JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

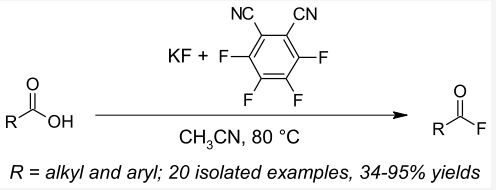
Deoxyfluorination of Carboxylic Acids with KF and Highly Electron-Deficient Fluoroarenes

Siyu Mao, Jordan H. Kramer, and Haoran Sun*

Cite This: J. Org. Chem. 2021, 86, 6066−6074 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A deoxyfluorination reaction of carboxylic acids using potassium fluoride (KF) and highly electron-deficient fluoroarenes is reported here, giving acyl fluorides in moderate to excellent yield (57−92% based on NMR integration and 34−95% for isolated examples).



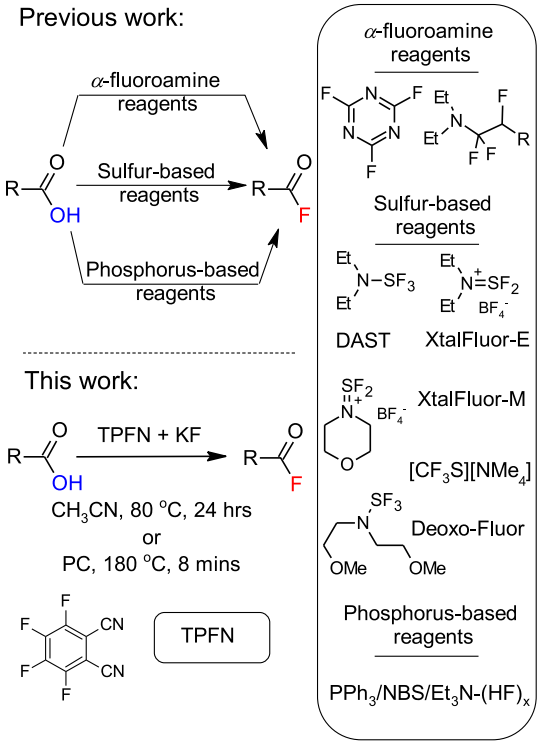
INTRODUCTION

Owing to unique physical, chemical, and biological properties, organofluorine compounds are vital for modern medicine and high-performance materials.[1−3] Developing new synthetic strategies and practices that utilize commonly available fluorinating reagents is the foundation for accessing a broader range of organofluorine compounds at different synthetic stages. Acyl fluorides, important carboxylic acid derivatives, are more stable and easier to handle than other acyl halides.[4] Acyl fluorides are useful intermediates for the preparation of sterically and/or electronically challenging amides and esters, accessing aldehydes, ketones, and α,β-unsaturated carbonyl compounds, peptide syntheses, trifluoromethylarenes, and transition-metal-catalyzed coupling reactions.[4−19] Acyl fluorides were recently used as starting materials to generate anhydrous fluoride salts *in situ* for S_NAr fluorination reactions.[20] Additionally, gaseous ^{18}F-acyl fluoride was utilized to transfer a hot fluoride source between a cyclotron unit and the radiochemistry labeling facility through a pipeline to facilitate the automation process of providing an anhydrous ^{18}F-fluoride source for radiotracer synthesis.[21]

Acyl fluorides can be prepared from acyl chlorides through chloride/fluoride exchange reactions with fluoride salts, preferably organic soluble anhydrous fluoride salts, for example, anhydrous tetrabutylammonium fluoride[22] or tetramethylammonium fluoride (TMAF).[23] Directly preparing acyl fluorides from carboxylic acids and their salts is often highly attractive and chemically lucrative for syntheses of complex target compounds. Representative methods and reagents for preparing acyl fluorides directly from carboxylic acids are listed in Scheme 1.

The first direct preparation of acyl fluorides from carboxylic acids was done by using cyanuric fluoride with Olah's seminal contribution in the early 1970s.[24] Sulfur-based deoxyfluorinating reagents, for example, SF_4, DAST, Deoxo-Fluor, XtalFluor-E, XtalFluor-M, and Fluolead, were developed and used in deoxyfluorination of alcohols, aldehydes, ketones, and

Scheme 1. Representative Methods and Reagents for Acyl Fluoride Preparation Directly from Carboxylic Acids



Received: November 25, 2020
Published: April 20, 2021

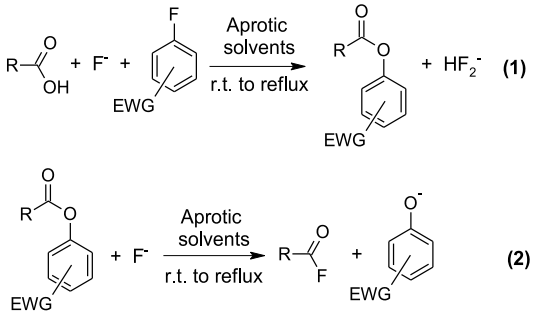
https://doi.org/10.1021/acs.joc.0c02491
J. Org. Chem. 2021, 86, 6066−6074

carboxylic acids and their derivatives over the past half-century.[25−34] While these reagents are effective and efficient in total deoxyfluorination, selective deoxyfluorination can also be achieved with careful temperature and stoichiometry control using those more reactive deoxyfluorinating reagents, for example, SF_4 and DAST.[26,27,29,30] In 2002, Olah's reagent, pyridine-$(HF)_x$, was combined with *N*,*N*′-dicyclohexylcarbodiimide for preparation of acyl fluorides, allowing access to both aliphatic and aromatic acyl fluorides efficiently.[35] Schoenebeck et al. recently broadened the utilization of an organic soluble tetramethylammonium trifluoromethanethiolate salt ($[Me_4N]SCF_3$), discovered by Tyrra et.al in 2003,[36] to the preparation of various acyl fluorides with an easy purification procedure, filtration.[37] Recent work by Prakash et al. utilizes an NBS/PPh_3/Et_3N-$(HF)_x$ protocol, perhaps the most accessible reagent for research laboratories preparing acyl fluorides through deoxyfluorination of carboxylic acids.[38] In 2020, Paquin's group developed an alternative method to generate a variety of acyl fluorides by utilizing XtalFluor-E and a catalytic amount of NaF at room temperature.[33] Lately, an article published by the same group provides a more comprehensive review on the synthesis of acyl fluorides.[39] A few new approaches were successfully identified for the preparation of acyl fluorides by using a sulfuryl fluoride/halide combination,[40] $CF_3SO_2OCF_3$,[41] and $Cu(O_2CCF_2SO_2F)_2$[42] while this paper was under preparation and review. Herein, we report a new alternative method for the synthesis of acyl fluorides from carboxylic acids using KF and highly electron-deficient fluoroarenes.

RESULTS AND DISCUSSION

A common key step for carboxylic acid deoxyfluorination is the removal of OH^-, by forming a strong X═O bond (X = S, P, C) in the side product during the reaction. We hypothesize that removal of OH^- can also be done if we convert this unfavorable leaving group into a relatively better leaving group where the negative charge on oxygen is stabilized by electron-withdrawing moieties and delocalization through resonance. A key strategy in our deoxyfluorination approach is to prepare an electron-deficient phenoxide as a better leaving group by using fluorinated electron-deficient aromatics as reaction mediators (Scheme 2). The fluorine bearing *ipso*-carbon in the highly electron-deficient fluoroarene is susceptible to nucleophilic aromatic substitution even with relatively weak nucleophiles, here, the carboxylates, forming esters (Scheme 2, first step). Then the highly reactive fluoride anion (anhydrous form) attacks the carbonyl carbon to form a C−F bond and break the ester C−O bond, forming the electron-deficient phenoxide (Scheme 2, second step) as a better leaving group.

Scheme 2. Deoxyfluorination of Carboxylic Acids

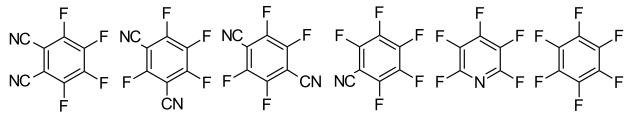


To test our hypothesis, we chose a simple highly electron-deficient fluoroaromatic, tetrafluorophthalonitrile (TFPN), as a reaction mediator that facilitates the formation of an ester intermediate in the first step and the formation of a better leaving group in the second step in Scheme 2. Two important factors we took into consideration for using TFPN are (1) the phenyl ring is highly electron-deficient due to the strong electron-withdrawing effects of both multiple fluorines and two cyano groups, leading to a faster S_NAr reaction in the first step and forming a better leaving group in the second step; (2) there is no acidic proton that can consume the highly reactive fluoride. Together with spray-dried KF, direct deoxyfluorination of carboxylic acids was achieved.

In a typical reaction, a carboxylic acid was mixed with 2.5 equiv of spray-dried KF and 1.2 equiv of TFPN in anhydrous acetonitrile, and the resulting mixture was heated at 80 °C. The reaction was monitored by both ^1H and ^{19}F NMR spectra periodically, and the final reaction yield was determined by integration of ^1H and/or ^{19}F NMR spectra with $TBAPF_6$ as the internal standard (see Supporting Information (SI) for details). Upon heating, the reaction typically finished within overnight to 24 h (see Figures S1−S6 for a typical example of reaction monitoring by NMR). Varying the amount of TFPN being used in the reaction, we found that 1 equiv of TFPN is needed. Given that TFPN also reacts with water to form the corresponding phenoxide (see SI, Figures S7 and S8), a competing reaction for the S_NAr reaction in the first step if the sample contains trace amounts of residual water, we utilize a slight excess of TFPN (1.2 equiv) in practice except noted otherwise.

Several other commercially available electron-deficient fluoroarenes that do not possess an active proton were also examined as reaction mediators (Chart 1). Using *para*-*N*,*N*-dimethylamino-benzoic acid as an example, we tested six different electron-deficient fluoroarenes under the same condition. Except for HFB, all these electron-deficient fluoroarenes work for the deoxyfluorination reaction, giving a similar result compared to TFPN (SI, Figures S9−S11) without reaction condition optimization. Estimated reactant conversion for those five working reactions is in the range of 57% to nearly quantitative based on the proton NMR integration ratio between reactant and product. When a relatively milder electron-deficient fluoroarene, e.g., *para*-fluorobenzonitrile, was used as the reaction mediator, the above reaction did not occur. Though searching for an electron-deficiency threshold for other fluoroarene mediators is theoretically important, we feel that reporting this new and practical method first will benefit a broad range of synthetic and medicinal chemistry communities to give researchers access to acyl fluorides through additional means. In addition, more reactive anhydrous fluoride salts (e.g., anhydrous TMAF) also can be used as the fluoride source to generate the target

Chart 1. Examples of Reaction Mediators



https://doi.org/10.1021/acs.joc.0c02491
J. Org. Chem. 2021, 86, 6066−6074

acyl fluoride product with 77% yield (SI, Figure S19); however, the cost is much higher than that of spray-dried KF.[43−45] Considering the reagent cost and easy to handle practice, we chose TFPN as the reaction mediator and spray-dried KF as the fluorinating reagent for the rest of the study in this report.[46]

Using *p*-methoxy-benzoic acid as the substrate, we further tested several solvents with boiling points (bp) ranging from 65 to 240 °C and both aprotic and protic solvents (Table 1). It

Table 1. Results from Reactions under Different Conditions[a]

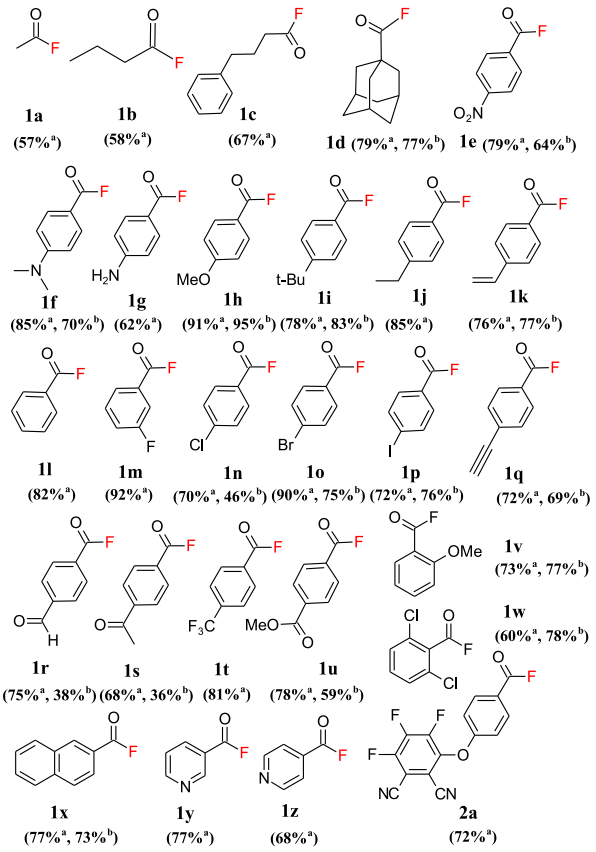
entry	solvent	TFPN (equiv)	F^- source (equiv)	yield[b] (%)
1	CH_3CN[c]	1.2	KF (2.5)	91
2	CH_3CN[d]	1.2	KF (2.5)	82
3	CH_3CN[d]	1.2	TMAF (2.5)	77
4	DMSO[d]	1.2	KF (2.5)	67
5	THF[d]	1.2	KF (2.5)	40
6	PC[d]	1.2	KF (2.5)	77
7	ethanol[d]	1.2	KF (2.5)	0

[a]All reactions were heated at 80 °C for 24 h; see SI for more detailed experimental procedures. [b]Yields were determined by ^{19}F NMR using $TBAPF_6$ as the internal standard. [c]Reaction was performed in an argon glovebox with anhydrous acetonitrile. [d]Reaction was performed on the benchtop with anhydrous acetonitrile directly out of the bottle.

is clear that alcohol-based solvents will not work for the corresponding deoxyfluorination of carboxylic acids as it (1) can form strong hydrogen bonding with fluoride to reduce the fluoride nucleophilicity dramatically, (2) competes for TFPN in the first S_NAr step with the carboxylic acid, and (3) potentially forms an ester under the basic condition. All other aprotic solvents tested worked, giving a yield ranging from 40% to 91% with reaction in THF giving the least yield, perhaps due to its low polarity. Considering the cost, workup procedure, and relatively easier removal of the solvent, we chose acetonitrile for the rest of the reactions in this paper. This is also likely a reasonable choice for a larger scale reaction where workup and isolation becomes more important than that of a smaller scale reaction.

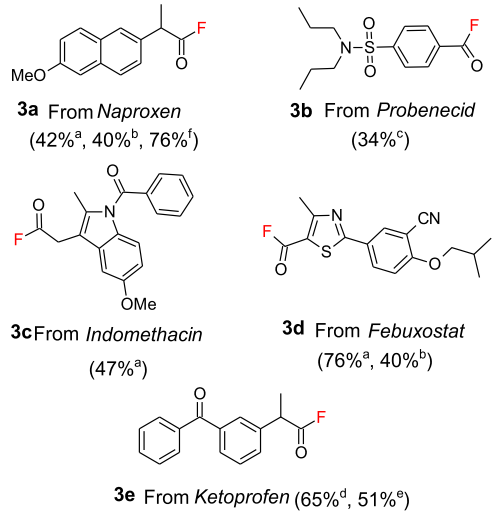
The presented deoxyfluorination strategy and reagents worked for both aliphatic and aromatic carboxylic acids with various functional groups (Chart 2). The reaction condition is tolerant to many functional groups, including cyano, trifluoromethyl, aryl halides, ketone, aldehyde, ether, ester, alkyne, and alkene. A key advantage of this TFPN/KF method for acyl fluoride preparation is shown by the high tolerance of the aldehyde and ketone functional groups. This is unlike other traditional deoxyfluorination reagents like SF_4, DAST, and XtalFluor which react with aldehydes and ketones as well. Such selectivity is particularly important for late-stage fluorination when multiple functional groups coexisted. Generally, the reaction yield ranges from moderate to excellent without further optimization of experimental conditions (Charts 2 and 3). Aliphatic carboxylic acids including sterically hindered carboxylic acids gave good yields. Substituted benzoic acids, with both electron-rich and electron-poor phenyl rings, give good to excellent yields (60−92%). It seems the electronic effects of the substituents on the phenyl rings do not have an observable impact on the product yields under current reaction conditions, though those substituents may affect the reaction kinetics. Substrates having amine groups made a slightly

Chart 2. List of Deoxyfluorination Products and Yield



[a]Yield was determined by ^{19}F NMR with the internal standard $TBAPF_6$. [b]Isolated yield with reaction condition of heating at 80 °C in CH_3CN for 24 h at 1 mmol scale.

Chart 3. Fluorinated Pharmaceutical Compounds



[a]Isolated yield with reaction condition of heating at 80 °C in CH_3CN for 24 h. [b]Isolated yield with reaction condition of heating at 180 °C in PC for 8 min. [c]1 g scale isolated yield with reaction condition of heating at 80 °C in CH_3CN for 24 h. [d]NMR quantified yield under the condition of heating at 80 °C in CH_3CN for 24 h. [e]NMR quantified yield under the condition of heating at 180 °C in PC for 8 min. [f]10 mmol (2.3 g) scale reaction, isolated yield with reaction condition of heating at 80 °C in CH_3CN for 24 h and with optimized purification procedure.

https://doi.org/10.1021/acs.joc.0c02491
J. Org. Chem. 2021, 86, 6066−6074

complicated case as the amine group could react with the acyl fluoride to form amide-based polymers. Monitoring the reaction by ^{1}H and ^{19}F NMR, followed by quenching the reaction at the appropriate time, gives us about 62% yield of *para*-aminobenzoyl fluoride. In the case of the *para*-hydroxyl-benzoic acid substrate, 2.2 equiv of TFPN and 3.5 equiv of KF are needed to convert the carboxylic acid into acyl fluoride. In this case, the *para* hydroxyl group was converted into a dicynano-trifluoro-phenoxyl group on the corresponding acyl fluoride product (**2a**) in 72% yield (SI, Figures S12−S16). Both nicotinic and *iso*-nicotinic acids were also converted to the corresponding acyl fluorides in good yield, 77% and 68%, respectively.

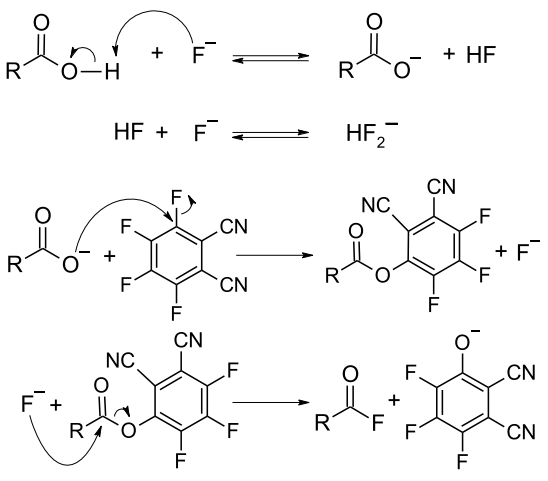
A practical scope of this methodology was further examined by running benchtop reactions under atmosphere conditions without the usage of a glovebox or a Schlenk line.[47] The results, as shown in Chart 2, demonstrated that a wide range of acyl fluorides were successfully synthesized and isolated under atmosphere conditions with commercially available dry solvents without using special equipment, i.e., glovebox nor Schlenk line, giving moderate to excellent yields (36−95%) after using methylene chloride or hexane to quench the reaction mixture and simple filtration through a silica plug. Side products, potassium bifluoride and potassium dicyanotri-fluorophenoxide, are insoluble in less- or nonpolar solvents such as CH_2Cl_2 and hexane. They can be filtered out after quenching the reaction with less- or nonpolar solvents, providing a pathway to recycle the side product, potassium dicyanotrifluorophenoxide. Further study of the usage of this highly electron-deficient phenoxide side product is underway in this lab.

To illustrate the synthetic scope of this method, we further demonstrated this deoxyfluorination strategy with several pharmaceutical compounds that contain carboxylic acid groups, giving moderate isolated yields (34−76%) of corresponding acyl fluorides (Chart 3) without optimization of reaction and isolation conditions. For this group of substrates, typically we used 0.5−4.0 mmol scale of substrates, 1.05 equiv of TFPN and 2.5 equiv of KF with appropriate solvents depending on the reaction temperature (see Experimental Section for details). To shorten the reaction time, a higher boiling point aprotic solvent, propylene carbonate (PC), was employed for rapid fluorination of these pharmaceutical compounds at 180 °C. Under this condition, a benchmark example, 4-(dimethylamino)benzoic acid, was fluorinated with 70% yield in about 15 min. In a PC solution at 180 °C, a nonsteroidal anti-inflammatory drug Naproxen, an inhibitor for cyclooxygenase-1 and -2, was fluorinated within 8 min with 40% isolated yield. Other pharmaceutical compounds (**3b**, **3c**, **3d**) containing sulfonamide, ketone, nitrile functional groups, and heterocycles were fluorinated in acetonitrile at 80 °C, giving 34−76% yield. Both pharmaceutical compounds (Naproxen and Febuxostat) demonstrated high compatibility with the high temperature reaction condition with 40% isolated yield. Furthermore, the scalability of this method has been demonstrated by directly using pharmaceutical com-pounds, Probenecid, with a 4 mmol scale (1.14 g) and obtained in 34% isolated yield and Naproxen with a 10 mmol scale (2.30 g) and obtained in 76% isolated yield under an optimized isolation procedure (see Experimental Section for more details). One precaution that must be taken into consideration is that the chiral center on the α carbon of the Naproxen was racemized during the reaction due to the basic condition of the fluoride and relative high proton acidity of the alpha proton on this compound. Searching for more reactive mediators and reducing the basicity of the reagents are current underway in this laboratory.

Converting an unfavorable leaving group into a better leaving group is the key for this successful deoxyfluorination strategy. The leaving ability of the corresponding phenoxide is mainly determined by its stability, or the acidity of its conjugate acid. Our initial DFT calculation of the gas phase proton affinity of the corresponding phenoxide from TFPN is about −293 kcal/mol compared to nonsubstituted phenoxide of −344 kcal/mol at room temperature (see SI for details). We estimated that the pK_a of the corresponding dicyano-trifluoro-phenol is about 37 pK_a units lower than that of nonsubstituted phenol in gas phase. With the IEFPCM solvation model, it is about 16 and 15 pK_a units lower than that of phenol in acetonitrile and water, respectively. These results indicate that dicyano-trifluoro-phenol is a very strong acid, resulting in the corresponding phenoxide as an excellent leaving group. Here, three fluorine and two cyano substituents serve the function of electron withdrawing and charge delocalization through resonance. There are still demands to further investigate and improve the mediator's S_NAr reactivity (step 1 in Scheme 1) and the corresponding phenoxide leaving group ability by introducing even stronger electron-withdrawing groups with better resonance onto the mediators. Practically speaking, TFPN is so far the most economical reaction mediator commercially available and works to generate a superior leaving group for this deoxyfluorination reaction.

During the reaction monitoring process, we observed the concentration of the key reaction intermediate ester was cumulated enough to be observed by NMR (SI, Figures S1−S6) and confirmed by GC-MS with a sample prepared at room temperature and quenched to exact the intermediate (SI, Figures S17 and S18). With this observation, we can reasonably propose that there are two key steps for this deoxyfluorination reaction in addition to the acid-base equilibrium reaction between acid and fluoride (Scheme 3). With the observation of the ester intermediate cumulating during the reaction, the first step S_NAr reaction is a faster step compared to the second step nucleophilic fluorination reaction. This indicates two major benefits of utilizing an electron-deficient fluoroarene as the reaction mediator: (1) converting

Scheme 3. Proposed Reaction Mechanism for Deoxyfluorination of Carboxylic Acids



https://doi.org/10.1021/acs.joc.0c02491
J. Org. Chem. 2021, 86, 6066−6074

the hydroxyl group into a better leaving group, electron-deficient phenoxide; and (2) facilitating the first step esterification process.

CONCLUSION

In summary, we have successfully demonstrated an alternative deoxyfluorination strategy for preparing acyl fluorides from carboxylic acids in moderate to excellent yields. A key rationale behind this success is that the electron-deficient fluoroarene mediator does coherently facilitate both functional group conversion and generating a better leaving group. The combined KF/electron-deficient fluoroarene reagent can be heated up, to at least 180 °C, in an aprotic solvent without compromising the deoxyfluorination reaction, providing a more workable space on reaction condition optimization. Many functional groups, including aldehyde, are compatible with the reaction conditions.

EXPERIMENTAL SECTION

General Information. Unless otherwise mentioned, all chemicals were purchased from commercial sources and used without further purification. Spray-dried KF purchased from Sigma-Aldrich was used without further purification. In some cases, spray-dried KF was heated under vacuum at 200 °C for a week under dynamic vacuum. However, the pretreatment of KF did not show any difference on the experimental result. Anhydrous acetonitrile was dried over flame-dried 4 Å molecular sieves. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer with a SmartProbe. Mass spectra (GC-MS) were recorded on a Shimadzu GC-2010 Plus mass spectrometer. High-resolution MS spectra were obtained from the Nebraska Center for Mass Spectrometry.

General Procedure for the Preparation of Acyl Fluorides from Carboxylic Acids and NMR Yield Determination. The following procedure was used in the preparation of acyl fluorides from the corresponding carboxylic acids and sodium carboxylates. Inside an argon glovebox (H_2O < 0.1 ppm; O_2 < 0.1 ppm), 1 mmol of carboxylic acid was weighed out into a screw cap vial. Next, 145 mg (2.5 mmol, 2.5 equiv) of KF and 240 mg (1.2 mmol, 1.2 equiv) of tetrafluorophthalonitrile were weighed out into the same vial; 2.5 mL of anhydrous acetonitrile (anhydrous propylene carbonate was used for high temperature experiments) was then added to the vial along with a small magnetic stir bar. In the case of using carboxylate salts (1 mmol) as the substrates, 87.15 mg (1.5 mmol, 1.5 equiv) of KF and 240 mg (1.2 mmol, 1.2 equiv) of tetrafluorophthalonitrile were used in the corresponding reaction set up. The vial was sealed with a screw cap and transferred outside the glovebox for heating. The sample was then heated for 20−24 h at 80−90 °C using a preheated oil bath (180 °C/8 min for high temperature experiments with PC as the solvent). After the reaction completion, the sample was cooled down to room temperature and 50 μL of 0.333 M $TBAPF_6/CH_3CN$ (6.5 mg, 0.017 mmol) solution was added as an internal standard. The mixture was sealed and stirred for 10 min at room temperature before an aliquot was taken and analyzed by ^{19}F NMR. The reported yields are determined by comparing the relative integration of the internal standard signal (PF_6^-) with the acyl fluoride product. ^{1}H and ^{19}F NMR spectra were obtained by monitoring the reaction mixture in CD_3CN solvent and/or by directly sampling the reaction mixture with $CDCl_3$ solvent without further purification. Upon mixing the reaction mixture with less polar $CDCl_3$ solvent, most side products KHF_2 and corresponding potassium phenoxide derivatives precipitated out of solution and separated with a syringe filter. Only small amounts of unreacted extra tetrafluorophthalonitrile were seen in the ^{19}F NMR without further purification.

General Procedure for the Preparation and Isolation of Acyl Fluorides. Carboxylic acid (1 mmol), 145 mg (2.5 mmol, 2.5 equiv) of KF, and 210 mg (1.05 mmol, 1.05 equiv) of tetrafluorophthalonitrile were weighed out into a small vial under atmosphere condition. Next, 2.5 mL of anhydrous acetonitrile (directly out of the bottle) was then added to the small vial along with a small magnetic stir bar. (In the case of using carboxylate salts (1 mmol) as the substrates, 87.15 mg (1.5 mmol, 1.5 equiv) of KF and 210 mg (1.05 mmol, 1.05 equiv) of tetrafluorophthalonitrile were used in the corresponding reaction.) The vial was capped tightly and stirred at 80 °C for 24 h. ***Caution!****Safety precaution must be taken because the vial is under pressure during the reaction. Please do not heat over the boiling point of the acetonitrile, and only heat the portion containing solution, not the top empty portion of the vial to allow adequate cooling above the solution surface. As an alternative, one can always use a small round-bottom flask to run the reaction with a condenser and a drying tube instead of a small vial.* After the reaction mixture was cooled down to room temperature, the vial was opened and the reaction mixture was diluted with 10 mL of anhydrous hexane and further stirred for 10 min at room temperature. The reaction mixture was purified by filtration over a silica plug (3 cm long with 2 cm in diameter). Subsequently, the silica plug was washed with anhydrous hexane or other appropriate mixture of solvent (see below for each compound). The filtrate was further concentrated under reduced pressure to give the final product without further purification.

Large Scale Acyl Fluoride Synthesis. Under atmosphere condition, Naproxen (10 mmol, 2.3 g), KF (2.5 equiv, 25 mmol,1.45 g), and TFPN (1.01 equiv, 10.1 mmol, 2.02 g) were weighed out into a 100 mL round-bottom flask under atmosphere condition. Next, 22 mL of anhydrous acetonitrile (directly out of the bottle) was then added to the round-bottom flask along with a small magnetic stir bar. The mixture was refluxed for 24 h. After the reaction mixture was cooled down to room temperature, the solvent of the reaction mixture was removed with a rotovap under reduced pressure. To the resulting yellow solid residual was added 20 mL of anhydrous hexane. The resulting mixture was filtered by vacuum filtration, and the solid was washed with 60 mL (3 × 20 mL) of anhydrous hexane. The combined filtrate was further concentrated under reduced pressure to give the final Naproxen fluoride product as a white powdery solid without further purification in 76% isolated yield. Characterization results are the same as those of the smaller sale reactions.

*Acetyl Fluoride (**1a**).*[48] The title compound was prepared in 57% yield as determined by ^{19}F NMR following the general preparation method. **^{1}H NMR** (400 MHz, CD_3CN) δ 2.26 (d, J = 7.41 Hz, 3H). **^{19}F NMR** (376 MHz, CD_3CN) δ 49.0 (q, J = 7.43 Hz, 1F). Note: The yield determined here is likely lower than the accurate reaction yield due to operational loss of highly volatile acetyl fluoride (bp is 21 °C).

*Butanoyl Fluoride (**1b**).*[38] The title compound was prepared in 58% yield as determined by ^{19}F NMR following the general preparation method. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.48 (td, J = 7.31, 0.91 Hz, 2H), 1.69 (sext, J = 7.34 Hz, 2H), 0.99 (td, J = 7.45, 0.93 Hz, 3H), **^{19}F NMR** (376 MHz, $CDCl_3$) δ 45.27 (s, 1F).

*4-Phenylbutanoyl Fluoride (**1c**).*[38] The title compound was prepared in 67% yield as determined by ^{19}F NMR following the general preparation method. **^{1}H NMR** (400 MHz, CD_3CN) δ 7.36−7.28 (m, 2H), 7.28−7.20 (m, 3H), 2.70 (t, J = 7.58 Hz, 2H), 2.59 (t, J = 7.35 Hz, 2H), 1.96 (p, J = 7.56 Hz, 2H). **^{19}F NMR** (376 MHz, CD_3CN) δ 43.36 (s, 1F).

*1-Adamantanecarboxylic Acid (**1d**).*[38] The title compound was prepared in 79% yield as determined by ^{19}F NMR following the general preparation method, using 1-adamantanecarboxylic acid (1 mmol, 180 mg), KF (2.5 mmol, 145 mg), and TFPN (1.05 mmol, 210 mg). The title compound was also isolated from a 1 mmol scale reaction under atmosphere condition described in the general procedure by filtration through a silica plug, washing the silica plug with anhydrous hexane as the eluent. Obtained as a low melting point white solid/gel in 77% isolated yield (139 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.12−2.04 (m, 3H), 2.03−1.93(m, 6H), 1.86−1.70(m, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 23.8 (s, 1F). **MS (EI)** m/z $[M]^+$ calculated for $C_{11}H_{15}FO$ = 182, found = 182.

*4-Nitrobenzoyl Fluoride (**1e**).*[37] The title compound was prepared in 79% yield as determined by ^{19}F NMR following the general preparation method. The title compound was also isolated from a 1 mmol scale reaction under atmosphere condition described in the

https://doi.org/10.1021/acs.joc.0c02491
J. Org. Chem. 2021, 86, 6066−6074

general procedure by filtration through a silica plug, washing the silica plug with a 4:1 anhydrous hexane/EtOAc mixture as the eluent. Obtained as a light yellow solid in 64% isolated yield (108 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.41 (d, J = 8.93 Hz, 2H), 8.28 (d, J = 8.84 Hz, 2H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 21.36 (s, 1F). **MS (EI)** m/z $[M]^+$ calculated for $C_7H_4FNO_3$ = 169, found = 169.

*4-(Dimethylamino)benzoyl Fluoride (**1f**).*[38] The title compound was prepared in 85% yield as determined by ^{19}F NMR following the general preparation method. The title compound was also isolated from a 1 mmol scale reaction under atmosphere condition described in the general procedure by filtration through a silica plug, washing the silica plug with anhydrous hexane as the eluent. Obtained as a light yellow solid in 70% isolated yield (117 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (d, J = 9.01 Hz, 2H), 6.69 (d, J = 9.11 Hz, 2H), 3.11 (s, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 12.37 (s, 1F). **MS (EI)** m/z $[M]^+$ calculated for $C_9H_{10}FNO$ = 167, found = 167.

*4-Aminobenzoyl Fluoride (**1g**).* The title compound was prepared in 62% yield as determined by ^{19}F NMR following the general preparation method, using 4-aminobenzoate (1 mmol, 159 mg), KF (1.5 mmol, 87 mg), and TFPN (2.05 mmol, 410 mg). 50 μL of $TBAPF_6$ standard solution was added, and 10 drops of the reaction mixture were diluted with 0.5 mL of CD_3CN before taking NMR. **^{1}H NMR** (400 MHz, CD_3CN) δ 7.76 (d, J = 8.77 Hz, 2H), 6.71(d, J = 8.79 Hz, 2H), 5.23 (s, 2H). **^{19}F NMR** (376 MHz, CD_3CN) δ 10.62 (s, 1F). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 157.7 (d, C-F, $1J_{C\text{-}F}$ = 334 Hz), 154.1, 133.6 (d, C-F, $3J_{C\text{-}F}$ = 5 Hz), 113.6 (d, C-F, $4J_{C\text{-}F}$ = 1 Hz), 111.6 (d, C-F, $2J_{C\text{-}F}$ = 61 Hz). **HRMS (EI)** m/z $[M]^+$ calculated for C_7H_6FNO = 139.0433, found = 139.0431.

*4-Methoxybenzoyl Fluoride (**1h**).*[38] The title compound was prepared in 91% yield as determined by ^{19}F NMR following the general preparation method. The title compound was also isolated from a 1 mmol scale reaction under atmosphere condition described in the general procedure by filtration through a silica plug, washing the silica plug with anhydrous hexane as the eluent. Obtained as a colorless oil in 95% isolated yield (146 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.75 Hz, 2H), 7.00 (d, J = 8.95 Hz, 2H), 3.92 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 15.94 (s, 1F). **MS (EI)** m/z $[M]^+$ calculated for $C_8H_7FO_2$ = 154, found = 154.

*4-tert-Butylbenzoyl Fluoride (**1i**).*[17] The title compound was prepared in 78% yield as determined by ^{19}F NMR following the general preparation method, using 4-*tert*-butylbenzoic acid (1 mmol, 178 mg), KF (2.5 mmol, 145 mg), and TFPN (1.05 mmol, 210 mg). The title compound was also isolated from a 1 mmol scale reaction under atmosphere condition described in the general procedure by filtration through a silica plug, washing the silica plug with anhydrous hexane as the eluent. Obtained as a colorless oil in 83% isolated yield (149 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02–7.97 (m, 2H), 7.60–7.54 (m, 2H), 1.38 (s, 9H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 17.65 (s, 1F). **MS (EI)** m/z $[M]^+$ calculated for $C_{11}H_{13}FO$ = 180, found = 180.

*4-Ethylbenzoyl Fluoride (**1j**).*[38] The title compound was prepared in 85% yield as determined by ^{19}F NMR following the general preparation method. **^{1}H NMR** (400 MHz, CD_3CN) δ 7.96 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 7.8 Hz, 2H), 2.76 (q, J = 7.60 Hz, 2H), 1.26 (t, J = 7.60 Hz, 3H). **^{19}F NMR** (376 MHz, CD_3CN) δ 16.0 (s, 1F).

*4-Vinylbenzoyl Fluoride (**1k**).*[38] The title compound was prepared in 76% yield as determined by ^{19}F NMR following the general preparation method without any heating and was stirred at r.t for 5 days, using 4-vinylbenzoic acid (1 mmol, 148 mg), KF (2.5 mmol, 145 mg), and TFPN (1.2 mmol, 240 mg). The title compound was also isolated from a 1 mmol scale reaction under atmosphere condition described in the general procedure by filtration through a silica plug, washing the silica plug with anhydrous hexane as the eluent. Obtained as a yellow oil in 77% isolated yield (116 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.52 Hz, 2H), 7.55 (d, J = 8.02 Hz, 2H), 6.79 (dd, J = 17.46, 10.94 Hz, 1H), 5.96 (d, J = 17.59, 1H), 5.51 (d, J = 10.98 Hz, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 17.80 (s, 1F). **MS (EI)** m/z $[M]^+$ calculated for C_9H_7FO = 150, found = 150.

*Benzoyl Fluoride (**1l**).*[38] The title compound was prepared in 82% yield as determined by ^{19}F NMR following the general preparation method. **^{1}H NMR** (400 MHz, CD_3CN) δ 8.05 (dd, J = 8.32, 1.14 Hz, 2H), 7.80 (tt, J = 7.60, 1.3 Hz, 1H), 7.64–7.57 (m, 2H). **^{19}F NMR** (376 MHz, CD_3CN) δ 16.5 (s, 1F). **MS (EI)** exact mass calculated for $[M]^{+\bullet}$: C_7H_5FO = 124.1124032, found = 124.

*3-Fluorobenzoyl Fluoride (**1m**).*[38] The title compound was prepared in 92% yield as determined by ^{19}F NMR following the general preparation method. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (d, J = 7.84 Hz, 1H), 7.74–7.68 (m, 1H), 7.57–7.50 (m, 1H), 7.46–7.38 (m, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 19.2 (d, J = 4.19 Hz, 1F), −110.74 (m, 1F). **MS (EI)** m/z $[M]^+$ calculated for $C_7H_4F_2O$ = 142, found = 142.

*4-Chlorobenzoyl Fluoride (**1n**).*[37] The title compound was prepared in 70% yield as determined by ^{19}F NMR following the general preparation method. The title compound was also isolated from a 1 mmol scale reaction under atmosphere condition described in the general procedure by filtration through a silica plug, washing the silica plug with anhydrous hexane as the eluent. Obtained as a white solid in 46% isolated yield (72 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05–7.98 (m, 2H), 7.58–7.51 (m, 2H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 18.43 (s, 1F). **MS (EI)** m/z $[M]^+$ calculated for C_7H_4ClFO = 158, found = 158 (for ^{35}Cl), 160 (for ^{37}Cl).

*4-Bromobenzoyl Fluoride (**1o**).*[38] The title compound was prepared in 90% yield as determined by ^{19}F NMR following the general preparation method. The title compound was also isolated from a 1 mmol scale reaction under atmosphere condition described in the general procedure by filtration through a silica plug, washing the silica plug with anhydrous hexane as the eluent. Obtained as a white solid in 75% isolated yield (152 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96–7.90 (m, 2H), 7.74–7.68 (m, 2H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 18.44 (s, 1F). **MS (EI)** m/z $[M]^+$ calculated for C_7H_4BrFO = 203, found = 204 (for ^{81}Br), 202 (for ^{79}Br).

*4-Iodobenzoyl Fluoride (**1p**).* The title compound was prepared in 72% yield as determined by ^{19}F NMR following the general preparation method. The title compound was also isolated from a 1 mmol scale reaction under atmosphere condition described in the general procedure by filtration through a silica plug, washing the silica plug with anhydrous hexane as the eluent. Obtained as a white solid in 76% isolated yield (190 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98–7.90 (m, 2H), 7.80–7.72 (m, 2H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 18.28 (s, 1F). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 157.1 (d, C-F, $1J_{C\text{-}F}$ = 343.1 Hz), 138.6, 132.5 (d, C-F, $3J_{C\text{-}F}$ = 4.0 Hz), 124.4 (d, C-F, $2J_{C\text{-}F}$ = 62.4 Hz), 104.01. **HRMS (EI-TOF)** m/z $[M]^+$ calculated for $C_7H_4F^{127}IO$ 249.9291; found 249.9297.

*4-Ethynylbenzoyl Fluoride (**1q**).* The title compound was prepared in 72% yield as determined by ^{19}F NMR following the general preparation method. The title compound was also isolated from a 1 mmol scale reaction under atmosphere condition described in the general procedure by filtration through a silica plug, washing the silica plug with anhydrous hexane as the eluent. Obtained as a light yellow solid in 69% isolated yield (101 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.32 Hz, 2H), 7.65 (d, J = 8.63 Hz, 2H), 3.36 (s, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 18.68 (s, 1F). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 155.3 (d, C-F, $1J_{C\text{-}F}$ = 344.2 Hz), 132.7, 131.3 (d, C-F, $3J_{C\text{-}F}$ = 4.4 Hz), 129.4, 124.8 (d, C-F, $2J_{C\text{-}F}$ = 62.1 Hz), 82.1, 81.9. **HRMS (EI-TOF)** m/z $[M]^+$ calculated for C_9H_5FO 148.0325; found 148.0328.

*4-Formylbenzoyl Fluoride (**1r**).*[41] The title compound was prepared in 75% yield as determined by ^{19}F NMR following the general preparation method. After reaction was finished, 50 μL of 0.333 M $TBAFP_6/CH_3CN$ standard solution was added into the vial. The title compound was also isolated from a 1 mmol scale reaction under atmosphere condition described in the general procedure by filtration through a silica plug, washing the silica plug with anhydrous hexane as the eluent. Obtained as a white solid in 38% isolated yield (57 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.27–8.22 (m, 2H), 8.10–8.04 (m, 2H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 20.57 (s, 1F). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 191.0, 156.3 (d, C-F, $1J_{C\text{-}F}$ = 346.1 Hz), 140.7, 136.0 (d, C-F, $3J_{C\text{-}F}$ = 3.7 Hz), 129.9, 129.7 (d, C-F, $2J_{C\text{-}F}$ = 61.7 Hz). **HRMS (EI-TOF)** m/z $[M]^+$ calculated for $C_8H_5FO_2$ = 152.0273; found = 152.0276.

https://doi.org/10.1021/acs.joc.0c02491
J. Org. Chem. 2021, 86, 6066–6074

*4-Acetylbenzoyl Fluoride (**1s**).*[38] The title compound was prepared in 68% yield as determined by ^{19}F NMR following the general preparation method. The title compound was also isolated from a 1 mmol scale reaction under atmosphere condition described in the general procedure by filtration through a silica plug, washing the silica plug with anhydrous hexane as the eluent. Obtained as a white solid in 36% isolated yield (60 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.43 Hz, 2H), 8.11 (d, J = 8.38 Hz, 2H), 2.70 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 20.23 (s, 1F). **MS (EI)** m/z $[M]^+$ calculated for $C_9H_7FO_2$ = 166, found = 166.

*4-(Trifluoromethyl)benzoyl Fluoride (**1t**).*[49] The title compound was prepared in 81% yield as determined by ^{19}F NMR following the general preparation method. After reaction was finished, 50 μL of 0.333 M $TBAFP_6/CH_3CN$ standard solution was added into the vial. **^{1}H NMR** (400 MHz, CD_3CN) δ 8.24 (d, J = 8.32 Hz, 2H), 7.93 (d, J = 8.29 Hz, 2H). **^{19}F NMR** (376 MHz, CD_3CN) δ 18.52 (s, 1F), 64.05 (s, 3F). **MS (EI)** m/z $[M]^+$ calculated for $C_8H_4F_4O$ = 192, found = 192.

*Methyl-4-(fluorocarbonyl)benzoate (**1u**).*[50] The title compound was prepared in 78% yield as determined by ^{19}F NMR following the general preparation method, using monomethyl terephthalate (1 mmol, 180 mg), KF (2.5 mmol, 145 mg), and TFPN (1.05 mmol, 210 mg). The title compound was also isolated from a 1 mmol scale reaction under atmosphere condition described in the general procedure by filtration through a silica plug, washing the silica plug with anhydrous hexane as the eluent. Obtained as a white solid in 59% isolated yield (107 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.28 Hz, 2H), 8.14 (d, J = 8.42 Hz, 2H), 4.00 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 20.08 (s, 1F). **MS (EI)** m/z $[M]^+$ calculated for $C_9H_7FO_3$ = 182, found = 182.

*2-Methoxybenzoyl Fluoride (**1v**).*[17] The title compound was prepared in 73% yield as determined by ^{19}F NMR following the general preparation method. The title compound was also isolated from a 1 mmol scale reaction under atmosphere condition described in the general procedure by filtration through a silica plug, washing the silica plug with anhydrous hexane as the eluent. Obtained as a colorless oil in 77% isolated yield (118 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (dd, J = 8.07, 1.35 Hz, 1H), 7.67−7.60 (m, 1H), 7.07−7.01 (m, 2H), 3.96 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 31.67 (s, 1F). **MS (EI)** m/z $[M]^+$ calculated for $C_8H_7FO_2$ = 154, found = 154.

*2,6-Dichlorobenzoyl Fluoride (**1w**).* The title compound was prepared in 60% yield as determined by ^{19}F NMR following the general preparation method. The title compound was also isolated from a 1 mmol scale reaction under atmosphere condition described in the general procedure by filtration through a silica plug, washing the silica plug with anhydrous hexane as the eluent. Obtained as a white solid in 78% isolated yield (152 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44−7.42 (m, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 53.33 (s, 1F). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 153.7 (d, C-F, $1J_{C\text{-}F}$ = 354.0 Hz), 132.8 (d, C-F, $3J_{C\text{-}F}$ = 1.5 Hz), 132.8, 129.0, 128.4. **MS (EI)** calculated for $[M]^{+\bullet}$:$C_7H_3Cl_2FO$ = 192 (for ^{35}Cl), found = 192 (for ^{35}Cl), 194 (for ^{35}Cl, ^{37}Cl), 196 (for ^{37}Cl). **HRMS (EI-TOF)** m/z $[M]^+$ calculated for $C_7H_3{}^{35}Cl_2FO$ 191.9545; found 191.9543.

*2-Naphthoyl Fluoride (**1x**).*[38] The title compound was prepared in 77% yield as determined by ^{19}F NMR following the general preparation method. The title compound was also isolated from a 1 mmol scale reaction under atmosphere condition described in the general procedure by filtration through a silica plug, washing the silica plug with anhydrous hexane as the eluent. Obtained as a white solid in 73% isolated yield (126 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.06−7.92 (m, 4H), 7.75−7.68 (m, 1H), 7.68−7.60 (m, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 18.07 (s, 1F). **MS (EI)** m/z $[M]^+$ calculated for $C_{11}H_7FO$ = 174, found = 174.

*3-Pyridinecarbonyl Fluoride (Nicotinoyl Fluoride) (**1y**).*[38] The title compound was prepared in 77% yield as determined by ^{19}F NMR following the general preparation method. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.23 (d, J = 2.00 Hz, 1H), 8.91 (dd, J = 4.95, 1.69 Hz, 1H), 8.34−8.29 (m, 1H), 7.51 (dd, J = 8.08, 4.90 Hz, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 20.60 (s, 1F).

*Isonicotinoyl Fluoride (**1z**).*[33] The title compound was prepared in 68% yield as determined by ^{19}F NMR following the general preparation method. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.92−8.88 (m, 2H), 7.88−7.83 (m, 2H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 20.93 (s, 1F).

*4-(2,3-Dicyano-4,5,6-trifluorophenoxy)benzoyl Fluoride (**2a**).* The title compound was prepared in 72% yield in the form of TFPN-substituted product as determined by ^{19}F NMR following the general preparation method, using sodium 4-hydroxybenzoate (1 mmol, 160 mg), KF (3.5 mmol, 203 mg), and TFPN (2.2 mmol, 440 mg). The final product showed mixed results in NMR as GC indicated the product as a reaction intermediate. The main product is identified by GC with 72% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.80 Hz, 2H), 7.13 (d, J = 8.78 Hz, 2H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 18.18 (s, 1F), −117.29 (dd, J = 11.27, 8.25 Hz, 1F), −125.80 (dd, J = 20.54, 10.94 Hz, 1F), −132.66 (dd, J = 20.45, 8.77 Hz, 1F). **HRMS (EI-TOF)** m/z $[M + Na]^+$ calculated for $C_{15}H_4F_4N_2O_2Na$ 343.01066; found 343.01042. The constitutional isomer of the product was also found in GC-MS with the same fragmentations (Figures S12−S16).

*2-(6-Methoxynaphthalen-2-yl)propanoyl Fluoride (Naproxen Fluoride) (**3a**).*[38] The title compound was prepared on the benchtop with 42% yield (40% with PC high temperature experiment) following the general preparation method with Naproxen (1 mmol, 230 mg), KF (2.5 mmol, 145 mg), and TFPN (1.05 mmol, 210 mg). The reaction was quenched with 10 mL of a 1:1 hexane and DCM mixture. The resulting mixture was then passed through a short pad of silica using hexane as the eluent. The collected filtrate was then concentrated under reduced pressure to saturation at about room temperature. Then the concentrated filtrate was cooled down to −18 °C for 15 min, followed by suction filtration, to collect the final solid product. Yield, 98 mg for reaction done in CH_3CN, and 93 mg for reaction done in PC. Because of the higher polarity of the PC than acetonitrile, we use a mixture of 42 mL of hexane and 7 mL of DCM to quench the reaction while other steps remained the same as for the reaction done in acetonitrile. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (d, J = 21.1 Hz, 1H), 7.76 (d, J = 3.4 Hz, 1H), 7.70 (d, J = 1.7 Hz, 1H), 7.39 (dd, J = 8.5, 1.9 Hz, 1H), 7.20 (dd, J = 8.9, 2.5 Hz, 1H), 7.16 (d, J = 2.5 Hz, 1H), 4.03 (q, J = 7.1 Hz, 1H), 3.95 (s, 3H), 1.69 (dd, J = 7.2, 0.8 Hz, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 39.63 (s, 1F). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 164.4 (d, C-F, $1J_{C\text{-}F}$ = 367.7 Hz), 158.1, 134.1, 132.4, 129.3, 128.9, 127.8, 126.4, 125.7, 119.5, 105.6, 55.4, 44.2 (d, C-F, $2J_{C\text{-}F}$ = 49.1 Hz), 18.1. **MS (EI)** m/z $[M]^+$ calculated for $C_{14}H_{13}FO_2$ = 232, found = 232.

*4-(Dipropylsulfamoyl)benzoyl Fluoride (Probenecid Fluoride) (**3b**).*[38] The title compound was prepared on the benchtop with 34% yield following the general preparation method with Probenecid (4 mmol, 1.14 g), KF (10 mmol, 0.58 g), TFPN (4.2 mmol, 0.84 g), and 8 mL of CH_3CN. The reaction mixture was first concentrated to 2 mL of total volume and then quenched with a mixture of 40 mL of hexane and 10 mL of DCM. Then the resulting mixture was passed through a short silica plug, and the silica plug was washed with a 1:1 hexanes/DCM mixture. The filtrate was then concentrated under reduced pressure to reach saturation at about room temperature. Then the concentrated filtrate was cooled down to −18 °C for 15 min, followed by suction filtration, to collect the final solid product. Yield, 390 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22−8.17(m, 2H), 8.0−7.95 (m, 2H), 3.14 (t, J = 7.65 Hz, 4H), 1.58 (h, J = 7.74 Hz, 4H), 0.89 (t, J = 7.4 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 20.2 (s, 1F). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 156.0 (d, C-F, $1J_{C\text{-}F}$ = 346.1 Hz), 146.7, 132.1 (d, C-F, $3J_{C\text{-}F}$ = 3.7 Hz), 128.1 (d, C-F, $2J_{C\text{-}F}$ = 62.1 Hz), 127.5, 50.0, 22.0, 11.1. **MS (EI)** m/z $[M]^+$ calculated for $C_{13}H_{18}NO_3FS$ = 287, found = 287.

*(1-Benzoyl-5-methoxy-2-methyl-1H-indol-3-yl)acetyl Fluoride (Indomethacin Fluoride) (**3c**).*[38] The title compound was prepared on the benchtop with 47% yield following the general preparation method with Indomethacin (1 mmol, 358 mg), KF (2.5 mmol, 145 mg), and TFPN (1.05 mmol, 210 mg). Upon the completion of the reaction, the reaction mixture was quenched with 10 mL of a 1:1 hexane and DCM mixture. Then the resulting mixture was filtrated

https://doi.org/10.1021/acs.joc.0c02491
J. Org. Chem. 2021, 86, 6066−6074

over a short pad of silica using a 1:1 hexanes/DCM mixture as the eluent. The filtrate was then concentrated under reduced pressure to saturation at about room temperature. The collected filtrate was cooled down to −18 °C for 15 min, followed by suction filtration, to collect the final yellow solid product. Yield, 170 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73−7.67 (m, 2H), 7.54−7.48 (m, 2H), 6.91 (d, J = 2.35 Hz, 1H), 6.87 (d, J = 9.0 Hz, 1H), 6.72 (dd, J = 9.0, 2.4, 1H), 3.89 (d, J = 2.45 Hz, 2H),3.87 (s, 3H), 2.44 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 44.41 (s, 1F). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 168.2, 160.5 (d, C-F, $1J_{C\text{-}F}$ = 364.2 Hz), 156.2, 139.6, 137.0, 133.5, 131.3, 130.7, 130.0, 129.2, 115.1, 112.1, 109.2 (d, C-F, $3J_{C\text{-}F}$ = 2.2 Hz), 100.7, 55.7, 28.3 (d, C-F, $2J_{C\text{-}F}$ = 58.0 Hz), 13.2.

*2-(3-Cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carbonyl Fluoride (Febuxostat Fluoride) (**3d**).*[38] The title compound was prepared on the benchtop with 76% (40% with PC high temperature experiment) yield following the general preparation method with Febuxostat (1 mmol, 316 mg), KF (2.5 mmol, 145 mg), TFPN (1.05 mmol, 210 mg), and 8 mL of CH_3CN. The reaction mixture was first condensed to 2 mL of total volume and then quenched with a mixture of 13.5 mL of hexane and 2.5 mL of DCM. The resulting mixture was passed through a short pad of silica using a 1:1 hexanes/DCM mixture as the eluent. The filtrate was then concentrated under reduced pressure to the saturation point at room temperature. The concentrated filtrate was then cooled down to −18 °C for 15 min, followed by suction filtration, to collect the final solid product. Yield, 241 mg for reaction done in CH_3CN, and 124 mg for reaction done in PC. Because of the higher polarity of the PC than acetonitrile, we use a mixture of 42 mL of hexane and 7 mL of DCM to quench the reaction while other steps remained the same as for the reaction done in acetonitrile. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.25 (d, J = 2.3 Hz, 1H), 8.13 (dd, J = 8.9, 2.4 Hz, 1H), 7.06 (d, J = 8.9 Hz, 1H) 3.94 (d, J = 6.5 Hz, 2H), 2.82 (s, 3H), 2.24 (non, J = 6.6 Hz, 1H), 1.12 (d, J = 6.7 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 37.63 (s, 1F). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 170.7, 166.6 (d, C-F, $3J_{C\text{-}F}$ = 6.6 Hz), 163.1, 152.0 (d, C-F, $1J_{C\text{-}F}$ = 329.5 Hz), 132.9, 132.5, 125.2, 115.5, 115.1, 112.8, 103.3, 75.8, 28.2, 19.0, 17.8 (d, C-F, $3J_{C\text{-}F}$ = 2.72 Hz). **MS (EI)** m/z $[M]^+$ calculated for $C_{16}H_{15}FN_2O_2S$ = 318, found = 318.

*2-(3-Benzoylphenyl)propionyl Fluoride (Ketoprofen Fluoride) (**3e**).*[38] The title compound was prepared in 65% yield as determined by ^{19}F NMR following the general preparation method, using Ketoprofen (1 mmol, 254 mg), KF (2.5 mmol, 145 mg), and TFPN (1.05 mmol, 210 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77−7.70 (m, 3H), 7.69 (dt, J = 7.22 Hz, 1.65 Hz, 1H), 7.61−7.55 (m, 1H), 7.53−7.43 (m, 4H), 3.95 (q, J = 7.19 Hz, 1H), 1.59 (d, J = 7.19 Hz, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 39.46 (s, 1F). **MS (EI)** m/z $[M]^+$ calculated for $C_{16}H_{13}FO_2$ = 256, found = 256.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02491.

Detailed experimental procedure, NMR and GC-MS results, and computational data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Haoran Sun − *Department of Chemistry & Center for Fluorinated Functional Materials, University of South Dakota, Vermillion, South Dakota 57069, United States;* orcid.org/0000-0001-5514-6144; Email: Haoran.Sun@usd.edu

Authors

Siyu Mao − *Department of Chemistry & Center for Fluorinated Functional Materials, University of South Dakota, Vermillion, South Dakota 57069, United States*

Jordan H. Kramer − *Department of Chemistry & Center for Fluorinated Functional Materials, University of South Dakota, Vermillion, South Dakota 57069, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02491

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the South Dakota Governor's Office of Economic Development for providing initial support through the Center for Fluorinated Functional Materials. Computational chemistry was performed on the Lawrence High Performance Computing System at the University of South Dakota, funded by the NSF (grant number ACI-1626516).

■ REFERENCES

(1) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. Organic fluorine compounds: a great opportunity for enhanced materials properties. *Chem. Soc. Rev.* **2011**, *40*, 3496−3508.

(2) O'Hagan, D. Understanding organofluorine chemistry. An introduction to the C-F bond. *Chem. Soc. Rev.* **2008**, *37*, 308−319.

(3) Hagmann, W. K. The Many Roles for Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2008**, *51*, 4359−4369.

(4) Ogiwara, Y.; Sakino, D.; Sakurai, Y.; Sakai, N. Acid Fluorides as Acyl Electrophiles in Suzuki−Miyaura Coupling. *Eur. J. Org. Chem.* **2017**, *2017*, 4324−4327.

(5) Ogiwara, Y.; Sakai, N. Acyl Fluorides in Late-Transition-Metal Catalysis. *Angew. Chem., Int. Ed.* **2020**, *59*, 574−594.

(6) Fu, L.; Chen, Q.; Wang, Z.; Nishihara, Y. Palladium-Catalyzed Decarbonylative Alkylation of Acyl Fluorides. *Org. Lett.* **2020**, *22*, 2350−2353.

(7) El-Faham, A.; Albericio, F. Peptide Coupling Reagents, More than a Letter Soup. *Chem. Rev.* **2011**, *111*, 6557−6602.

(8) Montalbetti, C. A. G. N.; Falque, V. Amide bond formation and peptide coupling. *Tetrahedron* **2005**, *61*, 10827−10852.

(9) Guo, W.; Huang, J.; Wu, H.; Liu, T.; Luo, Z.; Jian, J.; Zeng, Z. One-pot transition-metal free transamidation to sterically hindered amides. *Org. Chem. Front.* **2018**, *5*, 2950−2954.

(10) Due-Hansen, M. E.; Pandey, S. K.; Christiansen, E.; Andersen, R.; Hansen, S. V. F.; Ulven, T. A protocol for amide bond formation with electron deficient amines and sterically hindered substrates. *Org. Biomol. Chem.* **2016**, *14*, 430−433.

(11) Valeur, E.; Bradley, M. Amide bond formation: beyond the myth of coupling reagents. *Chem. Soc. Rev.* **2009**, *38*, 606−631.

(12) Kangani, C. O.; Kelley, D. E.; Day, B. W. One-pot synthesis of aldehydes or ketones from carboxylic acids via in situ generation of Weinreb amides using the Deoxo-Fluor reagent. *Tetrahedron Lett.* **2006**, *47*, 6289−6292.

(13) Kangani, C. O.; Kelley, D. E. One pot direct synthesis of amides or oxazolines from carboxylic acids using Deoxo-Fluor reagent. *Tetrahedron Lett.* **2005**, *46*, 8917−8920.

(14) Tunoori, A. R.; White, J. M.; Georg, G. I. A One-Flask Synthesis of Weinreb Amides from Chiral and Achiral Carboxylic Acids Using the Deoxo-Fluor Fluorinating Reagent. *Org. Lett.* **2000**, *2*, 4091−4093.

(15) Sakurai, S.; Yoshida, T.; Tobisu, M. Iridium-catalyzed Decarbonylative Coupling of Acyl Fluorides with Arenes and Heteroarenes via C-H Activation. *Chem. Lett.* **2019**, *48*, 94−97.

(16) Ogiwara, Y.; Iino, Y.; Sakai, N. Catalytic C-H/C-F Coupling of Azoles and Acyl Fluorides. *Chem. - Eur. J.* **2019**, *25*, 6513−6516.

(17) Ogiwara, Y.; Sakurai, Y.; Hattori, H.; Sakai, N. Palladium-Catalyzed Reductive Conversion of Acyl Fluorides via Ligand-Controlled Decarbonylation. *Org. Lett.* **2018**, *20*, 4204−4208.

(18) Craig, R.; Litvajova, M.; Cronin, S. A.; Connon, S. J. Enantioselective acyl-transfer catalysis by fluoride ions. *Chem. Commun.* **2018**, *54*, 10108−10111.
(19) Blanchard, N.; Bizet, V. Acid Fluorides in Transition-Metal Catalysis: A Good Balance between Stability and Reactivity. *Angew. Chem., Int. Ed.* **2019**, *58*, 6814−6817.
(20) Cismesia, M. A.; Ryan, S. J.; Bland, D. C.; Sanford, M. S. Multiple Approaches to the In Situ Generation of Anhydrous Tetraalkylammonium Fluoride Salts for SNAr Fluorination Reactions. *J. Org. Chem.* **2017**, *82*, 5020−5026.
(21) Jiang, H.; DiMagno, S. G.; DeGrado, T. R. Production and transport of gaseous 18F-synthons: 18F-acyl fluorides. *J. Fluorine Chem.* **2015**, *180*, 181−185.
(22) Sun, H.; DiMagno, S. G. Anhydrous Tetrabutylammonium Fluoride. *J. Am. Chem. Soc.* **2005**, *127*, 2050−2051.
(23) Christe, K. O.; Wilson, W. W.; Wilson, R. D.; Bau, R.; Feng, J. A. Syntheses, properties, and structures of anhydrous tetramethylammonium fluoride and its 1:1 adduct with trans-3-amino-2-butenenitrile. *J. Am. Chem. Soc.* **1990**, *112*, 7619−25.
(24) Olah, G. A.; Nojima, M.; Kerekes, I. Synthetic methods and reactions. IV. Fluorination of carboxylic acids with cyanuric fluoride. *Synthesis* **1973**, *1973*, 487−8.
(25) Umemoto, T.; Singh, R. P.; Xu, Y.; Saito, N. Discovery of 4-tert-Butyl-2,6-dimethylphenylsulfur Trifluoride as a Deoxofluorinating Agent with High Thermal Stability as Well as Unusual Resistance to Aqueous Hydrolysis, and Its Diverse Fluorination Capabilities Including Deoxofluoro-Arylsulfinylation with High Stereoselectivity. *J. Am. Chem. Soc.* **2010**, *132*, 18199−18205.
(26) Singh, R. P.; Shreeve, J. n. M. Recent advances in nucleophilic fluorination reactions of organic compounds using deoxofluor and DAST. *Synthesis* **2002**, 2561−2578.
(27) Messina, P. A.; Mange, K. C.; Middleton, W. J. Aminosulfur trifluorides: relative thermal stability. *J. Fluorine Chem.* **1989**, *42*, 137−43.
(28) Trofymchuk, S. A.; Kliukovskyi, D. V.; Semenov, S. V.; Khairulin, A. R.; Shevchenko, V. O.; Bugera, M. Y.; Tarasenko, K. V.; Volochnyuk, D. M.; Ryabukhin, S. V. Semi-Industrial Fluorination of *β*-Keto Esters with SF4: Safety vs Efficacy. *Synlett* **2020**, *31*, 565−574.
(29) Trofymchuk, S.; Bugera, M. Y.; Klipkov, A. A.; Razhyk, B.; Semenov, S.; Tarasenko, K.; Starova, V. S.; Zaporozhets, O. A.; Tananaiko, O. Y.; Alekseenko, A. N.; Pustovit, Y.; Kiriakov, O.; Gerus, I. I.; Tolmachev, A. A.; Mykhailiuk, P. K. Deoxofluorination of (Hetero)aromatic Acids. *J. Org. Chem.* **2020**, *85*, 3110−3124.
(30) Smith, W. C.; Tullock, C. W.; Muetterties, E. L.; Hasek, W. R.; Fawcett, F. S.; Engelhardt, V. A.; Coffman, D. D. Fluorination reactions of sulfur tetrafluoride. *J. Am. Chem. Soc.* **1959**, *81*, 3165−6.
(31) L'Heureux, A.; Beaulieu, F.; Bennett, C.; Bill, D. R.; Clayton, S.; La Flamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. Aminodifluorosulfinium Salts: Selective Fluorination Reagents with Enhanced Thermal Stability and Ease of Handling. *J. Org. Chem.* **2010**, *75*, 3401−3411.
(32) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. Bis(2-methoxyethyl)aminosulfur trifluoride: A new broad-spectrum deoxofluorinating agent with enhanced thermal stability. *J. Org. Chem.* **1999**, *64*, 7048−7054.
(33) Gonay, M.; Batisse, C.; Paquin, J.-F. Synthesis of Acyl Fluorides from Carboxylic Acids Using NaF-Assisted Deoxofluorination with XtalFluor-E. *J. Org. Chem.* **2020**, *85*, 10253−10260.
(34) Beaulieu, F.; Beauregard, L.-P.; Courchesne, G.; Couturier, M.; LaFlamme, F.; L'Heureux, A. Aminodifluorosulfinium Tetrafluoroborate Salts as Stable and Crystalline Deoxofluorinating Reagents. *Org. Lett.* **2009**, *11*, 5050−5053.
(35) Chen, C.; Chien, C.-T.; Su, C.-H. Preparation of acyl fluorides with hydrogen fluoride-pyridine and 1,3-dicyclohexylcarbodiimide. *J. Fluorine Chem.* **2002**, *115*, 75−77.
(36) Tyrra, W.; Naumann, D.; Hoge, B.; Yagupolskii, Y. L. A new synthesis of trifluoromethanethiolates-characterization and properties of tetramethylammonium, cesium and di(benzo-15-crown-5)cesium trifluoromethanethiolates. *J. Fluorine Chem.* **2003**, *119*, 101−107.
(37) Scattolin, T.; Deckers, K.; Schoenebeck, F. Direct Synthesis of Acyl Fluorides from Carboxylic Acids with the Bench-Stable Solid Reagent (Me4N)SCF3. *Org. Lett.* **2017**, *19*, 5740−5743.
(38) Munoz, S. B.; Dang, H.; Ispizua-Rodriguez, X.; Mathew, T.; Prakash, G. K. S. Direct Access to Acyl Fluorides from Carboxylic Acids Using a Phosphine/Fluoride Deoxyfluorination Reagent System. *Org. Lett.* **2019**, *21*, 1659−1663.
(39) Gonay, M.; Batisse, C.; Paquin, J.-F. Recent Advances in the Synthesis of Acyl Fluorides. *Synthesis* **2021**, *53*, 653−665.
(40) Foth, P. J.; Malig, T. C.; Yu, H.; Bolduc, T. G.; Hein, J. E.; Sammis, G. M. Halide-Accelerated Acyl Fluoride Formation Using Sulfuryl Fluoride. *Org. Lett.* **2020**, *22*, 6682−6686.
(41) Song, H.-X.; Tian, Z.-Y.; Xiao, J.-C.; Zhang, C.-P. Tertiary-Amine-Initiated Synthesis of Acyl Fluorides from Carboxylic Acids and CF3SO2OCF3. *Chem. - Eur. J.* **2020**, *26*, 16261−16265.
(42) Le, B.; Wu, H.; Hu, X.; Zhou, X.; Guo, Y.; Chen, Q.-Y.; Liu, C. Rapid synthesis of acyl fluorides from carboxylic acids with Cu(O2CCF2SO2F)2. *Tetrahedron Lett.* **2020**, *61*, 152624.
(43) Note: The cost of spray-dried KF (99%) is from about less than 20 cents per gram to about a dollar per gram from various vendors. The price of anhydrous TMAF (95%) is about $50 per gram with only few vendors offering it.
(44) Liang, T.; Neumann, C. N.; Ritter, T. Introduction of Fluorine and Fluorine-Containing Functional Groups. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214−8264.
(45) Adams, D. J.; Clark, J. H. Nucleophilic routes to selectively fluorinated aromatics. *Chem. Soc. Rev.* **1999**, *28*, 225−231.
(46) Note: To reduce the potential chance of HF gas generation during the deoxyfluorination of carboxylic acids, excess KF was used to maintain the basic reaction conditions.
(47) Note: Given the super-hygroscopic nature of KF, in the case of relative high humidity in the lab, precaution must be taken to avoid KF salt absorbing too much moisture to become a watery liquid. This is particularly important when dealing with small scale reactions under a high humidity enviroment. Weighing the KF salt quickly in a glovebag filled with argon or nitrogen is recommended.
(48) Švec, P.; Eisner, A.; Kolářová, L.; Weidlich, T.; Pejchal, V.; Růžička, A. Use of C,N-chelated di-n-butyltin(IV) fluoride for the synthesis of acyl fluorides, fluoroformates and fluorophosgene. *Tetrahedron Lett.* **2008**, *49*, 6320−6323.
(49) Meanwell, M.; Lehmann, J.; Eichenberger, M.; Martin, R. E.; Britton, R. Synthesis of acyl fluorides via photocatalytic fluorination of aldehydic C−H bonds. *Chem. Commun.* **2018**, *54*, 9985−9988.
(50) Boreux, A.; Indukuri, K.; Gagosz, F.; Riant, O. Acyl Fluorides as Efficient Electrophiles for the Copper-Catalyzed Boroacylation of Allenes. *ACS Catal.* **2017**, *7*, 8200−8204.

https://doi.org/10.1021/acs.joc.0c02491
J. Org. Chem. 2021, 86, 6066−6074