyridones (Scheme 1, B).[8] When there were methyl or

phenyl substituents at C6-position of 2-pyridones, however, a mixture of N-arylation and O-arylation products were obtained. From the work of Luo and Kim, it was shown that substituent effects on both 2-pyridones and arylation reagents were sensitive to the arylation reaction under copper catalysis, which might affect the oxidative addition or reductive elimination steps for copper species. During the studies on selective N- or O-arylation of N–O bond by diaryliodonium salts in our group,[9,10] to avoid the formation of copper species and figure out the limitation and scope of preparation of 2-aryloxypyridines, we surmised that a strong base might directly promote the arylation of 2-pyridones by diaryliodonium salts according to the p$K_a$ (about 17)[11] of 2-pyridone. Substituents at C6-position of 2-pyridones would favor access to O-arylation products due to the 'T-shape' of iodonium salts. Herein, we report a substituent effect-controlled O-arylation of 2-pyridones with diaryliodonium salts to prepare diverse 2-aryloxypyridines under transition-metal-free conditions (Scheme 1, C).

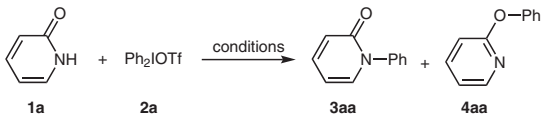



**Scheme 1** Arylation of 2-pyridones

Initially, we evaluated the arylation of 2-pyridone (**1a**) with diphenyliodonium triflate (**2a**) under transition-metal-free conditions. As shown in Table 1, when *t*-BuOK was used as a base in dichloroethane (DCE), N-arylation product **3aa** was obtained as a major product while O-arylation product **4aa** was formed as a minor product either at room temperature or higher; however, high yields of **3aa** and **4aa** were attained at increasing temperature (Table 1, entries 1–4).

Screening of bases revealed that bases such as KOH, $K_2CO_3$, or $Cs_2CO_3$ gave good yields of arylation products except that NaH and $Et_3N$ did not promote the reaction (entries 5–9). The best total yield of **3aa** and **4aa** was obtained in 99% by using $Cs_2CO_3$ (entry 8). Next, we examined the solvent effects for arylation of 2-pyridone (**1a**) (entry 8 vs entries 10–16). Products **3aa** and **4aa** were formed in high total yields in toluene, THF, DMF, and DMSO while lower yields were obtained in 1,4-dioxane, MeCN, and $H_2O$. The additives such as LiCl or $AlCl_3$ decreased the yield of **3aa** and **4aa** and did not affect the ratio of N-arylation or O-arylation products obviously (entries 17, 18). When diphenyliodonium triflate (**2a**) was replaced with $Ph_2IBF_4$, product **3aa** was obtained in 60% yield accompanied by **4aa** in 15% yield (entry 19). In all cases, the ratio of **3aa** and **4aa** ranged from 1:1 to 3:1. Although a mixture of N-arylation and O-arylation products was obtained, the two products can be easily purified

**Table 1** Optimization of the Reaction Conditions[a]



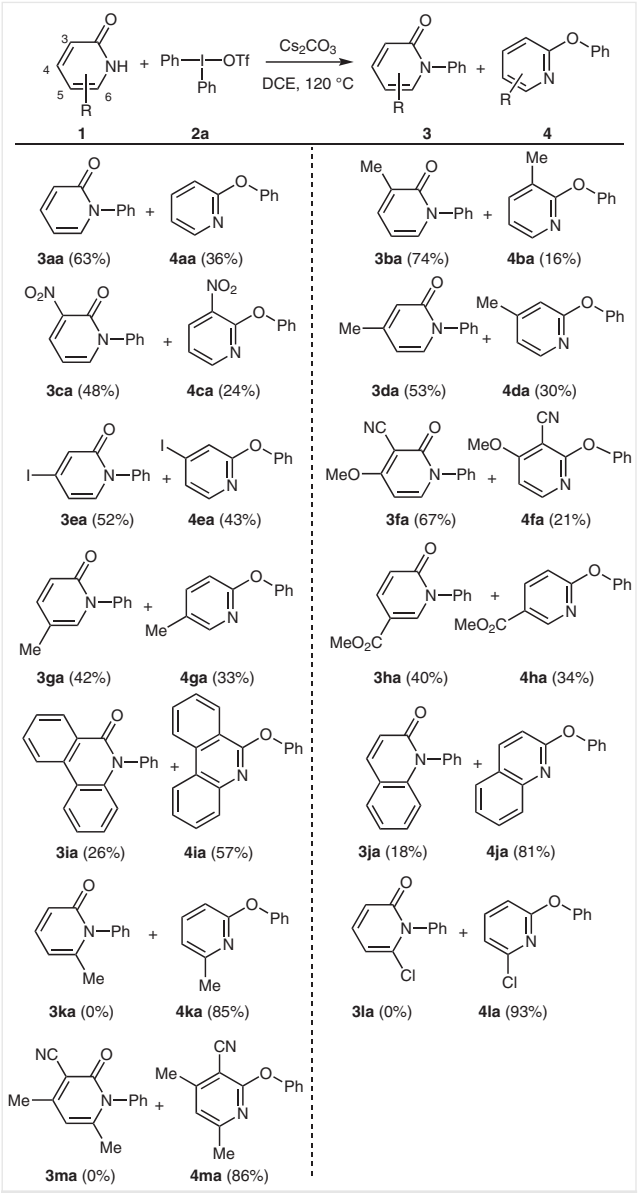

| Entry | Solvent | Base | Temp (°C) | **3aa** (%)[b] | **4aa** (%)[b] |
|---|---|---|---|---|---|
| 1 | DCE | *t*-BuOK | 25 | 33 | 14 |
| 2 | DCE | *t*-BuOK | 60 | 39 | 13 |
| 3 | DCE | *t*-BuOK | 100 | 47 | 15 |
| 4 | DCE | *t*-BuOK | 120 | 53 | 31 |
| 5 | DCE | KOH | 120 | 55 | 28 |
| 6 | DCE | $K_2CO_3$ | 120 | 39 | 31 |
| 7 | DCE | NaH | 120 | <5 | <5 |
| 8 | DCE | $Cs_2CO_3$ | 120 | 63 | 36 |
| 9 | DCE | $Et_3N$ | 120 | <5 | <5 |
| 10 | toluene | $Cs_2CO_3$ | 120 | 58 | 28 |
| 11 | THF | $Cs_2CO_3$ | 120 | 62 | 29 |
| 12 | MeCN | $Cs_2CO_3$ | 120 | 19 | 13 |
| 13 | 1,4-dioxane | $Cs_2CO_3$ | 120 | 35 | <5 |
| 14 | DMF | $Cs_2CO_3$ | 120 | 47 | 33 |
| 15 | DMSO | $Cs_2CO_3$ | 120 | 57 | 17 |
| 16 | $H_2O$ | $Cs_2CO_3$ | 120 | 6 | 10 |
| 17[c] | DCE | $Cs_2CO_3$ | 120 | 39 | 26 |
| 18[d] | DCE | $Cs_2CO_3$ | 120 | 40 | 29 |
| 19[e] | DCE | $Cs_2CO_3$ | 120 | 60 | 15 |

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol, 1.5 equiv), base (0.75 mmol, 1.5 equiv), solvent (5 mL), 2–18 h.
[b] Isolated yield.
[c] In the presence of LiCl.
[d] In the presence of $AlCl_3$.
[e] Triflate **2a** was replaced by $Ph_2IBF_4$.

by flash column chromatography. Finally, the optimal conditions for the arylation process were $Cs_2CO_3$ as base in DCE at 120 °C (entry 8).

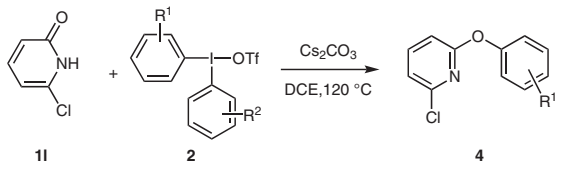
With the optimized conditions in hand, the substituent effects of 2-pyridones were evaluated. As shown in Scheme 2, substituted groups could be present at the 3-, 4-, 5-, or 6-position of 2-pyridones, and N-arylation product **3** and O-arylation product **4** were obtained in good to excellent total yields. For 5-methyl-2-pyridone (**1g**), N-arylation product **3ga** was achieved in 53% yield accompanied by O-arylation product **4ga** in 30% yield. Product **3ga** is known as Pirfenidone, a widely used antifibrotic agent for idiopathic pulmonary fibrosis.[12] The ratio of products **3** and **4** depended on the substituents of the 2-pyridone substrate. When there was a strongly electron-withdrawing group at C5-position, the ratio of products **3** and **4** was 1.1:1 (Scheme 2, **3ha** and **4ha**). Product **3ha** is a precursor for the synthesis of polymyxin lipopeptide.[13] 2-Pyridones **1i** and **1j** facilitated the formation of O-arylation products **4ia** and **4ja** as major products, while N-arylation products **3ia** and **3ja** were obtained as minor products. With a substituent at the C6-position, no N-arylation products were observed, whereas O-arylation products were obtained in excellent yields (Scheme 2, **4ka**, **4la**, and **4ma**). The reaction was compatible with diverse functional groups for 2-pyridones, such as halides, nitro, cyano, and ester groups. The results revealed that the substituent effects at the 6-position of 2-pyridones controlled the selectivity of O-arylation.

Encouraged by the highly selective O-arylation of 2-pyridones with substituents at the C6-position, a series of diaryliodonium salts were used to react with 2-pyridone **1l** to investigate the scope of O-arylation process. As shown in Table 2, various diaryliodonium salts containing electron-donating or electron-withdrawing groups with *para*, *meta*, and *ortho*-substituents delivered the corresponding O-arylation products in excellent yields. When iodonium salt **2b** with a methoxy group was used, the desired product **4lb** was obtained in 60% by extending the reaction time to 30 hours (Table 2, entry 2). In particular, iodonium salt **2n** with 2,4,6-trimethyl groups also resulted in product **4ln** in 99% yield, which could not be prepared by Luo's and Kim's methods (entry 14).[5a,8] It suggests that the steric effects of diaryliodonium salts have little influence on the metal-free selective O-arylation process, which is a good supplement for copper-catalyzed coupling reaction to prepare these *ortho*-substituted O-arylation products. When unsymmetrical diaryliodonium salts **2o** and **2q** were used, the electron-deficient aryl moieties were preferentially transferred to the desired products **4lm** and **4lq** in excellent yields (entries 15 and 17). Unsymmetrical diaryliodonium salts **2p** afforded product **4ln** in 92% yield, which suggested that the steric hindrance of aryl moiety was transferred to the desired products. These results show high chemoselectivity for unsymmetric diaryliodonium salts with both electronic effects and steric effects of substituents (entries 15–17). In all cases, the yield of the N-arylation product **3** was less than 5%. Furthermore, the reaction tolerated various functional groups such as chloro, bromo, fluoro, nitro, and ester groups. Particularly, the chloro-substituted group at C6-position of 2-pyridones will allow these products for more potential applications by $S_N2$ substitution or coupling reaction via transition-metal catalysis.




**Scheme 2** Reaction scope of 2-pyridones. *Reagents and conditions*: **1** (0.5 mmol), **2a** (0.75 mmol, 1.5 equiv), $Cs_2CO_3$ (0.75 mmol, 1.5 equiv), DCE (5 mL), 120 °C, 2–18 h. Isolated yields are shown.

**Table 2** Scope of O-Arylation for 6-Chloro-2-pyridone (**1l**)[a]



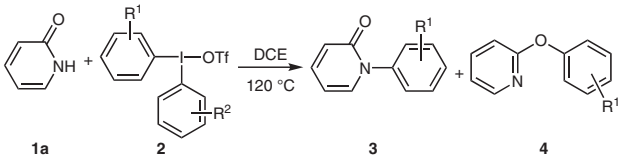

**1l** **2** **4**

| Entry | 2 | $R^1$ | $R^2$ | 4 | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **2a** | H | H | **4la** | 93 |
| 2 | **2b** | 4-MeO | 4-MeO | **4lb** | 60[c] |
| 3 | **2c** | 4-Me | 4-Me | **4lc** | 95 |
| 4 | **2d** | 4-Br | 4-Br | **4ld** | 92 |
| 5 | **2e** | 4-Cl | 4-Cl | **4le** | 95 |
| 6 | **2f** | 4-F | 4-F | **4lf** | 94 |
| 7 | **2g** | 4-$CF_3$ | 4-$CF_3$ | **4lg** | 86 |
| 8 | **2h** | 3-Me | 3-Me | **4lh** | 96 |
| 9 | **2i** | 3-Br | 3-Br | **4li** | 98 |
| 10 | **2j** | 3-$NO_2$ | 3-$NO_2$ | **4lj** | 92 |
| 11 | **2k** | 3,5-$Me_2$ | 3,5-$Me_2$ | **4lk** | 97 |
| 12 | **2l** | 2-Me | 2-Me | **4ll** | 87 |
| 13 | **2m** | 2-Br | 2-Br | **4lm** | 97 |
| 14 | **2n** | 2,4,6-$Me_3$ | 2,4,6-$Me_3$ | **4ln** | 99 |
| 15 | **2o** | 2-Br | 4-MeO | **4lm** | 89 |
| 16 | **2p** | 2,4,6-$Me_3$ | H | **4ln** | 92 |
| 17 | **2q** | 4-$CO_2$Me | H | **4lq** | 97 |

[a] Reaction conditions: **1l** (0.5 mmol), **2** (0.75 mmol, 1.5 equiv), $Cs_2CO_3$ (0.75 mmol, 1.5 equiv), DCE (5 mL), 120 °C, 1–18 h.
[b] Isolated yield.
[c] Reaction time: 30 h.

To better understand the substituent effect of diaryliodonium salts, some electron-donating or electron-withdrawing groups, as well as *ortho*-substituted diaryliodonium salts were reacted with 2-pyridone (**1a**) (Table 3). Both iodonium salts bearing electron-donating or electron-withdrawing groups gave a mixture of N-arylation product **3** and O-arylation product **4**, but affording N-arylation product **3** as the major product. Iodonium salts with *ortho*-substituted groups, such as **2l** and **2n**, also underwent N-arylation to afford N-arylation products as major products (Table 3, entries 3, 4). However, for unsymmetrical iodonium salt **2q**, the reaction showed high chemoselectivity and regioselectivity affording the N-arylation product **3aq** in 74% accompanied by less than 5% yield of O-arylation product **4aq** (entry 7). These results revealed that substituent of diaryliodonium salt moieties might favor N-arylation of 2-pyridone (**1a**). In particular, the electron-wtihdrawing group at diaryliodonium salt provided N-arylation product as a single product while steric effect of substituents did not improve the selectivity (entries 5–7).

**Table 3** Substituent Effects of Diaryliodonium Salts for 2-Pyridone (**1a**)[a]

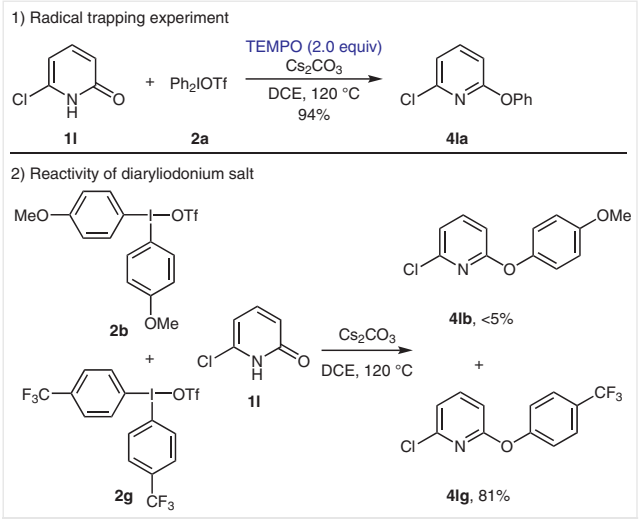



**1a** **2** **3** **4**

| Entry | 2 | $R^1$ | $R^2$ | 3 (%)[b] | 4 (%)[b] |
|---|---|---|---|---|---|
| 1 | **2c** | 4-Me | 4-Me | **3ac**, 60 | **4ac**, 23 |
| 2 | **2f** | 4-F | 4-F | **3af**, 71 | **4af**, 10 |
| 3 | **2l** | 2-Me | 2-Me | **3al**, 59 | **4al**, 19 |
| 4 | **2n** | 2,4,6-$Me_3$ | 2,4,6-$Me_3$ | **3an**, 33 | **4an**, 20 |
| 5 | **2o** | 2-Br | 4-MeO | **3ao**, 77 | **4ao**, 20 |
| 6 | **2p** | 2,4,6-$Me_3$ | H | **3an**, 54 | **4an**,18 |
| 7 | **2q** | 4-$CO_2$Me | H | **3aq**, 74 | **4aq**, <5 |

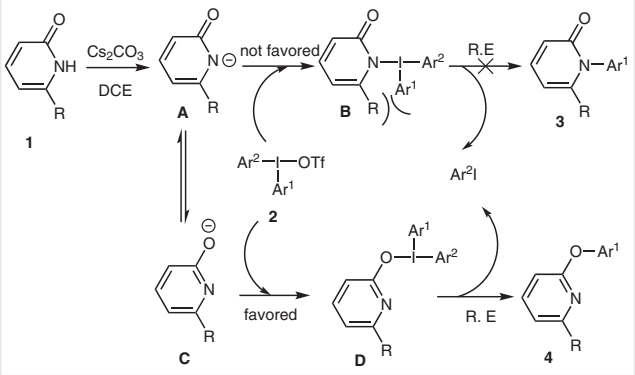
[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.75 mmol, 1.5 equiv), $Cs_2CO_3$ (0.75 mmol, 1.5 equiv), DCE (5 mL), 120 °C, 2–24 h.
[b] Isolated yield.

When 2-pyridone **1l** was reacted with **2a** in the presence of radical scavenger TEMPO (2.0 equiv) under the optimal conditions, product **4la** was still obtained in 94% yield (Scheme 3, 1). This result suggests that the arylation process might not involve a radical intermediate. When a 1:1 ratio of diaryliodonium salt **2b** with electron-donating group and **2g** with electron-withdrawing group reacted with 2-pyridone **1l** under the optimized conditions for 6 hours, the O-arylation product **4lg** was obtained in 81% yield while the O-arylation product **4lb** was formed in less than 5% yield (Scheme 3, 2). This result demonstrated that the O-arylation process showed more reactivity for diaryliodonium salt with electron-withdrawing group.



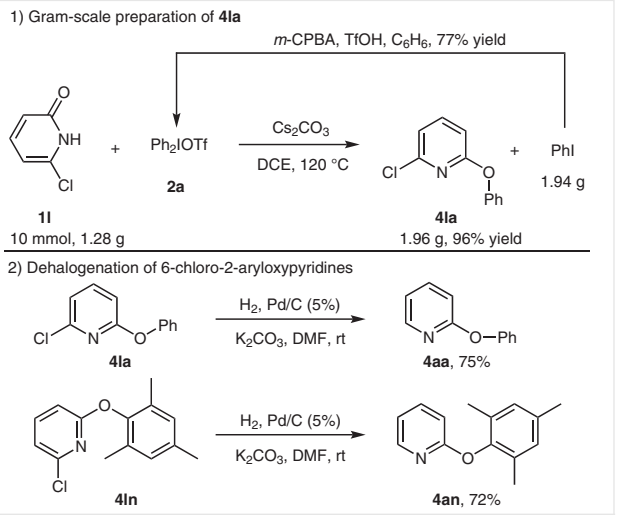

**Scheme 3** Control experiments

On the basis of experimental results, a possible mechanism of selective O-arylation of 6-substituted 2-pyridones is proposed (Scheme 4). Intermediate **A** is formed first by deprotonation under base conditions. Diaryliodonium salt is then attacked by intermediate **A** to give intermediate **B**. When a substituent group is present at the 6-position, diaryliodonium salt is unfavorable to be attacked to form intermediate **B**, which is also unfavorable to undergo reductive elimination (RE) to provide N-arylation product **3** due to the steric hindrance of 6-substituents and the 'T-shape' of iodonium salt. Consequently, intermediate **A** gets converted into intermediate **C** by isomerization.[14] Then, intermediate **C** attacks diaryliodonium salt to give the intermediate **D**, which favorably undergoes reductive elimination or 1,2-aryl migration to give the O-arylation product **4**.[6c,15]



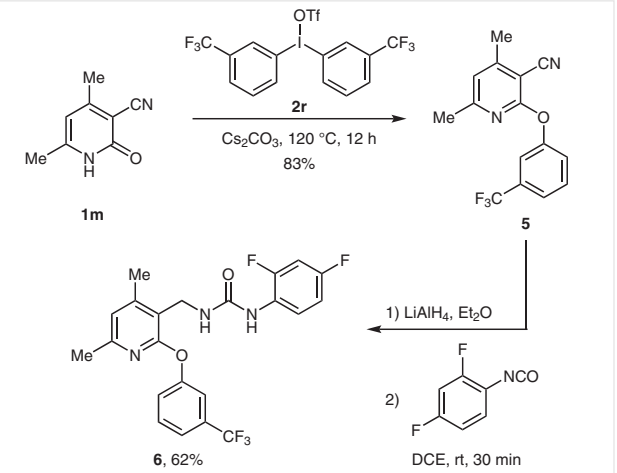

**Scheme 4** Possible mechanism for steric effects on O-arylation

Finally, inspired by the feasibility of the transition-metal-free O-arylation of 2-pyridones with diaryliodonium salts, a gram-scale procedure was performed. When 1.28 grams of 2-pyridone **1l** was reacted with **2a** under the optimal conditions, 1.96 grams of product **4la** was obtained in 96% yield accompanied by 1.94 grams of PhI (Scheme 5, 1). To make a green process, the producing PhI could be converted to iodonium salts **2a** in 77% yield following Olofsson's procedure.[16] Comparing Scheme 2, Table 2, and Table 3, we can see that O-arylation products can not be synthesized with high regioselectivity and yields when there was no substituent at C6-position of 2-pyridones. To figure out high-yielding unsubstituted 2-aryloxypyridines, dehalogenation of 6-chloro-2-aryloxypyridine products was performed (Scheme 5, 2). Treatment of compounds **4la** and **4ln** with 5% of Pd/C with $H_2$ at room temperature for 3 hours,[17] afforded **4aa** and **4an** in 75% and 72% yield, respectively, which were difficult to obtain by copper-catalysis, especially for *ortho*-substituted aryl groups. These results showed that 6-chloro-2-pyridone (**1l**) was a good precursor to access various unsubstituted 2-aryloxypyridines by highly selective O-arylation and sequential dehalogenation process.




**Scheme 5** Applications of O-arylation reaction

Next, we attempted to modify a lead compound for $P2Y_1$ (see Figure 1), which has demonstrated to possess good bioactivity.[18] As shown in Scheme 6, the O-arylation product **5** was obtained in 80% yield by reacting 2-pyridone **1m** and diaryliodonium salt **2r** under optimal conditions. Reduction of compound **5** with $LiAlH_4$ in $Et_2O$ for 2 hours and followed by addition of 2,4-difluoro-1-isocyanatobenzene gave the desired product **6** in 62% yield. This new approach to access $P2Y_1$ lead compound analogue is meaningful for future potential applications in pharmaceuticals.




**Scheme 6** Preparation of $P2Y_1$ lead compound analogue **6**

In summary, we have described a new synthetic method to prepare 2-aryloxypyridine derivatives by O-arylation of 2-pyridones and diaryliodonium salts under transition-metal-free conditions. It was found that 2-pyridones containing substituents at the 6-position definitely controlled the reaction selectivity to provide O-arylation products.

The O-arylation reaction was compatible with diaryliodonium salts containing various electron-donating or electron-withdrawing groups, as well as *ortho*-substituted groups. Furthermore, it is easy to be performed at gram-scale and a $P2Y_1$ lead compound analogue could be synthesized in two steps using the transition-metal-free O-arylation strategy.

All reactions were performed under an air atmosphere. Commercially available reagents were used without further purification. The NMR spectra were recorded in $CDCl_3$ or DMSO-$d_6$ using 400 or 500 MHz instrument with TMS as the internal standard. NMR data are represented as follows: chemical shift (pap), multiplicity (standard abbreviations), coupling constants (Hz), and integration. IR spectra were recorded on FT-IR spectrophotometer, and only major peaks are reported in $cm^{-1}$. HRMS were measured in ESI mode and the mass analyzer of the HRMS was TOF. Flash column chromatography was performed on silica gel (300–400 mesh). 2-Pyridones **1a–m** were purchased directly from Sigma-Aldrich. Diaryliodonium salts **2a–r**[10a,b] were prepared according to literature methods and their spectral data matched literature values.

### 2-Pyridones 3 and 4; General Procedure

A 25 mL Teflon-sealed flask was charged with the corresponding 2-pyridone **1** (0.5 mmol), diaryliodonium salt **2** (0.75 mmol, 1.5 equiv), and $Cs_2CO_3$ (0.75 mmol, 1.5 equiv) under an air atmosphere. DCE (5 mL) was added to the flask. Then, the reaction vessel was sealed with a Teflon cap. The reaction mixture was stirred at 120 °C until the 2-pyridone **1** was consumed completely (monitored by TLC). At this time, the solvent was removed in vacuo and the residue was purified by flash column chromatography (the crude residue was dry loaded on silica gel, 1:20 to 1:1, EtOAc/PE) to provide the desired products **3** and **4** (Scheme 2, Tables 2, 3).

### 1-Phenylpyridin-2(1*H*)-one (3aa)[19]

Yield: 0.054 g (63%); orange solid; mp 94–95 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.50–7.47 (m, 2 H), 7.43–7.36 (m, 4 H), 7.34 (d, *J* = 8.5 Hz, 1 H), 6.66 (d, *J* = 10.5 Hz, 1 H), 6.25 (t, *J* = 7.0 Hz, 1 H).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 162.3, 140.9, 139.8, 137.9, 129.2, 128.4, 126.4, 121.8, 105.8.

### 3-Methyl-1-phenylpyridin-2(1*H*)-one (3ba)[20]

Yield: 0.068 g (74%); yellow solid; mp 113–114 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.49 (t, *J* = 7.5 Hz, 2 H), 7.41–7.37 (m, 3 H), 7.27 (d, *J* = 5.0 Hz, 1 H), 7.23 (d, *J* = 7.0 Hz, 1 H), 6.17 (t, *J* = 7.5 Hz, 1 H), 2.19 (s, 3 H).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 162.8, 141.3, 136.9, 135.3, 130.8, 129.1, 128.2, 126.6, 105.5, 17.3.

### 3-Nitro-1-phenylpyridin-2(1*H*)-one (3ca)

Yield: 0.052 g (48%); orange solid; mp 140–141 °C.

IR (film): 3033, 2954, 1660, 1573, 1459, 1288, 1104, 734 $cm^{-1}$.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 8.38 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.73 (dd, *J* = 6.5, 1.5 Hz, 1 H), 7.53–7.49 (m, 3 H), 7.38 (d, *J* = 7.5 Hz, 2 H), 6.40 (t, *J* = 7.5 Hz, 1 H).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 154.3, 144.2, 139.6, 139.4, 138.8, 129.6, 129.5, 126.3, 103.2.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{11}H_9N_2O_3$: 217.0613; found: 217.0634.

### 4-Methyl-1-phenylpyridin-2(1*H*)-one (3da)[21]

Yield: 0.049 g (53%); orange solid; mp 104–105 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.49 (t, *J* = 7.5 Hz, 2 H), 7.41–7.35 (m, 3 H), 7.23 (d, *J* = 6.5 Hz, 1 H), 6.46 (s, 1 H), 6.09 (d, *J* = 6.0 Hz, 1 H), 2.23 (s, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 162.3, 151.5, 140.8, 136.7, 129.2, 128.2, 126.5, 120.0, 108.5, 21.2.

### 4-Iodo-1-phenylpyridin-2(1*H*)-one (3ea)

Yield: 0.077 g (52%); yellow oil.

IR (film): 3057, 2924, 1662, 1577, 1454, 1276, 1134, 632 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 2.0 Hz, 2 H), 7.51–7.41 (m, 4 H), 7.36 (d, *J* = 7.2 Hz, 2 H), 6.50 (d, *J* = 9.6 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 160.8, 147.2, 142.7, 140.0, 129.5, 128.9 126.4, 123.6, 64.4.

HRMS (ESI) *m*/*z* (M + H)$^+$ calcd for $C_{11}H_9INO$: 297.9729; found: 297.9719.

### 4-Methoxy-2-oxo-1-phenyl-1,2-dihydropyridine-3-carbonitrile (3fa)

Yield: 0.076 g (67%); white solid; mp 236–237 °C.

IR (film): 3098, 2216, 1657, 1524, 1340, 1239, 1106, 774 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.13 (d, *J* = 8.4 Hz, 1 H), 7.55–7.41 (m, 3 H), 7.42 (d, *J* = 8.4 Hz, 1 H), 4.06 (s, 3 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 173.7, 160.7, 145.9, 139.8, 129.6, 129.3, 127.3, 114.9, 95.2, 86.9, 58.4.

HRMS (ESI) *m*/*z* (M + H)$^+$ calcd for $C_{13}H_{11}N_2O_2$: 227.0821; found: 227.0813.

### 5-Methyl-1-phenylpyridin-2(1*H*)-one (3ga)[8]

Yield: 0.040 g (42%); yellow solid; mp 106–107 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.50 (t, *J* = 7.0 Hz, 2 H), 7.42–7.36 (m, 3 H), 7.28–7.25 (m, 1 H), 7.11 (s, 1 H), 6.62 (d, *J* = 9.0 Hz, 1 H), 2.10 (s, 3 H).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 161.7, 142.6, 141.1, 135.3, 129.3, 128.3, 126.6, 121.5, 114.8, 17.0.

### Methyl 6-Oxo-1-phenyl-1,6-dihydropyridine-3-carboxylate (3ha)[13]

Yield: 0.047 g (40%); yellow solid; mp 70–71 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.49 (m, 2 H), 7.46–7.37 (m, 4 H), 6.74 (d, *J* = 6.5 Hz, 1 H), 3.94 (s, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 164.9, 162.0, 140.8, 140.4, 138.1, 129.4, 128.8, 126.3, 123.8, 104.3, 52.9.

### 5-Phenylphenanthridin-6(5*H*)-one (3ia)[22]

Yield: 0.035 g (26%); orange solid; mp 106–107 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 7.8 Hz, 1 H), 8.35–8.30 (m, 2 H), 7.83 (t, *J* = 7.2 Hz, 1 H), 7.64 (t, *J* = 8.0 Hz, 3 H), 7.56 (t, *J* = 7.2 Hz, 1 H), 7.35–7.25 (m, 4 H), 6.71–6.69 (m, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 161.7, 139.1, 138.2, 133.9, 132.8, 130.1, 129.1, 129.0, 128.7, 128.1, 125.8, 122.9, 122.6, 121.7, 119.0, 117.0.

**1-Phenylquinolin-2(1*H*)-one (3ja)**[23]

Yield: 0.020 g (18%); yellow solid; mp 124–125 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 9.6 Hz, 1 H), 7.62–7.58 (m, 3 H), 7.54–7.50 (m, 1 H), 7.34–7.25 (m, 3 H), 7.21 (d, *J* = 7.2 Hz, 1 H), 6.80 (d, *J* = 9.6 Hz, 1 H), 6.66 (d, *J* = 8.8 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 162.3, 141.1, 139.8, 137.6, 130.2, 130.1, 128.9, 128.8, 128.2, 122.3, 122.2, 120.3, 115.9.

**1-(4-Methylphenyl)pyridin-2(1*H*)-one (3ac)**[20]

Yield: 0.055 g (60%); yellow oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.36 (m, 1 H), 7.32–7.24 (m, 5 H), 6.66 (d, *J* = 9.6 Hz, 1 H), 6.23 (t, *J* = 6.8 Hz, 1 H), 2.40 (s, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 162.5, 139.7, 138.4, 138.3, 138.0, 129.8, 126.1, 121.7, 105.7, 21.1.

**1-(4-Fluorophenyl)pyridin-2(1*H*)-one (3af)**[24]

Yield: 0.067 g (71%); yellow solid; mp 131–132 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.35 (m, 3 H), 7.32 (d, *J* = 4.0 Hz, 1 H), 7.20 (t, *J* = 6.8 Hz, 2 H), 6.67 (d, *J* = 7.2 Hz, 1 H), 6.26 (d, *J* = 5.2 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 163.4 (d, *J* = 247.1 Hz), 162.4, 140.0, 137.8, 136.8 (d, *J* = 3.1 Hz), 128.4 (d, *J* = 8.8 Hz), 121.9, 116.4 (d, *J* = 22.6 Hz), 106.2.

**1-*o*-Tolylpyridin-2(1*H*)-one (3al)**[4c]

Yield: 0.055 g (59%); yellow solid; mp 67–68 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.41 (m, 1 H), 7.34–7.31 (m, 3 H), 7.21 (t, *J* = 4.4 Hz, 2 H), 6.70 (d, *J* = 9.6 Hz, 1 H), 6.26 (d, *J* = 6.4 Hz, 1 H), 2.16 (s, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 162.0, 140.0, 139.9, 137.8, 134.8, 130.9, 128.9, 126.9, 126.8, 121.6, 105.7, 17.4.

**1-Mesitylpyridin-2(1*H*)-one (3an)**

Yield: 0.034 g (33%); yellow solid; mp 125–126 °C.

IR (film): 3055, 2923, 1667, 1580, 1501, 1274, 1008, 694 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.41 (m, 1 H), 7.08 (q, *J* = 5.6 Hz, 1 H), 6.98 (s, 2 H), 6.72 (d, *J* = 9.2 Hz, 1 H), 6.28 (t, *J* = 6.8 Hz, 1 H), 2.31 (s, 3 H), 2.05 (s, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 162.0, 140.0, 138.6, 137.8, 138.7, 134.3, 129.2, 122.1, 106.2. 20.9, 17.5.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{14}H_{16}NO$: 214.1232; found: 214.1242.

**1-(2-Bromophenyl)pyridin-2(1*H*)-one (3ao)**

Yield: 0.096 g (77%); yellow solid; mp 170–171 °C.

IR (film): 3045, 2938, 1665, 1578, 1496, 1236, 1022, 734 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.0 Hz, 1 H), 7.47–7.42 (m, 2 H), 7.37–7.31 (m, 2 H), 7.16 (d, *J* = 5.6 Hz, 1 H), 6.69 (d, *J* = 9.2 Hz, 1 H), 6.28 (t, *J* = 6.8 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 161.8, 140.3, 140.1, 137.7, 133.7, 130.5, 129.2, 128.6, 122.1, 121.6, 105.8.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{11}H_9BrNO$: 249.9868; found: 249.9870.

**Methyl 4-[2-Oxopyridin-1(2*H*)-yl]benzoate (3aq)**[25]

Yield: 0.084 g (74%); yellow oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 6.4 Hz, 2 H), 7.50 (d, *J* = 6.8 Hz, 2 H), 7.42 (t, *J* = 6.0 Hz, 1 H), 7.34 (d, *J* = 5.2 Hz, 1 H), 6.67 (d, *J* = 7.2 Hz, 1 H), 6.28 (q, *J* = 5.6 Hz, 1 H), 3.95 (s, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 166.1, 162.0, 144.6, 140.0, 137.2, 130.7, 130.1, 126.6, 122.1, 106.2, 52.3.

**2-Phenoxypyridine (4aa)**[2a]

Yield: 0.033 g (36%); yellow oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 4.0 Hz, 1 H), 7.69–7.64 (m, 1 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 7.21–7.12 (m, 3 H), 6.99–6.94 (m, 1 H), 6.90 (d, *J* = 8.2 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 163.7, 154.2, 147.7, 139.4, 129.6, 124.6, 121.1, 118.4, 111.5.

**3-Methyl-2-phenoxypyridine (4ba)**[2a]

Yield: 0.015 g (16%); yellow oil.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 4.0 Hz, 1 H), 7.52 (d, *J* = 7.0 Hz, 1 H), 7.39 (t, *J* = 7.5 Hz, 2 H), 7.18–7.15 (m, 1 H), 7.11 (d, *J* = 8.0 Hz, 2 H), 6.91–6.89 (m, 1 H), 2.34 (s, 3 H).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 161.8, 154.5, 144.7, 139.7, 129.4, 124.1, 122.0, 120.9, 118.6, 15.9.

**3-Nitro-2-phenoxypyridine (4ca)**[26]

Yield: 0.026 g (24%); yellow solid; mp 85–86 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.37 (t, *J* = 8.4 Hz, 2 H), 7.47 (t, *J* = 8.0 Hz, 2 H), 7.30 (t, *J* = 7.2 Hz, 1 H), 7.20–7.14 (m, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 155.9, 152.6, 151.7, 135.4, 134.6, 129.7, 125.8, 121.7, 118.2.

**4-Methyl-2-phenoxypyridine (4da)**[27]

Yield: 0.028 g (30%); orange oil.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 5.0 Hz, 1 H), 7.39 (t, *J* = 7.5 Hz, 2 H), 7.19 (t, *J* = 7.0 Hz, 1 H), 7.12 (d, *J* = 8.0 Hz, 2 H), 6.81 (d, *J* = 5.0 Hz, 1 H), 6.70 (s, 1 H), 2.32 (s, 3 H).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 164.0, 154.3, 150.9, 147.3, 129.6, 124.4, 121.0, 119.8, 111.7, 20.9.

**4-Iodo-2-phenoxypyridine (4ea)**

Yield: 0.065 g (43%); yellow oil.

IR (film): 3033, 2934, 1580, 1496, 1256, 1123, 734 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 2.0 Hz, 1 H), 7.92 (dd, *J* = 8.4 Hz, 2.0 H, 1 H), 7.42 (t, *J* = 8.0 Hz, 2 H), 7.23 (t, *J* = 7.6 Hz, 1 H), 7.13 (d, *J* = 8.0 Hz, 2 H), 6.76 (d, *J* = 8.2 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 163.2, 153.7, 153.6, 147.3, 129.7, 125.0, 121.1, 113.7, 84.1.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{11}H_9INO$: 297.9729; found: 297.9730.

**4-Methoxy-2-phenoxynicotinonitrile (4fa)**[28]

Yield: 0.024 g (21%); white solid; mp 236–237 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 6.0 Hz, 1 H), 7.44–7.10 (m, 2 H), 7.27–7.24 (m, 1 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 6.65 (d, *J* = 6.0 Hz, 1 H), 4.02 (s, 3 H).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 170.0, 165.6, 152.7, 152.1, 129.6, 125.6, 121.6, 112.4, 102.2, 86.6, 56.8.

**5-Methyl-2-phenoxypyridine (4ga)**[29]

Yield: 0.031 g (33%); orange oil.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 8.01 (s, 1 H), 7.48 (d, *J* = 6.5 Hz, 1 H), 7.38 (t, *J* = 8.0 Hz, 2 H), 7.17 (t, *J* = 8.0 Hz, 1 H), 7.11 (d, *J* = 7.0 Hz, 2 H), 6.80 (d, *J* = 8.5 Hz, 1 H), 2.27 (s, 3 H).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 161.8, 154.6, 147.4, 140.1, 129.5, 127.7, 124.2, 120.7, 111.0, 17.4.

**Methyl 6-Phenoxynicotinate (4ha)**[30]

Yield: 0.040 g (34%); yellow oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 4.0 Hz, 1 H), 7.53 (d, *J* = 4.0 Hz, 1 H), 7.43–7.40 (m, 2 H), 7.26–7.21 (m, 1 H), 7.15 (d, *J* = 6.8 Hz, 2 H), 3.95 (s, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 165.2, 164.5, 153.8, 148.5, 141.0, 129.8, 125.0, 121.2, 117.6, 111.4, 52.7.

**6-Phenoxyphenanthridine (4ia)**[31]

Yield: 0.078 g (57%); orange solid; mp 141–142 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 8.0 Hz, 1 H), 8.36–8.29 (m, 2 H), 7.84 (t, *J* = 7.2 Hz, 1 H), 7.64 (t, *J* = 8.0 Hz, 3 H), 7.56 (t, *J* = 7.2 Hz, 1 H), 7.35–7.26 (m, 4 H), 6.71–6.69 (m, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 161.7, 139.2, 138.3, 134.0, 132.8, 130.2, 129.1, 129.0, 128.8, 128.2, 125.9, 123.0, 122.6, 121.8, 119.0, 117.0.

**2-Phenoxyquinoline (4ja)**[32]

Yield: 0.089 g (81%); orange solid; mp 57–58 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.8 Hz, 1 H), 7.81 (d, *J* = 8.0 Hz, 1 H), 7.76 (d, *J* = 8.0 Hz, 1 H), 7.63–7.59 (m, 1 H), 7.44–7.41 (m, 3 H), 7.26–7.21 (m, 3 H), 7.08 (d, *J* = 8.8 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 161.5, 153.8, 146.3, 139.7, 129.7, 129.4, 127.8, 127.2, 125.6, 124.7, 124.6, 121.3, 116.2.

**2-Methyl-6-phenoxypyridine (4ka)**[2a]

Yield: 0.079 g (85%); yellow oil.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.54 (t, *J* = 7.5 Hz, 1 H), 7.38 (t, *J* = 8.0 Hz, 2 H), 7.18 (t, *J* = 7.5 Hz, 1 H), 7.13 (d, *J* = 7.5 Hz, 2 H), 6.87 (d, *J* = 7.5 Hz, 1 H), 6.57 (d, *J* = 8.5 Hz, 1 H), 2.46 (s, 3 H).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 163.2, 157.6, 154.7, 139.5, 129.6, 124.3, 120.7, 118.0, 107.6, 24.1.

**2-Chloro-6-phenoxypyridine (4la)**[27]

Yield: 0.097 g (93%); colorless oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.62 (t, *J* = 8.0 Hz, 1 H), 7.41 (t, *J* = 8.0 Hz, 2 H), 7.23 (t, *J* = 7.6 Hz, 1 H), 7.14 (t, *J* = 8.0 Hz, 2 H), 7.03 (d, *J* = 7.6 Hz, 1 H), 6.74 (t, *J* = 8.2 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 163.1, 153.7, 149.1, 141.4, 129.8, 125.0, 121.0, 118.4, 109.1.

**4,6-Dimethyl-2-phenoxynicotinonitrile (4ma)**

Yield: 0.096 g (86%); white solid; mp 96–97 °C.

IR (film): 3054, 2954, 2251, 1589, 1495, 1283, 1120, 783 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.38 (m, 2 H), 7.26–7.22 (m, 2 H), 7.18 (d, *J* = 8.0 Hz, 1 H), 6.80 (s, 1 H), 2.52 (s, 3 H), 2.35 (s, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 163.5, 161.1, 154.8, 153.0, 129.3, 125.9, 121.4, 119.1, 114.6, 95.1, 24.5, 20.1.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{14}H_{13}N_2O$: 225.1028; found: 225.1020.

**2-Chloro-6-(4-methoxyphenoxy)pyridine (4lb)**

Yield: 0.071 g (60%); colorless oil.

IR (film): 3055, 2956, 1590, 1430, 1256, 1167, 774 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.60 (t, *J* = 8.0 Hz, 1 H), 7.07 (d, *J* = 9.2 Hz, 2 H), 7.00 (d, *J* = 7.6 Hz, 1 H), 6.93 (d, *J* = 9.2 Hz, 2 H), 6.70 (d, *J* = 8.0 Hz, 1 H), 3.81 (s, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 163.6, 156.8, 149.0, 147.0, 141.3, 122.1, 118.0, 114.7, 108.6, 55.6.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{12}H_{11}ClNO_2$: 236.0478; found: 236.0483.

**2-Chloro-6-(*p*-tolyloxy)pyridine (4lc)**

Yield: 0.105 g (95%); colorless oil.

IR (film): 3032, 2923, 1960, 1582, 1428, 1287, 1159, 789 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.58 (t, *J* = 8.0 Hz, 1 H), 7.19 (t, *J* = 8.0 Hz, 2 H), 7.02–6.98 (m, 3 H), 6.70 (d, *J* = 7.6 Hz, 1 H), 2.35 (s, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 163.4, 151.3, 149.0, 141.3, 134.6, 130.2, 120.7, 118.1, 108.1, 20.8.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{12}H_{11}ClNO$: 220.0529; found: 220.0521.

**2-(4-Bromophenoxy)-6-chloropyridine (4ld)**

Yield: 0.131 g (92%); colorless oil.

IR (film): 3088, 2545, 2198, 1884, 1568, 1427, 1159, 792 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.64 (t, *J* = 8.0 Hz, 1 H), 7.50 (d, *J* = 8.0 Hz, 2 H), 7.04 (d, *J* = 8.8 Hz, 3 H), 6.80 (d, *J* = 8.0 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 162.5, 152.6, 149.0, 141.5, 132.7, 122.8, 118.8, 117.8, 109.5.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{11}H_8BrClNO$: 283.9478; found: 283.9467.

**2-Chloro-6-(4-chlorophenoxy)pyridine (4le)**

Yield: 0.113 g (95%); colorless oil.

IR (film): 3070, 1890, 1571, 1496, 1120, 798 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.58 (m, 1 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.08 (d, *J* = 8.4 Hz, 2 H), 7.03 (d, *J* = 7.6 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 162.4, 151.9, 148.8, 141.5, 130.0, 129.5, 122.3, 118.6, 109.3.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{11}H_8Cl_2NO$: 239.9983; found: 239.9990.

**2-Chloro-6-(4-fluorophenoxy)pyridine (4lf)**

Yield: 0.105 g (94%); white solid; mp 72–73 °C.

IR (film): 3077, 2345, 1585, 1427, 1288, 1155, 913, 768 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.64 (t, *J* = 8.0 Hz, 1 H), 7.13–7.02 (m, 5 H), 6.77 (d, *J* = 8.0 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 163.0, 161.0 (d, *J* = 241.0 Hz), 149.3 (d, *J* = 2.2 Hz), 149.0, 141.4, 122.6 (d, *J* = 8.0 Hz), 118.5, 116.4 (d, *J* = 2.4 Hz), 109.1.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{11}H_8FClNO$: 224.0278; found: 224.0271.

**2-Chloro-6-[4-(trifluoromethyl)phenoxy]pyridine (4lg)**

Yield: 0.118 g (86%); yellow oil.

IR (film): 3060, 2926, 1918, 1583, 1431, 1107, 1065, 783 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.65 (m, 3 H), 7.26 (d, *J* = 7.6 Hz, 2 H), 7.11 (d, *J* = 7.6 Hz, 1 H), 6.88 (d, *J* = 8.0 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 162.0, 156.3, 149.0, 141.7, 127.0 (q, *J* = 3.6 Hz), 125.4 (q, *J* = 269.8 Hz), 121.0, 120.9, 119.3, 110.1.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{12}H_8ClF_3NO$: 274.0247; found: 274.0236.

**2-Chloro-6-(*m*-tolyloxy)pyridine (4lh)**

Yield: 0.106 g (96%); colorless oil.

IR (film): 3055, 2919, 1943, 1580, 1427, 1281, 1138, 1213, 788 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.61 (t, *J* = 8.0 Hz, 1 H), 7.27 (t, *J* = 6.4 Hz, 1 H), 7.03 (d, *J* = 7.6 Hz, 2 H), 6.94 (d, *J* = 8.2 Hz, 2 H), 6.72 (d, *J* = 8.0 Hz, 1 H), 2.36 (s, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 163.3, 153.7, 149.2, 141.3, 140.0, 129.4, 125.9, 121.5, 118.3, 117.9, 109.0, 21.4.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{12}H_{11}ClNO$: 220.0529; found: 220.0520.

**2-(3-Bromophenoxy)-6-chloropyridine (4li)**

Yield: 0.140 g (98%); yellow oil.

IR (film): 3086, 2146, 1932, 1577, 1427, 1280, 1160, 786 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.66 (t, *J* = 8.0 Hz, 1 H), 7.35 (t, *J* = 8.0 Hz, 2 H), 7.28 (t, *J* = 8.4 Hz, 1 H), 7.10–7.05 (m, 2 H), 6.81 (d, *J* = 8.0 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 162.3, 154.3, 149.0, 141.6, 130.7, 128.1, 124.3, 122.6, 119.7, 119.0, 109.6.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{11}H_8BrClNO$: 283.9478; found: 283.9469.

**2-Chloro-6-(3-nitrophenoxy)pyridine (4lj)**

Yield: 0.115 g (92%); white solid; mp 50–51 °C.

IR (film): 3084, 2422, 1962, 1518, 1322, 1160, 1076, 793 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.0 Hz, 1 H), 8.02 (s, 1 H), 7.74 (t, *J* = 8.0 Hz, 1 H), 7.59–7.50 (m, 2 H), 7.13 (d, *J* = 7.6 Hz, 1 H), 6.94 (d, *J* = 8.0 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 161.7, 154.0, 149.0, 148.9, 141.9, 130.1, 127.4, 119.7, 119.5, 116.4, 110.1.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{11}H_8ClN_2O_3$: 251.0223; found: 251.0224.

**2-Chloro-6-(3,5-dimethylphenoxy)pyridine (4lk)**

Yield: 0.114 g (97%); colorless oil.

IR (film): 3021, 2737, 1979, 1574, 1295, 1260, 1023, 796 cm$^{-1}$.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.59 (t, *J* = 7.5 Hz, 1 H), 7.01 (d, *J* = 7.5 Hz, 1 H), 6.84 (s, 1 H), 6.73 (s, 2 H), 6.69 (d, *J* = 8.0 Hz, 1 H), 2.31 (s, 6 H).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 163.4, 153.6, 149.1, 141.2, 139.6, 126.8, 118.4, 118.2, 108.9, 21.2.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{13}H_{13}ClNO$: 234.0686; found: 234.0678.

**2-Chloro-6-(*o*-tolyloxy)pyridine (4ll)**

Yield: 0.096 g (87%); colorless oil.

IR (film): 3062, 2926, 1957, 1571, 1285, 1179, 1041, 787 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.60 (t, *J* = 8.0 Hz, 1 H), 7.28–7.21 (m, 2 H), 7.17 (t, *J* = 6.0 Hz, 1 H), 7.06 (d, *J* = 8.0 Hz, 1 H), 7.00 (d, *J* = 8.0 Hz, 1 H), 6.63 (d, *J* = 8.0 Hz, 1 H), 2.19 (s, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 162.2, 151.8, 149.3, 141.3, 131.5, 130.5, 127.2, 125.5, 121.5, 118.0, 108.0, 16.3.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{12}H_{11}ClNO$: 220.0529; found: 220.0520.

**2-(2-Bromophenoxy)-6-chloropyridine (4lm)**

Yield: 0.138 g (97%); yellow oil.

IR (film): 3088, 1589, 1426, 1281, 1157, 1045, 921, 785 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.62 (m, 2 H), 7.37 (t, *J* = 7.2 Hz, 1 H), 7.21 (d, *J* = 7.6 Hz, 1 H), 7.15 (t, *J* = 8.0 Hz, 1 H), 7.05 (d, *J* = 7.6 Hz, 1 H), 6.81 (d, *J* = 8.0 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 162.3, 150.5, 149.0, 141.5, 133.7, 128.6, 126.7, 123.6, 118.6, 116.3, 109.0.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{11}H_8ClBrNO$: 283.9478; found: 283.9480.

**2-Chloro-6-(mesityloxy)pyridine (4ln)**

Yield: 0.124 g (99%); yellow oil.

IR (film): 2919, 1985, 1582, 1427, 1281, 1197, 1034, 771 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.55 (t, *J* = 8.0 Hz, 1 H), 6.97 (d, *J* = 8.0 Hz, 1 H), 6.89 (s, 2 H), 6.51 (d, *J* = 8.0 Hz, 1 H), 2.29 (s, 3 H), 2.08 (s, 6 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 162.9, 149.4, 147.6, 141.3, 134.9, 130.4, 129.5, 117.5, 106.6, 20.7, 16.3.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{14}H_{15}ClNO$: 248.0842; found: 248.0832.

**Methyl 4-(6-Chloropyridin-2-yloxy)benzoate (4lq)**

Yield: 0.129 g (97%); yellow oil.

IR (film): 3080, 2944, 1927, 1720, 1579, 1424, 1276, 768 cm$^{-1}$.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.5 Hz, 2 H), 7.69 (t, *J* = 8.0 Hz, 1 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 7.10 (d, *J* = 8.0 Hz, 1 H), 6.86 (d, *J* = 8.5 Hz, 1 H), 3.92 (s, 3 H).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 166.4, 162.0, 157.6, 149.1, 141.7, 131.5, 126.6, 120.3, 119.3, 110.1, 52.1.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{13}H_{11}ClNO_3$: 264.0428; found: 264.0417.

**2-(4-Methylphenoxy)pyridine (4ac)**[2a]

Yield: 0.021 g (23%); yellow oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 4.0 Hz, 1 H), 7.66 (t, *J* = 6.8 Hz, 1 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 7.03 (d, *J* = 8.0 Hz, 2 H), 6.96 (t, *J* = 6.4 Hz, 1 H), 6.88 (d, *J* = 8.4 Hz, 1 H), 2.34 (s, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 164.0, 151.7, 147.6, 139.2, 134.1, 130.1, 130.0, 121.0, 118.1, 111.2, 20.8.

**2-(4-Fluorophenoxy)pyridine (4af)**[2a]

Yield: 0.010 g (10%); yellow oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 2.8 Hz, 1 H), 7.71–7.66 (m, 1 H), 7.12–7.07 (m, 4 H), 7.00–6.98 (m, 1 H), 6.92 (d, *J* = 6.4 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 163.6, 160.7 (d, *J* = 241.4 Hz), 149.8 (d, *J* = 2.9 Hz), 147.5, 139.4, 122.7 (d, *J* = 8.8 Hz), 118.4, 116.3 (d, *J* = 23.3 Hz), 111.3.

**2-(*o*-Tolyloxy)pyridine (4al)**[33]

Yield: 0.018 g (19%); yellow oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 3.6 Hz, 1 H), 7.68–7.63 (m, 1 H), 7.28–7.21 (m, 2 H), 7.16 (t, *J* = 7.2 Hz, 1 H), 7.06 (d, *J* = 7.6 Hz, 1 H), 6.96 (t, *J* = 6.4 Hz, 1 H), 6.86 (d, *J* = 8.4 Hz, 1 H), 2.18 (s, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 163.7, 152.2, 147.8, 139.3, 131.4, 130.7, 127.1, 125.2, 121.8, 117.9, 110.6, 16.3.

**2-(Mesityloxy)pyridine (4an)**[34]

Yield: 0.022 g (20%); yellow oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 3.6 Hz, 1 H), 7.65 (m, 1 H), 6.92 (t, *J* = 6.0 Hz, 3 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 2.29 (s, 3 H), 2.08 (s, 6 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 163.4, 147.9, 139.2, 134.6, 130.6, 129.4, 117.5, 109.7, 20.8, 16.4.

**2-(2-Bromophenoxy)pyridine (4ao)**[3d]

Yield: 0.026 g (20%); yellow solid; mp 68–69 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 3.6 Hz, 1 H), 7.72–7.68 (m, 1 H), 7.65 (d, *J* = 7.6 Hz, 1 H), 7.37 (d, *J* = 7.2 Hz, 1 H), 7.21 (d, *J* = 7.6 Hz, 1 H), 7.13 (t, *J* = 7.6 Hz, 1 H), 7.01–6.96 (m, 2 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 163.1, 154.8, 147.7, 139.6, 130.6, 127.7, 124.5, 122.6, 119.9, 119.0, 110.8.

**Dehalogenation of 4la and 4ln**

A mixture of **4la** or **4ln** (0.5 mmol), anhyd $K_2CO_3$ (80 mg), and 5% Pd/C (20 mg) in DMF (5 mL) was hydrogenated under atmospheric pressure at r.t. over a 3 h period. After the reaction was completed, $CH_2Cl_2$ (10 mL) and $H_2O$ (10 mL) were added to the mixture. The organic layer was separated, washed with 5% aq $Na_2CO_3$ (10 mL) and brine (10 mL), dried (anhyd $Na_2SO_4$) and filtered. The solvent was removed in vacuo and the residue was purified by flash column chromatography (the crude residue was dry loaded on silica gel, 1:10, EtOAc/PE) to provide the desired product **4aa** or **4an**.

**4,6-Dimethyl-2-[3-(trifluoromethyl)phenoxy]nicotinonitrile (5)**

A 100 mL Teflon-sealed flask was charged with the 2-pyridone **1m** (296 mg, 2.0 mmol), diaryliodonium salts **2r** (1.695 g, 3.0 mmol, 1.5 equiv), and $Cs_2CO_3$ (975 mg, 3.0 mmol, 1.5 equiv) under air atmosphere. DCE (20 mL) was then added to the flask. The reaction mixture was stirred at 120 °C until the 2-pyridone **1m** was consumed completely (monitored by TLC). At this time, the solvent was removed in vacuo and the residue was purified by flash column chromatography (the crude residue was dry loaded on silica gel, 1:10 EtOAc/PE) to provide the desired product **5**; yield: 485 mg (83%); white solid; mp 102–103 °C.

IR (film): 3073, 2922, 2229, 1600, 1449, 1327, 1179, 799 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.48 (m, 3 H), 7.39 (d, *J* = 7.2 Hz, 1 H), 6.86 (s, 1 H), 2.54 (s, 3 H), 2.37 (s, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 126.8, 161.1, 155.1, 152.9, 132.3 (q, *J* = 32.1 Hz), 129.9, 124.9, 122.2 (q, *J* = 269.1 Hz), 121.9 (q, *J* = 3.6 Hz), 119.7, 118.8 (q, *J* = 3.6 Hz), 114.3, 95.3, 24.4, 20.2.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{15}H_{12}F_3N_2O$: 293.0902; found: 293.0891.

***N*-(2,4-Difluorophenyl)-*N'*-({4,6-dimethyl-2-[3-(trifluoromethyl)-phenoxy]pyridin-3-yl}metyl)urea (6)**

A 100 mL round-bottom flask was charged with the nitrile **5** (292 mg, 1.0 mmol) under $N_2$ atmosphere. $Et_2O$ (10 mL) was then added to the flask. $LiAlH_4$ (152 mg, 4 mmol, 4.0 equiv) was added in portions. The reaction mixture was stirred at 25 °C until the nitrile **5** was consumed completely (monitored by TLC). At this time, the reaction was quenched by $H_2O$ (10 mL) and extracted with $Et_2O$ (3 × 10 mL). The combined organic extracts were dried ($Na_2SO_4$), filtered, and the solvent was removed under reduced pressure. The crude residue was dissolved in $CH_2Cl_2$ (5 mL) in a 25 mL round-bottom flask, and 2,4-difluoro-1-isocyanatobenzene (310 mg, 2.0 mmol, 2.0 equiv) was added. The reaction mixture was stirred at r.t. After completion of the reaction as monitored by TLC analysis, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (the crude residue was dry loaded on silica gel, 1:10 EtOAc/PE) to provide **6**; yield: 279 mg (62%); white solid; mp 174–175 °C.

IR (film): 3313, 2926, 1638, 1566, 1449, 1323, 1114, 694 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.86 (m, 1 H), 7.24 (s, 1 H), 7.19 (t, *J* = 8.0 Hz, 1 H), 7.10 (d, *J* = 7.8 Hz, 1 H), 6.96 (s, 1 H), 6.80 (d, *J* = 7.8 Hz, 1 H), 6.72–6.66 (m, 3 H), 5.98 (t, *J* = 5.6 Hz, 1 H), 4.44 (d, *J* = 5.6 Hz, 2 H), 2.57 (s, 3 H), 2.40 (s, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 160.7, 158.6 (d, *J* = 10.9 Hz), 156.2, 155.3, 154.8, 153.3 (d, *J* = 11.7 Hz), 151.4, 150.9 (d, *J* = 11.7 Hz), 132.0 (q, *J* = 32.1 Hz), 129.8, 124.8 (q, *J* = 271.3 Hz), 123.7 (dd, *J* = 10.2, 3.7 Hz), 122.7, 121.8 (d, *J* = 8.7 Hz), 121.4, 120.7, 120.1 (q, *J* = 3.7 Hz), 115.7 (q, *J* = 3.6 Hz), 110.9 (dd, *J* = 21.8, 3.6 Hz), 103.4 (dd, *J* = 26.1, 24.1 Hz), 34.9, 23.2, 19.3.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{22}H_{19}F_5N_3O_2$: 452.1397; found: 452.1391.

## Funding Information

Financial support from the 'Overseas 100 Talents Program' of Guangxi Higher Education, National Natural Science Foundation of China (21562005, 21602037), State Key Laboratory for Chemistry and Molecular Engineering of Medicinal Resources, Ministry of Science and Technology of China (CMEMR2015-A05), and Natural Science Foundation of Guangxi (2015GXNSFCA139001, 2016GXNSFFA380005) are greatly appreciated.

## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591884.

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