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Acyl Azolium Fluorides for Room Temperature Nucleophilic Aromatic Fluorination of Chloro- and Nitroarenes

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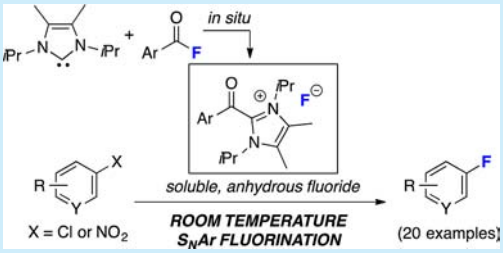
Supporting Information

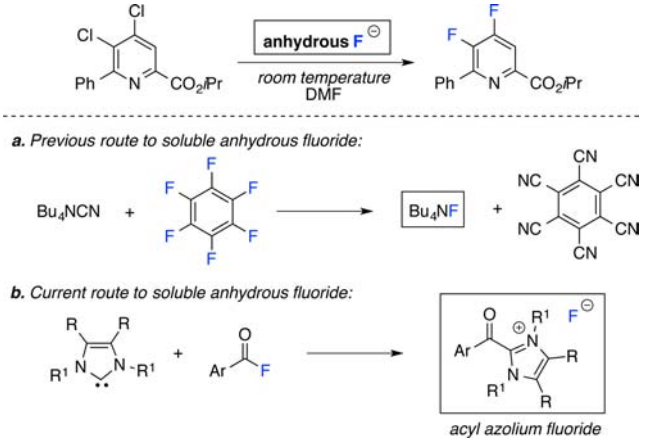
ABSTRACT: The reaction of acid fluorides with *N*-heterocyclic carbenes (NHCs) produces anhydrous acyl azolium fluorides. With appropriate selection of acid fluoride and NHC, these salts can be used for the room temperature S_NAr fluorination of a variety of aryl chlorides and nitroarenes.



The incorporation of fluorine atoms into biologically active molecules can significantly improve properties such as bioavailability, lipophilicity, and metabolic stability.[1] As a result, fluorinated molecules, particularly fluorinated aromatics and heteroaromatics, are common features of both pharmaceuticals and agrochemicals.[1,2] Nucleophilic aromatic fluorination (S_NAr) is a common method for the large-scale preparation of fluorinated aromatics/heteroaromatics.[3] S_NAr fluorination is typically achieved via the reaction of an electron-deficient aryl chloride or nitroarene with an anhydrous alkali metal fluoride salt. These reactions often require elevated temperatures (>130 °C) and long reaction times (>12 h) due to the low solubility and trace water content of the metal fluoride salts. These forcing conditions limit functional group tolerance and can lead to undesired side reactions. In principle, the use of a more soluble, anhydrous fluoride reagent, such as a tetraalkylammonium fluoride, should enable milder reaction conditions. However, such salts are generally only available as hydrates and often decompose upon dehydration in the solid state.[4]

In 2005, Sun and DiMagno reported an elegant strategy for the *in situ* generation of tetrabutylammonium fluoride from hexafluorobenzene (C_6F_6) and tetrabutylammonium cyanide (Scheme 1a).[5] This procedure forms a highly soluble and rigorously anhydrous source of fluoride ($TBAF_{anh}$) that participates in many S_NAr reactions *at room temperature*.[6] Our group has subsequently applied $TBAF_{anh}$ for the room temperature S_NAr fluorination of a variety of biologically relevant 3- and 5-fluoropyridines (Scheme 1).[7] This transformation enables S_NAr fluorination within 10 min under mild conditions in several process-chemistry friendly solvents. However, despite these advantages, the high cost of C_6F_6 and toxicity associated with cyanide limits the potential for process chemistry applications. In addition, the inaccessibility of ^{18}F labeled C_6F_6 precludes translation to radiolabeling applications.[8]

Scheme 1. Soluble Anhydrous Fluoride Sources for S_NAr Fluorination



To start addressing these limitations, we have focused on developing alternative approaches to soluble, anhydrous fluoride for low temperature S_NAr reactions. The reaction of acid fluorides with *N*-heterocyclic carbenes (NHCs) is known to produce acyl azolium fluoride salts (Scheme 1b).[9] In this report, we demonstrate that these acyl azolium fluorides can be used as anhydrous fluoride sources for the room temperature S_NAr fluorination of a variety of aryl chlorides and nitroarenes.[10] Furthermore, we demonstrate that the reactivity of the acyl azolium fluorides is strongly dependent on the structure of both the NHC and the acid fluoride used in this reaction.

Several recent reports have demonstrated that *N*-heterocyclic carbenes and acid fluorides react rapidly at room temperature to afford acyl azolium fluorides (AAFs).[9] We hypothesized that

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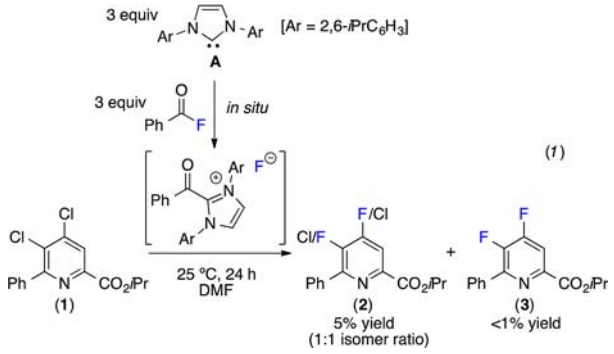
these AAFs should serve as soluble, anhydrous fluoride sources that could be exploited for room temperature S_NAr reactions. Importantly, acid fluorides are available from inexpensive carboxylic acid chlorides and HF or KF,[11] making them relatively affordable fluoride sources.[12] In addition, a straightforward route to ^{18}F-labeled acyl fluorides has recently been reported,[13] which could ultimately enable the translation of this chemistry to PET tracer synthesis.

Our initial studies focused on the use of AAFs for the S_NAr fluorination of 4,5-dichloropicolinate **1**. For comparison, we have previously shown that **1** reacts with 4 equiv of $TBAF_{anh}$ to form the difluorinated product **3** in 79% yield within 24 h at 25 °C in DMF.[7] We first examined the reaction of **1** with the AAF generated from the combination of benzoyl fluoride and carbene **A**[9] (eq 1). Benzoyl fluoride, **A**, and **1** were combined in



anhydrous DMF, and the resulting deep red solution was stirred for 16 h at room temperature. Analysis of the crude reaction mixture by ^{19}F NMR spectroscopy showed the formation of the monofluorinated product **2** in 5% yield as an approximately 1:1 mixture of isomers. The difluorinated product **3** was not detected. The experiment suggests that AAFs can participate in room temperature S_NAr reactions.

We hypothesized that reactivity could be enhanced by changing the structure of the NHC. Several literature reports have shown that the hydrogens on the imidazolium ring (**H**[1] in Figure 1) can serve as hydrogen bond donors.[10,14] A hydrogen

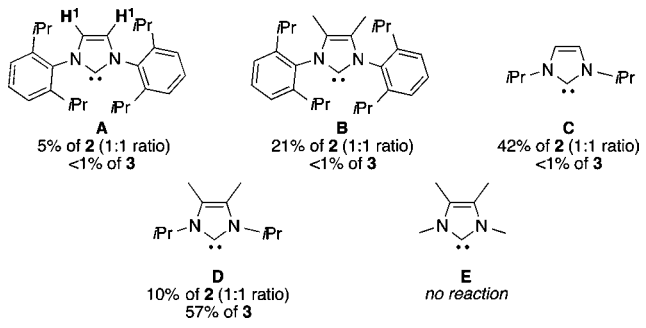


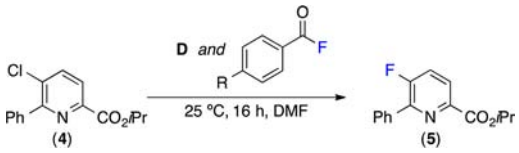
Figure 1. Impact of NHC structure on the S_NAr fluorination of **1** to form **2** and **3**. Conditions: 3 equiv of NHC, 3 equiv of benzoyl fluoride, 1 equiv of **1**, 16 h, 25 °C in DMF (0.2 M). Yields and product ratios determined by ^{19}F NMR analysis of the crude reaction mixtures.

bonding interaction with fluoride would be expected to significantly lower its nucleophilicity. Thus, we next examined carbene **B**, in which the backbone hydrogens are replaced with methyl groups. Under otherwise identical conditions, **B** provided an enhancement in the yield of the monofluorinated product **2** (21%, Figure 1).

We reasoned that the nitrogen substituents of the NHC might also impact the reaction, possibly by modulating the solubility and/or stability of the AAF intermediate. Indeed, changing from 2,6-di-*i*Pr phenyl substituents (in **A**) to *i*Pr substituents (in **C**) led to a substantial increase in the yield of **2** (from 5% to 44%). The best results were obtained with carbene **D**, which bears methyl groups on the imidazolium ring and *i*Pr substituents on the nitrogens. With **D**, the starting material **1** was completely consumed, and the difluorinated product **3** was formed in 57% yield, along with 10% of **2**.

Further optimization was carried out using the 5-chloropicolinate **4**. Substrate **4** is considerably less reactive than **1** toward S_NAr fluorination. For example, **4** does not react at all with carbenes **A**−**C**/benzoyl fluoride over 16 h at room temperature. However, the reaction of 1 equiv of **4** with 3 equiv of **D** and 3 equiv of benzoyl fluoride afforded a 75% yield of the fluorinated product **5** after 16 h at 25 °C in DMF (Table 1, entry 1). Analysis of the reaction mixture by GCMS showed that the mass balance is unreacted **4**. Changing the acid fluoride to the more electrophilic *p*-trifluoromethylbenzoyl fluoride led to a dramatic decrease in the yield of **5** (to 9%, entry 2). In contrast, the use of the more electron-rich *p*-methoxybenzoyl fluoride resulted in quantitative conversion and the formation of **5** in 99% yield as determined by ^{19}F NMR spectroscopy (entry 3). Using the combination of **D** and *p*-methoxybenzoyl fluoride, the loading of carbene and acid fluoride could be reduced to 2 equiv or even 1 equiv relative to **4** with minimal drop-off in yield (89% and 81%, respectively). For comparison, the S_NAr fluorination of **4** with NBu_4Cl/KF (2 equiv/2 equiv) affords an 86% yield after 24 h at 130 °C.[15] Using NBu_4CN/C_6F_6 (2 equiv/0.33 equiv), **4** is converted to **5** in 86% yield in 30 min at room temperature.[7]

Table 1. Effect of Acid Fluoride Structure on Conversion of 4 to 5



entry	R	equiv of **D**	equiv ArC(O)F	yield of **5**[a]
1	H	3	3	75%
2	CF_3	3	3	9%
3	OMe	3	3	99%
4	OMe	2	2	89%
5	OMe	1	1	81%

[a]Yields determined by ^{19}F NMR analysis of the crude reaction mixtures.

With optimal conditions in hand, we next explored the combination of carbene **D** and *p*-methoxybenzoyl fluoride as an anhydrous fluoride source for the S_NAr fluorination of different substrates. As summarized in Figure 2, a variety of 5- and 4,5-substituted chloropicolinate derivatives underwent fluorination to form products **3** and **5**−**9** in modest to excellent isolated yields. The modest yields with 4,5-dichloropicolinate substrates are due to the formation of byproduct **21** (Figure 3).[16] Methoxy, cyano, and trifluoromethyl substituents were compatible with the reaction conditions (see products **7**, **9**, **12**, **15**, **17**, and **20**). In addition, other aryl halide substituents (Cl, Br, and I) were well tolerated at less activated sites in the molecule (see products **6**, **8**, **10**, **14**, **18**, and **19**). Ethyl 3,6-

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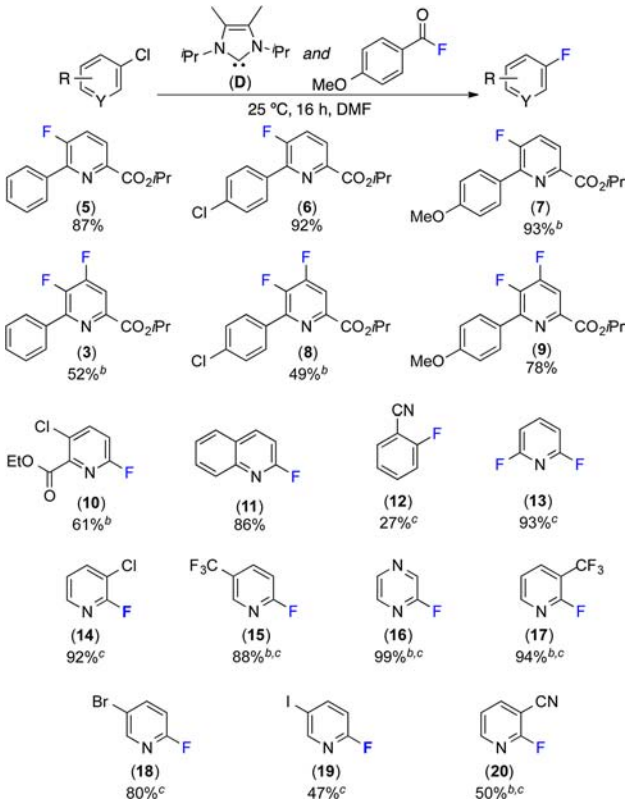

Figure 2. Substrate scope for conversion of aryl/heteroaryl chlorides to fluorides with **D** and *p*-methoxybenzoyl fluoride.[a] [a] General conditions: 1 equiv of aryl chloride, 3 equiv of **D** in DMF (0.2 M in aryl chloride), then 3 equiv of acid fluoride and stir for 16 h at 25 °C. [b] 3 equiv of **D** and 4 equiv of acid fluoride, with **D** added last. [c] Yield determined by ^{19}F NMR spectroscopy.

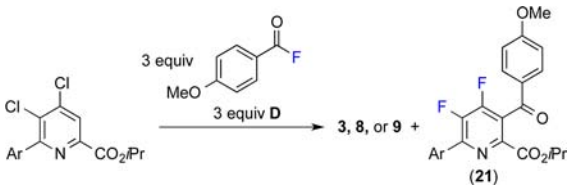

Figure 3. Side product formed along with products **3**, **8**, and **9**[16]

dichloropicolinate reacted to afford selective S_NAr fluorination at the more activated 6-position (product **10**), even in the presence of an excess of **D** and acid fluoride. 2-Chloroquinoline also underwent high yielding room temperature S_NAr fluorination to form **11**. The fluorination of 2-chlorobenzonitrile proceeded to produce **12**, albeit in modest 27% yield. In contrast, the less electrophilic substrate 4-chlorobenzophenone was unreactive.

We next applied **D**/*p*-methoxybenzoyl fluoride to the room temperature fluorodenitration reactions. Nitroarenes are well-known to be more reactive toward S_NAr fluorination than their chloroarene analogues based on the more electron-withdrawing nature of NO_2 versus Cl substituents.[3] Indeed, the use of 2-nitrobenzonitrile and 4-nitrobenzophenone as substrates afforded the corresponding fluorinated products **12** and **22** in high yields after 16 h at room temperature (Figure 4). Fluorodenitration of 2-nitro-5-bromopyridine as well as 4-nitroethylbenzoate also proceeded efficiently to afford products **18** and **23**.

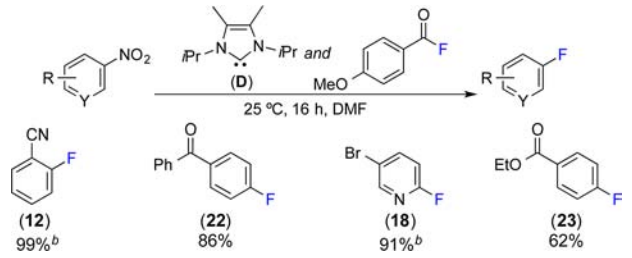

Figure 4. Fluorodenitration with **D** and *p*-methoxybenzoyl fluoride.[a] [a] General conditions: 1 equiv of nitroarene, 4 equiv of acid fluoride in DMF (0.2 M in nitroarene), then 3 equiv of **D** and stir for 16 h at 25 °C. [b] Yield determined by ^{19}F NMR spectroscopy.

In summary, this report demonstrates that the combination of *N*-heterocyclic carbenes and acid fluorides can react to form a fluoride source that participates in room temperature S_NAr fluorination reactions. We anticipate that this strategy will prove more broadly applicable to methods that require anhydrous fluoride reagents.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) See Supporting Information for a proposed mechanism for the formation of **21**.

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