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# Anhydrous Tetramethylammonium Fluoride for Room-Temperature $S_NAr$ Fluorination

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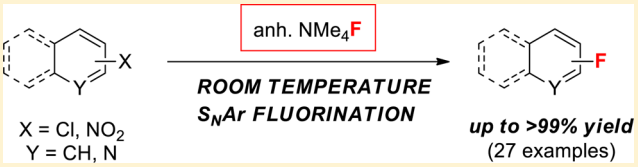
Supporting Information

**ABSTRACT:** This paper describes the room-temperature $S_NAr$ fluorination of aryl halides and nitroarenes using anhydrous tetramethylammonium fluoride ($NMe_4F$). This reagent effectively converts aryl-X (X = Cl, Br, I, $NO_2$, OTf) to aryl-F under mild conditions (often room temperature). Substrates for this reaction include electron-deficient heteroaromatics (22 examples) and arenes (5 examples). The relative rates of the reactions vary with X as well as with the structure of the substrate. However, in general, substrates bearing X = $NO_2$ or Br react fastest. In all cases examined, the yields of these reactions are comparable to or better than those obtained with CsF at elevated temperatures (i.e., more traditional halex fluorination conditions). The reactions also afford comparable yields on scales ranging from 100 mg to 10 g. A cost analysis is presented, which shows that fluorination with $NMe_4F$ is generally more cost-effective than fluorination with CsF.




## INTRODUCTION

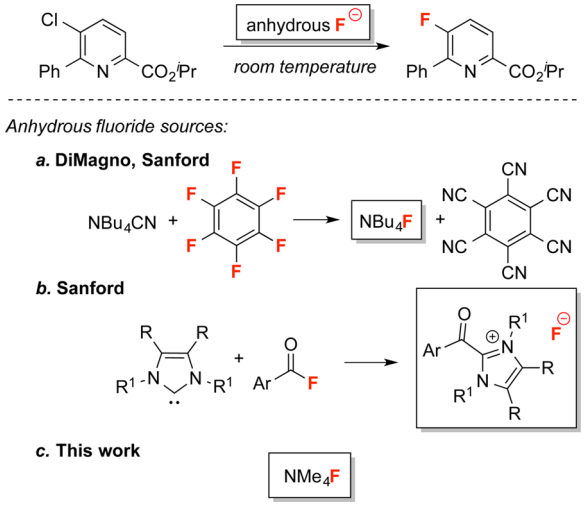
Fluorinated arenes and heteroarenes are finding increasing application in agrochemicals and pharmaceuticals.[1] The substitution of a hydrogen atom with a fluorine atom in biologically active molecules often imparts improvements in bioavailability and/or metabolic stability.[2] However, despite the importance of the incorporation of fluorine into organic molecules, there are relatively few selective and mild synthetic methods for C−F bond formation, particularly on a process scale.

One of the most common reactions for the industrial preparation of aryl and heteroaryl fluorides is nucleophilic aromatic fluorination ($S_NAr$).[3] This involves the reaction of an electron-deficient (hetero)aryl halide or nitroarene with a nucleophilic fluoride source to generate the corresponding aryl fluoride.[3,4] Anhydrous alkali metal fluorides (MF) are most typically employed as the fluoride source. However, these salts are poorly soluble in organic solvents. As a result, high temperatures and long reaction times are necessary to obtain high conversions. These forcing conditions often limit functional group tolerance and lead to the formation of undesired side products.[3]

Several recent reports have shown that replacing alkali metal fluorides with more soluble, anhydrous fluoride reagents can enable $S_NAr$ fluorination to proceed under significantly milder conditions. For example, DiMagno and co-workers have shown that anhydrous (anh) tetrabutylammonium fluoride ($NBu_4F$) can be generated in situ from tetrabutylammonium cyanide (TBACN) and hexafluorobenzene ($C_6F_6$).[5] This $NBu_4F$ (anh) participates in $S_NAr$ fluorination reactions with chloro- and nitroarenes at room temperature (Scheme 1a).[5,6] Similarly, our group has recently reported that the combination of acid fluorides and *N*-heterocyclic carbenes (NHCs) produces anhydrous acyl azolium fluorides that effect room-temperature $S_NAr$ fluorinations (Scheme 1b).[7,8] However, both of these methods are limited by the requirement for expensive stoichiometric reagents ($C_6F_6$, NHCs) that preclude implementation in an industrial-process scale.

To address this challenge, we have pursued anhydrous tetramethylammonium fluoride ($NMe_4F$) as a more practical

**Scheme 1. Soluble Anhydrous Fluoride Sources for Room-Temperature $S_NAr$ Fluorination**

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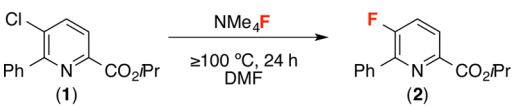
source of soluble anhydrous fluoride for $S_NAr$ fluorination. $NMe_4F$ (anh) offers the advantage that it can be prepared from inexpensive precursors (e.g., from $NMe_4Cl$ and KF or from $NMe_4OH$ and HF).[9] Furthermore, it can be rigorously dried at elevated temperatures (unlike $NBu_4F$, which is susceptible to Hoffman elimination upon heating).[10] Grushin and Marshall have reported that $NMe_4F$ (anh) reacts with unactivated aryl bromides in DMSO at 90−110 °C to form regioisomeric mixtures of fluoroarene products in 10−65% yield.[11] However, this transformation is proposed to proceed via an aryne mechanism rather than $S_NAr$. Clark has demonstrated a variety of examples of $S_NAr$ fluorodenitration reactions using anhydrous $NMe_4F$.[12,13] These reactions are typically conducted at temperatures ranging from 60 to 100 °C, and a variety of side products (e.g., arylethers, phenols) are formed in these systems. In contrast, there are very few literature reports of halide substitution with $NMe_4F$ (anh), and the scope of these transformations has not been extensively explored.[13a,b,14] Indeed, in some cases, the conversion of aryl chlorides to aryl fluorides is reported as an undesired side reaction during fluorodenitration processes.[13a,b]

Herein, we demonstrate the room-temperature $S_NAr$ fluorination of a variety of aryl halides and nitroarenes using anhydrous tetramethylammonium fluoride (Scheme 1c). We show that the reaction rates vary dramatically as a function of the leaving group, with nitroarenes and aryl bromides providing the fastest reactions. We demonstrate that $NMe_4F$ (anh) is effective for the $S_NAr$ fluorination of industrially relevant chloropicolinates as well as other electron-deficient (hetero)-aromatic substrates. The reactions generally proceed in excellent yield on scales ranging from 100 mg to 10 g, and the mild temperature limits the formation of side products derived from competing transesterification and/or deprotonation pathways. Finally, we provide a comparative cost analysis, which shows that $S_NAr$ fluorination with $NMe_4F$ (anh) is more cost-effective than analogous reactions with CsF.

## RESULTS AND DISCUSSION

Our initial investigations focused on the use of $NMe_4F$ (anh) for the $S_NAr$ fluorination of 5-chloropicolinate **1**, a structural motif found in many Dow AgroSciences products.[15] This transformation was initially examined at 140 °C (i.e, elevated temperature conditions similar to those commonly employed for $S_NAr$ fluorination).[3,16] As shown in Table 1, the reaction of **1** with 2 equiv of anhydrous $NMe_4F$ at 140 °C led to complete conversion of **1** but afforded only 66% yield of the fluoropicolinate product **2** (entry 1). At 100 °C, the conversion of **1** was again quantitative, but the yield of **2** was only 73% (entry 2). The major side products observed in these transformations are the carboxylic acid **2**-$CO_2H$, the isopropyl ether **1**-*i*PrO, and $CH_3F$[17] (eq 1).




(1)

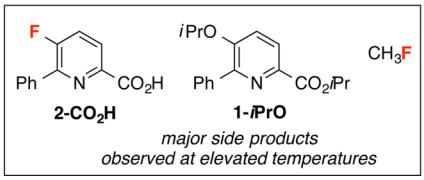
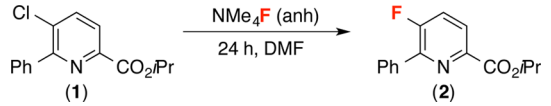



**Table 1. $S_NAr$ Fluorination of 1 with $NMe_4F$ (anh)**



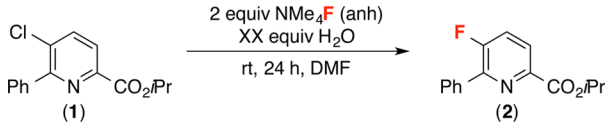

| entry[a] | equiv of $NMe_4F$ | temp | % conversion | % yield[b] |
|---|---|---|---|---|
| 1 | 2 | 140 °C | 100 | 66 |
| 2 | 2 | 100 °C | 100 | 73 |
| 3 | 2 | 60 °C | 100 | 85 |
| 4 | 2 | 40 °C | 100 | 95 |
| 5 | 2 | rt | 100 | 99 |
| 6 | 2[c] | rt | 0 | <1 |
| 7 | 1 | rt | 80 | 80 |

[a]Conditions: Substrate **1** (0.1 mmol) and anhydrous $NMe_4F$ were stirred in DMF for 24 h. [b]Yield determined by $^{19}F$ NMR spectroscopy using 1,3,5-trifluorobenzene as a standard. [c]$NMe_4F{\cdot}4H_2O$ was used in place of anhydrous $NMe_4F$.

We hypothesized that competing side product formation could be limited by lowering the reaction temperature (entries 2−5). Gratifyingly, *at room temperature* we observed full conversion of **1**, along with a quantitative yield of **2** (entry 5). Furthermore, with only 1 equiv of anhydrous $NMe_4F$, the $S_NAr$ fluorination of **1** proceeded to 80% yield at room temperature (entry 7). These results demonstrate that $NMe_4F$ (anh) has comparable reactivity to previously reported anhydrous $NBu_4F$[6] and acyl azolium fluoride[7] reagents.

The use of $NMe_4F{\cdot}4H_2O$ under otherwise analogous conditions afforded none of the fluorinated product (Table 1, entry 6). On the basis of this result, we next systematically explored the effect of $H_2O$ on the room-temperature reaction of **1** with $NMe_4F$ (anh). In this study, various quantities of water were added to reactions that were set up under anhydrous conditions (Table 2). The addition of 1 equiv of

**Table 2. Effect of Water on the Reaction of 1 with $NMe_4F$**




| entry[a] | equiv of $H_2O$ | % yield[b] |
|---|---|---|
| 1 | 0 | 99 |
| 2 | 1 | 76 |
| 3 | 2 | 1 |
| 4 | 5 | <1 |

[a]Conditions: Substrate **1** (0.1 mmol) and anhydrous $NMe_4F$ (0.2 mmol) were combined in a 4 mL vial. DMF (0.2 M) and water were combined and added as a solution to the solids. The reaction was stirred at room temperature for 24 h. [b]Yield was determined by $^{19}F$ NMR spectroscopy using 1,3,5-trifluorobenzene as an internal standard.

water resulted in an approximately 25% reduction in the reaction yield (from 99% to 76%, entries 1 and 2, respectively). However, the addition of ≥2 equiv of water completely shut down the reaction (entries 3 and 4). Bifluoride ($HF_2^-$) was the major species detected by $^{19}F$ NMR spectroscopic analysis under the conditions in entries 3 and 4 ($^{19}F$ NMR resonance at −152.0 ppm in $CH_2Cl_2$).

We next examined the scope of leaving groups that can be employed in this $S_NAr$ fluorination with $NMe_4F$ (anh). Our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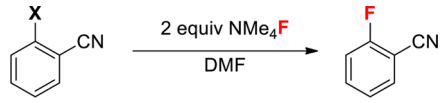
first study focused on a series of commercially available 2-substituted-benzonitrile substrates with Cl, Br, I, $NO_2$, and OTf as leaving groups (**3a–e**). Compounds **3a–e** react slowly with 2 equiv of $NMe_4F$ (anh) at room temperature, affording **4** in 2–95% yield after 48 h (Table 3). In most cases, significantly

**Table 3. Comparison of Reactions of 3a–e with $NMe_4F$ (anh) and CsF**




X = Cl (**3a**)
X = Br (**3b**)
X = I (**3c**)
X = $NO_2$ (**3d**)
X = OTf (**3e**)

(**4**)

| | | % yield | | |
|---|---|---|---|---|
| entry | substrate | 24 h, 25 °C[a] | 3 h, 80 °C[b] | CsF, 140 °C[c] |
| 1 | **3a** | 32 | 94 | 52 |
| 2 | **3b** | 48 | 95 | 49 |
| 3 | **3c** | 8 | 88 | 22 |
| 4 | **3d** | 95 | 97 | 73 |
| 5 | **3e** | 2 | 8 | 73 |

[a]Conditions: Substrate (0.1 mmol) and anhydrous $NMe_4F$ (0.2 mmol) stirred in DMF (0.2 M) at 25 °C for 24 h. [b]Conditions: Substrate (0.1 mmol) and anhydrous $NMe_4F$ (0.2 mmol) stirred in DMF (0.2 M) at 80 °C for 3 h. [c]Conditions: Substrate (0.1 mmol) and CsF (0.2 mmol) stirred in DMF (0.2 M) at 140 °C for 24 h. All yields were determined by $^{19}F$ NMR spectroscopy using 1,3,5-trifluorobenzene as an internal standard.

faster rates were observed at 80 °C, and **3a–d** reacted to afford **4** in 88–97% yield after 3 h at 80 °C (Table 3, entries 1–4). In contrast, aryl triflate **3e** showed minimal reactivity at 80 °C, even at reaction times up to 48 h (entry 5). Notably, aryl bromides and aryl iodides have previously been reported as poor substrates for $S_NAr$ fluorination reactions.[18] However, the current study shows that they can react with $NMe_4F$ (anh) to afford comparable yields of the fluorinated product.

Time studies were conducted to obtain more detailed insight into the relative rates of fluorination of substrates **3a–e**. Notably, there are relatively few systematic studies of the rate of $S_NAr$ fluorination reactions as a function of leaving group, and most of these have been conducted in the context of radiofluorination.[19] As shown in Figure 1, the relative rates were $NO_2 \gg Br > Cl > I \gg OTf$. 2-Nitrobenzonitrile **3d** reacted to afford a nearly quantitative yield of **4** in just 5 min at 80 °C, while all three of the halide substrates afforded quantitative conversion within 3 h under otherwise analogous conditions.

We also compared the reactions of **3a–e** with $NMe_4F$ (anh) to those with CsF, a more traditional reagent for $S_NAr$ fluorination. In all cases, CsF afforded <5% yield of the fluorinated product **4** after 24 h at 80 °C. At 140 °C (more typical conditions for CsF halex reactions),[3,20] the aryl halides **3a–c** reacted with CsF to form **4** in moderate yields after 24 h (22–52%, entries 1–3). In all of these reactions, unreacted starting material remained after 24 h at 140 °C. The fluorodenitration of 2-nitrobenzonitrile (**3d**) with CsF at 140 °C afforded **4** in 73% yield (entry 4). In this case, the conversion of **3d** was quantitative, but a variety of aryl ether side products were formed (as determined by GCMS analysis

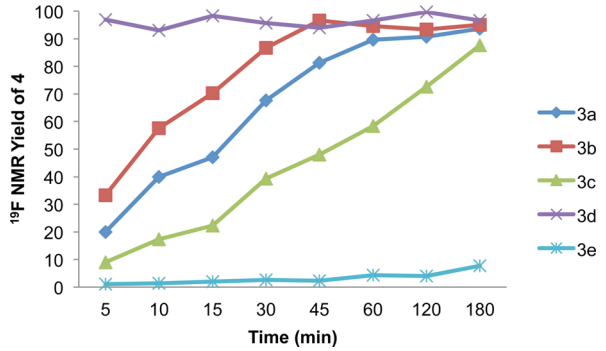



**Figure 1.** Reaction profiles for the reactions of **3a–e** with anhydrous $NMe_4F$ to form **4**. Conditions: Substrate (0.1 mmol, 1 equiv) and anhydrous $NMe_4F$ (0.2 mmol, 2 equiv) were stirred in DMF (0.2 M) at 80 °C for the given time. Yields determined by $^{19}F$ NMR spectroscopy using 1,3,5-trifluorobenzene as a standard.

of the crude reaction mixture). Such side products are common in fluorodenitration reactions, as the displaced nitrite ion can act as a nucleophile.[12,13] Finally, aryl triflate **3e** afforded a significantly better yield with CsF at 140 °C (73%) than with $NMe_4F$ (anh) at 80 °C (8%). Overall, these results highlight the advantages of the current method as well as its complementarity to more conventional $S_NAr$ fluorination with CsF.

We conducted an analogous set of studies with the 2-substituted pyridines **5a–e**. Similar to our results using **3a–e**, the reactions of 2-chloro, 2-bromo, 2-iodo, and 2-nitropyridine (**5a–d**) with $NMe_4F$ (anh) at 80 °C afforded 2-fluoropyridine **6** in good to excellent yield (72–98%) (Table 4, entries 1–4).

**Table 4. Comparison of Reactions of 5a–e with $NMe_4F$ (anh) and CsF**


X = Cl (**5a**)
X = Br (**5b**)
X = I (**5c**)
X = $NO_2$ (**5d**)
X = OTf (**5e**)

(**6**)

| | | % yield | |
|---|---|---|---|
| entry | substrate | 4 h, 80 °C[a] | CsF, 140 °C[b] |
| 1 | **5a** | 72 | 9 |
| 2 | **5b** | 96 | 17 |
| 3 | **5c** | 91 | 19 |
| 4 | **5d** | 98 | 100 |
| 5 | **5e** | 43 | 87 |

[a]Conditions: Substrate (0.1 mmol) and anhydrous $NMe_4F$ (0.2 mmol) stirred in DMF (0.2 M) at 80 °C for 4 h. [b]Conditions: Substrate (0.1 mmol) and CsF (0.2 mmol) stirred in DMF (0.2 M) at 140 °C for 24 h. All yields were determined by $^{19}F$ NMR spectroscopy using 1,3,5-trifluorobenzene as an internal standard.

In all of these cases, the results compare favorably to those obtained with CsF at 140 °C (9–100% yield for **5a–d**, Table 4). Pyridin-2-yl trifluoromethanesulfonate (**5e**) underwent fluorination with $NMe_4F$ (anh) to afford **6** in moderate 43% yield. With this substrate, side products (most significantly aryl ether derivatives) were detected by GCMS. Interestingly, the CsF conditions afforded a significantly improved yield of 87%



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with substrate **5e**. These data suggest that (hetero)aryl triflates are particularly good substrates for CsF halex reactions.

Time studies for the reactions of **5a**–**e** with $NMe_4F$ (anh) are shown in Figure 2. In this system, the impact of leaving

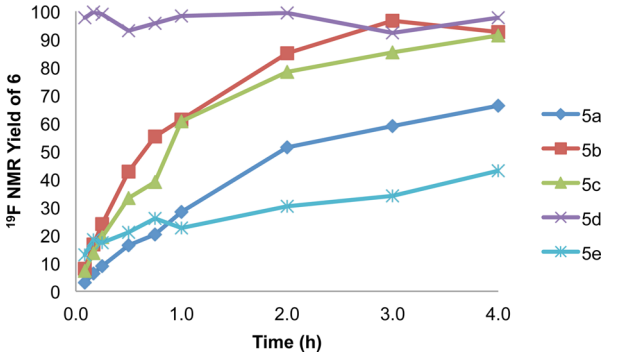


**Figure 2.** Reaction profiles for the reaction **5a**–**e** with anhydrous $NMe_4F$ to form **6**. General conditions: Substrate (0.1 mmol, 1 equiv) and anhydrous $NMe_4F$ (0.2 mmol, 2 equiv) were stirred in DMF (0.2 M) at 80 °C for the given time. Yield was determined by $^{19}F$ NMR spectroscopy using 1,3,5-trifluorobenzene as a standard.

group on reaction rate is slightly different from that observed for **3a**–**e**, with the order of reactivity being $NO_2 \gg Br \approx I > Cl > OTf$. Notably, the initial rate with triflate substrate **5e** is actually comparable to that of the aryl bromide; however, the reaction stalls after about 20 min. A related time study of $S_NAr$ fluorination as a function of leaving group has been reported for the radiofluorination of 2-substituted pyridines with $K^{18}F$. Similar to our observations, this study showed that 2-nitropyridine and 2-bromopyridine reacted faster than the other 2-halopyridines.[19d] Overall, a key finding from the time studies in Figures 1 and 2 is that leaving-group effects on reaction rates are substrate-dependent.

The substrate scope of $S_NAr$ fluorination with $NMe_4F$ (anh) was next investigated. As shown in Chart 1, a variety of monochloropicolinates and dichloropicolinates react to afford the corresponding mono- and difluorinated products **2** and **7**–**11** in good to excellent isolated yields. These transformations were all conducted at room temperature over 24 h, and the reactions of dichloropicolinate substrates required only 1.5 equiv of $NMe_4F$ per chloride. The fluorination of **1** has been conducted on a 138 mg, a 2 g, and a 10 g scale. Comparable yields were obtained in all of these cases [82% (isolated), 93% (in pot), and 85% (isolated), respectively].

Chloroquinoline, chloroisoquinoline, and chloropyridazine substrates also undergo room-temperature fluorination to form **12**–**16** in excellent yields. The high-yielding synthesis of 8-(benzyloxy)-2-fluoroquinoline (**15**) is particularly noteworthy, as $^{18}F$-**15** has been used for the PET imaging of amyloid plaques.[21,22] Methoxy, cyano, and trifluoromethyl substituents are compatible with the reaction conditions (products **8**, **11**, **13**, and **17**–**21**). In addition, halide (Cl, Br, and I) and nitro substituents at less-activated positions in the molecule are well-tolerated, even in the presence of excess $NMe_4F$ (products **7**, **10**, and **23**–**26**). Less-activated aryl chlorides require higher temperatures to form the desired product (products **4**, **28**, and **29**). $S_NAr$ fluorination with $NMe_4F$ (anh) can be used to produce 2- and 4-fluorobenzonitrile (**4** and **29**) in excellent yields, while 3-fluorobenzonitrile **28** is formed in low yield. This latter result is consistent with previous reports showing that meta-positioned electron-withdrawing groups do not activate aryl rings for $S_NAr$ reactions.[5a] While ethyl 4-chlorobenzoate and 4-chlorobenzophenone are not sufficiently activated for the $S_NAr$ fluorination with $NMe_4F$ (even at 80 °C), the nitro analogs react to afford high yields of the fluorinated products at room temperature (**30** and **31**).

Finally, we conducted a cost analysis in order to compare $NMe_4F$ (anh) to CsF for process scale $S_NAr$ fluorinations.[23] The cost of manufacturing (COM) for each of the cases studied was computed using the equation shown below:[24−26]

$$\text{COM} = \text{raw material cost} + \text{waste treatment cost} + \text{conversion cost}$$

The calculations were performed for several different substrates **3a**, **5b**, **5d**, in order to demonstrate how the reaction yield impacts this analysis. All calculations were performed by assuming a product volume of 200 t per year. The results are summarized in Table 5.

With substrates **3a** and **5b**, the yield of fluorinated product is much higher with $NMe_4F$ (anh). As a result, the use of CsF is 3−10-fold more costly and thus not economically competitive. For substrate **5d**, the reaction yields are similar to the two fluorinating reagents. Here, $NMe_4F$ (anh) still offers a significant advantage over CsF, since the mass of CsF required to achieve high yield is quite large. As such, the mass (and thus cost) required to deliver each fluorinating equivalent is higher than that with $NMe_4F$ (anh). Overall, for difficult fluorinations, $NMe_4F$ (anh) appears to offer a cost-effective alternative to CsF.

## ■ CONCLUSION

This report describes the use of $NMe_4F$ (anh) as a broadly useful reagent for low-temperature $S_NAr$ fluorination reactions. We demonstrate that diverse aryl halides and nitroarenes react with $NMe_4F$ (anh) to yield aryl fluoride products at temperatures ranging from room temperature to 80 °C. The relative rates vary as a function of leaving group and substrate, but aryl bromide and nitroarene substrates generally afford the fastest rates and highest yields in these transformations. $NMe_4F$ (anh) has been compared directly to CsF, and it generally affords comparable or enhanced reaction yields and smaller quantities of byproducts. This latter effect is likely due to the lower operating temperature required for $S_NAr$ fluorinations with $NMe_4F$ (25−80 °C) versus with CsF (140 °C). A cost analysis projects that $NMe_4F$ (anh) is economically superior to CsF for the $S_NAr$ reactions presented herein. Overall, the use of $NMe_4F$ (anh) addresses many of the prior limitations of process-scale $S_NAr$ fluorination reactions (e.g., high temperatures, side product formation, and costly reagents).

## ■ EXPERIMENTAL SECTION

**Materials and Methods.** NMR spectra were obtained on a 400 MHz (400.52 MHz for $^1H$, 376.87 MHz for $^{19}F$, 100.71 MHz for $^{13}C$), a 500 MHz (500.01 MHz for $^1H$, 125.75 MHz for $^{13}C$, 470.56 MHz for $^{19}F$), a 700 MHz (699.76 MHz for $^1H$, 175.95 MHz for $^{13}C$), or a 500 MHz (499.90 MHz for $^1H$, 125.70 for $^{13}C$) NMR spectrometer. $^1H$ and $^{13}C$ chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference ($CDCl_3$; $^1H$ $\delta$ 7.26 ppm, $^{13}C$ $\delta$ 77.16 ppm). $^{19}F$ NMR spectra are referenced to the internal standard 1,3,5-trifluorobenzene, which appears at −108.33 ppm. Multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublets (dd), doublet of triplets (dt). Coupling constants ($J$) are


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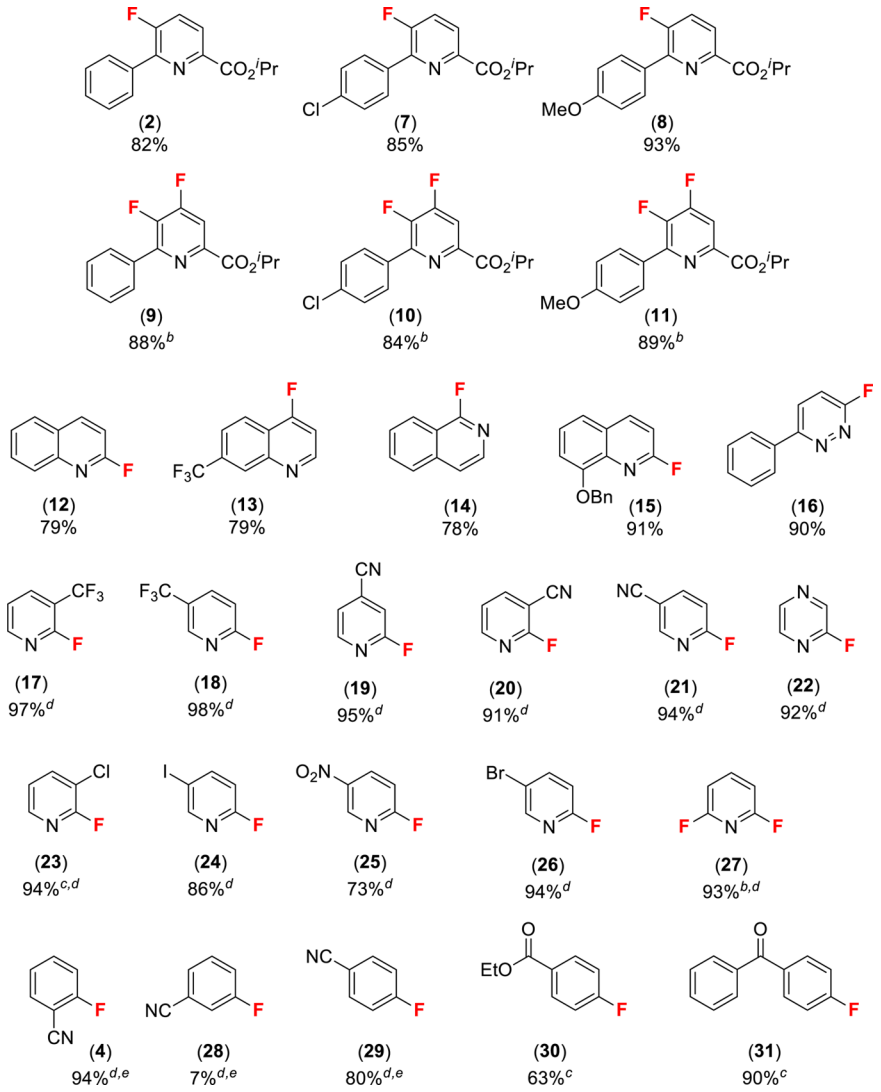
**Chart 1. Substrate Scope for $S_NAr$ Fluorination with $NMe_4F$ (anh)**[a]




[a]Conditions: anhydrous $NMe_4F$ (2 equiv) and substrate (1 equiv) were stirred in DMF at 25 °C for 24 h. [b]With 3 equiv of anhydrous $NMe_4F$. [c]The corresponding nitroarene was used as the substrate. [d]Yield determined by $^{19}F$ NMR spectroscopy using 1,3,5-trifluorobenzene as a standard. [e]Reaction was stirred at 80 °C for 24 h.

**Table 5. Cost Analysis for $S_NAr$ Fluorination of 3a, 5b, and 5d with CsF and $NMe_4F$ (anh)**

| fluorinating agent (equiv) | substrate | % yield | consumption of fluorinating agent (kg/kg product) | cost contribution of fluorinating agent ($/kg product) | total estimated cost ($/kg product) |
|---|---|---|---|---|---|
| $NMe_4F$ (2) | **3a** | 94 | 1.6 | 53 | 74 |
| CsF (2) | **3a** | 52 | 4.8 | 237 | 260 |
| $NMe_4F$ (1) | **3a** | 78 | 0.99 | 32 | 53 |
| CsF (1) | **3a** | 51 | 2.56 | 121 | 143 |
| $NMe_4F$ (2) | **5b** | 96 | 2.0 | 65 | 127 |
| CsF (2) | **5b** | 17 | 18.42 | 902 | 1185 |
| $NMe_4F$ (2) | **5d** | 98 | 1.96 | 64 | 214 |
| CsF (2) | **5d** | 100 | 3.13 | 153 | 297 |

reported in hertz. For GCMS analysis, the products were separated on a crossbond 5% diphenyl–95% dimethyl polysiloxane column (30 m length by 0.25 mm i.d., 0.25 $\mu$m df). Helium was employed as the carrier gas, with a constant column flow of 1.5 mL/min. The injector temperature was held constant at 250 °C. The GC oven temperature program for low molecular weight compounds was as follows: 32 °C, hold for 5 min, ramp 15 °C/min to 250 °C, and hold for 1.5 min. The GC oven temperature program for medium molecular weight compounds was as follows: 60 °C, hold for 4 min, ramp 15 °C/min to 250 °C. Melting points are uncorrected. High-resolution mass spectra were recorded on a Magnetic Sector mass spectrometer.

Commercial reagents were used as received unless otherwise noted. Anhydrous tetramethylammonium fluoride was obtained from Sigma-Aldrich. Anhydrous *N*,*N*-dimethylformamide was obtained from Alfa Aesar. Isopropyl chloroarylpicolinates were prepared using previously described methods.[6] 2-Cyanophenyl trifluoromethanesulfonate,[27]



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pyridine-2-yl trifluoromethanesulfonate,[28] and 8-(benzyloxy)-2-chloroquinoline[21] were prepared using literature procedures and dried over $P_2O_5$ prior to use.

**General Procedures for Fluorination Reactions.** *General Procedure A: Experimental Details for Fluorination Reactions Reported in Table 1.* In a drybox, substrate **1** (0.1 mmol, 1.0 equiv) and anhydrous tetramethylammonium fluoride ($NMe_4F$) were weighed into a 4 mL vial equipped with a microsized stir bar. DMF (0.5 mL) was added, and the reaction vial was sealed with a Teflon-lined cap, removed from the drybox, and stirred at the designated temperature for 24 h. The reaction was then cooled to room temperature and diluted with dichloromethane (2.5 mL), and an internal standard (1,3,5-trifluorobenzene, 100 $\mu$L of a 0.5 M solution in toluene) was added. An aliquot was removed for analysis by $^{19}$F NMR spectroscopy.

*General Procedure B: Experimental Details for Fluorination Reactions Reported in Table 2.* A solution of anhydrous DMF (2 mL) and deionized water that was sparged with $N_2$ was prepared in a Schlenk flask and sparged with $N_2$ for 15 min. The Schlenk tube was then pumped into a drybox. In a drybox, substrate **1** (0.1 mmol, 1.0 equiv) and anhydrous $NMe_4F$ (0.2 mmol, 2.0 equiv) were weighed into a 4 mL vial equipped with a microsized stir bar. The water−DMF solution was then added (0.5 mL), and the reaction vial was sealed with a Teflon-lined cap, removed from the drybox, and stirred at room temperature for 24 h. The reaction was then diluted with dichloromethane (2.5 mL), and an internal standard (1,3,5-trifluorobenzene, 100 $\mu$L of a 0.5 M solution in toluene) was added. An aliquot was removed for analysis by $^{19}$F NMR spectroscopy.

*General Procedure C: Experimental Details for Fluorination Reactions Reported in Tables 3 and 4 and Figures 1 and 2.* For reactions with anhydrous $NMe_4F$, in a drybox, substrate **3a−e** or **5a−e** (0.1 mmol, 1.0 equiv) and anhydrous $NMe_4F$ (0.2 mmol, 2 equiv) were weighed into a 4 mL vial equipped with a microsized stir bar. DMF (0.5 mL) was added, and the reaction vial was sealed with a Teflon-lined cap, removed from the drybox, and stirred at the given temperature for the given time. The reactions were cooled at 0 °C and diluted with dichloromethane (2.5 mL), and an internal standard (1,3,5-trifluorobenzene, 100 $\mu$L of a 0.5 M solution in toluene) was added. An aliquot was removed for analysis by $^{19}$F NMR spectroscopy.

For reactions with CsF, in a drybox, substrate **3a−e** or **5a−e** (0.1 mmol, 1.0 equiv) and CsF (0.2 mmol, 2 equiv) were weighed into a 4 mL vial equipped with a microsized stir bar. DMF (0.5 mL) was added, and the reaction vial was sealed with a Teflon-lined cap, removed from the drybox, and stirred at 140 °C for 24 h. The reactions were cooled to room temperature and diluted with dichloromethane (2.5 mL), and an internal standard (1,3,5-trifluorobenzene, 100 $\mu$L of a 0.5 M solution in toluene) was added. An aliquot was removed for analysis by $^{19}$F NMR spectroscopy.

*General Procedure D: Experimental Details for Isolated Yields Reported in Chart 1.* In a drybox, anhydrous $NMe_4F$ (93 mg, 1 mmol, 2 equiv) and the appropriate aryl chloride or nitroarene substrate (0.5 mmol, 1 equiv) were weighed into a 4 mL vial equipped with a microsized stir bar. DMF (2.5 mL) was added, and the reaction vial was sealed with a Teflon-lined cap, removed from the drybox, and stirred at room temperature for 24 h. 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 magnesium sulfate, and concentrated in vacuo. The crude mixture was purified by flash column chromatography on silica gel using gradients of hexanes and either diethyl ether or ethyl acetate as eluent.

*General Procedure E: General Experimental Details for NMR Yields Reported in Chart 1.* In a drybox, anhydrous $NMe_4F$ (18.6 mg, 0.2 mmol, 2 equiv) and the appropriate aryl chloride or nitroarene substrate (0.1 mmol, 1 equiv) were weighed into a 4 mL vial equipped with a microsized stir bar. DMF (0.5 mL) was added, and the reaction vial was sealed with a Teflon-lined cap, removed from the drybox, and stirred at room temperature unless otherwise noted for 24 h. The reaction was cooled to room temperature and an internal standard (1,3,5-trifluorobenzene, 100 $\mu$L of a 0.5 M solution in toluene) was added. An aliquot was removed for analysis by $^{19}$F NMR spectroscopy and GCMS.

**Product Synthesis and Characterization.** *Isopropyl 5-Fluoro-6-phenylpicolinate (**2**).* General procedure D was followed using isopropyl 5-chloro-6-phenylpicolinate (**1**) (138 mg, 0.5 mmol, 1 equiv), providing **2** as a colorless oil (106 mg, 82% yield, $R_f$ = 0.61 in 70% hexanes/30% $Et_2O$). $^1$H, $^{13}$C, and $^{19}$F NMR experimental data match those reported in the literature.[6] HRMS ESI$^+$ ($m/z$): $[M + H]^+$ calcd for $C_{15}H_{15}FNO_2$ 260.1081, found 260.1080. The yield reported in Chart 1 (82%) represents an average of two runs (82% and 81%).

*Isopropyl 5-Fluoro-6-phenylpicolinate (**2**) on a 10 g Scale.* A 250 mL three-necked round-bottom flask equipped with a magnetic stir bar was evacuated and purged about three times with nitrogen. The vessel was charged with isopropyl 5-chloro-6-phenylpicolinate (10.11 g, 36.67 mmol, 1 equiv) and then anhydrous DMF (100 mL) was added by cannula transfer under vacuum. Anhydrous $NMe_4F$ (5.02 g, 53.92 mmol, 1.47 equiv) was added in a single portion, and the mixture was allowed to stir overnight (23 h) at ambient temperature. The reaction mixture was filtered and the filtrate was partitioned between 200 mL of distilled water and 120 mL of toluene in a 1 L separatory funnel. The bottom cloudy aqueous layer was separated and then subsequently extracted with two 50 mL portions of toluene. The three organic layers were combined and then washed with two 50 mL portions of distilled water. The upper toluene layer was separated and concentrated under vacuum. Purification by column chromatography provided the product as a colorless oil (8.04 g, 85% yield, CombiFlash using a 220 g RediSep Silica column, 90% hexanes/10% ethyl acetate). $^1$H, $^{13}$C, and $^{19}$F NMR experimental data match those reported in the literature.[6]

*Isopropyl 5-Fluoro-6-(p-chlorophenyl)picolinate (**7**).* General procedure D was followed using isopropyl 5-chloro-6-(*p*-chlorophenyl)picolinate (122 mg, 0.5 mmol, 1 equiv), providing **7** as a white solid (122 mg, 83% yield, $R_f$ = 0.59 in 70% hexanes/30% $Et_2O$, mp = 73−76 °C). $^1$H, $^{13}$C, and $^{19}$F NMR experimental data match those reported in the literature.[7] HRMS ESI$^+$ ($m/z$): $[M + H]^+$ calcd for $C_{15}H_{14}ClFNO_2$ 294.0692, found 294.0689. The yield reported in Chart 1 (85%) represents an average of two runs (83% and 87%).

*Isopropyl 5-Fluoro-6-(p-methoxyphenyl)picolinate (**8**).* General procedure D was followed using isopropyl 5-chloro-6-(*p*-methoxyphenyl)picolinate (153 mg, 0.5 mmol, 1 equiv), providing **8** as a white solid (138 mg, 96% yield, $R_f$ = 0.38 in 70% hexanes/30% $Et_2O$, mp = 46−48 °C). $^1$H, $^{13}$C, and $^{19}$F NMR experimental data match those reported in the literature.[7] HRMS ESI$^+$ ($m/z$): $[M + H]^+$ calcd for $C_{16}H_{17}FNO_3$ 290.1187, found 290.1185. The yield reported in Chart 1 (93%) represents an average of two runs (96% and 90%).

*Isopropyl 4,5-Difluoro-6-phenylpicolinate (**9**).* General procedure D was followed using isopropyl 4,5-dichloro-6-phenylpicolinate (155 mg, 0.5 mmol, 1 equiv) and anhydrous $NMe_4F$ (140 mg, 1.5 mmol, 3 equiv), providing **9** as a colorless oil (121 mg, 87% yield, $R_f$ = 0.64 in 70% hexanes/30% $Et_2O$). $^1$H, $^{13}$C, and $^{19}$F NMR experimental data match those reported in the literature.[6] HRMS ESI$^+$ ($m/z$): $[M + H]^+$ calcd for $C_{15}H_{14}F_2NO_2$ 278.0987, found 278.0986. The yield reported in Chart 1 (88%) represents an average of two runs (87% and 88%).

*Isopropyl 4,5-Difluoro-6-(p-chlorophenyl)picolinate (**10**).* General procedure D was followed using isopropyl 4,5-dichloro-6-(*p*-chlorophenyl)picolinate (172 mg, 0.5 mmol, 1 equiv) and anhydrous $NMe_4F$ (140 mg, 1.5 mmol, 3 equiv), providing **10** as a white solid (138 mg, 89% yield, $R_f$ = 0.69 in 70% hexanes/30% $Et_2O$, mp = 74−76 °C). $^1$H, $^{13}$C, and $^{19}$F NMR experimental data match those reported in the literature.[6] HRMS ESI$^+$ ($m/z$): $[M + H]^+$ calcd for $C_{15}H_{13}ClF_2NO_2$ 312.0597, found 312.0597. The yield reported in Chart 1 (84%) represents an average of two runs (89% and 79%).

*Isopropyl 4,5-Difluoro-6-(p-methoxyphenyl)picolinate (**11**).* General procedure D was followed using isopropyl 4,5-dichloro-6-(*p*-methoxyphenyl)picolinate (170 mg, 0.5 mmol, 1 equiv) and anhydrous $NMe_4F$ (140 mg, 1.5 mmol, 3 equiv), providing **11** as a white solid (136 mg, 89% yield, $R_f$ = 0.61 in 70% hexanes/30% $Et_2O$, mp = 37−38 °C). $^1$H, $^{13}$C, and $^{19}$F NMR experimental data match those reported in the literature.[6] HRMS ESI$^+$ ($m/z$): $[M + H]^+$ calcd


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for $C_{16}H_{16}F_2NO_3$ 308.1093, found 308.1091. The yield reported in Chart 1 (89%) represents an average of two runs (89% and 88%).

*2-Fluoroquinoline (**12**).* General procedure D was followed using 2-chloroquinoline (82 mg, 0.5 mmol, 1 equiv), providing **12** as a colorless oil (56 mg, 77% yield, $R_f$ = 0.51 in 70% hexanes/30% $Et_2O$). $^1H$, $^{13}C$, and $^{19}F$ NMR experimental data match those reported in the literature.[6] HRMS ESI$^+$ ($m/z$): $[M + H]^+$ calcd for $C_9H_7FN$ 148.0557, found 148.0555. The yield reported in the text (79%) represents an average of two runs (77% and 80%).

*4-Fluoro-7-(trifluoromethyl)quinoline (**13**).* General procedure D was followed using 4-chloro-7-(trifluoromethyl)quinoline (116 mg, 0.5 mmol, 1 equiv), providing **13** as a white solid (88 mg, 82% yield, $R_f$ = 0.38 in 70% hexanes/30% $Et_2O$, mp = 84−86 °C). $^1H$, $^{13}C$, and $^{19}F$ NMR experimental data match those reported in the literature.[6] HRMS ESI$^+$ ($m/z$): $[M + H]^+$ calcd for $C_{10}H_6F_4N$ 216.0431, found 216.0430. The yield reported in Chart 1 (79%) represents an average of two runs (82% and 75%).

*1-Fluoroisoquinoline (**14**).* General procedure D was followed using 1-chloroisoquinoline (82 mg, 0.5 mmol, 1 equiv), providing **14** as a colorless oil (59 mg, 80% yield, $R_f$ = 0.53 in 70% hexanes/30% $Et_2O$). $^1H$, $^{13}C$, and $^{19}F$ NMR experimental data match those reported in the literature.[7] HRMS ESI$^+$ ($m/z$): $[M + H]^+$ calcd for $C_9H_7FN$ 148.0557, found 148.0555. The yield reported in Chart 1 (78%) represents an average of two runs (80% and 76%).

*8-(Benzyloxy)-2-fluoroquinoline (**15**).* General procedure D was followed using 8-(benzyloxy)-2-chloroquinoline (134.5 mg, 0.1 mmol, 1 equiv), providing **15** as a white solid (120 mg, 95% yield, $R_f$ = 0.38 in 70% hexanes/30% $Et_2O$, mp = 67−69 °C). $^1H$ and $^{19}F$ NMR experimental data match those reported in the literature.[22] $^{13}C$ NMR (125.75 MHz, $CDCl_3$): $\delta$ 161.5 (d, $J$ = 242 Hz), 153.4, 142.0 (d, $J$ = 9.5 Hz), 138.7, 137.6 (d, $J$ = 15.3 Hz), 136.8, 128.6, 128.0 (d, $J$ = 1.9 Hz), 127.0, 126.9, 126.1 (d, $J$ = 2.9 Hz), 119.6, 111.6, 110.6 (d, $J$ = 42.9 Hz), 70.7. HRMS ESI$^+$ ($m/z$): $[M + H]^+$ calcd for $C_{16}H_{13}FNO$ 254.0976, found 254.0975. The yield reported in Chart 1 (91%) represents an average of two runs (95% and 86%).

*3-Fluoro-6-phenylpyridazine (**16**).* General procedure D was followed using 3-chloro-6-phenylpyridzaine (95 mg, 0.5 mmol, 1 equiv), providing **16** as a white solid (79 mg, 91% yield, $R_f$ = 0.38 in 70% hexanes/30% $Et_2O$, mp = 129−131 °C). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 8.01−7.98 (multiple peaks, 3H), 7.53−7.49 (multiple peaks, 3H), 7.29 (dd, $J$ = 9.5, 2.0 Hz, 1H). $^{13}C$ NMR (175.95 MHz, $CDCl_3$): $\delta$ 166.7 (d, $J$ = 245 Hz), 159.2 (d, $J$ = 3.5 Hz), 135.1 (d, $J$ = 2.1 Hz), 130.2, 129.5 (d, $J$ = 7.6 Hz), 129.0, 127.0, 116.1 (d, $J$ = 33.4 Hz). $^{19}F$ NMR (100 MHz, $CDCl_3$): − 84.8 (d, $J$ = 1.5 Hz). IR (cm$^{-1}$): 1584, 1556, 1450, 1427, 1278, 1108, 852, 778, 739. HRMS ESI$^+$ ($m/z$): $[M + H]^+$ calcd for $C_{10}H_7FN_2$ 175.0666, found 175.0663. The yield reported in Chart 1 (90%) represents an average of two runs (91% and 88%).

*2-Fluoro-3-(trifluoromethyl)pyridine (**17**).* General procedure E was followed using 2-chloro-3-(trifluoromethyl)pyridine (18.1 mg, 0.1 mmol, 1 equiv), providing **17** in 100% yield as determined by $^{19}F$ NMR spectroscopic analysis of the crude reaction mixture. The product showed a $^{19}F$ NMR signals at −63.42 (3F) and −68.06 (1F) ppm in DCM [lit.[5a] −60.62 (3F), −63.01 (1F) ppm in DMSO]. The identity of the product was further confirmed by GCMS analysis ($m/z$ = 165). The yield reported in Chart 1 (97%) represents an average of two runs (100% and 94%).

*2-Fluoro-5-(trifluoromethyl)pyridine (**18**).* General procedure E was followed using 2-chloro-5-(trifluoromethyl)pyridine (18.1 mg, 0.1 mmol, 1 equiv), providing **18** in 95% yield as determined by $^{19}F$ NMR spectroscopic analysis of the crude reaction mixture. The product showed $^{19}F$ NMR signals at −62.68 (3F) and −63.51 (1F) ppm in DCM [lit.[5a] −60.62 (3F), −63.01 (1F) ppm in DMSO]. The identity of the product was further confirmed by GCMS analysis ($m/z$ = 165). The yield reported in Chart 1 (98%) represents an average of two runs (95% and 100%).

*2-Fluoro-4-cyanopyridine (**19**).* General procedure E was followed using 2-chloro-4-cyanopyridine (13.8 mg, 0.1 mmol, 1 equiv), providing **19** in 100% yield as determined by $^{19}F$ NMR spectroscopic analysis of the crude reaction mixture. The $^{19}F$ NMR spectral data matched that of an authentic sample (Synthonix; s, −64.94 ppm). The identity of the product was further confirmed by GCMS analysis ($m/z$ = 122). The yield reported in Chart 1 (95%) represents an average of two runs (100% and 89%).

*2-Fluoro-3-cyanopyridine (**20**).* General procedure E was followed using 2-chloro-3-cyanopyridine (13.8 mg, 0.1 mmol, 1 equiv), providing **20** in 93% yield as determined by $^{19}F$ NMR spectroscopic analysis of the crude reaction mixture. The product showed a $^{19}F$ NMR signal at −62.66 ppm in DCM (lit.[29] −60.0 ppm in $CDCl_3$). The identity of the product was further confirmed by GCMS analysis ($m/z$ = 122). The yield reported in Chart 1 (91%) represents an average of two runs (93% and 88%).

*2-Fluoro-5-cyanopyridine (**21**).* General procedure E was followed using 2-chloro-5-cyanopyridine (13.8 mg, 0.1 mmol, 1 equiv), providing **21** in 87% yield as determined by $^{19}F$ NMR spectroscopic analysis of the crude reaction mixture. The $^{19}F$ NMR spectral data matched that of an authentic sample (Matrix Scientific; s, −59.41 ppm). The identity of the product was further confirmed by GCMS analysis ($m/z$ = 122). The yield reported in the text (94%) represents an average of two runs (87% and 100%).

*2-Fluoropyrazine (**22**).* General procedure E was followed using 2-chloropyrazine (11.4 mg, 0.1 mmol, 1 equiv), providing **22** in 99% yield as determined by $^{19}F$ NMR spectroscopic analysis of the crude reaction mixture. The product showed a $^{19}F$ NMR signal at −81.00 ppm in DCM (lit.[5a] −80.4 ppm in DMSO). The identity of the product was further confirmed by GCMS analysis ($m/z$ = 98). The yield reported in Chart 1 (92%) represents an average of two runs (99% and 84%).

*2-Fluoro-3-chloropyridine (**23**).* General procedure E was followed using 2-nitro-3-chloropyridine (15.8 mg, 0.1 mmol, 1 equiv), providing **23** in 94% yield as determined by $^{19}F$ NMR spectroscopic analysis of the crude reaction mixture. The product showed a $^{19}F$ NMR signal at −72.54 ppm in DCM (lit.[5a] −73.03 ppm in DMSO). The identity of the product was further confirmed by GCMS analysis ($m/z$ = 131). The yield reported in Chart 1 (94%) represents an average of two runs (94% and 94%).

*2-Fluoro-5-iodopyridine (**24**).* General procedure E was followed using 2-chloro-5-iodopyridine (23.9 mg, 0.1 mmol, 1 equiv), providing **24** in 85% yield as determined by $^{19}F$ NMR spectroscopic analysis of the crude reaction mixture. The $^{19}F$ NMR spectral data matched that of an authentic sample (Sigma-Aldrich; m, −71.28 ppm). The identity of the product was further confirmed by GCMS analysis ($m/z$ = 223). The yield reported in Chart 1 (86%) represents an average of two runs (85% and 87%).

*2-Fluoro-5-nitropyridine (**25**).* General procedure E was followed using 2-chloro-5-nitropyridine (15.8 mg, 0.1 mmol, 1 equiv), providing **25** in 70% yield as determined by $^{19}F$ NMR spectroscopic analysis of the crude reaction mixture. The $^{19}F$ NMR spectral data matched that of an authentic sample (Oakwood Chemicals; s, −59.14 ppm). The identity of the product was further confirmed by GCMS analysis ($m/z$ = 142). The yield reported in Chart 1 (73%) represents an average of two runs (70% and 76%).

*2-Fluoro-5-bromopyridine (**26**).* General procedure E was followed using 2-chloro-5-bromopyridine (19.1 mg, 0.1 mmol, 1 equiv), providing **26** in 100% yield as determined by $^{19}F$ NMR spectroscopic analysis of the crude reaction mixture. The $^{19}F$ NMR spectral data matched that of an authentic sample (Oakwood Products; s, −71.69 ppm). The identity of the product was further confirmed by GCMS analysis ($m/z$ = 175). The yield reported in Chart 1 (94%) represents an average of two runs (100% and 88%).

*2,6-Difluoropyridine (**27**).* General procedure E was followed using 2,6-dichloropyridine (14.7 mg, 0.1 mmol, 1 equiv) and anhydrous $NMe_4F$ (28 mg, 0.3 mmol, 3 equiv), providing **27** in 91% yield as determined by $^{19}F$ NMR spectroscopic analysis of the crude reaction mixture. The $^{19}F$ NMR spectral data matched that of an authentic sample (Alfa Aesar; m, −68.91 ppm). The identity of the product was further confirmed by GCMS analysis ($m/z$ = 115). The yield reported in Chart 1 (93%) represents an average of two runs (91% and 95%).

*2-Fluorobenzonitrile (**4**).* General procedure E was followed using 2-chlorobenzonitrile (13.7 mg, 0.1 mmol, 1 equiv) at 80 °C, providing


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**4** in 98% yield as determined by $^{19}F$ NMR spectroscopic analysis of the crude reaction mixture. The $^{19}F$ NMR spectral data matched that of an authentic sample (Ark Pharm; m, −108.02 ppm). The identity of the product was further confirmed by GCMS analysis ($m/z$ = 121). The yield reported in Chart 1 (94%) represents an average of three runs (98%, 83%, and 100%).

*3-Fluorobenzonitrile (**28**).* General procedure E was followed using 3-chlorobenzonitrile (13.7 mg, 0.1 mmol, 1 equiv) at 80 °C, providing **28** in 6% yield as determined by $^{19}F$ NMR spectroscopic analysis of the crude reaction mixture. The $^{19}F$ NMR spectral data matched that of an authentic sample (Oakwood Chemicals; m, −111.18 ppm). The identity of the product was further confirmed by GCMS analysis ($m/z$ = 121). The yield reported in Chart 1 (7%) represents an average of two runs (6% and 7%).

*4-Fluorobenzonitrile (**29**).* General procedure E was followed using 4-chlorobenzonitrile (13.7 mg, 0.1 mmol, 1 equiv) at 80 °C, providing **29** in 79% yield as determined by $^{19}F$ NMR spectroscopic analysis of the crude reaction mixture. The $^{19}F$ NMR spectral data matched that of an authentic sample (Oakwood Chemicals; m, −103.89 ppm). The identity of the product was further confirmed by GCMS analysis ($m/z$ = 121). The yield reported in Chart 1 (80%) represents an average of two runs (79% and 81%).

*Ethyl 4-Fluorobenzoate (**30**).* General procedure D was followed using ethyl 4-nitrobenzoate (98 mg, 0.5 mmol, 1 equiv), providing **30** as a colorless oil (51 mg, 61% yield, $R_f$ = 0.58 in 90% hexanes/10% EtOAc). $^1H$, $^{13}C$, and $^{19}F$ NMR experimental data match those reported in the literature.[7] HRMS ESI$^+$ ($m/z$): $[M]^+$ calcd for $C_9H_9FO_2$ 168.0587, found 168.0584. The yield reported in Chart 1 (63%) represents an average of two runs (61% and 65%).

*4-Fluorobenzophenone (**31**).* General procedure D was followed using 4-nitrobenzophenone (114 mg, 0.5 mmol, 1 equiv), providing **31** as a white solid (89 mg, 89% yield, $R_f$ = 0.54 in 90% hexanes/10% EtOAc, mp = 47−48 °C). $^1H$, $^{13}C$, and $^{19}F$ NMR experimental data match those reported in the literature.[7] HRMS ESI$^+$ ($m/z$): $[M + H]^+$ calcd for $C_{13}H_{10}FO$ 201.0710, found 201.0708. The yield reported in Chart 1 (90%) represents an average of two runs (89% and 90%).

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02075.

Further description of the cost analysis and NMR spectra of isolated products **2**, **7**−**16**, **30**, and **31** (PDF)

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### Notes

The authors declare no competing financial interest.

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