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Mild Fluorination of Chloropyridines with in Situ Generated Anhydrous Tetrabutylammonium Fluoride

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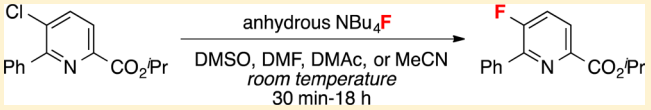
Supporting Information

ABSTRACT: This paper describes the fluorination of nitrogen heterocycles using anhydrous NBu_4F. Quinoline derivatives as well as a number of 3- and 5-substituted pyridines undergo high-yielding fluorination at room temperature using this reagent. These results with anhydrous NBu_4F compare favorably to traditional halex fluorinations using alkali metal fluorides, which generally require temperatures of ≥100 °C.



Fluorinated pyridines are widely prevalent in commercial agrochemicals and pharmaceuticals,[1] and pyridines containing a fluorine substituent at the 3- and/or 5-position are particularly common in biologically active molecules (Figure 1).[2−5] However, the carbon−fluorine bond in such molecules is often challenging to install. The most common method for fluorinating pyridine derivatives involves nucleophilic halide exchange (halex) between the corresponding aryl chloride and an alkali metal fluoride salt (MF).[6−8] Since the 3- and 5-positions of pyridine are relatively electron-rich sites, such transformations generally require forcing conditions (≥100 °C) and often involve the use of expensive CsF. For instance, as shown in Scheme 1A, the fluorination of 5-chloropicolinate **1** with 2 equiv of CsF requires 24 h at 100 °C to proceed to completion.

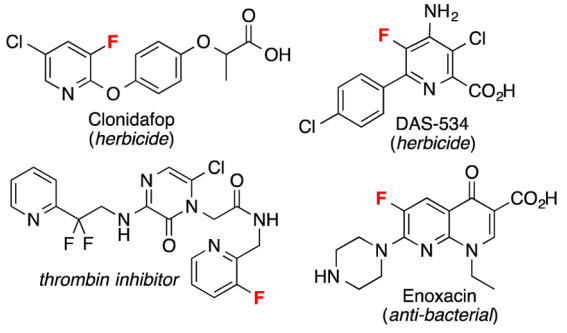
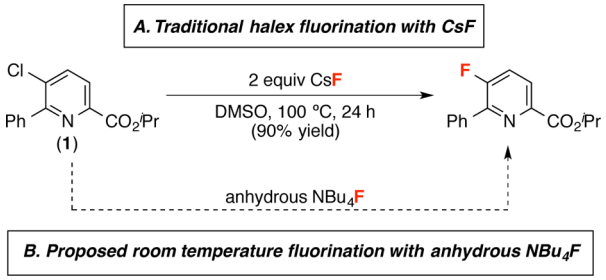


Figure 1. Examples of biologically active molecules containing 3- or 5-fluoropyridines.

An attractive alternative to high-temperature halex reactions with metal fluorides involves the use of anhydrous tetrabutylammonium fluoride.[9] Sun and DiMagno have shown that anhydrous TBAF can participate in S_NAr reactions with a variety of electron-deficient arene substrates *at room temperature*.[10] Furthermore, this reagent can be preformed through the combination of tetrabutylammonium cyanide (TBACN) and hexafluorobenzene (C_6F_6) in DMSO.[11]

Scheme 1. Fluorination of 1 via (A) Traditional Halex Fluorination with CsF and (B) Proposed Room-Temperature Fluorination with Anhydrous TBAF



We aimed to use anhydrous TBAF to achieve both mild and high-yielding fluorinations of challenging 3- and 5-chloropyridine substrates (Scheme 1B). We report herein a convenient adaptation of DiMagno's anhydrous TBAF fluorination procedure that enables the room-temperature fluorination of a variety of nitrogen heterocycles. This method offers the additional advantages that it can be performed in one pot and that a variety of solvents can be used.

Our initial studies focused on the fluorination of 5-chloropicolinate **1**, a structural motif that appears in a variety of Dow Agrosciences products.[12] As shown in Table 1, the reaction of **1** with a preformed solution of anhydrous TBAF (1 equiv generated from 0.167 equiv of C_6F_6 and 1 equiv of NBu_4CN in DMSO per DiMagno's procedure)[7] resulted in 82% yield of fluoropicolinate **2** within 24 h at room temperature (Table 1, entry 2). The yield of this transformation increased to near quantitative with 2 equiv or more of the preformed anhydrous TBAF (entries 3, 4). Furthermore, with 2 equiv of anhydrous TBAF, the fluorination of **1** proceeded to 84% yield within 30 min at room temperature (entry 5). Importantly, these conditions compare favorably to the

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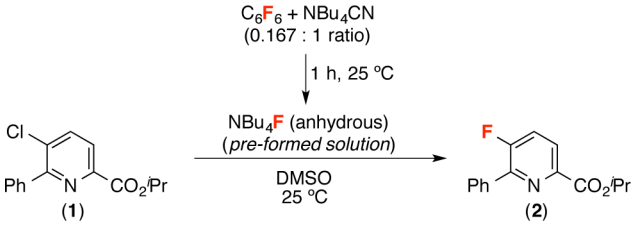
Table 1. Fluorination of 1 with Preformed Anhydrous TBAF



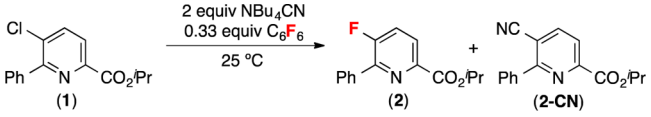
entry[a]	equiv NBu_4F	time	yield[b] (%)
1	0.5	24 h	43
2	1	24 h	82
3	2	24 h	>99
4	4	24 h	>99
5	2	30 min	84
6	2	5 min	53

[a]Conditions: C_6F_6 and NBu_4CN stirred for 1 h in DMSO at 25 °C, and then substrate **1** added to this solution. [b]Yield determined by ^{19}F NMR spectroscopy using trifluorotoluene as a standard.

requirements for the corresponding reaction with CsF (100 °C for 24 h, Scheme 1A).

Further investigations revealed that preformation of anhydrous TBAF is not necessary to achieve room temperature fluorination of **1**. Simply weighing the substrate and TBACN into the reaction vessel followed by the addition of DMSO and C_6F_6 furnished **2** in quantitative yield within 6 h (Table 2, entries 2 and 3). No cyanation to form **2-CN** was observed under these conditions. Good results were also obtained using less expensive NBu_3MeCN in place of NBu_4CN (70% yield after 24 h at 25 °C, entry 4). In addition, the one-pot generation of anhydrous TBAF could be applied to achieve rapid, high-yielding, room-temperature fluorination of **1** in a variety of solvents, including DMF, DMAc, and MeCN (Table 2, entries 5−13). The use of MeCN at room temperature is particularly appealing from a process chemistry perspective.[13]

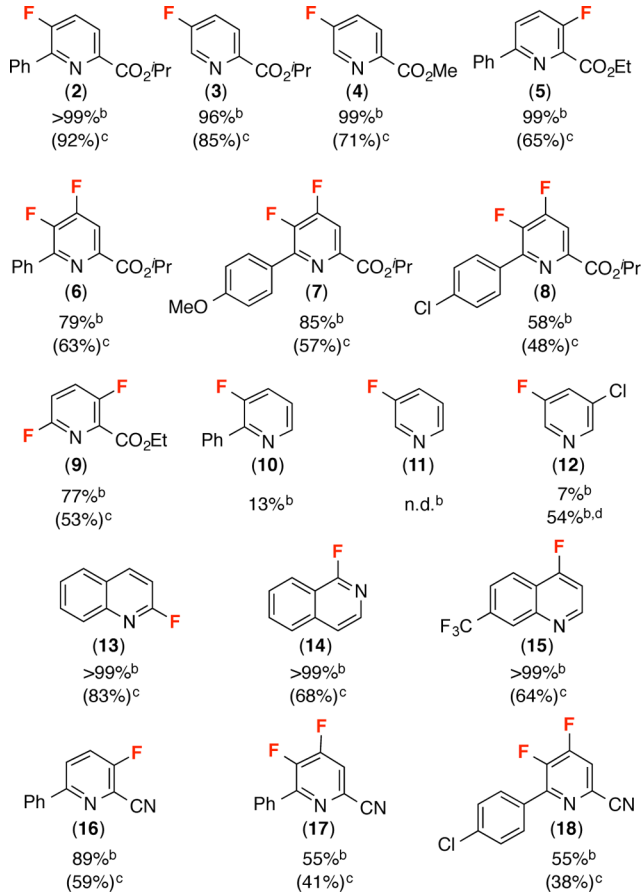
Table 2. One-Pot Room-Temperature Fluorination of 1 with Anhydrous TBAF in a Variety of Solvents



entry[a]	solvent	time	yield **2**[b] (%)	yield 2-CN[c,d] (%)
1	DMSO	10 min	66	n.d.
2	DMSO	6 h	>99	n.d.
3	DMSO	24 h	>99	n.d.
4[e]	DMSO	24 h	70	n.d.
5	DMF	10 min	95	n.d.
6	DMF	6 h	>99	n.d.
7	DMF	24 h	>99	n.d.
8	DMAc	10 min	87	<1
9	DMAc	6 h	98	<1
10	DMAc	24 h	>99	<1
11	MeCN	10 min	5	n.d.
12	MeCN	6 h	57	n.d.
13	MeCN	24 h	>99	n.d.

[a]Conditions: all reagents combined together in the appropriate solvent and stirred at 25 °C for 10 min to 24 h. [b]Yield determined by ^{19}F NMR spectroscopy using trifluorotoluene as a standard. [c]Yields determined by GC using 2-phenylpyridine as a standard. [d]n.d. = not detected. [e]NBu_3MeCN was used in place of NBu_4CN.

Table 3. Substrate Scope for in Situ Generated Fluorination with Anhydrous TBAF



[a]Conditions: C_6F_6 and NBu_4CN were stirred for 5 min in DMSO at 25 °C, and then the chloropyridine or chloroquinoline substrate was added to this solution. The resulting reaction mixtures were then stirred for 24 h at 25 °C. Two equivalents of anhydrous TBAF were added per chlorine on the pyridine/quinolone ring. [b]Yield determined by ^{19}F NMR spectroscopy using trifluorotoluene as a standard; n.d. = not detected. [c]Isolated yield. [d]Reaction time was 60 h.

We next investigated the scope of this room-temperature fluorination reaction with various chloropyridine and chloroquinoline derivatives (Table 3). In order to avoid competing cyanation (which was problematic with a few of the more activated substrates), we used a general procedure that involves prestirring a DMSO solution of 2 equiv of NBu_4CN and 0.33 equiv of C_6F_6 for 5 min and then adding the chloropyridine substrate. Both monofluorination of electron-deficient 3- or 5-chloropyridines (to afford **2**−**5**) and difluorination of electron-deficient 4,5-dichloropyridines (to afford **6**−**8**) proceeded in high yield. The fluorination of ethyl 3-chloro-6-phenylpicolinate to form **5** is particularly remarkable, since this product was obtained in low yield under more traditional halex conditions with CsF. For instance, the reaction of ethyl 3-chloro-6-phenylpicolinate with 2 equiv of CsF in DMSO for 24 h at 130 °C afforded only 35% yield of **5** along with unreacted starting material. Fluorination also proceeded smoothly when the ester group of **5**, **6**, and **8** was replaced with a CN substituent (products **16**−**18**). Furthermore, difluorination of

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the isopropyl ester of the broad leaf herbicide chlopyralid proceeded to form **9** in high yield. Importantly, all of these difluorination reactions were carried out using 2 equiv of anhydrous TBAF per chloride in the starting material.

As anticipated on the basis of DiMagno's earlier work,[8] less activated 3- and 3,5-chloropyridine substrates afforded modest yields under these conditions. For example, only 7% of **12** was detected after 24 h. However, increasing the reaction time to 60 h resulted in 54% yield of **12**. Finally, chloroquinoline derivatives were also good substrates for these room-temperature fluorination reactions, and **13**−**15** were formed in >99% yield from the reactions of anhydrous TBAF with the corresponding chloroquinolines.

In conclusion, this report describes the nucleophilic fluorination of chloropyridine and chloroquinoline substrates using anhydrous NBu_4F. A variety of 3- and 5-chloropyridines undergo high-yielding fluorination at room temperature using this reagent. These results compare very favorably to traditional alkali metal fluoride halex fluorinations of these challenging substrates, which typically require temperatures of ≥100 °C.

EXPERIMENTAL SECTION

Materials and Methods. NMR spectra were recorded on a 700 MHz (699.76 MHz for ^{1}H; 175.95 MHz for ^{13}C), 500 MHz (500.10 MHz for ^{1}H; 125.75 MHz for ^{13}C, 470.56 MHz for ^{19}F), or 400 MHz (400.52 MHz for ^{1}H; 100.71 for ^{13}C; 376.87 MHz for ^{19}F) NMR spectrometer with the residual solvent peak ($CDCl_3$; ^{1}H δ = 7.26 ppm, ^{13}C δ = 77.16 ppm) used as the internal reference unless otherwise noted. Chemical shifts are reported in parts per million (ppm) (δ) relative to tetramethylsilane. Multiplicities are reported as follows: br (broad resonance), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Coupling constants (J) are reported in hertz. Infrared (IR) spectroscopy peaks are reported in cm^{-1}. Melting points are uncorrected. All stock solutions were made using volumetric glassware. All liquid reagents were dispensed by difference from syringes. All reagents were weighed out in a nitrogen-filled drybox with exclusion of air and moisture, unless otherwise noted. All reagents were purchased from common suppliers and dried over P_2O_5 prior to use unless otherwise noted. Tetrabutylammonium cyanide was dried at 40 °C under vacuum for 12 h before use.[7] Thin layer chromatography (TLC) was performed on plates precoated with silica gel 60 F_{254}.

Substrate Synthesis. *Isopropyl 5-Chloro-6-phenylpicolinate (1).* A 500 mL 3-neck round bottomed flask equipped with a mechanical overhead stirrer was charged with KF·2H_2O (18.1 g, 192.6 mmol), tap water (70 mL), and acetonitrile (280 mL). The mixture was stirred until all of the solids dissolved. To this biphasic mixture was added phenylboronic acid (9.39 g, 77.1 mmol) and then isopropyl 5,6-dichloropicolinate (15.0 g, 64.2 mmol). The resulting suspension was sparged with N_2 for 15 min, and then bis(triphenylphosphine) palladium dichloride (1.13 g, 1.61 mmol) was added. The resulting bright yellow suspension was sparged with N_2 for an additional 15 min, and then the mixture was heated to 65 °C. After 6 h, the heating mantle was removed, and the mixture was cooled to ambient temperature. The reaction was diluted with EtOAc (150 mL) and water (50 mL). The layers were separated, and SiO_2 (48 g) was added to the organic layer. The solvent was then removed by rotary evaporation. The product was purified by semiautomated silica gel chromatography (column: RediSep Silica 330 g; mobile phase: hexanes/EtOAc gradient elution from 5% to 20% EtOAc; flow rate: 200 mL/min) to afford a thick oil (15.63 g, 88% yield). Crystallization was induced by seeding with a pure crystal to afford an off-white crystalline solid (15.03 g, 85% yield, mp = 43−45 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.80−7.77 (m, 2H), 7.49−7.44 (m, 3H), 5.31 (hept, J = 6.4 Hz, 1H), 1.41 (d, J = 6.4 Hz, 6H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.0, 156.7, 146.8, 138.8, 137.6, 133.5, 129.8, 129.2, 128.1, 124.2, 69.8, 22.0. HRMS ESI$^+$ (m/z): [M + H]$^+$ calcd for $C_{15}H_{15}ClNO_2$ 276.0786; found 276.0794.

Isopropyl 4,5-Dichloro-6-phenylpicolinate. A 300 mL 3-neck round bottomed flask equipped with a mechanical overhead stirrer was charged with CsF (8.19 g, 53.9 mmol), tap water (40 mL), acetonitrile (120 mL), phenylboronic acid (4.39 g, 36.0 mmol), and isopropyl 4,5,6-trichloropicolinate (5.44 g, 18.8 mmol, 92% purity). The resulting suspension was sparged with N_2 gas for 15 min, and then bis(triphenylphosphine) palladium dichloride (0.51 g, 0.72 mmol) was added. The resulting bright yellow suspension was sparged with N_2 for an additional 15 min, and then the mixture was heated to 55 °C. After 24 h, the heating mantle was removed, and the mixture was cooled to ambient temperature and then diluted with EtOAc (150 mL) and water (40 mL). The layers were separated, and SiO_2 (30 g) was added to the organic layer. The solvent was then removed by rotary evaporation. The product was purified by semiautomated silica gel chromatography (column: RediSep Silica 330 g; mobile phase: hexanes/EtOAc gradient elution from 0% to 10% EtOAc; flow rate: 200 mL/min) to afford a white solid (5.50 g, 95% yield, mp = 95 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.74−7.71 (m, 2H), 7.49−7.46 (m, 3H), 5.31 (hept, J = 6.4 Hz, 1H), 1.41 (d, J = 6.4 Hz, 6H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) 163.2, 158.8, 146.7, 144.5, 137.7, 132.3, 129.7, 129.5, 128.2, 125.1, 70.3, 21.9. IR (cm^{-1}): 3067, 2986, 1715, 1309, 1216, 817. HRMS ESI$^+$ (m/z): [M + Na]$^+$ calcd for $C_{15}H_{13}Cl_2NNaO_2$ 332.0216; found 332.0240.

Isopropyl 4,5-Dichloro-6-(p-methoxyphenyl)picolinate. A 300 mL 3-necked round bottomed flask equipped with a mechanical overhead stirrer was charged with CsF (8.19 g, 53.9 mmol), tap water (40 mL), acetonitrile (120 mL), 4-methoxyphenylboronic acid (4.23 g, 27.8 mmol), and isopropyl 5,6-dichloropicolinate (5.44 g, 18.8 mmol, 92% purity). The resulting suspension was sparged with N_2 gas for 15 min, and then bis(triphenylphosphine) palladium dichloride (0.51 g, 0.72 mmol) was added. The resulting bright yellow suspension was sparged with N_2 for an additional 15 min, and then the mixture was heated to 55 °C. After 6 h, the heating mantle was removed, and the mixture was cooled to ambient temperature. The reaction was diluted with EtOAc (150 mL) and water (40 mL). The layers were separated, and SiO_2 (31 g) was added to the organic layer. The solvent was then removed by rotary evaporation. The product was purified by semiautomated silica gel chromatography (column: RediSep Silica 220 g; mobile phase: hexanes/EtOAc gradient elution from 5% to 15% EtOAc; flow rate: 150 mL/min) to afford a white solid (5.70 g, 89% yield, mp = 105−106 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.74 (dt, J = 8.8, 2.4 Hz, 2H), 6.99 (dt, J = 8.8, 2.4 Hz, 2H), 5.30 (hept, J = 6.0 Hz, 1H), 3.87 (s, 3H, OCH_3), 1.41 (d, J = 6.0 Hz, 6H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.3, 160.7, 158.3, 146.5, 144.4, 131.9, 131.4, 130.1, 124.6, 113.5, 70.2, 55.5, 21.9. IR (cm^{-1}): 3061, 2980, 2837, 1717, 1214, 1179, 1104, 825. HRMS ESI$^+$ (m/z): [M + Na]$^+$ calcd for $C_{16}H_{15}Cl_2NNaO_3$ 362.0321; found 362.0331.

Isopropyl 4,5-Dichloro-6-(p-chlorophenyl)picolinate. A 300 mL 3-neck round bottomed flask equipped with a mechanical overhead stirrer was charged with CsF (8.19 g, 53.9 mmol), tap water (40 mL), acetonitrile (120 mL), 4-chlorophenylboronic acid (4.22 g, 27.0 mmol), and isopropyl 5,6-dichloropicolinate (5.00 g, 18.0 mmol, 96% purity). The resulting suspension was sparged with N_2 gas for 15 min, and then bis(triphenylphosphine) palladium dichloride (0.47 g, 0.67 mmol) was added. The resulting bright yellow suspension was sparged with N_2 for an additional 15 min, and then the mixture was heated to 55 °C. After 5 h, the mixture was cooled to ambient temperature. The reaction was diluted with EtOAc (120 mL) and water (40 mL). The layers were separated, and SiO_2 (34 g) was added to the organic layer. The solvent was then removed by rotary evaporation. The product was purified by semiautomated silica gel chromatography (column: RediSep Silica 330 g; mobile phase: hexanes/EtOAc gradient elution from 5% to 15% EtOAc; flow rate: 200 mL/min) to afford a white solid (4.90 g, 79% yield, mp = 134−138 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.69 (dt, J = 8.8, 2.4 Hz, 2H), 7.90 (dt, J = 8.8, 2.4 Hz, 2H), 5.31 (hept, J = 6.4 Hz, 1H), 1.41 (d, J = 6.0 Hz, 6H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.1, 157.5, 146.8, 144.7, 136.0, 135.8, 132.2, 131.2, 128.5, 125.3, 70.4, 21.9. IR (cm^{-1}): 3069,

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2990, 1717, 1312, 1216, 830, 820. HRMS ESI$^+$ (m/z): [M + Na]$^+$ calcd for $C_{15}H_{12}Cl_3NNaO_2$ 365.9826; found 332.9830.

Ethyl 3,6-Dichloropicolinate. This compound was prepared using a modification of a literature procedure.[14] 3,6-Dichloropicolinic acid (12.0 g, 62.5 mmol, 1.0 equiv) was weighed into a 100 mL round bottomed flask equipped with a magnetic stir bar. Absolute ethanol (25 mL) and sulfuric acid (0.5 mL) were added, and a reflux condenser was attached. The reaction was heated at reflux for 5 h. After completion, the reaction mixture was cooled to room temperature, diluted with Na_2CO_3 (5% aqueous solution, 100 mL), and transferred to a separatory funnel. The crude material was diluted with ethyl acetate (50 mL), and the organic layer was washed with brine (1 × 50 mL), dried over sodium sulfate, and concentrated in vacuo to provide the product as a colorless oil (12.0 g, 73% yield, R_f = 0.59 in 70% hexanes/30% Et_2O). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.74 (d, J = 8.5 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 4.46 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H). ^{13}C NMR (700 MHz, $CDCl_3$) δ 163.3, 149.0, 147.9, 141.0, 129.4, 127.1, 62.6, 14.1. HRMS ESI$^+$ (m/z): [M + H]$^+$ calcd for $C_8H_8Cl_2NO_2$ 219.9927; found 219.9926.

Ethyl 3-Chloro-6-phenylpicolinate. Phenylboronic acid (381 mg, 3.13 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (75 mg, 0.065 mmol, 0.025 equiv), and potassium fluoride (500 mg, 8.61 mmol, 3.3 equiv) were combined in a Schlenk flask equipped with a magnetic stir bar. The flask was evacuated and backfilled with nitrogen three times. Ethyl 3,6-dichloropicolinate (576 mg, 2.6 mmol, 1.0 equiv) was added as a solution in toluene (10.5 mL, purged with N_2), and the resulting reaction mixture was refluxed at 120 °C for 12 h. Upon cooling, the mixture was diluted with ethyl acetate and transferred to a separatory funnel. The organic layer was washed with water (2 × 50 mL) and brine (1 × 50 mL), dried over sodium sulfate, and concentrated in vacuo. The resulting residue was purified by flash column chromatography using a gradient elution of 0−20% EtOAc in hexanes, providing the product as a colorless oil (355 mg, 52% yield, R_f = 0.65 in 70% hexanes/30% Et_2O). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.00−7.99 (multiple peaks, 2H), 7.82 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.47−7.43 (multiple peaks, 3H), 4.51 (q, J = 7.1 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H). ^{13}C NMR (700 MHz, $CDCl_3$) δ 165.1, 155.5, 148.4, 139.0, 137.4, 129.8, 129.0, 128.6, 127.2, 122.8, 62.3, 14.3. HRMS ESI+ (m/z): [M + H]$^+$ calcd for $C_{14}H_{13}ClNO_2$ 262.06291; found 262.0629.

2-Phenyl-3-chloropyridine. 2,3-Dichloropyridine (500 mg, 3.38 mmol, 1.0 equiv), phenylboronic acid (494 mg, 4.05 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (98 mg, 0.085 mmol, 0.025 equiv), and potassium fluoride (648 mg, 11.15 mmol, 3.3 equiv) were combined in a Schlenk flask equipped with a magnetic stir bar. The flask was evacuated and backfilled with nitrogen three times. Toluene (10.5 mL, purged with N_2) was added, and the mixture was refluxed at 120 °C for 12 h. Upon cooling, the mixture was diluted with ethyl acetate and transferred to a separatory funnel. The organic layer was washed with water (2 × 50 mL) and brine (1 × 50 mL), dried over sodium sulfate, and concentrated in vacuo. The residue was purified by flash column chromatography using a gradient elution of 0−20% EtOAc in hexanes to provide the product as a colorless oil (396 mg, 62% yield, R_f = 0.65 in 70% hexanes/30% Et_2O). The ^{1}H and ^{13}C NMR spectroscopic data match that reported in the literature.[15]

3-Chloro-6-phenylpicolinonitrile. To a 125 mL round bottomed flask were added potassium fluoride (1.46 g, 18.9 mmol), H_2O (13 mL), MeCN (50 mL), 3,6-dichloro-2-pyridinecarbonitrile (1.45 g, 8.4 mmol), and phenylboronic acid (1.54 g, 12.6 mmol). The resulting colorless solution was sparged with N_2 for 20 min, and then bis(triphenylphosphine)palladium dichloride (296 mg, 0.44 mmol) was added. The yellow solution was sparged for 15 min and then heated to 40 °C for 24 h. The mixture was then cooled to room temperature and diluted with H_2O (30 mL) and EtOAc (100 mL). The layers were separated, and the aqueous layer extracted with EtOAc (2 × 50 mL). The organic layers were combined, and SiO_2 (35 g) was added. The solvent was removed under vacuum, and the crude product was purified by semiautomated silica gel chromatography (column: RediSep Silica 330 g; mobile phase: hexanes/EtOAc (with 0.1% Et_3N) gradient elution from 0% to 15% EtOAc (with 0.1% Et_3N); flow rate: 200 mL/min) to give a white solid (1.32 g, 73% yield, mp = 99−101 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01−7.99 (m, 2H), 7.89 (d, J = 0.4 Hz, 2H), 7.52−7.48 (m, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.0, 138.3, 136.2, 134.1, 132.9, 130.6, 129.2, 127.1, 124.2, 115.0. IR (cm^{-1}): 3077, 3061, 2239, 1573, 1547, 1451, 1434, 1364, 1304, 1251, 1185, 1159, 1076, 1040, 840, 773, 744, 698, 692, 650, 606. HRMS calcd for $C_{12}H_7ClN_2$ [M + H]$^+$: 215.0376; found 215.0388.

4,5-Dichloro-6-phenylpicolinonitrile. To a 125 mL round bottomed flask were added potassium fluoride (4.20 g, 72.3 mmol), H_2O (20 mL), MeCN (60 mL), 4,5,6-trichloro-2-pyridinecarbonitrile (5.00 g, 24.1 mmol), and phenylboronic acid (4.41 g, 36.2 mmol). The resulting colorless solution was sparged with N_2 for 20 min, and then bis(triphenylphosphine)palladium(II) chloride (845 mg, 1.2 mmol) was added. The yellow solution was sparged for 15 min and then heated to 45 °C for 21 h. To the reaction mixture were added additional phenylboronic acid (200 mg, 1.64 mmol) and additional bis(triphenylphosphine)palladium dichloride (35 mg, 0.05 mmol). The mixture was then stirred for an additional 4 h at 45 °C. The mixture was allowed to cool to room temperature and then diluted with H_2O (75 mL) and EtOAc (150 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 60 mL). The organic layers were combined, and SiO_2 (58 g) added. The solvent was removed under vacuum, and the crude product was purified by semiautomated silica gel chromatography (column: RediSep Silica 330 g; mobile phase: hexanes/EtOAc (0.1% Et_3N) gradient elution from 0% to 15% EtOAc (0.1% Et_3N); flow rate: 200 mL/min) to give a white solid (5.38 g, 90% yield, mp = 100−103 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.71−7.68 (m, 2H), 7.52−7.49 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.4, 144.9, 136.5, 133.4, 131.4, 130.2, 129.4, 128.4, 128.1, 115.8. IR (cm^{-1}): 3107, 3054, 2245 1532, 1497, 1450, 1283, 1159, 1123, 1037, 902, 885, 815, 778, 778, 744, 686, 641, 599. HRMS calcd for $C_{12}H_6Cl_2N_2$ [M + H]$^+$: 248.9986; found 248.9996.

4,5-Dichloro-6-(4-chlorophenyl)picolinonitrile. To a 125 mL round bottomed flask were added potassium fluoride (840 mg, 14.5 mmol), H_2O (5 mL), MeCN (20 mL), 4,5,6-trichloro-2-pyridine-carbonitrile (1.00 g, 4.82 mmol), and 4-chlorophenyboronic acid (1.13 g, 7.23 mmol). The resulting colorless solution was sparged with N_2 for 20 min, and then bis(triphenylphosphine)palladium dichloride (169 mg, 0.24 mmol) was added. The yellow solution was sparged for 15 min and then heated to 40 °C for 21 h. The mixture was allowed to cool to room temperature and then was diluted with H_2O (25 mL) and EtOAc (75 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 25 mL). The organic layers were combined, and SiO_2 (18.2 g) was added. The solvent was removed under vacuum, and the crude product was purified by semiautomated silica gel chromatography (column: RediSep Silica 120 g; mobile phase: hexanes/EtOAc (0.1% Et_3N) gradient elution from 0% to 25% EtOAc (0.1% Et_3N); flow rate: 85 mL/min) to give a white solid (0.99 g, 72% yield, mp = 132−134 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.67 (dt, J = 8.8, 2.2 Hz, 2H), 7.48 (dt, J = 8.6, 2.2 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.1, 145.2, 136.6, 134.8, 133.3, 131.5, 131.0, 128.7, 128.3, 115.7. IR (cm^{-1}): 3110, 3061, 2235, 1593, 1533, 1489, 1371, 1323, 1286, 1217, 1159, 1371, 1323, 1286, 1217, 1159, 1124, 1090, 1040, 1031, 1019, 903, 883, 820, 760, 717, 640, 604, 586. HRMS calcd for $C_{12}H_5Cl_3N_2$ [M + H]$^+$: 282.9597; found 282.9607.

General Procedures for Fluorination Reactions. *General Procedure A: Experimental Details for Fluorination Reactions Reported in Table 1.* In a drybox, tetrabutylammonium cyanide (TBACN) was weighed into a 4 mL vial (Vial 1). DMSO (0.5 mL) was added, and the mixture was stirred at room temperature until all of the TBACN dissolved (<5 min). Hexafluorobenzene (0.167 equiv with respect to TBACN) was then added, resulting in a rapid color change from light yellow to dark red/brown. This solution was stirred at room temperature for 1 h. Substrate **1** (0.1 mmol, 1.0 equiv) was weighed into a separate 4 mL vial equipped with a micro stirbar, and the appropriate amount of preformed anhydrous TBAF from vial 1 (0.5−4.0 equiv) was added via syringe. The reaction vial was sealed

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with a Teflon-lined cap, removed from the drybox, and stirred at room temperature for the indicated time. The reaction was then diluted with dichloromethane (2.5 mL), and an internal standard (trifluorotoluene, 10 mL, 0.081 mmol, 0.81 equiv) was added. An aliquot (~0.6 mL) was removed for analysis by ^{19}F NMR spectroscopy.

General Procedure B: Experimental Details for Fluorination Reactions Reported in Table 2. In a drybox, substrate **1** (0.1 mmol, 1.0 equiv) and tetrabutylammonium cyanide (0.2 mmol, 2.0 equiv) were combined in a 4 mL vial equipped with a micro stir bar. Solvent (0.5 mL) was added, and the mixture was stirred at room temperature until all of the solids dissolved (<5 min). Hexafluorobenzene (3.8 μL, 0.033 mmol, 0.33 equiv) was then added via microliter syringe, resulting in a rapid color change from light yellow to dark red/brown. The reaction vial was sealed with a Teflon-lined cap, removed from the drybox, and stirred at room temperature for the indicated time. The reaction was then diluted with dichloromethane (2.5 mL), and internal standards (both trifluorotoluene, 10 mL, 0.081 mmol, 0.81 equiv and 2-phenylpyridine, 14.3 mL, 0.1 mmol, 1.0 equiv) were added. An aliquot (~0.6 mL) was removed for analysis by both ^{19}F NMR spectroscopy and gas chromatography. The reaction with NBu_3MeCN (entry 4) was carried out on a slightly larger scale (0.18 mmol of **1**, 0.36 mmol NBu_3MeCN, 0.06 mmol C_6F_6, 0.75 mL DMSO) but under otherwise identical conditions.

General Procedure C: Experimental Details for Isolated Yields Reported in Table 3. In a drybox, tetrabutylammonium cyanide (268 or 536 mg, 1.0 or 2.0 mmol, 2.0 or 4.0 equiv) was weighed into 4 mL vial equipped with a micro stir bar. DMSO (2.5 mL) was added, and the mixture was stirred at room temperature until all of the solids dissolved (<5 min). Hexafluorobenzene (31 or 63 mg, 0.17 or 0.33 mmol, 0.33 or 0.67 equiv) was then added, resulting in a rapid color change from light yellow to dark red/brown. The reaction mixture was stirred at room temperature for ~5 min. The appropriate chloropyridine or chloroquinoline substrate (0.5 mmol, 1.0 equiv) was then added, and the reaction vial was sealed with a Teflon-lined cap, removed from the drybox, and stirred at room temperature for the indicated time. The reaction was then diluted with dichloromethane (~15 mL) and transferred to a separatory funnel. The organic layer was washed with water (3 × 25 mL) and brine (1 × 25 mL), dried over sodium sulfate, and concentrated in vacuo. The crude mixture was purified by flash column chromatography using gradients of hexanes and either diethyl ether or ethyl acetate as eluent.

General Procedure D: General Experimental Details for NMR Yields Reported in Table 3. In a drybox, tetrabutylammonium cyanide (54 or 108 mg, 0.2 or 0.4 mmol, 2.0 or 4.0 equiv) was weighed into 4 mL vial equipped containing a micro stir bar. DMSO (0.5 mL) was added, and the mixture was stirred at room temperature until all of the solids dissolved (<5 min). Hexafluorobenzene (6.1 or 12.4 mg, 0.033 or 0.066 mmol, 0.33 or 0.67 equiv) was then added, resulting in a rapid color change from light yellow to dark red/brown. The reaction mixture was stirred at room temperature for 5 min. The appropriate chloropyridine or chloroquinoline substrate (0.1 mmol, 1.0 equiv) was then added, and the reaction vial was sealed with a Teflon-lined cap, removed from the drybox, and stirred at room temperature for the indicated time. The reaction was then diluted with dichloromethane (2.5 mL), and an internal standard (trifluorotoluene, 10 mL, 0.81 equiv) was added. An aliquot (~0.6 mL) was removed for analysis by ^{19}F NMR spectroscopy.

Product Synthesis and Characterization. *Isopropyl 5-Fluoro-6-phenylpicolinate (**2**).* General procedure C was followed using isopropyl 5-chloro-6-phenylpicolinate (**1**) (138 mg, 0.5 mmol, 1 equiv) with a reaction time of 24 h, providing **2** as a colorless oil (121 mg, 91% yield, R_f = 0.61 in 70% hexanes/30% Et_2O). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.05−8.03 (multiple peaks, 3H), 7.54 (dd, J = 10.5, 8.4 Hz, 1H), 7.49−7.46 (m, 2H), 7.45−7.42 (m, 1H) 5.31 (septet, J = 6.3 Hz, 1H), 1.41 (d, J = 6.3 Hz, 6H). ^{13}C NMR (700 MHz, $CDCl_3$) δ 163.7, 159.0 (d, J = 270 Hz), 146.2 (d, J = 11 Hz), 144.4 (d, J = 4.0 Hz), 134.5 (d, J = 5.0 Hz), 129.6, 129.0 (d, J = 6.0 Hz), 128.4, 125.3 (d, J = 6.0 Hz), 124.5 (d, J = 21 Hz), 69.3, 21.8. ^{19}F NMR (470 MHz, $CDCl_3$) δ −117.8 (m). IR (cm^{-1}): 1734, 1712, 1463, 1438, 1358, 1313, 1285, 1213, 1138, 1101, 1052, 909, 795, 723, 692. HRMS ESI$^+$ (m/z): $[M + H]^+$ calcd for $C_{15}H_{15}FNO_2$ 260.1081; found 260.1084.

*Isopropyl 5-Fluoropicolinate (**3**).* General procedure C was followed using isopropyl 5-chloropicolinate (100 mg, 0.5 mmol, 1.0 equiv) with a reaction time of 24 h, providing **3** as a white solid (78 mg, 85% yield, R_f = 0.44 in 70% hexanes/30% Et_2O, mp = 36−38 °C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.60 (d, J = 2.8 Hz, 1H), 8.17 (dd, J = 8.4, 4.2 Hz, 1H), 7.51 (ddd, J = 8.4, 8.4, 2.8 Hz, 1H), 5.33 (septet, J = 6.3 Hz, 1H), 1.42 (d, J = 6.3 Hz, 6H). ^{13}C NMR (700 MHz, $CDCl_3$): 163.6, 161.0 (d, J = 160 Hz), 144.8 (d, J = 4.0 Hz), 138.4 (d, J = 25 Hz), 126.8 (d, J = 5.0 Hz), 123.3 (d, J = 19 Hz), 69.7, 21.8. ^{19}F NMR (470 MHz, $CDCl_3$) δ −120.40 (m). IR (cm^{-1}): 1716, 1584, 1480, 1374, 1353, 1294, 1227, 1137, 1100, 908, 856, 725, 697. HRMS ESI+ (m/z): $[M + Na]^+$ calcd for $C_9H_{10}FNO_2Na$ 206.0588; found 206.0589.

*Methyl 5-Fluoropicolinate (**4**).* General procedure C was followed using methyl 5-chloropicolinate (86 mg, 0.5 mmol, 1.0 equiv) with a reaction time of 24 h, providing **4** as a white solid (55 mg, 71% yield, R_f = 0.29 in 70% hexanes/30% Et_2O, mp = 30−32 °C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.55 (d, J = 2.8 Hz, 1H), 8.16 (dd, J = 8.4, 4.9 Hz, 1H), 7.50 (ddd, J = 8.4, 8.4, 2.8 Hz, 1H), 3.97 (s, 3H). ^{13}C NMR (700 MHz, $CDCl_3$) δ 164.5, 161.1 (d, J = 260 Hz), 144.1 (d, J = 4.0 Hz), 138.5 (d, J = 24 Hz), 126.9 (d, J = 5.0 Hz), 123.5 (d, J = 18 Hz), 53.0. ^{19}F NMR (470 MHz, $CDCl_3$) δ −119.73 (m). IR (cm^{-1}): 2362, 2337, 1717, 1700, 1653, 1559, 1437, 1314, 1228, 1197, 1129, 1100, 854, 790, 692. HRMS ESI+ (m/z): $[M + H]^+$ calcd for $C_7H_7FNO_2$ 156.0455; found 156.0454.

*Ethyl 3-Fluoro-6-phenylpicolinate (**5**).* General procedure C was followed using ethyl 3-chloro-6-phenylpicolinate (125 mg, 0.5 mmol, 1 equiv) with a reaction time of 24 h, providing **5** as a colorless oil (80 mg, 65% yield, R_f = 0.49 in 70% hexanes/30% Et_2O). ^{1}H NMR (700 MHz, $CDCl_3$): 7.99 (m, 2H), 7.88 (dd, J = 8.7, 3.4 Hz, 1H), 7.58 (dd, J = 9.5, 8.7 Hz, 1H), 7.47 (m, 2H) 7.42 (m, 1H), 4.50 (q, J = 7.1 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H). ^{13}C NMR (700 MHz, $CDCl_3$) δ 163.4, 158.3 (d, J = 270 Hz), 153.4 (d, J = 4.0 Hz), 137.5, 136.8 (d, J = 10 Hz), 129.3, 128.8, 127.0, 126.0 (d, J = 21 Hz), 124.7 (d, J = 5.0 Hz), 62.0, 14.2. ^{19}F NMR (470 MHz, $CDCl_3$) δ −121.96 (m). IR (cm^{-1}): 1729, 1459, 1313, 1254, 1216, 1094, 907, 725, 692. HRMS ESI+ (m/z): $[M + H]^+$ calcd for $C_{14}H_{13}FNO_2$ 246.0925; found 246.0926.

*Isopropyl 4,5-Difluoro-6-phenylpicolinate (**6**).* General procedure C was followed using isopropyl 4,5-difluoro-6-phenylpicolinate (155 mg, 0.5 mmol, 1.0 equiv) with a reaction time of 24 h, providing **6** as a colorless oil (88 mg, 63% yield, R_f = 0.75 in 70% hexanes/30% Et_2O). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.04 (m, 2H), 7.89 (dd, J = 9.4, 5.2 Hz, 1H), 7.53−7.45 (multiple peaks, 3H), 5.31 (septet, J = 6.3 Hz, 1H), 1.42 (d, J = 6.3 Hz, 6H). ^{13}C NMR (700 MHz, $CDCl_3$) δ 162.8 (d, J = 4.0 Hz), 156.7 (dd, J = 260, 12 Hz), 148.5 (d, J = 8.0 Hz), 148.0 (dd, J = 270, 10 Hz), 145.4 (t, J = 6.0 Hz), 133.8 (dd, J = 5.0, 3.0 Hz), 130.1, 129.0 (d, J = 6.0 Hz), 128.6, 113.5 (d, J = 16 Hz), 70.1, 21.8. ^{19}F NMR (470 MHz, $CDCl_3$) δ −125.2 (m), −144.7 (m). IR (cm^{-1}): 1742, 1714, 1605, 1576, 1471, 1435, 1417, 1371, 1226, 1135, 1094, 974, 909, 879, 730, 713, 690. HRMS ESI+ (m/z): $[M + H]^+$ calcd for $C_{15}H_{14}F_2NO_2$ 278.0987; found 278.0992.

*Isopropyl 4,5-Difluoro-6-(p-methoxyphenyl)picolinate (**7**).* General procedure C was followed using isopropyl 4,5-dichloro-6-(*p*-methoxyphenyl)picolinate (170 mg, 0.5 mmol, 1.0 equiv) with a reaction time of 24 h, providing **7** as a colorless oil (90 mg, 57% yield, R_f = 0.56 in 70% hexanes/30% Et_2O). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.04 (m, 2H), 7.82 (dd, J = 9.4, 5.2 Hz, 1H), 7.00 (m, 2H), 5.29 (septet, J = 6.3 Hz, 1H), 3.86 (s, 3H), 1.41 (d, J = 6.3 Hz, 6H). ^{13}C NMR (700 MHz, $CDCl_3$) δ 162.9 (d, J = 3.0 Hz), 161.2, 156.6 (dd, J = 260, 13 Hz), 148.0 (d, J = 8.0 Hz), 147.7 (dd, J = 270, 11 Hz), 145.1 (t, J = 7.0 Hz), 130.4 (d, J = 7.0 Hz), 126.4 (dd, J = 6.0, 3.0 Hz), 114.0, 112.8 (d, J = 16 Hz), 70.0, 55.3, 21.8. ^{19}F NMR (470 MHz, $CDCl_3$) δ −125.7 (m), −145.3 (m). IR (cm^{-1}): 1741, 1714, 1598, 1517, 1464, 1411, 1371, 1222, 1179, 1133, 1107, 1091, 1029, 973, 880, 834, 786, 729, 697. HRMS ESI+ (m/z): $[M + H]^+$ calcd for $C_{16}H_{16}F_2NO_3$ 308.1093; found 308.1096.

*Isopropyl 4,5-Difluoro-6-(p-chlorophenyl)picolinate (**8**).* General procedure C was followed using isopropyl 4,5-dichloro-6-(*p*-

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chlorophenyl)picolinate (172 mg, 0.5 mmol, 1 equiv) with a reaction time of 24 h, providing **8** as a white solid (75 mg, 48% yield, R_f = 0.61 in 70% hexanes/30% Et_2O, mp = 46−48 °C). ^1H NMR (700 MHz, $CDCl_3$) δ 8.01 (m, 2 H), 7.90 (dd, J = 9.0, 4.9 Hz, 1 H), 7.48 (m, 2 H), 5.31 (septet, J = 5.6 Hz, 1 H), 1.42 (d, J = 6.3 Hz, 6 H). ^{13}C NMR (700 MHz, $CDCl_3$) δ 162.7 (d, J = 3.0 Hz), 156.7 (dd, J = 270, 13 Hz), 148.0 (dd, J = 270, 11 Hz), 147.0 (d J = 9.0 Hz), 145.5 (t, J = 7.0 Hz), 136.4, 132.2 (dd, J = 5.0, 3.0 Hz), 130.3 (d, J = 6.0 Hz), 128.9, 113.8 (d, J = 16 Hz), 70.2, 21.8. ^{19}F NMR (470 MHz, $CDCl_3$) δ −124.7 (m), −144.4 (m). IR (cm^{-1}): 1714, 1593, 1462, 1393, 1371, 1239, 1221, 1103, 1089, 1014, 974, 909, 877, 829, 788, 753, 736. HRMS ESI+ (m/z): $[M + H]^+$ calcd for $C_{15}H_{13}ClF_2NO_2$ 312.0601; found 312.0601.

*Ethyl 3,6-Difluoropicolinate (**9**).* General procedure C was followed using ethyl 3,6-dichloropicolinate (110 mg, 0.5 mmol, 1 equiv) with a reaction time of 24 h, providing **9** as a white solid (49 mg, 53% yield, R_f = 0.20 in 70% hexanes/30% Et_2O, mp = 24−27 °C). ^1H NMR (700 MHz, $CDCl_3$) δ 7.66 (app. td, J = 8.4, 5.6 Hz, 1H), 7.14 (ddd, J = 8.4, 4.2, 2.8, 1H), 4.43 (q, J = 7.0 Hz, 2H), 1.39 (t, J = 7.0 Hz, 3H). ^{13}C NMR (700 MHz, $CDCl_3$) δ 161.8 (d, J = 6.0 Hz), 157.7 (dd, J = 240, J = 6.0 Hz), 157.2 (dd, J = 270, 4.0 Hz), 133.5 (t, J = 13 Hz), 131.4 (dd, J = 24, 8.0 Hz), 115.3 (dd, J = 36, 6.0 Hz), 62.4, 14.2. ^{19}F NMR (470 MHz, $CDCl_3$) δ −69.4 (m), −122.5 (m). IR (cm^{-1}): 1729, 1459, 1418, 1228, 1084, 1018, 912, 834, 766, 722, 662. HRMS ESI+ (m/z): $[M + H]^+$ calcd for $C_8H_8F_2NO_2$ 188.0518; found 188.0518.

*2-Phenyl-3-fluoropyridine (**10**).* General procedure D was followed using 2-phenyl-3-chloropyridine (18.9 mg, 0.1 mmol, 1.0 equiv) with a reaction time of 60 h, providing **10** in 13% yield as determined by ^{19}F NMR spectroscopy. The identity of **10** was confirmed by synthesis of an authentic sample from arylation of 2-chloro-3-fluoropyridine with phenylboronic acid. ^1H and ^{13}C NMR data match those previously reported in the literature.[16] ^1H NMR (700 MHz, $CDCl_3$) δ 8.51 (dt, J = 4.5, 1.6 Hz, 1H), 8.01 (dt, J = 8.1, 1.4 Hz, 2H), 7.50 (td, J = 7.0, 1.6 Hz, 2H), 7.44 (m, 2H), 7.20 (ddd, J = 8.3, 4.5, 3.8 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 157.5 (d, J = 260.7 Hz), 146.2 (d, J = 10.2 Hz), 145.4 (d, J = 5.4 Hz), 135.4 (d, J = 5.6 Hz), 129.2, 128.8 (d, J = 5.7 Hz), 128.5, 124.0 (d, J = 20.6 Hz), 123.4 (d, J = 3.9 Hz). ^{19}F NMR (400 MHz, $CDCl_3$) δ −122.9 (m). IR (cm^{-1}): 1595, 1444, 1430, 1249, 1187, 1101, 907, 798, 728, 691. HRMS ESI+ (m/z): $[M + H]^+$ calcd for $C_{11}H_9FN$ 174.0714; found 174.0716.

*3-Fluoropyridine (**11**).* General procedure D was followed using 3-chloropyridine (9.7 mg, 0.1 mmol, 1.0 equiv) with a reaction time of 24 h. None of product **11** was detected by ^{19}F NMR spectroscopy in the crude reaction mixture by comparison to an authentic sample of **11** [^{19}F NMR (470 MHz, CH_2Cl_2) δ −128.1 (m)].

*3-Chloro-5-fluoropyridine (**12a**) and 3,5-Difluoropyridine (**12b**).* General procedure D was followed using 3,5-dichloropyridine (15 mg, 0.1 mmol, 1.0 equiv) with a reaction time of 24 h, providing **12a** in 7% yield as determined by ^{19}F NMR spectroscopy (none of product **12b** was detected). The same reaction was repeated with a reaction time of 60 h, providing the fluorinated products as a mixture of **12a** and **12b** in 54% and 5% yield as determined by ^{19}F NMR spectroscopy. The ^{19}F NMR spectral data for **12a** and **12b** matched those of authentic samples [**12a**, ^{19}F NMR (400 MHz, CH_2Cl_2) δ −126.5 (d, J = 8.3 Hz); **12b**, ^{19}F NMR (400 MHz, CH_2Cl_2) δ −124.9 (d, J = 8.6 Hz)].

*2-Fluoroquinoline (**13**).* General procedure C was followed using 2-chloroquinoline (82 mg, 0.5 mmol, 1 equiv) with a reaction time of 24 h, providing **13** as a colorless oil (61 mg, 83% yield, R_f = 0.50 in 70% hexanes/30% Et_2O). ^1H and ^{13}C experimental data match those reported in the literature.[17] ^1H NMR (700 MHz, $CDCl_3$) δ 8.19 (t, J = 8.4 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.80 (m, 1H), 7.70 (m, 1H), 7.50 (m, 1H), 7.03 (dd, J = 8.7, 2.8 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 161.2 (d, J = 242.1 Hz), 145.8 (d, J = 16.8 Hz), 142.0 (d, J = 10.0 Hz), 130.7, 128.1 (d, J = 1.2 Hz), 127.6, 126.9 (d, J = 1.9 Hz), 126.2 (d, J = 2.4 Hz), 110.0 (d, J = 42.4 Hz). ^{19}F NMR (400 MHz, $CDCl_3$) δ −61.7. IR (cm^{-1}): 1620, 1593, 1579, 1507, 1472, 1428, 1309, 1230, 1205, 1107, 967, 906, 815, 777, 753, 727, 705. HRMS ESI + (m/z): $[M + H]^+$ calcd for C_9H_7FN 148.0557; found 148.0554.

*1-Fluoroisoquinoline (**14**).* General procedure C was followed using 1-chloroisoquinoline (82 mg, 0.5 mmol, 1.0 equiv) with a reaction time of 24 h, providing **14** as a colorless oil (50 mg, 68% yield, R_f = 0.44 in 70% hexanes/30% Et_2O). ^1H and ^{13}C NMR experimental data match those reported in the literature.[13] ^1H NMR (700 MHz, $CDCl_3$) δ 8.16 (d, J = 8.3 Hz, 1H), 8.05 (m, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.76 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.52 (d, J = 5.7 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 160.0 (d, J = 246.5 Hz), 139.7 (d, J = 5.9 Hz), 139.3 (d, J = 16.1 Hz), 131.6, 128.0, 126.4 (d, J = 3.8 Hz), 123.2, 119.4 (d, J = 4.9 Hz), 117.8 (d, J = 32.4 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ −71.3 (s). IR (cm^{-1}): 1637, 1591, 1573, 1497, 1371, 1348, 1269, 1051, 819, 749, 720, 658. HRMS ESI+ (m/z): $[M + H]^+$ calcd for C_9H_7FN 148.0557; found 148.0554.

*4-Fluoro-7-(trifluoromethyl)quinoline (**15**).* General procedure C was followed using 4-chloro-7-(trifluoromethyl)quinoline (116 mg, 0.5 mmol, 1.0 equiv) with a reaction time of 24 h, providing **15** as a white solid (68 mg, 64% yield, R_f = 0.33 in 70% hexanes/30% Et_2O, mp = 54−56 °C). ^1H NMR (700 MHz, $CDCl_3$) δ 8.92 (ddd, J = 8.1, 5.0, 2.0 Hz, 1H), 8.39 (s, 1H), 8.16 (dd, J = 8.7, 2.8 Hz, 1H), 7.73 (dd, J = 8.7, 2.1 Hz, 1H), 7.17 (ddd, J = 9.4, 4.9, 2.1 Hz, 1H). ^{13}C NMR (700 MHz, $CDCl_3$) δ 164.9 (d, J = 170 Hz 152.9 (d, J = 8.0 Hz), 149.3 (d, J = 4.0 Hz), 132.3 (q, J = 33 Hz), 126.7 (quin, J = 4.0 Hz), 123.5 (q, J = 260 Hz), 122.5 (d, J = 2.0 Hz), 121.9 (d, J = 5.0 Hz), 121.1 (d, J = 120 Hz), 107.3 (d, J = 14 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.1 (s), −111.6 (m). IR (cm^{-1}): 1616, 1562, 1512, 1456, 1383, 1367, 1322, 1297, 1250, 1172, 1109, 1090, 904, 844, 831, 683. HRMS ESI+ (m/z): $[M + H]^+$ calcd for $C_{10}H_6F_4N$ 216.0431; found 216.0430.

*3-Fluoro-6-phenyl-2-pyridinecarbonitrile (**16**).* General procedure C was followed using 3-chloro-6-phenyl-2-pyridinecarbonitrile (680 mg, 3.15 mmol, 1.0 equiv) with a reaction time of 15 h. The mixture was purified by semiautomated silica gel chromatography. First purification (column: RediSep Silica 40 g; mobile phase: hexanes/EtOAc gradient elution from 0% to 10% EtOAc; flow rate: 40 mL/min) provided 249 mg of **16**. Remaining fractions were concentrated, and the residue was purified a second time by semiautomated silica gel chromatography (column: RediSep Silica 40 g; mobile phase: hexanes/EtOAc gradient elution from 0% to 4.8% EtOAc; flow rate: 40 mL/min) providing an additional 117 mg of **16** (total: 366 mg, 59% yield, mp = 114−115 °C). ^1H NMR (400 MHz, $CDCl_3$) δ) δ 7.99−7.95 (multiple peaks, 3H), 7.65 (dd, J = 9.0, 7.9 Hz, 1H), 7.52−7.45 (multiple peaks, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6 (d, J = 269.3 Hz), 155.4 (d, J = 4.3 Hz), 136.4, 130.2, 129.2, 127.0, 125.6 (d, J = 4.5 Hz), 125.4 (d, J = 18.2 Hz), 122.3 (d, J = 15.5 Hz), 113.3 (d, J = 5.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −119.7. IR (cm^{-1}): 3074, 2236, 1462, 1453, 1269, 1119, 776, 743. HRMS ESI+ (m/z): $[M + H]^+$ calcd for $C_{12}H_8FN_2$ 199.0666; found 199.0665.

*4,5-Difluoro-6-phenyl-2-pyridinecarbonitrile (**17**).* General procedure C was followed using 4,5-dichloro-6-phenyl-2-pyridinecarbonitrile (500 mg, 2.01 mmol, 1.0 equiv) with a reaction time of 24 h. The mixture was purified by semiautomated silica gel chromatography (column: RediSep Silica 80 g; mobile phase: hexanes/EtOAc gradient elution from 0% to 1.5% EtOAc; flow rate: 60 mL/min), providing **17** as a white solid (177 mg, 44% yield, mp = 73−74 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (m, 2H), δ 7.53 (multiple peaks, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (dd, J = 267.5, 13.0 Hz), 150.9 (dd, J = 8.8, 2.0 Hz), 148.3 (dd, J = 271.7, 10.5 Hz), 132.8 (dd, J = 5.2, 3.1 Hz), 131.1, 130.0 (dd, J = 8.9, 7.8 Hz), 129.1 (d, J = 6.2 Hz), 129.0, 117.1 (d, J = 17.6 Hz), 115.9 (d, J = 3.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.5 (d, J = 19.2 Hz), −141.3 (d, J = 19.1 Hz). IR (cm^{-1}): 3097, 2240, 1594, 1573, 1431, 1235, 977, 790. HRMS ESI+ (m/z): $[M + H]^+$ calcd for $C_{12}H_7F_2N_2$ 217.0572; found 217.0572.

*4,5-Difluoro-6-(p-chlorophenyl)-2-pyridinecarbonitrile (**18**).* General procedure C was followed using 4,5-dichloro-6-(4-chlorophenyl)-2-pyridinecarbonitrile (1.00 g, 3.54 mmol, 1.0 equiv) with a reaction time of 22 h. The mixture was purified by semiautomated silica gel chromatography (column: RediSep Silica 80 g; mobile phase: hexanes/EtOAc gradient elution from 0% to 2.1% EtOAc; flow rate: 60 mL/min)providing **18** as a white solid (333 mg, 38% yield, mp = 88−89 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2H), 7.54 (dd, J = 8.2, 5.0 Hz, 1H), 7.49 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (dd, J = 267.8, 13.1 Hz), 150.0−146.6 (m, 2 carbons), 137.6, 131.1 (dd, J = 5.4, 3.2 Hz), 130.4 (d, J = 6.7 Hz), 130.1 (dd, J = 9.0,

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7.7 Hz), 129.3, 117.29 (d, J = 17.5 Hz), 115.7 (d, J = 3.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.0 (d, J = 19.1 Hz), −140.9 (d, J = 19.1 Hz). IR (cm^{-1}): 3075, 2246, 1738, 1596, 1583, 1461, 1237, 1092, 980, 843. HRMS ESI+ (m/z): $[M + H]^+$ calcd for $C_{12}H_6ClF_2N_2$ 251.0182; found 251.0185.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectral data for all new substrates and for isolated products **2**−**17**. 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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