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Copper-Mediated Direct Alkoxylation of Arenes Using an *N,O*-Bidentate Directing System

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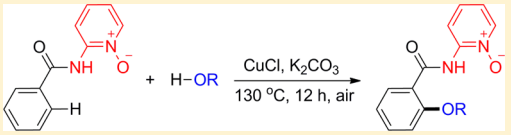
Supporting Information

ABSTRACT: Highly effective CuCl-mediated C—H alkoxylation of arenes and heteroarenes has been developed by using a 2-aminopyridine 1-oxide moiety as an *N,O*-bidentate directing group. The reaction proceeds smoothly using a broad range of substrates to afford *o*-alkoxylated benzoic and heteroaromatic amide products. Moreover, the reaction system shows remarkable compatibility when hexafluoroisopropanol is used as a coupling parter; halogen, nitro, ether, alkoxy, ester, and sulfonyl functional groups are all tolerated. The directing group can be easily removed by base hydrolysis, affording *o*-alkoxylated benzoic acids.



INTRODUCTION

Diverse C—H bond functionalization methodologies have been developed in the past two decades.[1] Compared to traditional methods, direct C—H functionalization offers more efficient ways of constructing complex chemical frameworks without prefunctionalization of the starting materials. Recently, tremendous C—C,[2] C—N,[3] and C—O[4] bond-forming reactions have proven the practical utility and feasibility of direct functionalization protocols. However, most examples of direct functionalization of C—H bonds have been performed by applying expensive metal catalysts such as palladium,[5] rhodium,[6] or ruthenium.[7] On the other hand, copper salts are abundant and inexpensive alternatives to the rare metals described above and have been reported in Cu-catalyzed or Cu-mediated cross-dehydrogenative coupling reactions by Miura[8] and other groups[9] recently.

Aryl ethers are common structural motifs in many natural products, pharmaceuticals, and functional materials.[10] From a synthetic perspective, dehydrogenative cross coupling between arenes and alcohols compares favorably with classical methods such as Pd-catalyzed Buchwald–Harting couplings,[11] and Cu-catalyzed Ullmann,[12] Chan–Evans–Lam,[13] Williamson,[14] and Mitsunobu[15] reactions. Considering the fact that fruitful strategies for direct hydroxylations,[16] acetoxylations,[17] and even phenoxylations[4a−d] have been developed, the alkoxylation of arenes remains a challenging topic because alkanols are easily oxidized to their corresponding aldehydes, ketones, or carboxylic acids.[18] In general, palladium salt is a highly active catalyst for this type of transformation.[19] Recently, pioneering copper-catalyzed dehydrogenative alkoxylation of arenes has been reported by Gooßen.[20] Moreover, Stahl and co-workers[21] have observed the etherification of a macrocyclic copper ligand on the addition of alkanols and have performed a fundamental mechanistic study on Cu(II)-mediated methoxylation of 8-aminoquinoline benzamide using 2 equiv of $Cu(OAc)_2$.

In 2005, Daugulis and co-workers employed picolinamide and 8-aminoquinoline as *N,N*-bidentate directing groups for palladium-catalyzed C—H bond functionalization.[22] Recently, methods for chelating-assisted C—H bond functionalization by employing a bidentate directing group have been developed by the groups of Daugulis,[23] Miura,[8b,c] Nakamura,[24] Chatani,[25] Chen,[26] and others.[27] The noteworthy advantage of these transformations is that abundant, relatively cheap first-row transition metals, including copper, iron, and nickel, are used.[28] Moreover, our laboratory was the first to report the 2-aminopyridine 1-oxide moiety as an *N,O*-bidentate directing group for selective mono- or diaryloxylation of benzamides by applying a stoichiometric copper acetate.[29] Encouraged by the notable progress in C—H bond functionalization methodologies mentioned above, we studied the alkoxylation of C—H bonds as a complementary alternative for the synthesis of *o*-alkoxylated benzoic acids.

RESULTS AND DISCUSSION

We first investigated the reaction of 2-benzamidopyridine 1-oxide (**1a**) with ethanol (**2a**). The results are summarized in Table 1.

When **1a** was treated with stoichiometric $Cu(OAc)_2$ in ethanol (**2a**) at 130 °C, desired ethoxylated product **3aa** was obtained in 21% yield (entry 1). As we had previously observed a beneficial effect of base composition on the aryloxylation of benzamide substrates,[29] we next tested various bases (entries 2−9). Among them, K_2CO_3 proved to be effective and led to an increase in the yield to 49% (entry 9). Subsequently, a series of

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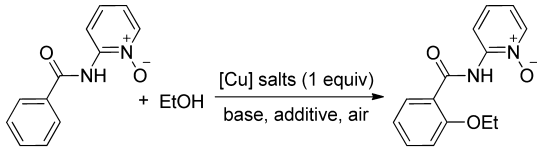
Table 1. Optimization of Reaction Conditions[a]



1a 2a 3aa

entry	Cu salt	base	additive[b]	solvent[b]	yield (%)[c]
1	$Cu(OAc)_2$			EtOH	21
2	$Cu(OAc)_2$	KO-*t*Bu		EtOH	38
3	$Cu(OAc)_2$	NaOEt		EtOH	33
4	$Cu(OAc)_2$	KOH		EtOH	25
5	$Cu(OAc)_2$	DBU		EtOH	20
6	$Cu(OAc)_2$	TMG		EtOH	36
7	$Cu(OAc)_2$	Cs_2CO_3		EtOH	44
8	$Cu(OAc)_2$	Na_2CO_3		EtOH	45
9	$Cu(OAc)_2$	K_2CO_3		EtOH	49
10	$Cu(acac)_2$	K_2CO_3		EtOH	trace
11	$CuBr_2$	K_2CO_3		EtOH	trace
12	$CuCl_2$	K_2CO_3		EtOH	22
13	$Cu(ClO_4)_2$	K_2CO_3		EtOH	nr
14	$Cu(OTf)_2$	K_2CO_3		EtOH	nr
15	CuF_2	K_2CO_3		EtOH	57
16	CuI	K_2CO_3		EtOH	53
17	CuCl	K_2CO_3		EtOH	61
18	CuCl	K_2CO_3	DMAP	EtOH	49
19	CuCl	K_2CO_3	bpy	EtOH	51
20	CuCl	K_2CO_3	TMEDA	EtOH	54
21	CuCl	K_2CO_3	Py	EtOH	77
22	**CuCl**	**K_2CO_3**		**EtOH/Py (1:1)**	**84**
23[d]	CuCl	K_2CO_3		EtOH/Py (1:1)	66
24[e]	CuCl	K_2CO_3		EtOH/Py (1:1)	60
25		K_2CO_3		EtOH/Py (1:1)	nr
26[f]	CuCl	K_2CO_3		EtOH/Py (1:1)	trace

[a]Reaction conditions: [Cu] (0.2 mmol), additive (0.2 mmol), base (0.1 mmol), **1a** (0.2 mmol), solvent (1.5 mL), air atmosphere, 130 °C, 12 h, unless otherwise noted. [b]Py = pyridine. [c]Isolated yields; nr = no reaction. [d]CuCl (0.1 mmol). [e]Run at 110 °C. [f]Under argon atmosphere.

copper salts were investigated in the reaction, including $Cu(acac)_2$ (acac = acetylacetonate), $CuBr_2$, $CuCl_2$, $Cu(ClO_4)_2$, $Cu(OTf)_2$, CuF_2, CuI, and CuCl (entries 10–17, respectively). The use of CuCl resulted in a significant increase in yield (entry 17). The addition of N donor ligands to stabilize the copper salts resulted in slightly decreased yields (entries 18–20). However, the use of pyridine as an additive substantially influenced the yields to give a superior result (entry 21), similar to the observation of Daugulis in copper-catalyzed fluorination reactions.[23a] When pyridine was used as a cosolvent, and the ratio of pyridine to ethanol was changed to 1:1 (v/v), the yield increased to 84% (entry 22). Unfortunately, decreasing the amount of CuCl or lowering the reaction temperature reduced the yields (entries 23 and 24). Control experiments revealed that no reaction took place without copper salts and that air atmosphere was crucial (entries 25 and 26). Furthermore, the 2-aminopyridine 1-oxide motif appeared to be more effective under the current identical conditions compared to other bidentate coordinating groups (Figure 1**A**–**C**). Noteworthily, 8-aminoquinoline benzamide **A** was inefficient during the dehydrogenative ethoxylation process (yield <5%) regardless of the optimized reaction conditions that Daugulis employed for

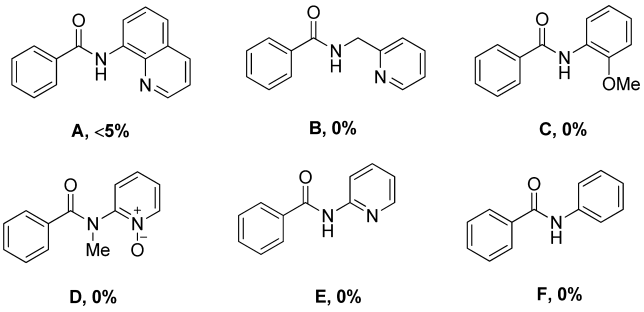
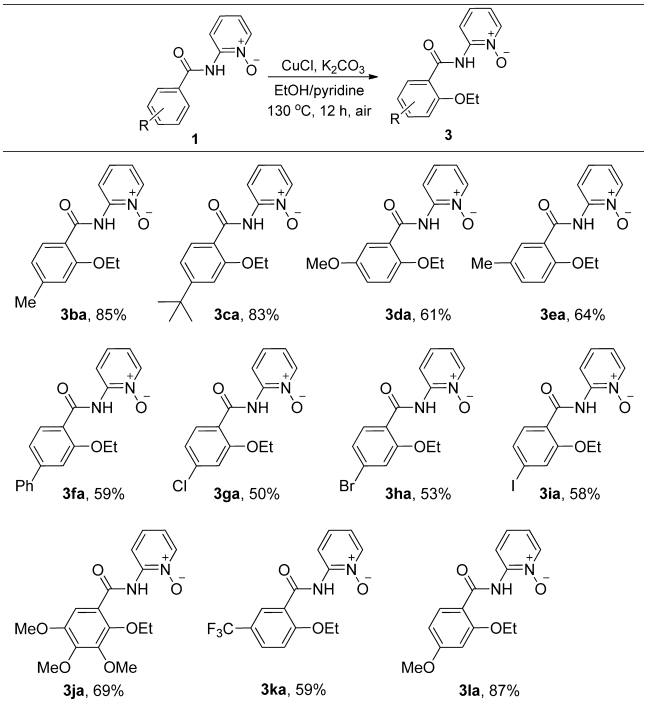


Figure 1. Varieties of directing groups.

copper-catalyzed alkoxylation.[23d] Structurally similar monodentate directing groups (Figure 1**D**–**F**) failed to promote this reaction either, indicating that the *N*,*O*-bidentate coordinating group is essential for transformation.

With the optimized reaction conditions for ethoxylation in hand, we tested the reactions of a series of 2-benzamidopyridine 1-oxide derivatives bearing different functional groups with ethanol. The results are listed in Scheme 1. A wide range of aryl

Scheme 1. Reaction Scope with Respect to Amides[a]



[a]Reaction conditions: CuCl (0.20 mmol), amide (0.20 mmol), K_2CO_3 (0.1 mmol), EtOH (0.75 mL), pyridine (0.75 mL), at 130 °C, under air, for 12 h. Isolated yield.

substrates bearing electron-withdrawing or -donating groups underwent monoethoxylation smoothly to afford their corresponding products (**3ba**–**3la**) in 50–87% yields. Diethoxylated products were not observed in all cases. The *o*-substituted substrates, such as *o*-methylbenzamide **1q** and *o*-chlorobenzamide **1r**, did not work. Furthermore, 2-benzamidopyridine 1-oxide derivatives possessing electron-donating functional groups in the *p*-position gave good yields (**3ba**, **3ca**, and **3la**). Electron-withdrawing functional groups such as chloro (**1g**), bromo (**1h**), and iodo (**1i**) also provided the desired products (**3ga**–**3ia**), albeit in moderate yields. Significantly, the

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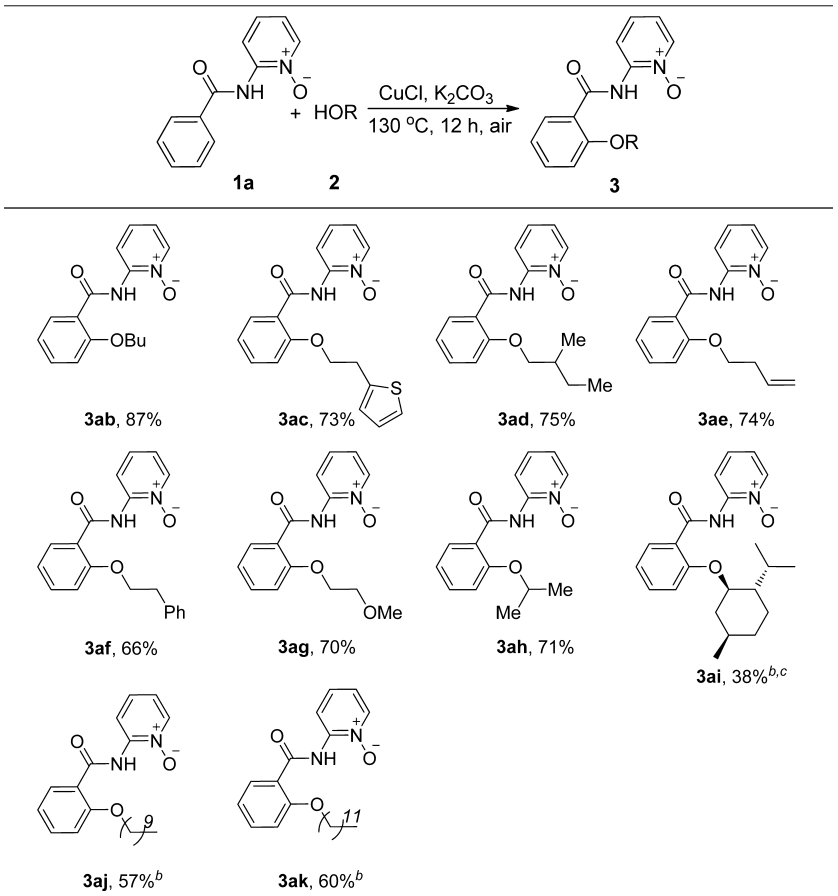
Scheme 2. Reaction Scope with Respect to Alcohols[a]



[a]Reaction conditions: CuCl (0.20 mmol), **1a** (0.20 mmol), K_2CO_3 (0.1 mmol), alcohols (0.75 mL), pyridine (0.75 mL), at 130 °C, under air, for 12 h. [b]Pyridine solvent. Alcohols (2 mmol). [c]The configuration is determined on a Daicel Chiralpak AD-H column with hexane/2-propanol (90:10). Flow rate = 0.1 mL/min, UV wavelength = 254 nm, and retention time = 6.0 min (one signal).

halo-substituted benzamide moiety remained intact. Strong electron-withdrawing functional groups, such as NO_2, inhibited the reaction and could not yield the target product under the optimized reaction conditions. These results add to the growing evidence that the electron density of substrates plays a more important role than steric hindrance factors. For *m*-substituted substrates (**1d**, **1e**, and **1k**), selective ethoxylation occurred at the less-hindered position to give a good yield and excellent regioselectivity.

We next explored a variety of alcohols in copper-mediated, direct alkoxylation of **1a** (Scheme 2) and found that the strategy of direct dehydrogenative alkoxylation coupling has broad applications. Both primary and secondary alcohols could proceed smoothly, affording their corresponding alkoxylated products in moderate to good yields (**3ab**−**3ah**). The reaction system tolerated a range of functional groups, such as heteroaromatic (**2c**), branched (**2d**), and olefin (**2e**) alcohols. The chiral alcohol menthol (**2i**) could react while retaining its configuration. The benzylic alcohols did not give the desired products because they were easily oxidized at high temperature.[30] Long-chain alcohols (**2j** and **2k**) also provided the corresponding ethers **3aj** and **3ak** in moderate yields when pyridine was used as the solvent. To our surprise, hexafluoroisopropanol (HFIP) also underwent alkoxylation to give monoalkoxylated product **3al** and dialkoxylated product **3'al** in a 2.8:1 ratio and 93% combined yield.

In light of the extraordinary potential for fluorine-containing molecules in medicinal chemistry and chemical biology,[31] we examined the use of HFIP as the coupling partner (Scheme 3). When changing the ratio of pyridine and HFIP to 1:4 (v/v), we found that a variety of aryl amide substrates **1** with electron-withdrawing or -donating groups were hexafluoroisopropoxylated to give good to excellent yields. Doubly alkoxylated products **3'** were detected for substrates that bear functional groups at the para position of the aromatic ring (**3il** and **3ll**−**3ol**). Similar to ethoxylation, excellent regioselectivity was obtained for *m*-substituted substrates, and alkoxylation only occurred at the less-congested site (**3el**, **3kl**, and **3ul**−**3wl**). For *o*-substituted substrates, single monoalkoxylated products (**3ql**−**3tl**) were isolated with 54−93% yields. It is worth noting that substrate **1s**, which bears the strong electron-withdrawing NO_2 functional group, also underwent alkoxylation smoothly and transformed into its corresponding product in a synthetically useful yield (**3sl**). The naphthyl substrate (**1x**) could be successfully reacted with HFIP with regioselectively at the 2-position in 81% yield. We were pleased to find that heteroaryl substrates (**1o**, **1y**, and **1z**) proceeded smoothly to give their corresponding products in good yields (75, 74, and 38%, respectively).

To obtain more insight into the mechanism, some controlled experiments were performed. The addition of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) as a radical quencher completely inhibited the reaction (Scheme 4, eq 1), suggesting that the reaction involved a radical pathway. TEMPOH rather

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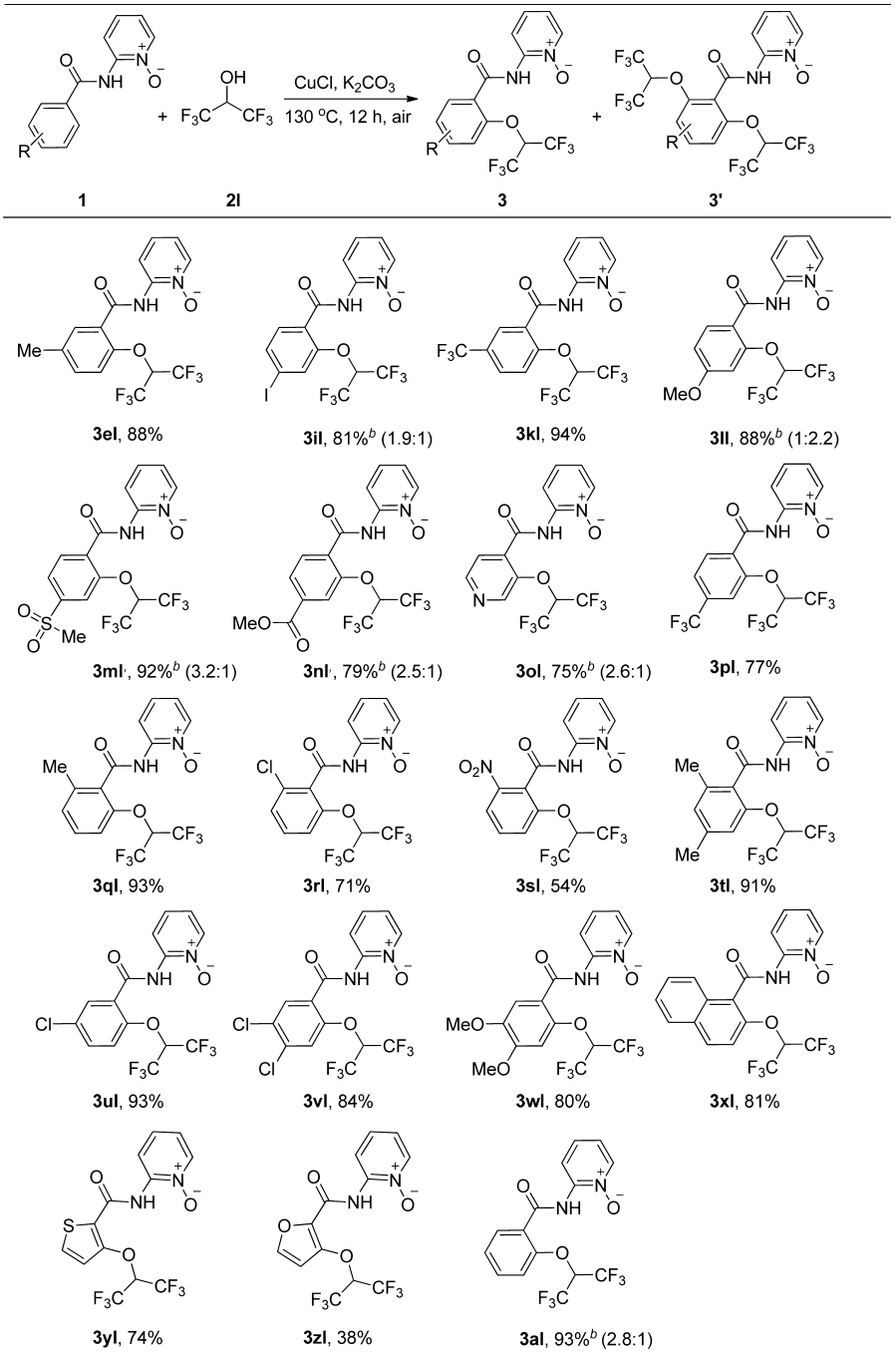
Scheme 3. Exceptional Compatibility with HFIP[a]



[a]Reaction conditions: CuCl (0.20 mmol), **1** (0.20 mmol), K_2CO_3 (0.1 mmol), pyridine (0.3 mL), HFIP (1.2 mL). [b]The combined isolated yield of **3** and **3'** is given. The ratio of **3**/**3'** is in parentheses and is determined by ^{1}H NMR analysis of the crude reaction mixture; **3** and **3'** were separated by silica gel column chromatography.

than TEMPOOEt was detected by LC-MS, which is in agreement with findings by Stahl and co-workers.[18a] Next, treatment of a 1:1 mixture of [$\mathbf{D_5}$]-**1a** and **1a** with ethanol resulted in a kinetic isotope effect (KIE) of 2.5 (Scheme 4, eq 2). This finding indicated that the C—H activation of the arene is rate limiting. The single-electron-transfer (SET) mechanism proposed by Yu in copper-mediated chlorination reactions, in which a low kinetic isotope effect had been found, could be ruled out.[4a] A hydroxyarene intermediate resulting from an attack of H_2O on the benzamide was excluded based on the fact that 2-(2-hydroxybenzamido)pyridine 1-oxide (**1A**) was not transformed into **3aa** under the standard reaction conditions (Scheme 4, eq 3). Moreover, 2-(thiophen-2-yl)-acetaldehyde **4** was obtained from 2-thiopheneethanol under the reaction conditions in the absence of substrate **1a**, which can be used as indirect evidence of alkoxy radical formation (Scheme 4, eq 4). However, when TEMPO was added to the reaction mixture under the optimized conditions using HFIP as the coupling partner, it did not inhibit the reaction. Moreover, treatment of a 1:1 mixture of [$\mathbf{D_5}$]-**1a** and **1a** with HFIP provided a KIE of 2.1. HFIP (pK_a = 9.3) is more acidic, which differs from ethanol (pK_a = 15.9), and is actually more similar

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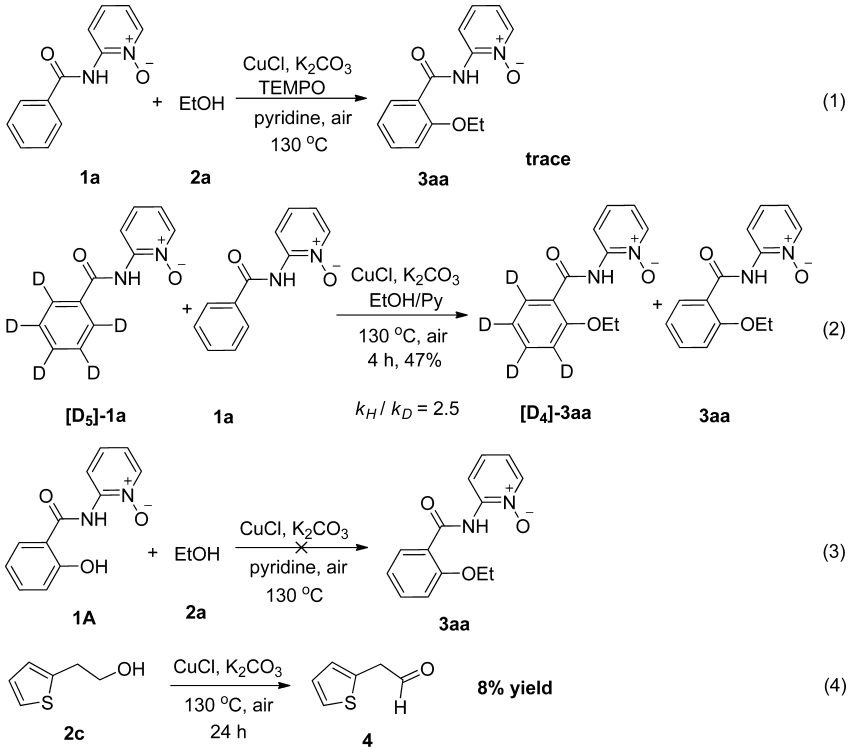
Scheme 4. Controlled Experiments



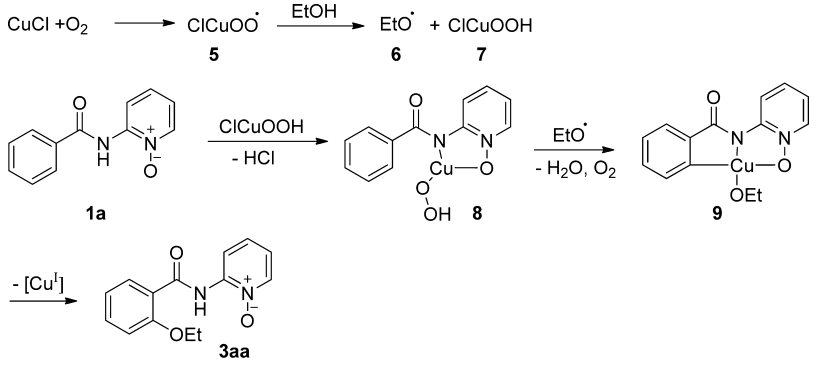
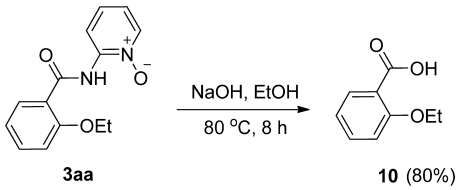


Figure 2. Plausible mechanism for *o*-alkoxylation.

Scheme 5. Removal of the Directing Group



to phenol (pK_a = 9.9). It seems that the reaction proceeds via a CNO-pincer Cu(III) intermediate, which we have clarified in the aryloxylation of benzamides.[29]

On the basis of these investigations, we searched the literature[8b,20b,21] and developed a plausible reaction mechanism (Figure 2). First, CuCl is oxidated via the formation of Cu(II)-superoxo species **5**,[32] which could be easily reduced to produce hydroperoxo form **7** after protonation while alkoxy radical **6** is simultaneously formed in the process.[33] Then, ligand exchange with **1a** occurs to form *N*,*O*-chelated complex **8**. The alkoxy radical is transferred to Cu(II) species **8** to give Cu(III) complex **9**. Finally, intermediate **9** furnishes desired product **3aa** by reductive elimination.

The 2-aminopyridine 1-oxide directing group can be easily removed by base hydrolysis. For example, treatment of **3aa** with NaOH in EtOH at 80 °C for 8 h affords 2-ethoxybenzoic acid **10** in high yield (Scheme 5).

■ CONCLUSIONS

In summary, we have developed a copper-mediated coupling of benzamides and alcohols with the aid of an *N*,*O*-bidentate directing group derived from 2-aminopyridine 1-oxide. This new-fashioned strategy is operationally simple and possesses a broad substrate scope, thus providing a convenient synthetic route to *o*-alkoxylated benzoic and heteroaromatic acids. Moreover, the exceptional compatibility of the alkoxylation reaction with HFIP renders this reaction highly valuable for the synthesis of medicinal fluorine-containing compounds. Further exploration extending this strategy to sp^3 C—H groups of aliphatic substrates through a detailed mechanistic study is currently in progress.

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EXPERIMENTAL SECTION

General. Unless otherwise noted, all solvents and reagents were purchased commercially and used directly. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded at 400, 100, and 376 MHz, respectively, using tetramethylsilane as an internal standard. Chemical shift multiplicities are represented as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentalet, m = multiplet, dd = double doublet, bs = broad singlet. HRMS spectra were obtained on a Q-TOF mass spectrometer using the ESI technique.

Amide substrates **1a**−**1z** were prepared according to published procedures.[29]

2-(4-(*tert*-Butyl)benzamido)pyridine 1-Oxide (1c). Purified by column chromatography on silica gel with CH_2Cl_2/acetone (5:1) as an eluent (R_f = 0.37) to afford a white solid (1.20 g, 74%, mp 123−124 °C from 1:3 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.91 (s, 1H), 8.63 (dd, J = 8.5, 1.7 Hz, 1H), 8.32 (dd, J = 6.5, 1.1 Hz, 1H), 7.97−7.94 (m, 2H), 7.56−7.53 (m, 2H), 7.42−7.38 (m, 1H), 7.04−7.00 (m, 1H), 1.36 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 160.5, 159.7, 137.5, 129.4, 128.1, 118.6, 117.3, 115.5, 115.0, 35.2, 30.9. HRMS (positive ESI): calcd for $C_{16}H_{19}N_2O_2$ [M + H], 271.1447; found, 271.1442.

2-(4-Bromobenzamido)pyridine 1-Oxide (1h). Purified by column chromatography on silica gel with CH_2Cl_2/acetone (5:1) as an eluent (R_f = 0.37) to afford a white solid (1.32 g, 75%, mp 188−189 °C from 1:3 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.92 (s, 1H), 8.58 (dd, J = 8.5, 1.7 Hz, 1H), 8.30 (dd, J = 6.5, 1.0 Hz, 1H), 7.90−7.88 (m, 2H), 7.74−7.71 (m, 2H), 7.42−7.38 (m, 1H), 7.07−7.03 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 144.4, 137.2, 132.4, 132.0, 129.3, 128.6, 128.1, 119.0, 115.0. HRMS (positive ESI): calcd for $C_{12}H_{10}BrN_2O_2$ [M + H], 292.9926; found, 292.9919.

2-(4-Iodobenzamido)pyridine 1-Oxide (1i). Purified by column chromatography on silica gel with CH_2Cl_2/acetone (5:1) as an eluent (R_f = 0.39) to afford a white solid (1.55 g, 76%, mp 198−199 °C from 1:3 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.92 (s, 1H), 8.58 (dd, J = 8.5, 1.6 Hz, 1H), 8.30 (dd, J = 6.5, 1.0 Hz, 1H), 7.89−7.85 (m, 2H), 7.68−7.65 (m, 2H), 7.42−7.38 (m, 1H), 7.06−7.02 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 144.3, 138.2, 137.1, 132.5, 129.1, 128.3, 118.9, 114.8, 100.5. HRMS (positive ESI): calcd for $C_{12}H_{10}IN_2O_2$ [M + H], 340.9787; found, 340.9781.

2-(4-(Methoxycarbonyl)benzamido)pyridine 1-Oxide (1n). Purified by column chromatography on silica gel with CH_2Cl_2/acetone (5:1) as an eluent (R_f = 0.44) to afford a white solid (1.22 g, 75%, mp 131−132 °C from 1:3 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.99 (s, 1H), 8.61 (dd, J = 8.5, 1.7 Hz, 1H), 8.32 (dd, J = 6.5, 1.0 Hz, 1H), 8.21−8.19 (m, 2H), 8.09−8.06 (m, 2H), 7.45−7.40 (m, 1H), 7.09−7.05 (m, 1H), 3.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 164.4, 144.3, 137.1, 136.8, 134.0, 130.2, 128.4, 127.7, 119.1, 114.9, 52.6. HRMS (positive ESI): calcd for $C_{14}H_{13}N_2O_4$ [M + H], 273.0875; found, 273.0871.

2-(2-Chlorobenzamido)pyridine 1-Oxide (1r). Purified by column chromatography on silica gel with CH_2Cl_2/acetone (5:1) as an eluent (R_f = 0.38) to afford a white solid (1.07 g, 72%, mp 151−152 °C from 1:3 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.82 (s, 1H), 8.63 (dd, J = 8.4, 1.7 Hz, 1H), 8.30 (dd, J = 6.5, 1.0 Hz, 1H), 7.79 (dd, J = 7.6, 1.4 Hz, 1H), 7.52−7.45 (m, 2H), 7.44−7.38 (m, 2H), 7.08−7.04 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 144.2, 137.3, 133.7, 132.5, 131.4, 130.8, 130.3, 128.3, 127.3, 119.2, 115.2. HRMS (positive ESI): calcd for $C_{12}H_{10}ClN_2O_2$ [M + H], 249.0431; found, 249.0426.

2-(2-Nitrobenzamido)pyridine 1-Oxide (1s). Purified by column chromatography on silica gel with CH_2Cl_2/acetone (4:1) as an eluent (R_f = 0.30) to afford a yellow solid (780 mg, 51%, mp 203−204 °C from 1:3 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.50 (s, 1H), 8.54 (dd, J = 8.4, 1.2 Hz, 1H), 8.19 (d, J = 5.8 Hz, 1H), 8.13 (d, J = 7.9 Hz, 1H), 7.76−7.72 (m, 1H), 7.67−7.64 (m, 2H), 7.42−7.38 (m, 1H), 7.07−7.03 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 146.4, 143.9, 137.2, 134.0, 131.6, 131.5, 128.5, 128.3, 124.8, 119.5, 115.3. HRMS (positive ESI): calcd for $C_{12}H_{10}N_3O_4$ [M + H], 260.0671; found, 260.0667.

2-(Thiophene-2-carboxamido)pyridine 1-Oxide (1y). Purified by column chromatography on silica gel with CH_2Cl_2/acetone (4:1) as an eluent (R_f = 0.35) to afford a white solid (924 mg, 70%, mp 142−143 °C from 1:3 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.90 (s, 1H), 8.55 (d, J = 8.4 Hz, 1H), 8.30 (d, J = 6.5 Hz, 1H), 7.62−7.61 (m, 1H), 7.40−7.36 (m, 1H), 7.34−7.33 (m, 1H), 7.05−7.01 (m, 1H), 6.61−6.60 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 146.9, 145.7, 144.1, 137.3, 128.1, 118.9, 117.0, 114.9, 112.9. HRMS (positive ESI): calcd for $C_{10}H_9N_2O_2S$ [M + H], 221.0385; found, 221.0379.

2-(Furan-2-carboxamido)pyridine 1-Oxide (1z). Purified by column chromatography on silica gel with CH_2Cl_2/acetone (4:1) as an eluent (R_f = 0.40) to afford a white solid (881 mg, 72%, mp 137−138 °C from 1:3 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.79 (s, 1H), 8.53 (dd, J = 8.5, 1.7 Hz, 1H), 8.30 (dd, J = 6.5, 1.1 Hz, 1H), 7.80 (dd, J = 3.8, 1.0 Hz, 1H), 7.66 (dd, J = 5.0, 1.0 Hz, 1H), 7.41−7.37 (m, 1H), 7.19−7.17 (m, 1H), 7.05−7.01 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 144.2, 138.0, 137.0, 132.7, 130.1, 128.3, 128.2, 118.6, 114.7. HRMS (positive ESI): calcd for $C_{10}H_9N_2O_3$ [M + H], 205.0613; found, 205.0608.

Typical Procedure for Copper-Mediated Dehydrogenative Alkoxylated Coupling. A screw cap vial was equipped with a magnetic stir bar and charged with benzamide substrate **1** (0.2 mmol), CuCl (19.8 mg, 0.2 mmol), freshly distilled anhydrous alcohol (0.75 mL), and freshly distilled pyridine (0.75 mL). The resulting mixture was stirred at 35 °C for 30 min followed by the addition of K_2CO_3 (13.8 mg, 0.1 mmol) and stirring for an additional 5 min at 35 °C. Then, the suspension was kept stirring for 12 h at 130 °C. The resulting crude mixture was allowed to cool to room temperature and quenched with 2 M HCl aqueous solution (5 mL). The mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in a vacuum. The resulting residue was purified by column chromatography with eluent to give corresponding alkyl-aryl ether **3**.

2-(2-Ethoxybenzamido)pyridine 1-Oxide (3aa). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (6:1) as an eluent (R_f = 0.35) to afford a white solid (43 mg, 84%, mp 140−141 °C from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.30 (s, 1H), 8.74 (dd, J = 8.5, 1.8 Hz, 1H), 8.31−8.28 (m, 2H), 7.55−7.51 (m, 1H), 7.38−7.34 (m, 1H), 7.13−7.09 (m, 1H), 7.07 (d, J = 8.4 Hz, 1H), 7.02−6.98 (m, 1H), 4.35 (q, J = 7.0 Hz, 2H), 1.72 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 157.5, 145.4, 137.4, 134.3, 132.7, 127.8, 121.1, 120.5, 118.5, 115.9, 112.4, 65.4, 14.8. HRMS (positive ESI): calcd for $C_{14}H_{15}N_2O_3$ [M + H], 259.1083; found, 259.1081.

2-(4-Methyl-2-ethoxybenzamido)pyridine 1-Oxide (3ba). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (3:1) as an eluent (R_f = 0.32) to afford a white solid (46 mg, 85%, mp 162−163 °C from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.16 (s, 1H), 8.66 (d, J = 8.4 Hz, 1H), 8.20−8.18 (m, 1H), 8.09−8.07 (d, J = 8.0 Hz, 1H), 7.26−7.23 (m, 1H), 6.91−6.88 (m, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.77 (s, 1H), 4.24 (q, J = 7.0 Hz, 2H), 2.32 (s, 3H), 1.63 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 157.4, 145.5, 137.4, 132.5, 127.9, 122.0, 118.3, 117.8, 115.7, 113.0, 65.2, 21.9, 14.8. HRMS (positive ESI): calcd for $C_{15}H_{17}N_2O_3$ [M + H], 273.1239; found, 273.1234.

2-(4-*tert*-Butyl-2-ethoxybenzamido)pyridine 1-Oxide (3ca). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (3:1) as an eluent (R_f = 0.42) to afford a white solid (52 mg, 83%, mp 127−128 °C from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.27 (s, 1H), 8.75 (dd, J = 8.5, 1.7 Hz, 1H), 8.29 (dd, J = 6.5, 1.0 Hz, 1H), 8.20 (d, J = 8.3 Hz, 1H), 7.37−7.33 (m, 1H), 7.14 (dd, J = 8.4, 1.7 Hz, 1H), 7.05 (d, J = 1.6 Hz, 1H), 7.00−6.96 (m, 1H), 4.37 (q, J = 7.0 Hz, 2H), 1.73 (t, J = 7.0 Hz, 3H). 1.36 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 158.6, 157.3, 145.5, 137.3, 132.3, 127.8, 118.4, 118.3, 117.8, 115.8, 109.4, 65.1, 35.4, 31.1, 14.8. HRMS (positive ESI): calcd for $C_{18}H_{23}N_2O_3$ [M + H], 315.1709; found, 315.1705.

2-(5-Methoxy-2-ethoxybenzamido)pyridine 1-Oxide (3da). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (3:1) as an eluent (R_f = 0.31) to afford a white solid (35 mg, 61%, mp 179−180 °C

from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.40 (s, 1H), 8.73 (dd, J = 8.5, 1.7 Hz, 1H), 8.30−8.29 (m, 1H), 7.81 (d, J = 3.2 Hz, 1H), 7.38−7.34 (m, 1H), 7.11−7.08 (m, 1H), 7.02−7.00 (m, 2H), 4.31 (q, J = 7.0 Hz, 2H), 3.85 (s, 3H), 1.69 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 153.6, 151.9, 145.4, 137.4, 127.8, 121.3, 120.8, 118.6, 115.8, 115.4, 114.0, 65.8, 55.9, 14.8. HRMS (positive ESI): calcd for $C_{15}H_{17}N_2O_4$ [M + H], 289.1188; found, 289.1185.

2-(5-Methyl-2-ethoxybenzamido)pyridine 1-Oxide (3ea). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (3:1) as an eluent (R_f = 0.33) to afford a white solid (35 mg, 64%, mp 191−192 °C from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.32 (s, 1H), 8.74 (dd, J = 8.5, 1.8 Hz, 1H), 8.30−8.28 (m, 1H), 8.08 (d, J = 2.2 Hz, 1H), 7.38−7.31 (m, 2H), 7.01−6.97 (m, 1H), 6.96 (d, J = 8.6 Hz, 1H), 4.31 (q, J = 7.0 Hz, 2H), 2.36 (s, 3H), 1.70 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 155.5, 145.5, 137.3, 134.9, 132.7, 130.4, 127.8, 120.0, 118.4, 115.9, 112.4, 65.3, 20.4, 14.8. HRMS (positive ESI): calcd for $C_{15}H_{17}N_2O_3$ [M + H], 273.1239; found, 273.1236.

2-(3-Ethoxy-[1,1′-biphenyl]-4-ylcarboxamido)pyridine 1-Oxide (3fa). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (3:1) as an eluent (R_f = 0.36) to afford a white solid (39 mg, 59%, mp 174−175 °C from 1:3 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.32 (s, 1H), 8.76 (dd, J = 8.6, 1.7 Hz, 1H), 8.34 (d, J = 8.2 Hz, 1H), 8.31−8.29 (m, 1H), 7.64−7.62 (m, 2H), 7.50−7.46 (m, 2H), 7.43−7.41 (m, 1H), 7.36−7.32 (m, 2H), 7.25−7.24 (m, 1H), 7.02−6.98 (m, 1H), 4.43 (q, J = 7.0 Hz, 2H), 1.75 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 157.7, 147.4, 145.4, 139.9, 137.3, 133.2, 129.0, 128.4, 127.9, 127.3, 119.9, 119.2, 118.5, 115.9, 111.1, 65.5, 14.8. HRMS (positive ESI): calcd for $C_{20}H_{19}N_2O_3$ [M + H], 335.1396; found, 335.1392.

2-(4-Chloro-2-ethoxybenzamido)pyridine 1-Oxide (3ga). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (3:1) as an eluent (R_f = 0.36) to afford a white solid (29 mg, 50%, mp 210−211 °C from 1:3 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.19 (s, 1H), 8.71 (dd, J = 8.5, 1.4 Hz, 1H), 8.30−8.28 (m, 1H), 8.23 (d, J = 8.5 Hz, 1H), 7.38−7.34 (m, 1H), 7.10 (dd, J = 8.5, 1.8 Hz, 1H), 7.06 (d, J = 1.8 Hz, 1H), 7.03−6.99 (m, 1H), 4.34 (q, J = 7.0 Hz, 2H), 1.73 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 157.8, 145.2, 140.2, 137.4, 133.8, 128.0, 121.5, 119.1, 118.7, 115.9, 113.1, 66.0, 14.6. HRMS (positive ESI): calcd for $C_{14}H_{14}ClN_2O_3$ [M + H], 293.0693; found, 293.0690.

2-(4-Bromo-2-ethoxybenzamido)pyridine 1-Oxide (3ha). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (3:1) as an eluent (R_f = 0.39) to afford a white solid (36 mg, 53%, mp 195−196 °C from 1:3 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.18 (s, 1H), 8.72−8.70 (m, 1H), 8.30−8.28 (m, 1H), 8.14 (d, J = 8.5 Hz, 1H), 7.38−7.34 (m, 1H), 7.26 (dd, J = 8.5, 1.7 Hz, 1H), 7.22 (d, J = 1.6 Hz, 1H), 7.03−6.99 (m, 1H), 4.34 (q, J = 7.0 Hz, 2H), 1.73 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 157.7, 145.2, 137.4, 133.9, 128.6, 128.0, 124.5, 119.5, 118.7, 116.0, 115.8, 66.0, 14.6. HRMS (positive ESI): calcd for $C_{14}H_{14}BrN_2O_3$ [M + H], 337.0188; found, 337.0184.

2-(2-Ethoxy-4-iodobenzamido)pyridine 1-Oxide (3ia). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (3:1) as an eluent (R_f = 0.39) to afford a white solid (45 mg, 58%, mp 163−164 °C from 1:3 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.17 (s, 1H), 8.72−8.69 (m, 1H), 8.29−8.28 (m, 1H), 7.96 (d, J = 8.3 Hz, 1H), 7.47 (dd, J = 8.3, 1.3 Hz, 1H), 7.40 (d, J = 1.1 Hz, 1H), 7.37−7.33 (m, 1H), 7.03−6.99 (m, 1H), 4.33 (q, J = 7.0 Hz, 2H), 1.72 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 157.3, 145.2, 137.4, 133.8, 130.6, 127.9, 121.9, 120.2, 118.7, 115.8, 101.1, 66.0, 14.7. HRMS (positive ESI): calcd for $C_{14}H_{14}IN_2O_3$ [M + H], 385.0049; found, 385.0044.

2-(2-Ethoxy-3,4,5-trimethoxybenzamido)pyridine 1-Oxide (3ja). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (3:1) as an eluent (R_f = 0.45) to afford a white solid (48 mg, 69%, mp 98−99 °C from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.58 (s, 1H), 8.69 (dd, J = 8.5, 1.7 Hz, 1H), 8.30 (dd, J = 6.5, 1.1 Hz, 1H), 7.53 (s, 1H), 7.39−7.34 (m, 1H), 7.03−6.99 (m, 1H), 4.37 (q, J = 7.0 Hz, 2H), 4.00 (s, 3H), 3.94 (s, 3H), 3.93 (s, 3H), 1.58 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 149.3, 147.5, 146.8, 146.4, 145.2, 137.4, 127.7, 119.5, 118.6, 115.7, 107.9, 71.3, 61.4, 61.3, 56.1, 15.5. HRMS (positive ESI): calcd for $C_{17}H_{21}N_2O_6$ [M + H], 349.1400; found, 349.1392.

2-(2-Ethoxy-5-(trifluoromethyl)benzamido)pyridine 1-Oxide (3ka). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (3:1) as an eluent (R_f = 0.41) to afford a white solid (38 mg, 59%, mp 190−191 °C from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.25 (s, 1H), 8.73−8.71 (m, 1H), 8.59−8.58 (m, 1H), 8.30−8.29 (m, 1H), 7.77 (dd, J = 8.7, 2.2 Hz, 1H), 7.40−7.36 (m, 1H), 7.17 (d, J = 8.7 Hz, 1H), 7.05−7.02 (m, 1H), 4.41 (q, J = 7.0 Hz, 2H), 1.75 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5, 158.5, 144.0, 136.3, 130.0 (q, J_{C-F} = 3.4 Hz), 129.3 (q, J_{C-F} = 3.7 Hz), 127.0, 122.8 (q, J_{C-F} = 269.9 Hz), 122.5 (q, J_{C-F} = 33.3 Hz), 119.8, 117.9, 114.9, 111.8, 65.1, 13.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −61.92. HRMS (positive ESI): calcd for $C_{15}H_{14}F_3N_2O_3$ [M + H], 327.0957; found, 327.0953.

2-(2-Ethoxy-4-methoxybenzamido)pyridine 1-Oxide (3la). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (2:1) as an eluent (R_f = 0.29) to afford a white solid (50 mg, 87%, mp 196−197 °C from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.16 (s, 1H), 8.74 (dd, J = 8.5, 1.3 Hz, 1H), 8.29−8.27 (m, 1H), 8.24 (d, J = 8.9 Hz, 1H), 7.36−7.32 (m, 1H), 6.99−6.96 (m, 1H), 6.63 (dd, J = 8.8, 2.2 Hz, 1H), 6.54 (d, J = 2.2 Hz, 1H), 4.31 (q, J = 7.0 Hz, 2H), 3.83 (s, 3H), 1.72 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 163.7, 159.0, 145.6, 137.3, 134.4, 128.1, 118.1, 115.7, 113.5, 105.7, 99.1, 65.4, 55.6, 14.7. HRMS (positive ESI): calcd for $C_{15}H_{17}N_2O_4$ [M + H], 289.1188; found, 289.1185.

2-(2-Butoxybenzamido)pyridine 1-Oxide (3ab). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (10:1) as an eluent (R_f = 0.40) to afford a white solid (50 mg, 87%, mp 90−91 °C from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.26 (s, 1H), 8.73 (dd, J = 8.5, 1.7 Hz, 1H), 8.30−8.27 (m, 2H), 7.55−7.51 (m, 1H), 7.37−7.33 (m, 1H), 7.13−7.07 (m, 2H), 7.01−6.97 (m, 1H), 4.29 (t, J = 7.1 Hz, 2H), 2.14−2.07 (m, 2H), 1.60−1.50 (m, 2H), 1.02 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 157.6, 145.4, 137.4, 134.3, 132.7, 127.7, 121.0, 120.6, 118.5, 115.8, 112.5, 69.6, 30.6, 19.3, 13.8. HRMS (positive ESI): calcd for $C_{16}H_{19}N_2O_3$ [M + H], 287.1396; found, 287.1401.

2-(2-(2-(Thiophen-2-yl)ethoxy)benzamido)pyridine 1-Oxide (3ac). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (5:1) as an eluent (R_f = 0.30) to afford a white solid (50 mg, 73%, mp 123−124 °C from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.26 (s, 1H), 8.74 (dd, J = 8.4, 1.1 Hz, 1H), 8.30−8.26 (m, 2H), 7.53−7.49 (m, 1H), 7.38−7.34 (m, 1H), 7.14−7.10 (m, 2H), 7.04−6.99 (m, 2H), 6.97−6.96 (m, 1H), 6.93−6.91 (m, 1H), 4.45 (t, J = 7.3 Hz, 2H), 3.70 (t, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 157.1, 145.3, 139.7, 137.3, 134.3, 132.7, 127.8, 126.9, 126.1, 124.1, 121.5, 120.7, 118.5, 115.8, 112.5, 70.4, 29.6. HRMS (positive ESI): calcd for $C_{18}H_{17}N_2O_3S$ [M + H], 341.0960; found, 341.0955.

2-(2-(2-Methylbutoxy)benzamido)pyridine 1-Oxide (3ad). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (6:1) as an eluent (R_f = 0.30) to afford a white solid (45 mg, 75%, mp 117−118 °C from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.19 (s, 1H), 8.73 (dd, J = 8.5, 1.8 Hz, 1H), 8.30−8.25 (m, 2H), 7.54−7.50 (m, 1H), 7.36−7.32 (m, 1H), 7.12−7.06 (m, 2H), 7.01−6.97 (m, 1H), 4.19−4.15 (m, 1H), 4.04−3.99 (m, 1H), 2.39−2.31 (m, 1H), 1.66−1.56 (m, 1H), 1.40−1.29 (m, 1H), 1.09 (d, J = 6.7 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 157.7, 145.3, 137.4, 134.2, 132.6, 127.5, 121.0, 120.7, 118.5, 115.8, 112.6, 74.9, 33.7, 26.3, 16.8, 11.0. HRMS (positive ESI): calcd for $C_{17}H_{21}N_2O_3$ [M + H], 301.1552; found, 301.1547.

2-(2-(But-3-en-1-yloxy)benzamido)pyridine 1-Oxide (3ae). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (10:1) as an eluent (R_f = 0.29) to afford a white solid (42 mg, 74%, mp 107−108 °C from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.23 (s, 1H), 8.73 (dd, J = 8.5, 1.7 Hz, 1H), 8.30−8.27 (m, 2H), 7.55−7.51 (m, 1H), 7.37−7.33 (m, 1H), 7.14−7.06 (m, 2H),

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7.01−6.98 (m, 1H), 6.02−5.92 (m, 1H), 5.24−5.19 (m, 1H), 5.13−5.10 (m, 1H), 4.31 (t, J = 7.2 Hz, 2H), 2.93−2.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 157.3, 145.4, 137.3, 134.3, 133.8, 132.7, 127.7, 121.2, 120.6, 118.5, 117.6, 115.8, 112.5, 69.0, 33.1. HRMS (positive ESI): calcd for $C_{16}H_{17}N_2O_3$ [M + H], 285.1239; found, 285.1237.

2-(2-Phenethoxybenzamido)pyridine 1-Oxide (3af). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (5:1) as an eluent (R_f = 0.33) to afford a white solid (44 mg, 66%, mp 153−154 °C from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.28 (s, 1H), 8.74 (dd, J = 8.5, 1.6 Hz, 1H), 8.32−8.26 (m, 2H), 7.52−7.48 (m, 1H), 7.39−7.27 (m, 5H), 7.24−7.20 (m, 1H), 7.13−7.10 (m, 1H), 7.03−6.99 (m, 2H), 4.42 (t, J = 7.8 Hz, 2H), 3.47 (t, J = 7.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 157.3, 145.3, 137.5, 137.4, 134.3, 132.7, 129.2, 129.0, 128.5, 127.9, 126.6, 126.4, 121.3, 120.7, 118.6, 115.8, 112.6, 70.7, 35.5. HRMS (positive ESI): calcd for $C_{20}H_{19}N_2O_3$ [M + H], 335.1396; found, 335.1392.

2-(2-(2-Methoxyethoxy)benzamido)pyridine 1-Oxide (3ag). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (2:1) as an eluent (R_f = 0.44) to afford a white solid (40 mg, 70%, mp 114−115 °C from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.24 (s, 1H), 8.72 (dd, J = 8.5, 1.8 Hz, 1H), 8.30−8.27 (m, 2H), 7.56−7.51 (m, 1H), 7.37−7.33 (m, 1H), 7.15−7.10 (m, 2H), 7.01−6.97 (m, 1H), 4.42 (t, J = 4.7 Hz, 2H), 4.10 (t, J = 4.9 Hz, 2H), 3.48 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 157.4, 145.4, 137.3, 134.3, 132.7, 127.6, 121.5, 120.8, 118.5, 115.8, 112.8, 70.4, 69.0, 59.1. HRMS (positive ESI): calcd for $C_{15}H_{17}N_2O_4$ [M + H], 289.1188; found, 289.1185.

2-(2-Isopropoxybenzamido)pyridine 1-Oxide (3ah). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (5:1) as an eluent (R_f = 0.40) to afford a white solid (39 mg, 71%, mp 138−139 °C from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.28 (s, 1H), 8.75 (dd, J = 8.5, 1.8 Hz, 1H), 8.31−8.28 (m, 2H), 7.54−7.50 (m, 1H), 7.37−7.33 (m, 1H), 7.11−7.07 (m, 2H), 7.01−6.97 (m, 1H), 4.96−4.90 (m, 1H), 1.60 (d, J = 6.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 156.5, 145.4, 137.4, 134.2, 132.8, 127.7, 121.2, 120.9, 118.5, 115.9, 113.6, 72.3, 21.9. HRMS (positive ESI): calcd for $C_{15}H_{17}N_2O_3$ [M + H], 273.1239; found, 273.1237.

2-(2-(((1*R*,2*R*,5*R*)-2-Isopropyl-5-methylcyclohexyl)oxy)-benzamido)pyridine 1-Oxide (3ai). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (10:1) as an eluent (R_f = 0.49) to afford a white solid (28 mg, 38%, mp 133−134 °C from 1:2 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.29 (s, 1H), 8.74 (dd, J = 8.5, 1.7 Hz, 1H), 8.31−8.28 (m, 2H), 7.53−7.49 (m, 1H), 7.34−7.30 (m, 1H), 7.13−7.06 (m, 2H), 6.99−6.95 (m, 1H), 4.45−4.39 (m, 1H), 2.25−2.16 (m, 3H), 1.83−1.79 (m, 1H), 1.73−1.72 (m, 1H), 1.52−1.49 (m, 1H), 1.44−1.38 (m, 1H), 1.15−1.10 (m, 2H), 0.95 (d, J = 3.0 Hz, 3H), 0.93 (d, J = 2.5 Hz, 3H), 0.76 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 157.1, 145.4, 137.4, 134.3, 132.9, 127.3, 121.2, 120.7, 118.4, 115.8, 113.3, 79.7, 46.4, 39.9, 34.0, 31.7, 26.3, 23.6, 22.0, 20.6, 16.5. HRMS (positive ESI): calcd for $C_{22}H_{29}N_2O_3$ [M + H], 369.2178; found, 369.2178.

2-(2-*n*-Decoxybenzamido)pyridine 1-Oxide (3aj). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (10:1) as an eluent (R_f = 0.45) to afford a white solid (42 mg, 57%, mp 83−84 °C from 1:3 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.27 (s, 1H), 8.73 (dd, J = 8.5, 1.7 Hz, 1H), 8.30−8.26 (m, 2H), 7.55−7.50 (m, 1H), 7.37−7.32 (m, 1H), 7.12−7.06 (m, 2H), 7.01−6.97 (m, 1H), 4.27 (t, J = 7.2 Hz, 2H), 2.15−2.08 (m, 2H), 1.52−1.49 (m, 2H), 1.42−1.35 (m, 2H), 1.28−1.24 (m, 10H), 0.87 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 157.6, 145.4, 137.3, 134.3, 132.6, 127.6, 121.0, 120.6, 118.5, 115.8, 112.5, 69.9, 31.9, 29.6, 29.5, 29.3, 29.2, 28.6, 26.0, 22.7, 14.1. HRMS (positive ESI): calcd for $C_{22}H_{31}N_2O_3$ [M + H], 371.2335; found, 371.2332.

2-(2-Dodecoxybenzamido)pyridine 1-Oxide (3ak). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (10:1) as an eluent (R_f = 0.45) to afford a white solid (48 mg, 60%, mp 78−79 °C from 1:2 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.27 (s, 1H), 8.73 (dd, J = 8.5, 1.7 Hz, 1H), 8.30−8.26 (m, 2H), 7.55−7.50 (m, 1H), 7.37−7.32 (m, 1H), 7.13−7.06 (m, 2H), 7.01−6.97 (m, 1H), 4.27 (t, J = 7.2 Hz, 2H), 2.15−2.08 (m, 2H), 1.51−1.45 (m, 2H), 1.42−1.35 (m, 2H), 1.29−1.24 (m, 14H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 157.6, 145.4, 137.3, 134.3, 132.6, 127.6, 121.0, 120.6, 118.5, 115.8, 112.5, 69.9, 31.9, 29.6, 29.4, 29.2, 28.6, 26.0, 22.7, 14.1. HRMS (positive ESI): calcd for $C_{24}H_{35}N_2O_3$ [M + H], 399.2648; found, 399.2645.

2-(2-((Hexafluoropropan-2-yl)oxy)benzamido)pyridine 1-Oxide (3al). Purified by analytical TLC on silica gel with petroleum ether/ethyl acetate (1:1) as an eluent (R_f = 0.30 and 0.38 for **3al** and **3′al**, respectively) to afford a white solid (52 mg, 68%, and mp 138−139 °C from 1:2 hexane/dichloromethane for **3al**; 26 mg, 24%, and mp 196−197 °C from 1:2 hexane/dichloromethane for **3′al**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.22 (s, 1H), 8.63 (dd, J = 8.5, 1.8 Hz, 1H), 8.32−8.30 (m, 1H), 8.09−8.06 (m, 1H), 7.62−7.58 (m, 1H), 7.39−7.31 (m, 2H), 7.17 (d, J = 8.4 Hz, 1H), 7.05−7.01 (m, 1H), 5.14−5.08 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 154.7, 144.5, 137.3, 134.0, 132.3, 127.6, 125.1, 125.0, 120.7 (q, J_{C-F} = 285.8 Hz), 119.0, 115.4, 115.3, 76.4 (p, J_{C-F} = 33.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −72.78. HRMS (positive ESI): calcd for $C_{15}H_{11}F_6N_2O_3$ [M + H], 381.0674; found, 381.0672.

2-(2,6-(Bis(hexafluoropropan-2-yl)oxy)benzamido)pyridine 1-Oxide (3′al). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.41−8.37 (m, 2H), 7.70−7.66 (m, 1H), 7.52−7.49 (m, 1H), 7.29 (d, J = 8.6 Hz, 2H), 7.24−7.21 (m, 1H), 6.67−6.63 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.0, 153.4, 142.9, 137.6, 132.0, 127.4, 121.0 (q, J_{C-F} = 285.8 Hz), 120.1, 118.0, 114.2, 109.8, 72.6 (p, J_{C-F} = 32.4 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ −72.90. HRMS (positive ESI): calcd for $C_{18}H_{11}F_{12}N_2O_4$ [M + H], 547.0527; found, 547.0526.

2-(2-((Hexafluoropropan-2-yl)oxy)-5-methylbenzamido)-pyridine 1-Oxide (3el). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (10:1) as an eluent (R_f = 0.33) to afford a white solid (69 mg, 88%, mp 159−160 °C from 1:4 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.20 (s, 1H), 8.63 (dd, J = 8.5, 1.8 Hz, 1H), 8.30 (d, J = 6.2 Hz, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.38−7.34 (m, 2H), 7.07−7.01 (m, 2H), 5.09−5.04 (m, 1H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 152.7, 144.6, 137.3, 135.0, 134.5, 132.4, 127.6, 124.6, 120.8 (q, J_{C-F} = 285.2 Hz), 118.9, 115.5, 115.3, 76.7 (p, J_{C-F} = 34.0 Hz), 20.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −72.84. HRMS (positive ESI): calcd for $C_{16}H_{13}F_6N_2O_3$ [M + H], 395.0830; found, 395.0828.

2-(2-((Hexafluoropropan-2-yl)oxy)-4-iodobenzamido)-pyridine 1-Oxide (3il). Purified by analytical TLC on silica gel with petroleum ether/ethyl acetate (1:1) as an eluent (R_f = 0.28 and 0.60 for **3al** and **3′al**, respectively) to afford a white solid (54 mg, 53%, and mp 99−100 °C from 1:4 hexane/dichloromethane for **3il**; 38 mg, 28%, and mp 138−139 °C from 1:4 hexane/dichloromethane for **3′il**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.21 (s, 1H), 8.60 (dd, J = 8.5, 1.5 Hz, 1H), 8.31−8.30 (m, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.70−7.68 (m, 1H), 7.50 (s, 1H), 7.39−7.35 (m, 1H), 7.06−7.02 (m, 1H), 5.13−5.09 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 154.4, 144.3, 137.3, 134.6, 133.4, 127.6, 124.7, 124.5, 120.7 (q, J_{C-F} = 280.0 Hz), 119.2, 115.4, 99.6, 76.5 (p, J_{C-F} = 33.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −72.66. HRMS (positive ESI): calcd for $C_{15}H_{10}F_6IN_2O_3$ [M + H], 506.9640; found, 506.9644.

2-(2,6-Bis((hexafluoropropan-2-yl)oxy)-4-iodobenzamido)-pyridine 1-Oxide (3′il). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.39−8.33 (m, 2H), 7.72 (s, 2H), 7.50−7.46 (m, 1H), 7.24−7.20 (m, 1H), 6.72−6.66 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.7, 153.4, 143.0, 137.7, 127.2, 120.8 (q, J_{C-F} = 282.4 Hz), 120.2, 118.5, 118.0, 114.6, 96.7, 72.5 (p, J_{C-F} = 32.8 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ −72.91. HRMS (positive ESI): calcd for $C_{18}H_{10}F_{12}IN_2O_4$ [M + H], 672.9499; found, 672.9493.

2-(2-((Hexafluoropropan-2-yl)oxy)-5-(trifluoromethyl)-benzamido)pyridine 1-Oxide (3kl). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (6:1) as an eluent (R_f = 0.45) to afford a white solid (84 mg, 94%, mp 110−111 °C from 1:4 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.30 (s, 1H), 8.62 (dd, J = 8.5, 1.7 Hz, 1H), 8.40 (d, J = 2.1 Hz, 1H), 8.32−8.30 (m, 1H), 7.86 (dd, J = 8.8, 2.2 Hz, 1H), 7.41−7.37 (m, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.09−7.05 (m, 1H), 5.25−5.20 (m, 1H). ^{13}C NMR

(100 MHz, $CDCl_3$): δ 161.6, 156.4, 144.1, 137.2, 130.9 (q, J_{C-F} = 3.4 Hz), 130.1 (q, J_{C-F} = 3.4 Hz), 127.7, 127.4 (q, J_{C-F} = 33.7 Hz), 125.2, 123.1 (q, J_{C-F} = 270.7 Hz), 120.5 (q, J_{C-F} = 282.4 Hz), 119.5, 115.5, 115.4, 75.8 (p, J_{C-F} = 34.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.45, −72.62. HRMS (positive ESI): calcd for $C_{16}H_{10}F_9N_2O_3$ [M + H], 449.0548; found, 449.0553.

2-(2-((Hexafluoropropan-2-yl)oxy)-4-methoxybenzamido)-pyridine 1-Oxide (3ll). Purified by analytical TLC on silica gel with petroleum ether/ethyl acetate (1:1) as an eluent (R_f = 0.23 and 0.50 for **3ll** and **3'll**, respectively) to afford a white solid (23 mg, 28%, and mp 157−158 °C from 1:4 hexane/dichloromethane for **3ll**; 69 mg, 60%, and mp 182−183 °C from 1:4 hexane/dichloromethane for **3'll**). ^1H NMR (400 MHz, $CDCl_3$): δ 11.28 (s, 1H), 8.63 (dd, J = 8.4, 1.4 Hz, 1H), 8.31−8.29 (m, 1H), 8.12 (d, J = 8.8 Hz, 1H), 7.34−7.32 (m, 1H), 7.02−6.99 (m, 1H), 6.83−6.81 (m, 1H), 6.65 (d, J = 2.1 Hz, 1H), 5.21−5.15 (m, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 162.7, 156.1, 144.8, 137.3, 134.5, 127.6, 120.7 (q, J_{C-F} = 285.3 Hz), 118.7, 116.8, 115.4, 109.2, 101.9, 76.1 (p, J_{C-F} = 34.0 Hz), 55.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −72.67. HRMS (positive ESI): calcd for $C_{16}H_{13}F_6N_2O_4$ [M + H], 411.0780; found, 411.0784.

2-(2,6-Bis((hexafluoropropan-2-yl)oxy)-4-methoxybenzamido)-pyridine 1-Oxide (3'll). ^1H NMR (400 MHz, DMSO-d_6): δ 8.42−8.34 (m, 2H), 7.52−7.48 (m, 1H), 7.23−7.20 (m, 1H), 6.91 (s, 2H), 6.71−6.65 (m, 2H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.2, 160.7, 154.4, 143.0, 137.4, 127.5, 120.9 (q, J_{C-F} = 281.7 Hz), 119.8, 113.9, 110.5, 96.2, 72.3 (p, J_{C-F} = 32.5 Hz), 56.3. ^{19}F NMR (376 MHz, DMSO-d_6): δ −72.94. HRMS (positive ESI): calcd for $C_{19}H_{13}F_{12}N_2O_5$ [M + H], 577.0633; found, 577.0638.

2-(2-((Hexafluoropropan-2-yl)oxy)-4-(methylsulfonyl)-benzamido)pyridine 1-Oxide (3ml). Purified by analytical TLC on silica gel with petroleum ether/ethyl acetate (1:1) as an eluent (R_f = 0.25 and 0.55 for **3ml** and **3'ml**, respectively) to afford a white solid (64 mg, 70%, and mp 206−207 °C from 1:4 hexane/dichloromethane for **3ml**; 27 mg, 22%, and mp 291−292 °C from 1:4 hexane/dichloromethane for **3'ml**). ^1H NMR (400 MHz, DMSO-d_6): δ 8.45−8.41 (m, 2H), 8.08 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 1.0 Hz, 1H), 7.90−7.88 (m, 1H), 7.53−7.48 (m, 1H), 7.26−7.22 (m, 1H), 6.95−6.89 (m, 1H), 3.35 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.2, 153.2, 144.6, 143.1, 137.5, 132.0, 129.6, 127.3, 122.9, 120.9 (q, J_{C-F} = 282.3 Hz), 120.3, 114.9, 114.2, 73.5 (p, J_{C-F} = 33.0 Hz), 43.2. ^{19}F NMR (376 MHz, DMSO-d_6): δ −72.44. HRMS (positive ESI): calcd for $C_{16}H_{13}F_6N_2O_5S$ [M + H], 459.0449; found, 459.0456.

2-(2,6-Bis((hexafluoropropan-2-yl)oxy)-4-(methylsulfonyl)-benzamido)pyridine 1-Oxide (3'ml). ^1H NMR (400 MHz, DMSO-d_6): δ 8.38−8.36 (m, 2H), 7.82 (s, 2H), 7.50−7.46 (m, 1H), 7.25−7.21 (m, 1H), 6.89−6.83 (m, 2H), 3.35 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.4, 153.7, 143.7, 143.1, 137.9, 127.1, 122.7, 120.8 (q, J_{C-F} = 281.0 Hz), 114.9, 110.5, 108.6, 72.8 (p, J_{C-F} = 33.0 Hz), 43.2. ^{19}F NMR (376 MHz, DMSO-d_6): δ −72.77. HRMS (positive ESI): calcd for $C_{19}H_{13}F_{12}N_2O_6S$ [M + H], 625.0303; found, 625.0305.

2-(2-((Hexafluoropropan-2-yl)oxy)-4-(methoxycarbonyl)-benzamido)pyridine 1-Oxide (3nl). Purified by analytical TLC on silica gel with petroleum ether/ethyl acetate (1:1) as an eluent (R_f = 0.22 and 0.46 for **3nl** and **3'nl**, respectively) to afford a white solid (49 mg, 56%, and mp 173−174 °C from 1:4 hexane/dichloromethane for **3nl**; 28 mg, 23%, and mp 163−164 °C from 1:4 hexane/dichloromethane for **3'nl**). ^1H NMR (400 MHz, $CDCl_3$): δ 11.24 (s, 1H), 8.62 (dd, J = 8.5, 1.6 Hz, 1H), 8.33−8.31 (m, 1H), 8.14 (d, J = 8.1 Hz, 1H), 7.97−7.95 (m, 1H), 7.83 (s, 1H), 7.40−7.36 (m, 1H), 7.08−7.04 (m, 1H), 5.29−5.24 (m, 1H), 3.98 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 162.3, 154.2, 144.2, 137.3, 135.2, 132.6, 128.6, 127.6, 125.7, 120.6 (q, J_{C-F} = 282.0 Hz), 119.3, 115.8, 115.4, 75.9 (p, J_{C-F} = 34.0 Hz), 52.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −72.72. HRMS (positive ESI): calcd for $C_{17}H_{13}F_6N_2O_5$ [M + H], 439.0729; found, 439.0727.

2-(2,6-Bis((hexafluoropropan-2-yl)oxy)-4-(methoxycarbonyl)-benzamido)pyridine 1-Oxide (3'nl). ^1H NMR (400 MHz, $CDCl_3$): δ 10.30 (s, 1H), 8.57 (dd, J = 8.4, 1.4 Hz, 1H), 8.29−8.27 (m, 1H), 7.58 (s, 2H), 7.44−7.39 (m, 1H), 7.10−7.06 (m, 1H), 5.11−5.05 (m, 2H), 4.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 159.8, 154.6, 143.5, 137.2, 134.2, 128.1, 123.2, 120.5 (q, J_{C-F} = 282.7 Hz), 119.6, 114.9, 111.5, 75.6 (p, J_{C-F} = 33.9 Hz), 53.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.04. HRMS (positive ESI): calcd for $C_{20}H_{13}F_{12}N_2O_6$ [M + H], 605.0582; found, 605.0583.

2-(3-((Hexafluoropropan-2-yl)oxy)isonicotinamido)pyridine 1-Oxide (3ol). Purified by analytical TLC on silica gel with petroleum ether/ethyl acetate (1:1) as an eluent (R_f = 0.22 and 0.60 for **3ol** and **3'ol**, respectively) to afford a white solid (41 mg, 54%, and mp 138−139 °C from 1:4 hexane/dichloromethane for **3ol**; 23 mg, 21%, and mp 250−251 °C from 1:4 hexane/dichloromethane for **3'ol**). ^1H NMR (400 MHz, $CDCl_3$): δ 11.24 (s, 1H), 8.68−8.65 (m, 2H), 8.59 (dd, J = 8.4, 1.6 Hz, 1H), 8.32−8.31 (m, 1H), 7.90 (d, J = 4.7 Hz, 1H), 7.42−7.38 (m, 1H), 7.11−7.07 (m, 1H), 5.31−5.25 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 149.9, 147.0, 143.9, 139.1, 137.3, 131.7, 127.7, 124.3, 120.5 (q, J_{C-F} = 280.0 Hz), 119.7, 115.5, 76.9 (p, J_{C-F} = 34.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −72.77. HRMS (positive ESI): calcd for $C_{14}H_{10}F_6N_3O_3$ [M + H], 382.0626; found, 382.0623.

2-(2,6-Bis((hexafluoropropan-2-yl)oxy)isonicotinamido)-pyridine 1-Oxide (3'ol). ^1H NMR (400 MHz, DMSO-d_6): δ 8.62 (s, 2H), 8.39−8.35 (m, 2H), 7.50−7.46 (m, 1H), 7.26−7.22 (m, 1H), 6.82−6.76 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.6, 149.0, 143.0, 138.0, 127.0, 125.3, 120.8 (q, J_{C-F} = 279.8 Hz), 120.6, 115.2, 73.3 (p, J_{C-F} = 32.8 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ −72.85. HRMS (positive ESI): calcd for $C_{17}H_{10}F_{12}N_3O_4$ [M + H], 548.0480; found, 548.0473.

2-(2-((Hexafluoropropan-2-yl)oxy)-4-(trifluoromethyl)-benzamido)pyridine 1-Oxide (3pl). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (10:1) as an eluent (R_f = 0.40) to afford a white solid (69 mg, 77%, mp 119−120 °C from 1:1 hexane/dichloromethane). ^1H NMR (400 MHz, $CDCl_3$): δ 11.19 (s, 1H), 8.62−8.60 (m, 1H), 8.30−8.29 (m, 1H), 8.18−8.16 (m, 1H), 7.60−7.58 (m, 1H), 7.42−7.38 (m, 2H), 7.09−7.05 (m, 1H), 5.26−5.20 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.9, 154.4, 144.1, 137.2, 135.6 (q, J_{C-F} = 33.5 Hz), 133.1, 128.4, 127.7, 122.7 (q, J_{C-F} = 271.6 Hz), 121.9 (q, J_{C-F} = 3.5 Hz), 120.5 (q, J_{C-F} = 280.9 Hz), 119.5, 115.4, 112.6, 76.3 (p, J_{C-F} = 34.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.23, −72.76. HRMS (positive ESI): calcd for $C_{16}H_{10}F_9N_2O_3$ [M + H], 449.0548; found, 449.0550.

2-(2-((Hexafluoropropan-2-yl)oxy)-6-methylbenzamido)-pyridine 1-Oxide (3ql). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (10:1) as an eluent (R_f = 0.35) to afford a white solid (73 mg, 93%, mp 95−96 °C from 1:4 hexane/dichloromethane). ^1H NMR (400 MHz, $CDCl_3$): δ 10.20 (s, 1H), 8.63−8.61 (m, 1H), 8.25−8.24 (m, 1H), 7.42−7.35 (m, 2H), 7.09−7.04 (m, 2H), 6.93 (d, J = 8.4 Hz, 1H), 4.97−4.91 (m, 1H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 153.6, 144.0, 138.1, 137.3, 131.1, 128.2, 127.8, 126.7, 120.8 (q, J_{C-F} = 284.9 Hz), 119.1, 114.9, 112.2, 76.0 (p, J_{C-F} = 33.5 Hz), 19.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.20. HRMS (positive ESI): calcd for $C_{16}H_{13}F_6N_2O_3$ [M + H], 395.0830; found, 395.0828.

2-(2-Chloro-6-((hexafluoropropan-2-yl)oxy)benzamido)-pyridine 1-Oxide (3rl). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (10:1) as an eluent (R_f = 0.40) to afford a white solid (59 mg, 71%, mp 141−142 °C from 1:4 hexane/dichloromethane). ^1H NMR (400 MHz, $CDCl_3$): δ 10.28 (s, 1H), 8.60 (dd, J = 8.4, 1.6 Hz, 1H), 8.27−8.26 (m, 1H), 7.46−7.39 (m, 2H), 7.30−7.28 (m, 1H), 7.10−7.04 (m, 2H), 5.02−4.96 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8, 154.3, 143.7, 137.3, 132.8, 131.2, 128.1, 127.7, 126.0, 120.6 (q, J_{C-F} = 285.4 Hz), 119.5, 115.0, 113.7, 76.1 (p, J_{C-F} = 33.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.09. HRMS (positive ESI): calcd for $C_{15}H_{10}ClF_6N_2O_3$ [M + H], 415.0284; found, 415.0281.

2-(2-((Hexafluoropropan-2-yl)oxy)-6-nitrobenzamido)-pyridine 1-Oxide (3sl). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (6:1) as an eluent (R_f = 0.35) to afford a yellow solid (46 mg, 54%, mp 162−163 °C from 1:4 hexane/dichloromethane). ^1H NMR (400 MHz, $CDCl_3$): δ 10.42 (s, 1H), 8.56 (dd, J = 8.4, 1.2 Hz, 1H), 8.24−8.22 (m, 1H), 8.06 (d, J = 8.2 Hz, 1H), 7.71−7.67 (m, 1H), 7.50−7.41 (m, 2H), 7.10−7.06 (m, 1H), 5.13−5.08 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 154.2, 146.6, 143.7, 137.2, 131.9, 128.4, 123.7, 121.2, 120.5, 120.5 (q, J_{C-F} = 282.4 Hz), 119.5, 115.1,

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76.2 (p, J_{C-F} = 33.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −72.95. HRMS (positive ESI): calcd for $C_{15}H_{10}F_6N_3O_5$ [M + H], 426.0525; found, 426.0524.

2-(2-((Hexafluoropropan-2-yl)oxy)-4,6-dimethylbenzamido)-pyridine 1-Oxide (3tl). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (10:1) as an eluent (R_f = 0.39) to afford a white solid (74 mg, 91%, mp 105−106 °C from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.17 (s, 1H), 8.62−8.60 (m, 1H), 8.26−8.25 (m, 1H), 7.40−7.36 (m, 1H), 7.06−7.03 (m, 1H), 6.89 (s, 1H), 6.72 (s, 1H), 4.97−4.91 (m, 1H), 2.37 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 153.7, 144.1, 141.9, 137.9, 137.3, 128.1, 127.5, 125.0, 120.8 (q, J_{C-F} = 285.1 Hz), 119.0, 114.8, 112.9, 76.0 (p, J_{C-F} = 33.4 Hz), 21.6, 19.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.22. HRMS (positive ESI): calcd for $C_{17}H_{15}F_6N_2O_3$ [M + H], 409.0987; found, 409.0986.

2-(5-Chloro-2-((hexafluoropropan-2-yl)oxy)benzamido)-pyridine 1-Oxide (3ul). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (10:1) as an eluent (R_f = 0.41) to afford a white solid (77 mg, 93%, mp 127−128 °C from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.24 (s, 1H), 8.60 (dd, J = 8.6, 1.7 Hz, 1H), 8.31−8.29 (m, 1H), 8.05 (d, J = 2.7 Hz, 1H), 7.54 (dd, J = 8.9, 2.7 Hz, 1H), 7.40−7.36 (m, 1H), 7.15 (d, J = 8.9 Hz, 1H), 7.08−7.04 (m, 1H), 5.15−5.09 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7, 153.1, 144.2, 137.2, 133.7, 132.1, 130.7, 127.7, 126.3, 120.6 (q, J_{C-F} = 285.3 Hz), 119.3, 117.0, 115.4, 76.6 (p, J_{C-F} = 33.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −72.77. HRMS (positive ESI): calcd for $C_{15}H_{10}ClF_6N_2O_3$ [M + H], 415.0284; found, 415.0283.

2-(4,5-Dichloro-2-((hexafluoropropan-2-yl)oxy)benzamido)-pyridine 1-Oxide (3vl). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (10:1) as an eluent (R_f = 0.49) to afford a white solid (75 mg, 84%, mp 137−138 °C from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.26 (s, 1H), 8.60−8.58 (m, 1H), 8.31−8.29 (m, 1H), 8.20 (s, 1H), 7.40−7.36 (m, 1H), 7.32 (s, 1H), 7.08−7.05 (m, 1H), 5.17−5.12 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 152.9, 144.2, 137.9, 137.3, 133.7, 129.6, 127.7, 124.5, 120.4 (q, J_{C-F} = 282.6 Hz), 119.4, 117.8, 115.5, 76.7 (p, J_{C-F} = 34.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −72.64. HRMS (positive ESI): calcd for $C_{15}H_9Cl_2F_6N_2O_3$ [M + H], 448.9894; found, 448.9889.

2-(2-((Hexafluoropropan-2-yl)oxy)-4,5-dimethoxybenzamido)-pyridine 1-Oxide (3wl). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (5:1) as an eluent (R_f = 0.32) to afford a white solid (71 mg, 80%, mp 170−171 °C from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.36 (s, 1H), 8.62 (dd, J = 8.5, 1.6 Hz, 1H), 8.31−8.29 (m, 1H), 7.58 (s, 1H), 7.37−7.33 (m, 1H), 7.03−7.00 (m, 1H), 6.62 (s, 1H), 5.04−4.99 (m, 1H), 3.97 (s, 3H), 3.95 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 153.5, 149.7, 146.2, 144.7, 137.3, 127.5, 120.7 (q, J_{C-F} = 283.0 Hz), 118.8, 116.6, 115.2, 113.1, 100.0, 77.7 (p, J_{C-F} = 33.5 Hz), 56.4, 56.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ −72.67. HRMS (positive ESI): calcd for $C_{17}H_{15}F_6N_2O_5$ [M + H], 441.0885; found, 441.0886.

2-(2-((Hexafluoropropan-2-yl)oxy)-1-naphthamido)pyridine 1-Oxide (3xl). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (10:1) as an eluent (R_f = 0.47) to afford a white solid (70 mg, 81%, mp 106−107 °C from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.41 (s, 1H), 8.73−8.71 (m, 1H), 8.25−8.23 (m, 1H), 7.98 (d, J = 9.2 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.59−7.50 (m, 2H), 7.44−7.40 (m, 1H), 7.30 (d, J = 9.1 Hz, 1H), 7.07−7.04 (m, 1H), 5.14−5.08 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 150.8, 144.0, 137.3, 132.9, 130.7, 130.5, 128.7, 128.3, 128.1, 126.4, 124.5, 123.2, 120.8 (q, J_{C-F} = 285.1 Hz), 119.3, 115.2, 115.0, 76.6 (p, J_{C-F} = 33.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.08. HRMS (positive ESI): calcd for $C_{19}H_{13}F_6N_2O_3$ [M + H], 431.0830; found, 431.0826.

2-(3-((Hexafluoropropan-2-yl)oxy)thiophene-2-carboxamido)-pyridine 1-Oxide (3yl). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (6:1) as an eluent (R_f = 0.37) to afford a white solid (57 mg, 74%, mp 161−162 °C from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.29 (s, 1H), 8.57 (d, J = 7.5 Hz, 1H), 8.31−8.30 (m, 1H), 7.63 (d, J = 5.6 Hz, 1H), 7.35−7.31 (m, 1H), 7.04−7.00 (m, 1H), 6.97 (d, J = 5.6 Hz, 1H), 5.18−5.13 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 152.6, 144.5, 137.3, 132.2, 127.7, 120.6, 120.5 (q, J_{C-F} = 280.0 Hz), 118.9, 115.8, 115.3, 76.8 (p, J_{C-F} = 34.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −72.81. HRMS (positive ESI): calcd for $C_{13}H_9F_6N_2O_3S$ [M + H], 387.0238; found, 387.0235.

2-(3-((Hexafluoropropan-2-yl)oxy)furan-2-carboxamido)-pyridine 1-Oxide (3zl). Purified by analytical TLC on silica gel with CH_2Cl_2/acetone (6:1) as an eluent (R_f = 0.44) to afford a white solid (28 mg, 38%, mp 153−154 °C from 1:5 hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.94 (s, 1H), 8.55 (d, J = 7.8 Hz, 1H), 8.31−8.30 (m, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.38−7.34 (m, 1H), 7.06−7.03 (m, 1H), 6.51 (d, J = 2.0 Hz, 1H), 6.09−6.03 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 151.0, 144.7, 144.0, 137.3, 131.2, 128.2, 120.8 (q, J_{C-F} = 284.6 Hz), 119.0, 114.9, 107.2, 76.5 (p, J_{C-F} = 33.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.32. HRMS (positive ESI): calcd for $C_{13}H_9F_6N_2O_4$ [M + H], 371.0467; found, 371.0462.

General Procedure for Removal of the Directing Group. A mixture of 2-(2-ethoxybenzamido)pyridine 1-oxide (51.6 mg, 0.2 mmol) and NaOH (120 mg, 3 mmol) in EtOH (2 mL) was stirred at 80 °C for 8 h. After completion of the reaction, the resulting dark red solution was cooled to room temperature and quenched with 2 M HCl aqueous solution (15 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, and filtered, and the solvent was evaporated under a vacuum. Purification by silica gel column chromatography (CH_2Cl_2/methanol, 20:1) afforded 2-ethoxybenzoic acid **10** as a light yellow oil (27 mg, 80%, CAS: 134-11-2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.97 (bs, 1H), 8.18 (dd, J = 7.8, 1.8 Hz, 1H), 7.58−7.54 (m, 1H), 7.15−7.11 (m, 1H), 7.05 (d, J = 8.3 Hz, 1H), 4.34 (q, J = 7.0 Hz, 2H), 1.57 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 157.4, 135.1, 133.7, 122.2, 117.7, 112.6, 66.0, 14.7.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds. 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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