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Multiple Approaches to the In Situ Generation of Anhydrous Tetraalkylammonium Fluoride Salts for S_NAr Fluorination Reactions

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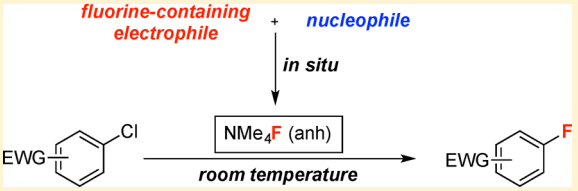
Supporting Information

ABSTRACT: This article focuses on the development of practical approaches to the in situ generation of anhydrous fluoride salts for applications in nucleophilic aromatic substitution (S_NAr) reactions. We report herein that a variety of combinations of inexpensive nucleophiles (e.g., tetraalkylammonium cyanide and phenoxide salts) and fluorine-containing electrophiles (e.g., acid fluoride, fluoroformate, benzenesulfonyl fluoride, and aryl fluorosulfonate derivatives) are effective for this transformation. Ultimately, we demonstrate that the combination of tetramethylammonium 2,6-dimethylphenoxide and sulfuryl fluoride (SO_2F_2) serves as a particularly practical route to anhydrous tetramethylammonium fluoride. This procedure is applied to the S_NAr fluorination of a range of electron-deficient aryl and heteroaryl chlorides as well as nitroarenes.



INTRODUCTION

Fluorinated arenes and heteroarenes appear in a variety of pharmaceuticals and agrochemicals.[1] In many cases, the replacement of a C−H bond with a C−F bond is used to increase the bioavailability, metabolic stability, and/or lipophilicity of these biologically active molecules.[2] However, despite their prevalence, many aryl and heteroaryl fluorides remain challenging to synthesize, particularly under mild conditions and with inexpensive reagents.

One of the most common methods for the formation of aryl fluorides is nucleophilic aromatic substitution (S_NAr fluorination). These transformations typically involve the reaction of an aryl chloride or nitroarene with an alkali metal fluoride salt (MF).[3,4] Elevated temperatures (>100 °C) and long reaction times are often required,[5] mainly due to the low solubility of MF under the anhydrous reaction conditions.[6] This can result in poor functional group tolerance and undesired side reactions. As such, significant recent effort has focused on developing inexpensive and practical routes to more soluble anhydrous fluoride sources for S_NAr fluorination reactions (Scheme 1a).

Tetraalkylammonium fluoride salts are attractive targets as anhydrous fluoride sources for this application.[7−10] However, these salts are generally synthesized under aqueous conditions, resulting in strongly hydrated (and thus weakly nucleophilic) NR_4F.[11] Furthermore, the elevated temperatures required to dehydrate $NR_4F{\cdot}(H_2O)_n$ often lead to decomposition via E_2 or S_N2 reactions of the NR_4 cation.[11,12] In an effort to address these challenges, DiMagno pioneered the in situ formation of anhydrous NR_4F starting from a tetraalkylammonium nucleophile and a fluorine-containing electrophile.[13] As shown in Scheme 1b, DiMagno's original report involved the combination of tetrabutylammonium cyanide (NBu_4CN) and hexafluorobenzene (C_6F_6) to generate anhydrous NBu_4F at room temperature. This reagent proved highly reactive for the S_NAr fluorination of electron-deficient aryl chlorides and nitroarenes.[13,14] However, widespread application of this method remains limited by both cost (C_6F_6) and toxicity (NBu_4CN) considerations.

Our overall objective is to develop more practical and potentially scalable approaches to the in situ generation of anhydrous fluoride salts for S_NAr reactions (Scheme 1c). We report herein that a variety of combinations of inexpensive nucleophiles and fluorine-containing electrophiles are effective for this transformation. Ultimately, we demonstrate that the reaction of tetramethylammonium 2,6-dimethylphenoxide with sulfuryl fluoride (SO_2F_2) serves as a particularly practical route to anhydrous tetramethylammonium fluoride (NMe_4F). This procedure is applied to the in situ generation of NMe_4F and subsequent S_NAr fluorination of a range of electron-deficient aryl and heteroaryl chlorides as well as nitroarenes.

RESULTS AND DISCUSSION

The 5-chloropicolinate **1-Cl** was selected as a model S_NAr substrate for our initial investigations. The resulting fluorinated product **1-F** is a close analogue of several agrochemicals.[15] Furthermore, **1-Cl** has been used as a substrate for our previous studies of S_NAr fluorination,[8,14,16,17] thus enabling a direct comparison to the current systems. We first evaluated the S_NAr fluorination of **1-Cl** using the combination of acid fluoride **A-1** and a variety of neutral nucleophiles, which were expected to form fluoride salts of general structure **B** (Table 1).[16,18] For the initial screening, equimolar quantities of the acid fluoride **A-1** and the nucleophile were combined in anhydrous DMF, and

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Scheme 1. Methods for the In Situ Generation of Anhydrous Fluoride for S_NAr Fluorination

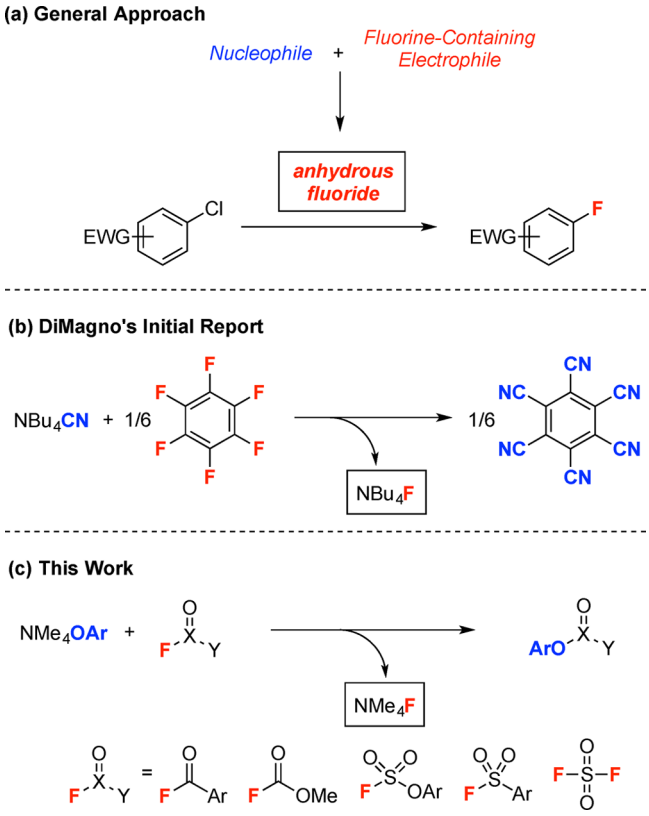
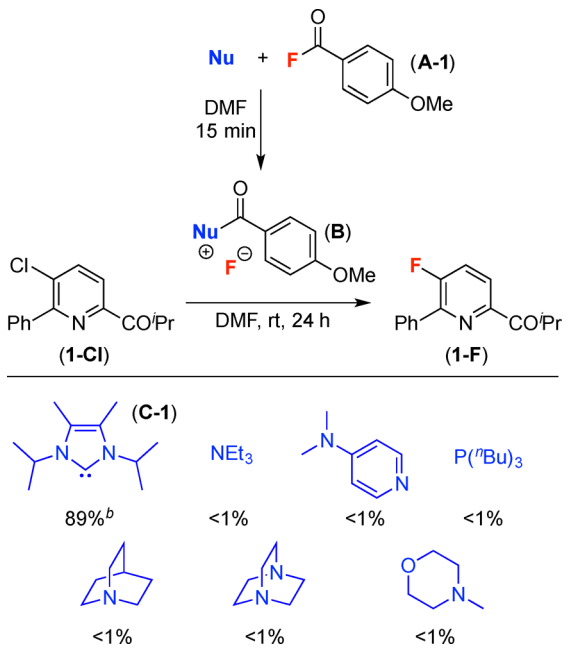


Table 1. Reaction of A-1 with Neutral Nucleophiles To Generate Anhydrous Fluoride for the S_NAr Fluorination of 1-Cl[a]

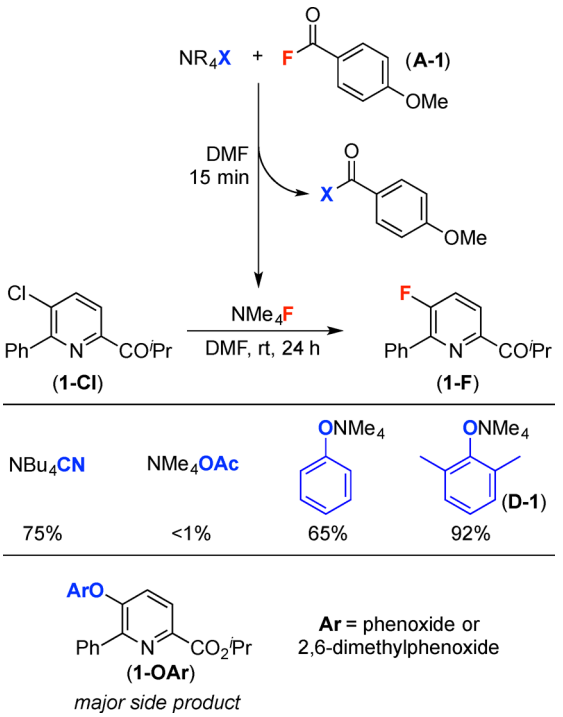


[a]Conditions: **A-1** (2 equiv) and nucleophile (2 equiv) stirred in DMF for 15 min at rt; **1-Cl** (1 equiv) added and stirred for an additional 24 h at rt. Yield of **1-F** determined by ^{19}F NMR spectroscopy. [b]Yield from ref 16.

this mixture was allowed to stir for 15 min. Substrate **1-Cl** was then added, and the reaction was stirred at room temperature for an additional 24 h and then analyzed by ^{19}F NMR spectroscopy to determine the yield of **1-F**. Among the nucleophiles examined, only the N-heterocyclic carbene **C-1** formed a reactive fluorinating reagent under these conditions,[19] affording 89% yield of **1-F**.[16] In contrast, <1% of **1-F** was formed using the amine, phosphine, and pyridine derivatives in Table 1. In all these systems, significant quantities of acid fluoride (>90%) remained at the end of the reaction, suggesting that very little of **B** is formed.

We next examined the reactions of **A-1** with tetraalkylammonium (NR_4) salts of anionic nucleophiles in an effort to form anhydrous NR_4F (Table 2). This in situ generated

Table 2. Reaction of A-1 with Anionic Nucleophiles To Generate Anhydrous NR_4F for the S_NAr Fluorination of 1-Cl[a]



[a]Conditions: **A-1** (2 equiv) and nucleophile (2 equiv) stirred in DMF for 15 min at rt; then **1-Cl** (1 equiv) added and reaction stirred for an additional 24 h at rt. Yields of **1-F** determined by ^{19}F NMR spectroscopy.

fluoride was then utilized for the S_NAr fluorination of **1-Cl**. Whereas NMe_4OAc was ineffective for this transformation, the more nucleophilic salts NBu_4CN and NMe_4OPh led to 75 and 65% yield of **1-F**, respectively. In the latter transformation, the major side product was **1-OPh**, which results from an S_NAr reaction between the residual nucleophile and either the starting material **1-Cl** or the fluorinated product **1-F**.[20] We hypothesized that this side product could be limited (and thus the yield of **1-F** could be improved) through the use of a more hindered phenoxide. Indeed, under otherwise identical conditions, tetramethylammonium 2,6-dimethylphenoxide (**D-1**) afforded 92% yield of **1-F**, along with <10% of **1-OAr** (Ar = 2,6-dimethylphenoxide).[21] The formation of **1-OAr** could be further minimized by changing the ratio of **A-1** to 2,6-dimethylphenoxide from 1:1 to 1.3:1. Using these optimized

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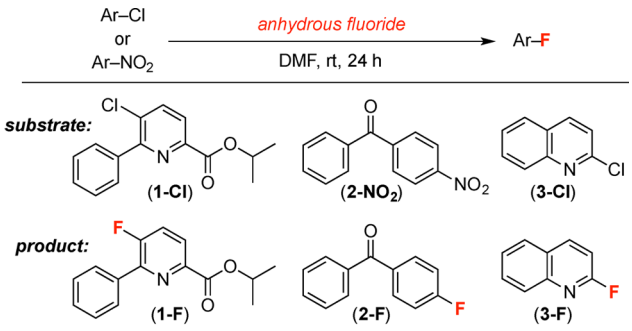
conditions, **1-OAr** was not detected, and product **1-F** was formed in >95% yield as determined by ^{19}F NMR spectroscopy and isolated in 89% yield.

We next applied the combination of **A-1** and tetramethylammonium 2,6-dimethylphenoxide (**D-1**) to the S_NAr fluorination of several other substrates and compared the results to those reported in the literature (Table 3). As shown in Table 3, column 1, the S_NAr fluorination of **1-Cl** with **A-1**/**D-1** afforded an isolated yield comparable to that with the in situ generated acyl azolium fluoride (**B** with Nu = **C-1**)[16] or with isolated anhydrous NMe_4F[8] (89, 87, and 82% yield, respectively). These three methods also provided comparable isolated yields for the fluorodenitration of **2-NO$_2$** (column 2) as well as the halex fluorination of 2-chloroquinoline (**3-Cl**, column 3).

Table 3. Comparison with Other S_NAr Fluorination Methods



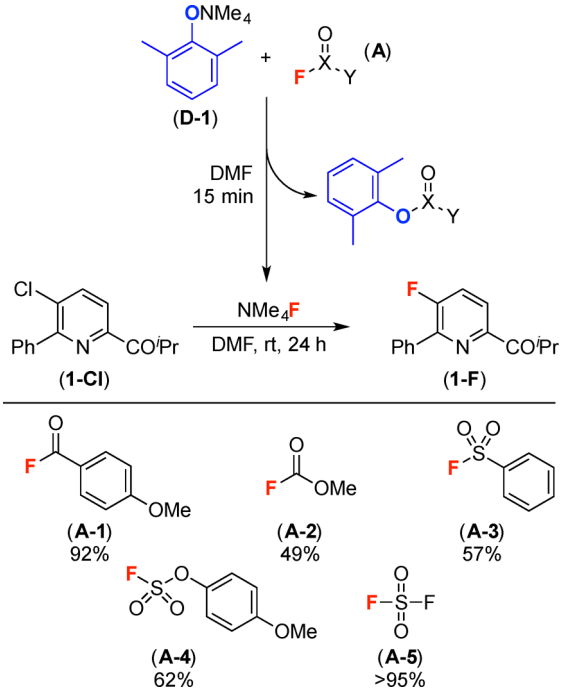
fluoride source			
A-1/**D-1**[a]	89%	76%	70%
A-1/**C-1**[b]	87%	86%	86%
NMe_4F[c]	82%	90%	70%

[a]Conditions: **A-1** (2 equiv) and **D-1** (1.5 equiv) stirred in DMF for 15 min at rt; then substrate (1 equiv) added and reaction stirred for a further 24 h at rt. Isolated yields are reported. [b]Isolated yields from ref 16. [c]Isolated yields from ref 8.

We next probed a series of fluorine-containing electrophiles that could react with tetramethylammonium 2,6-dimethylphenoxide (**D-1**) to release NMe_4F. These reactions were conducted by stirring 2 equiv of **A** and 2 equiv of **D-1** in DMF for 15 min at room temperature, followed by the addition of 1 equiv of **1-Cl**. As shown in Table 4, methyl fluoroformate (**A-2**), benzenesulfonyl fluoride (**A-3**),[22] and 4-methoxyphenyl sulfurofluoridate (**A-4**) were all effective precursors to anhydrous fluoride under these conditions, affording **1-F** in 49, 57, and 62% yield, respectively. However, the best results were obtained with sulfuryl fluoride (**A-5**), which afforded >95% yield of **1-F**.[23] This is a particularly significant result because sulfuryl fluoride is an inexpensive commercial insecticide that is produced on multi-ton scale annually.[24] As such, this method serves as a practical and potentially scalable route to anhydrous NMe_4F.

We next used the combination of tetramethylammonium 2,6-dimethylphenoxide (**D-1**) and sulfuryl fluoride (**A-5**) for the S_NAr fluorination of a variety of different substrates. Notably, in most cases, prestirring the tetramethylammonium 2,6-dimethylphenoxide and sulfuryl fluoride was found to be unnecessary. As such, the standard conditions involved combining 2 equiv of **D-1**, 3 equiv of **A-5**,[25] and 1 equiv of substrate in a single pot and then stirring for 24 h at room temperature. As summarized in Table 5, substrates **1-Cl**, **2-NO$_2$**, and **3-Cl** all reacted under our standard conditions to afford **1-F**, **2-F**, and **3-F** in 95, 91, and 81% isolated yield, respectively. Other heteroaryl chlorides, including quinolines **4-Cl** and **5-Cl** as well as pyridazine **6-Cl**, underwent S_NAr fluorination in 81, 75, and 74% isolated yield, respectively. This method was also effective for the S_NAr fluorination of aryl chlorides and nitroarenes bearing electron-withdrawing cyano (**7-Cl**, **9-NO$_2$**, and **11-NO$_2$**), ester (**8-NO$_2$**), and amide (**10-NO$_2$**) substituents. Finally, this method enabled the synthesis of 4-fluoro-*N*-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)-*N*-(pyridin-2-yl)benzamide (MPPF, **10-F**), a serotonin 1A receptor ligand, and 3-fluoro-5-(pyridin-2-ylethynyl)-benzonitrile (PEB-F, **11-F**), a metabotropic glutamate receptor subtype 5 ligand. Both of these are analogues to positron emission tomography (PET) radiotracers.

Table 4. Reaction of Different Fluorine-Containing Electrophiles A with D-1 To Generate Anhydrous NMe_4F for the S_NAr Fluorination of 1-Cl[a]



[a]Conditions: **A** (2 equiv) and **D-1** (2 equiv) stirred in DMF for 15 min at rt; then substrate (1 equiv) added and reaction stirred for a further 24 h at rt. Yields of **1-F** determined by ^{19}F NMR spectroscopy.

CONCLUSION

Overall, this report demonstrates that a variety of different combinations of nucleophiles and electrophilic fluorine sources can be used to generate anhydrous fluoride at room temperature. In particular, the combination of tetramethylammonium 2,6-dimethylphenoxide (**D-1**) and sulfuryl fluoride (**A-5**) rapidly generates anhydrous tetramethylammonium fluoride, which can then be employed for the S_NAr fluorination of a variety of different substrates. This method offers the advantages that it employs inexpensive, readily available reagents and that it is operationally straightforward. As such, we anticipate that it has the potential for applications in pharmaceutical and agrochemical syntheses.

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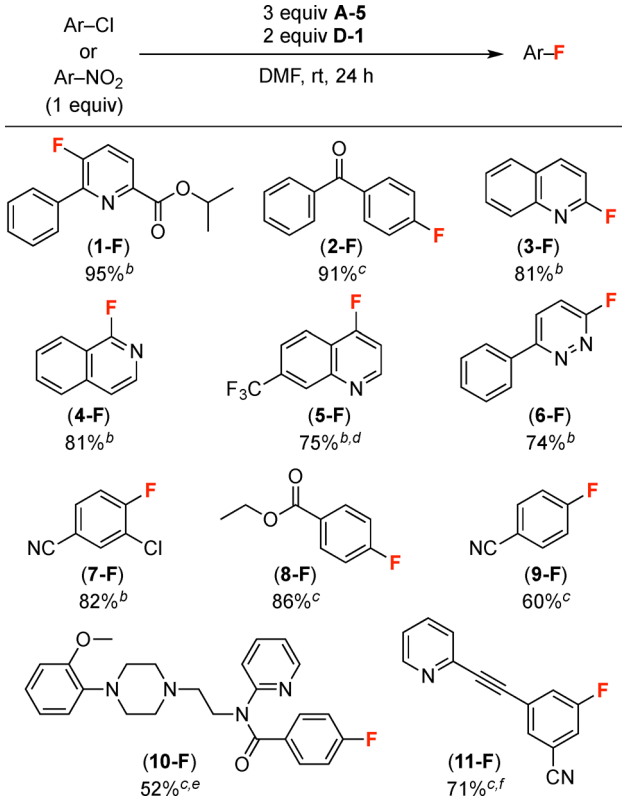
Table 5. Substrate Scope for S_NAr Fluorination with Tetramethylammonium 2,6-Dimethylphenoxide (D-1) and Sulfuryl Fluoride (A-5)[a]



[a]Conditions: **A-5** (3 equiv) in a DMF solution was added to the substrate (1 equiv) and **D-1** (2 equiv) and stirred for 24 h at rt. Isolated yields are reported. [b](Hetero)aryl chloride was used as the substrate. [c]Nitroarene was used as the substrate. [d]With 15 min prestir of **A-5**/**D-1** salt before substrate addition. [e]Conducted at 100 °C with 6 equiv of **A-5** and 4 equiv of **D-1**. [f]Conducted at 80 °C for 4 h.

EXPERIMENTAL SECTION

Materials and Methods. NMR spectra were obtained on a 400 MHz (400.52 MHz for ^{1}H, 376.87 MHz for ^{19}F, 100.71 MHz for ^{13}C) or a 500 MHz (500.01 MHz for ^{1}H, 470.56 MHz for ^{19}F, 125.75 MHz for ^{13}C) NMR spectrometer. ^{1}H, ^{19}F, and ^{13}C NMR chemical shifts are reported in parts per million (ppm) relative to the residual solvent peak ($CDCl_3$: ^{1}H δ 7.26 ppm, ^{13}C δ 77.16 ppm; DMSO-d_6: ^{1}H δ 2.50 ppm, ^{13}C δ 39.52 ppm). Multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), heptet (hept), multiplet (m), doublet of doublets (dd), double of doublet of doublets (ddd). Coupling constants (J) are reported in hertz (Hz). Melting points are uncorrected. High-resolution mass spectra were recorded on a Magnetic Sector mass spectrometer.

Commercial reagents and solvents were used as received unless otherwise stated. Anhydrous acetonitrile and anhydrous *N*,*N*-dimethylformamide were purchased from Alfa Aesar. Spray-dried potassium fluoride was received from The Dow Chemical Company. Sulfuryl fluoride was purchased from SynQuest Laboratories. 1,3-Diisopropyl-4,5-dimethyl-1*H*-imidazol-3-ium-2-ide,[16] isopropyl 5-chloro-6-phenylpicolinate,[14] 4-methoxyphenyl sulfurofluoridate,[26] *N*-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)-4-nitro-*N*-(pyridin-2-yl)-benzamide,[27] and 3-nitro-5-(pyridin-2-ylethynyl)benzonitrile[28] were prepared as previously described. Phenol and 2,6-dimethylphenol were purified by column chromatography before use. Nitroarenes and (hetero)aryl chlorides were dried under vacuum in the presence of P_2O_5 overnight before use. All fluorination reactions were set up in a drybox due to the sensitivity of this system to water.[8]

A 1.5 wt % solution of sulfuryl fluoride in DMF was prepared by bubbling sulfuryl fluoride through a 100 mL AcroSeal bottle of dry DMF for 15 min or until 1.5 g of sulfuryl fluoride was added. Excess sulfuryl fluoride was passed through a knockout pot containing an aqueous 1 M NaOH solution. **Caution: sulfuryl fluoride is a highly toxic gas.** As such, all preparations of sulfuryl fluoride solutions were carried out in a well-ventilated fume hood and in the presence of a sulfuryl fluoride detector.

*4-Methoxybenzoyl fluoride (**A-1**).* Spray-dried potassium fluoride (1.63 g, 28.1 mmol, 2 equiv) was suspended in anhydrous acetonitrile (10 mL). 4-Methoxybenzoyl chloride (1.9 mL, 14.0 mmol, 1 equiv) was added, and the reaction was stirred vigorously for 3 days. The reaction mixture was then filtered through a silica plug and concentrated in vacuo to yield the product as a clear oil (1.94 g, 90% yield, R_f = 0.60 in 5:1 pentane/diethyl ether). ^{1}H, ^{13}C, and ^{19}F NMR characterization data match those reported in the literature.[29] HRMS ESI (m/z): $[M]^+$ calcd for $C_8H_7FO_2$ 154.0430; found 154.0434.

Tetramethylammonium Phenoxide. Phenol (726 mg, 7.7 mmol, 1 equiv) was dissolved in water (5 mL). Tetramethylammonium hydroxide (25 wt % in H_2O, 2.8 g, 7.7 mmol, 1 equiv) was added, and the reaction was stirred for 1 min before the water was removed in vacuo. The resulting salt was dried at 70 °C under vacuum for 3 days and then overnight at room temperature in the presence of P_2O_5 to yield the product as an off-white solid (1.3 g, quantitative yield, mp = 69.5–70.8 °C). The salt was stored in a drybox. ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.78 (t, J = 7.5 Hz, 2H), 6.24 (d, J = 7.0 Hz, 2H), 6.03 (m, 1H), 3.10 (s, 12H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 169.0, 128.7, 118.0, 108.9, 55.28 (t, J = 3.9 Hz).

*Tetramethylammonium 2,6-Dimethylphenoxide (**D-1**).* Under a N_2 atmosphere, tetramethylammonium hydroxide (25 wt % in H_2O, 7.2 mL, 20 mmol, 1 equiv) was added to a round-bottom flask containing 2,6-dimethylphenol (2.5 g, 20 mmol, 1 equiv). The reaction was stirred until it became homogeneous, and then the water was removed in vacuo. The resulting salt was dried at 70 °C under vacuum for 3 days and then overnight at room temperature in the presence of P_2O_5 to yield the product as an off-white solid (3.8 g, 96% yield, mp = decomp). The salt was stored in a drybox. ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.54 (d, J = 7.0 Hz, 2H), 5.61 (t, J = 7.0 Hz, 1H), 3.09 (s, 12H), 1.88 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 170.1, 126.9, 123.1, 103.8, 51.5 (t, J = 3.9 Hz), 18.7. HRMS EI (m/z): $[M]^-$ calcd for C_8H_9O 121.0659, found 121.0655. HRMS EI (m/z): $[M]^+$ calcd for $C_4H_{12}N$ 74.0964, found 74.0969.

*Methyl Fluoroformate (**A-2**).* Spray-dried potassium fluoride (3.0 g, 52 mmol, 2 equiv) was suspended in anhydrous acetonitrile (12 mL). Methyl chloroformate (2.1 mL, 27 mmol, 1 equiv) was added, and the reaction was stirred vigorously for 4 days. The reaction mixture was filtered through a cotton pipet plug to remove most of the KCl byproduct. Distillation of the resulting solution at 90 °C under N_2 yielded the product as a 27 wt % solution in acetonitrile (2.44 g, 31% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.88 (s, 3H, **A-2**), 1.90 (s, 3H, MeCN). ^{13}C NMR (126 MHz, $CDCl_3$): δ 145.9 (d, J = 280.9 Hz, **A-2**), 116.5 (MeCN), 57.5 (**A-2**), 1.5 (MeCN). ^{19}F NMR (470 MHz, $CDCl_3$): δ −18.42 (s, 1 F). ^{19}F NMR characterization data match those reported in the literature.[30]

General Procedures of Fluorination Reactions. *General Procedure A: Reactions Reported in Tables 1 and 2.* In a drybox, 4-methoxybenzoyl fluoride (**A-1**, 0.2 mmol, 2 equiv), nucleophile (0.2 mmol, 2 equiv), and DMF (0.5 mL) were added to a 1 dram vial equipped with a stir bar. This mixture was stirred for 15 min at rt, and then **1-Cl** (0.1 mmol, 1 equiv) was added. The vial was sealed with a Teflon-lined cap and removed from the drybox, and then the reaction was stirred for 24 h at rt. The reaction was then diluted with dichloromethane, and a standard (25 μL of 4-fluoroanisole) was added. An aliquot was removed for analysis by ^{19}F NMR spectroscopy.

General Procedure B: Reactions Reported in Table 3. In a drybox, 4-methoxybenzoyl fluoride (**A-1**, 0.4 mmol, 2 equiv), tetramethylammonium 2,6-dimethylphenoxide (**D-1**, 0.3 mmol, 1.5 equiv), and DMF (1.0 mL) were combined in a 1 dram vial equipped with a stir bar. This mixture was stirred for 15 min at rt, and then the substrate (0.2

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mmol, 1 equiv) was added. The vial was sealed with a Teflon-lined cap and removed from the drybox, and then the reaction was stirred for 24 h at rt. The reaction mixture was diluted with diethyl ether (10 mL), and the organic layer was washed with water (3 × 10 mL), dried over magnesium sulfate, and concentrated in vacuo. The crude reaction mixture was purified by flash column chromatography on silica gel using a gradient of hexane and ethyl acetate or pentane and diethyl ether.

General Procedure C: Reactions Reported in Table 4. In a drybox, the fluoride source (**A**, 0.2 mmol, 2 equiv), **D-1** (0.2 mmol, 2 equiv), and DMF (0.5 mL) were combined in a 1 dram vial equipped with a stir bar. For the reaction with **A-5** (sulfuryl fluoride solution in DMF), no additional DMF was added. The reaction was stirred for 15 min at rt, and then **1-Cl** (0.1 mmol, 1 equiv) was added. The vial was sealed with a Teflon-lined cap and removed from the drybox, and the reaction was stirred for 24 h at rt. The reaction was then diluted with dichloromethane, and a standard (25 μL of 4-fluoroanisole) was added. An aliquot was removed for analysis by ^{19}F NMR spectroscopy.

General Procedure D: Reactions Reported in Table 5. In a drybox, substrate (0.2 mmol, 1 equiv), **D-1** (0.4 mmol, 2 equiv), and sulfuryl fluoride (**A-5**, 4.3 mL of a 0.14 M solution in DMF, 3 equiv) were added to a 2 dram vial equipped with a stir bar. The vial was sealed with a Teflon-lined cap and removed from the drybox, and the reaction was stirred for 24 h at rt. The reaction mixture was then diluted with diethyl ether (10 mL), and the organic layer was washed with water (3 × 10 mL), dried over magnesium sulfate, and concentrated in vacuo. The crude reaction mixture was purified by flash column chromatography on silica gel using a gradient of hexane and ethyl acetate or pentane and diethyl ether.

Product Synthesis and Characterization. *Isopropyl 5-Fluoro-6-phenylpicolinate (1-F).* General procedure B was followed using isopropyl 5-chloro-6-phenylpicolinate (**1-Cl**) (55.1 mg, 0.2 mmol, 1 equiv), **A-1** (62.2 mg, 0.4 mmol, 2 equiv), and **D-1** (58.8 mg, 0.3 mmol, 1.5 equiv), providing **1-F** as a colorless oil (45.1 mg, 87% yield, R_f = 0.40 in 5:1 pentane/diethyl ether). ^{1}H, ^{13}C, and ^{19}F NMR characterization data match those reported in the literature.[14] HRMS ESI (m/z): $[M + H]^+$ calcd for $C_{15}H_{15}FNO_2$ 260.1081, found 260.1082. The yield reported in Table 3 (89%) represents an average of two runs (87 and 90%).

General procedure D was followed using isopropyl 5-chloro-6-phenylpicolinate (**1-Cl**) (55.1 mg, 0.2 mmol, 1 equiv), **D-1** (78.0 mg, 0.4 mmol, 2 equiv), and **A-5** (4.3 mL of a 0.14 M solution in DMF, 3 equiv), providing **1-F** as a colorless oil (47.8 mg, 92% yield). The yield reported in Table 5 (95%) represents an average of two runs (92 and 98%).

4-Fluorobenzophenone (2-F). General procedure B was followed using 4-nitrobenzophenone (45.4 mg, 0.2 mmol, 1 equiv), **A-1** (61.7 mg, 0.4 mmol, 2 equiv), and **D-1** (58.7 mg, 0.3 mmol, 1.5 equiv), providing **2-F** as a white solid (29.5 mg, 74% yield, R_f = 0.63 in 5:1 pentane/diethyl ether, mp = 42.0–43.9 °C). ^{1}H, ^{13}C, and ^{19}F NMR characterization data match those reported in the literature.[16] HRMS ESI (m/z): $[M + H]^+$ calcd for $C_{13}H_{10}FO$ 201.0710, found 201.0712. The yield reported in Table 3 (76%) represents an average of two runs (74 and 77%).

General procedure D was followed using 4-nitrobenzophenone (45.6 mg, 0.2 mmol, 1 equiv), **D-1** (78.4 mg, 0.4 mmol, 2 equiv), and **A-5** (4.3 mL of a 0.14 M solution in DMF, 3 equiv), providing **2-F** as a white solid (31.8 mg, 89% yield). The yield reported in Table 5 (91%) represents an average of two runs (89 and 93%).

2-Fluoroquinoline (3-F). General procedure B was followed using 2-chloroquinoline (32.5 mg, 0.2 mmol, 1 equiv), **A-1** (62.8 mg, 0.4 mmol, 2 equiv), and **D-1** (58.9 mg, 0.3 mmol, 1.5 equiv), providing **3-F** as a colorless oil (19.3 mg, 66% yield, R_f = 0.51 in 5:1 pentane/diethyl ether). ^{1}H, ^{13}C, and ^{19}F NMR characterization data match those reported in the literature.[14] HRMS ESI (m/z): $[M + H]^+$ calcd for C_9H_7FN 148.0557, found 148.0557. The yield reported in Table 3 (70%) represents an average of two runs (66 and 73%).

General procedure D was followed using 2-chloroquinoline (32.8 mg, 0.2 mmol, 1 equiv), **D-1** (78.2 mg, 0.4 mmol, 2 equiv), and **A-5** (4.3 mL of a 0.14 M solution in DMF, 3 equiv), providing **3-F** as a colorless oil (23.0 mg, 78% yield). The yield reported in Table 5 (81%) represents an average of two runs (78 and 84%).

1-Fluoroisoquinoline (4-F). General procedure D was followed using 2-chloroisoquinoline (32.9 mg, 0.2 mmol, 1 equiv), **D-1** (78.5 mg, 0.4 mmol, 2 equiv), and **A-5** (4.3 mL of a 0.14 M solution in DMF, 3 equiv), providing **4-F** as a colorless oil (23.7 mg, 80% yield, R_f = 0.48 in 5:1 pentane/diethyl ether). ^{1}H, ^{13}C, and ^{19}F NMR characterization data match those reported in the literature.[16] HRMS ESI (m/z): $[M + H]^+$ calcd for C_9H_7FN 148.0557, found 148.0557. The yield reported in Table 5 (81%) represents an average of two runs (80 and 82%).

4-Fluoro-7-(trifluoromethyl)quinoline (5-F). General procedure D was followed, with the exception that **D-1** and **A-5** were stirred together at rt for 15 min prior to addition of **5-Cl**, using 4-chloro-7-(trifluoromethyl)quinoline (46.4 mg, 0.2 mmol, 1 equiv), **D-1** (78.4 mg, 0.4 mmol, 2 equiv), and **A-5** (4.3 mL of a 0.14 M solution in DMF, 3 equiv), providing **5-F** as a white solid (31.9 mg, 74% yield, R_f = 0.26 in 5:1 pentane/diethyl ether, mp = 81.6–82.3 °C). ^{1}H, ^{13}C, and ^{19}F NMR experimental data match those reported in the literature.[14] HRMS ESI (m/z): $[M + H]^+$ calcd for $C_{10}H_6F_4N$ 216.0431, found 216.0432. The yield reported in Table 5 (75%) represents an average of two runs (74 and 75%).

3-Fluoro-6-phenylpyridazine (6-F). General procedure D was followed using 3-chloro-6-phenylpyridazine (38.2 mg, 0.2 mmol, 1 equiv), **D-1** (78.1 mg, 0.4 mmol, 2 equiv), and **A-5** (4.3 mL of a 0.14 M solution in DMF, 3 equiv), providing **6-F** as a white solid (25.1 mg, 72% yield, R_f = 0.14 in 5:1 pentane/diethyl ether, mp = 127.2–128.4 °C). ^{1}H, ^{13}C, and ^{19}F NMR characterization data match those reported in the literature.[8] HRMS ESI (m/z): $[M + H]^+$ calcd for $C_{10}H_8FN_2$ 175.0666, found 175.0666. The yield reported in Table 5 (74%) represents an average of two runs (72 and 76%).

3-Chloro-4-Fluorobenzonitrile (7-F). General procedure D was followed using 3,4-dichlorobenzonitrile (34.6 mg, 0.2 mmol, 1 equiv), **D-1** (78.5 mg, 0.4 mmol, 2 equiv), and **A-5** (4.3 mL of a 0.14 M solution in DMF, 3 equiv), providing **7-F** as a white solid (24.8 mg, 79% yield, R_f = 0.57 in 5:1 pentane/diethyl ether, mp = 65.7–66.2 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (dd, J = 6.7, 2.0 Hz, 1H), 7.58 (ddd, J = 8.5, 4.3, 2.0 Hz, 1H), 7.27 (t, J = 8.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.9 (d, J = 259.0 Hz), 134.8, 132.7 (d, J = 8.5 Hz), 123.0 (d, J = 19.0 Hz), 118.0 (d, J = 22.6 Hz), 116.9, 109.7 (d, J = 4.4 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ −104.8 (m, 1F). HRMS EI (m/z): $[M]^+$ calcd for C_7H_3ClFN 154.9938, found 154.9943. The yield reported in Table 5 (82%) represents an average of two runs (79 and 85%).

Ethyl-4-fluorobenzoate (8-F). General procedure D was followed using ethyl-4-nitrobenzoate (39.1 mg, 0.2 mmol, 1 equiv), **D-1** (78.3 mg, 0.4 mmol, 2 equiv), and **A-5** (4.3 mL of a 0.14 M solution in DMF, 3 equiv), providing **8-F** as a colorless oil (30.1 mg, 89% yield, R_f = 0.71 in 5:1 pentane/diethyl ether). ^{1}H, ^{13}C, and ^{19}F NMR characterization data match those reported in the literature.[16] HRMS EI (m/z): $[M]^+$ calcd for $C_9H_9FO_2$ 168.0587, found 168.0594. The yield reported in Table 5 (86%) represents an average of two runs (89 and 82%).

4-Fluorobenzonitrile (9-F). General procedure D was followed using 4-nitrobenzonitrile (29.3 mg, 0.2 mmol, 1 equiv), **D-1** (78.0 mg, 0.4 mmol, 2 equiv), and **A-5** (4.3 mL of a 0.14 M solution in DMF, 3 equiv), providing **9-F** as a white solid (13.6 mg, 57% yield, R_f = 0.57 in 5:1 pentane/diethyl ether, mp = 32.7–33.3 °C). ^{1}H, ^{13}C, and ^{19}F NMR characterization data match those reported in the literature.[31] HRMS EI (m/z): $[M]^+$ calcd for C_7H_4FN 121.0328, found 121.0326. The yield reported in Table 5 (60%) represents an average of two runs (57 and 62%).

4-Fluoro-N-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)-N-(pyridin-2-yl)benzamide (10-F). General procedure D was followed using *N*-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)-4-nitro-*N*-(pyridin-2-yl)benzamide (46.3 mg, 0.1 mmol, 1 equiv), **D-1** (78.1 mg, 0.4 mmol, 4 equiv), and **A-5** (4.3 mL of a 0.14 M solution in DMF, 6 equiv). The reaction was heated to 100 °C for 24 h, and the workup was conducted using dichloromethane in place of diethyl ether (6 × 10 mL) to afford **10-F** as a brown oil (22.3 mg, 51% yield, R_f = 0.29 in

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J. Org. Chem. XXXX, XXX, XXX–XXX

diethyl ether). ^{1}H, ^{13}C, and ^{19}F NMR characterization data match those reported in the literature.[9] HRMS ESI (m/z): $[M + H]^+$ calcd for $C_{24}H_{28}FN_4O_2$ 435.2191, found 435.2190. The yield reported in Table 5 (52%) represents an average of two runs (51 and 53%).

3-Fluoro-5-(pyridin-2-ylethynyl)benzonitrile (11-F). General procedure D was followed using 3-nitro-5-(pyridin-2-ylethynyl)-benzonitrile (49.4 mg, 0.2 mmol, 1 equiv), **D-1** (78.1 mg, 0.4 mmol, 2 equiv), and **A-5** (4.3 mL of a 0.14 M solution in DMF, 3 equiv). The reaction was heated to 80 °C for 4 h and provided **11-F** as a white solid (30.0 mg, 68% yield, R_f = 0.80 in diethyl ether, mp = 95.7−96.7 °C). ^{1}H, ^{13}C, and ^{19}F NMR characterization data match those reported in the literature.[26,32] HRMS ESI (m/z): $[M + H]^+$ calcd for $C_{14}H_8FN_2$ 223.0666, found 223.0663. The yield reported in Table 5 (71%) represents an average of two runs (68 and 73%).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00481.

NMR spectral data for all new substrates and for isolated products (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (b) Jeschke, P. *Pest Manage. Sci.* **2010**, *66*, 10. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (d) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (e) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (f) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (g) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071.

(2) (a) Special Issue: Fluorine in the Life Sciences *ChemBioChem* **2004**, *5*, 557−726. (b) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3.

(3) (a) Langlois, B.; Gilbert, L.; Forat, G. Fluorination of aromatic compounds by halogen exchange with fluoride anions ("halex" reaction). In *Industrial Chemistry Library*; Jean-Roger, D., Serge, R., Eds.; Elsevier: New York, 1996; pp 244−292. (b) Clark, J. H.; Wails, D.; Bastock, T. W. *Aromatic Fluorination*; CRC Press: Boca Raton, FL, 1996. (c) Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. *Chem. Rev.* **2015**, *115*, 9073.

(4) (a) Kuduk, S. D.; DiPardo, R. M.; Bock, M. G. *Org. Lett.* **2005**, *7*, 577. (b) Boechat, N.; Clark, J. H. *J. Chem. Soc., Chem. Commun.* **1993**, 921. (c) Adams, D. J.; Clark, J. H.; McFarland, H. *J. Fluorine Chem.* **1998**, *92*, 127. (d) Clark, J. H.; Wails, D. *J. Fluorine Chem.* **1995**, *70*, 201. (e) Clark, J. H.; Wails, D. *Tetrahedron Lett.* **1993**, *34*, 3901. (f) Clark, J. H.; Wails, D.; Jones, C. W.; Smith, H.; Boechat, N.; Mayer, L. U.; Mendonca, J. S. *J. Chem. Res.* **1994**, 478. (g) Adams, D. J.; Clark, J. H.; Nightingale, D. J. *Tetrahedron* **1999**, *55*, 7725. (h) Adams, D. J.; Clark, J. H.; McFarland, H.; Nightingale, D. J. *J. Fluorine Chem.* **1999**, *94*, 51. (i) Maggini, M.; Passudetti, M.; Gonzales-Trueba, G.; Prato, M.; Quintily, U.; Scorrano, G. *J. Org. Chem.* **1991**, *56*, 6406.

(5) Adams, D. J.; Clark, J. H. *Chem. Soc. Rev.* **1999**, *28*, 225.

(6) (a) Wynn, D. A.; Roth, M. M.; Pollard, B. D. *Talanta* **1984**, *31*, 1036. (b) Vlasov, V.-M. *J. Fluorine Chem.* **1993**, *61*, 193.

(7) Sun, H.; Koch, A. S.; DiMagno, S. G. *Fluorinated Heterocycles*; American Chemical Society: Washington DC, 2009; Chapter 5, pp 85−104.

(8) Schimler, S. D.; Ryan, S. J.; Bland, D. C.; Anderson, J. E.; Sanford, M. S. *J. Org. Chem.* **2015**, *80*, 12137.

(9) Schimler, S. D.; Cismesia, M. A.; Hanley, P. S.; Froese, R. D. J.; Jansma, M. J.; Bland, D. C.; Sanford, M. S. *J. Am. Chem. Soc.* **2017**, *139*, 1452.

(10) Grushin, V. V.; Marshall, W. J. *Organometallics* **2008**, *27*, 4825.

(11) (a) Lawson, A. T.; Collie, N. J. *J. Chem. Soc., Trans.* **1888**, *53*, 624. (b) Dermeik, S.; Sasson, Y. *J. Org. Chem.* **1989**, *54*, 4827. (c) Christe, K. O.; Wilson, W. W.; Wilson, R. D.; Bau, R.; Feng, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 7619. (d) Urban, G.; Dötzer, R. Method of producing onium fluorides selected from the group consisting of nitrogen, antimony, boron, and arsenic. Patent US3388131A1, June 11, 1968.

(12) Sharma, R. K.; Fry, J. L. *J. Org. Chem.* **1983**, *48*, 2112.

(13) (a) Sun, H.; DiMagno, S. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2720. (b) Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc.* **2005**, *127*, 2050. (c) DiMagno, S. G.; Sun, H. Anhydrous Fluoride Salts and Reagents and Methods for Their Production. Patent US20060089514A1, April 27, 2006.

(14) Allen, L. J.; Muhuhi, J. M.; Bland, D. C.; Merzel, R.; Sanford, M. S. *J. Org. Chem.* **2014**, *79*, 5827.

(15) (a) Eckelbarger, J. D.; Epp, J. B.; Schmitzer, P. R.; Siddall, T. L. 3-Alkenyl-6-halo-4-aminopicolinates and their use as herbicides. Patent US20120190548A1, July 25, 2012. (b) Whiteker, G. T.; Arndt, K. E.; Renga, J. M.; Yuanming, Z.; Lowe, C. T.; Siddall, T. L.; Podhorez, D. E.; Roth, G. A.; West, S. P.; Arndt, C. Process for the preparation of 4-amino-5-fluoro-3-halo-6-(substituted)picolinates. Patent US20120190860, July 26, 2012. (c) Yerkes, C. N.; Lowe, C. T.; Eckelbarger, J. D.; Epp, J. B.; Guenthenspberger, K. A.; Siddall, T. L.; Schmitzer, P. R. Aryl alkyl esters of 4-amino-6-(substitutedphenyl)-4-picolinates and 6-amino-2-(substituted phenyl)-4-pyrimidinecarboxylates and their use as selective herbicides for crops. Patent US20150025238A1, January 22, 2015. (d) Eckelbarger, J. D.; Epp, J. B.; Schmitzer, P. R. 6-Amino-2-substituted-5-vinylsilylpyrimidine-4-carboxylic acids and esters and 4-amino-6-substituted-3-vinylsilylpyridine-2-carboxylic acids and esters as herbicides. Patent US20120190549A1, July 26, 2012. (e) Epp, J. B.; Schmitzer, P. R.; Balko, T. W.; Ruiz, J. M.; Yerkes, C. N.; Siddall, T. L.; Lo, W. C. 2-Substituted 6-amino-5-alkyl, alkenyl or alkynyl-4-pyrimidinecarboxylic acids and 6-substituted-4-amino-3-alkyl, alkenyl or alkynyl picolinic acids and their use as herbicides. Patent US20090088322A1, April 2, 2009. (f) Walsh, T. A.; Hicks, G.; Honma, M.; Davies, J. P. Resistance to auxinic herbicides. Patent US20070220629A1, September 20, 2007.

(16) Ryan, S. J.; Schimler, S. D.; Bland, D. C.; Sanford, M. S. *Org. Lett.* **2015**, *17*, 1866.

(17) Allen, L. J.; Lee, S. H.; Cheng, Y.; Hanley, P. S.; Muhuhi, J. M.; Kane, E.; Powers, S. L.; Anderson, J. E.; Bell, B. M.; Roth, G. A.; Sanford, M. S.; Bland, D. C. *Org. Process Res. Dev.* **2014**, *18*, 1045.

(18) For a related approach for the nucleophilic fluorination of phenols, see: (a) Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482. (b) Fujimoto, T.; Becker, F.; Ritter, T. *Org. Process Res. Dev.* **2014**, *18*, 1041. (c) Fujimoto, T.; Ritter, T. *Org. Lett.* **2015**, *17*, 544. (d) Neumann, C. N.; Hooker, J. M.; Ritter, T. *Nature* **2016**, *534*, 369.

(19) We cannot exclude the possibility of a covalent C−F bond formed between **C-1** and **A-1** as the active fluorinating reagent.

(20) Peaks corresponding to starting material **1-Cl** (m/z = 275) and side product **1-OPh** (m/z = 333) were observed by GCMS.

(21) A peak corresponding to side product **1-OAr** (m/z = 361) was observed by GCMS.

(22) A similar arylsulfonyl fluoride has been reported in the deoxyfluorination of alcohols. See: Nielsen, M. K.; Ugaz, C. R.; Li, W.; Doyle, A. G. *J. Am. Chem. Soc.* **2015**, *137*, 9571.

(23) Peaks corresponding to both 2,6-dimethylphenyl sulfurofluoridate (m/z = 204) and bis(2,6-dimethylphenyl) sulfate (m/z = 306) byproducts from the reaction of **D-1** and **A-5** were observed by

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J. Org. Chem. XXXX, XXX, XXX−XXX

GCMS, indicating that both fluorines of **A-5** can be converted to NMe_4F.
(24) Kenaga, E. E. Fumigation with sulfuryl fluoride. Patent US2875127, February 24, 1959.
(25) Three equivalents of **A-5** was used to ensure no S_NAr byproducts were formed.
(26) Hanley, P. S.; Ober, M. S.; Krasovskiy, A. L.; Whiteker, G. T.; Kruper, W. J. *ACS Catal.* **2015**, *5*, 5041.
(27) Zhuang, Z.-P.; Kung, M.-P.; Kung, H. F. *J. Med. Chem.* **1994**, *37*, 1406.
(28) Alagille, D.; DaCosta, H.; Chen, Y.; Hemstapat, K.; Rodriguez, A.; Baldwin, R. M.; Conn, J. P.; Tamagnan, G. D. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3243.
(29) Arisawa, M.; Igarashi, Y.; Kobayashi, H.; Yamada, T.; Bando, K.; Ichikawa, T.; Yamaguchi, M. *Tetrahedron* **2011**, *67*, 7846.
(30) Tordeux, M.; Wakselman, C. *Synth. Commun.* **1982**, *12*, 513.
(31) Anbarasan, P.; Neumann, H.; Beller, M. *Chem. - Eur. J.* **2011**, *17*, 4217.
(32) Mossine, A. V.; Brooks, A. F.; Makaravage, K. J.; Miller, J. M.; Ichiishi, N.; Sanford, M. S.; Scott, P. J. H. *Org. Lett.* **2015**, *17*, 5780.

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J. Org. Chem. XXXX, XXX, XXX−XXX