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Nucleophilic Deoxyfluorination of Phenols via Aryl Fluorosulfonate Intermediates

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Supporting Information

ABSTRACT: This report describes a method for the deoxyfluorination of phenols with sulfuryl fluoride (SO_2F_2) and tetramethylammonium fluoride (NMe_4F) via aryl fluorosulfonate (ArOFs) intermediates. We first demonstrate that the reaction of ArOFs with NMe_4F proceeds under mild conditions (often at room temperature) to afford a broad range of electronically diverse and functional group-rich aryl fluoride products. This transformation was then translated to a one-pot conversion of phenols to aryl fluorides using the combination of SO_2F_2 and NMe_4F. Ab initio calculations suggest that carbon−fluorine bond formation proceeds via a concerted transition state rather than a discrete Meisenheimer intermediate.

Aryl and heteroaryl fluorides are common components of numerous pharmaceuticals and agrochemicals.[1] The unique properties of fluorine (high electronegativity, small size, inertness of C−F bonds)[2,3] can impact biological activity by modulating lipophilicity, binding affinity, and/or metabolic stability.[4] However, despite the importance of (hetero)aryl fluorides in medicinal and agricultural chemistry, very few mild, general, and selective synthetic methods exist for the construction of C(sp^2)−F bonds.

From a cost and practicality perspective, the ideal C(sp^2)−F bond-forming reaction would involve the coupling of a nucleophilic fluoride source with a readily available (hetero)aryl electrophile. In addition, the ideal transformation would proceed with a wide scope of electronically diverse substrates under mild reaction conditions and without the requirement for expensive transition metal catalysts or stoichiometric reagents. There are currently three major synthetic methods available for the nucleophilic fluorination of aryl electrophiles: (A) the S_NAr fluorination of aryl chlorides or nitroarenes,[5−7] (B) the Pd-catalyzed fluorination of aryl bromides or triflates,[8−10] and (C) the PhenoFluor-mediated deoxyfluorination of phenols.[11,12] However, none of these methods meet all of the criteria outlined above. As summarized in Figure 1A−C, they each suffer from at least one major limitation with respect to substrate scope, forcing reaction conditions, the formation of isomeric side-products, and/or the requirement for expensive reagents/catalysts.

We report herein the development of a new method for the nucleophilic fluorination of phenol derivatives (ArOH). Notably, phenols are particularly attractive starting materials because many

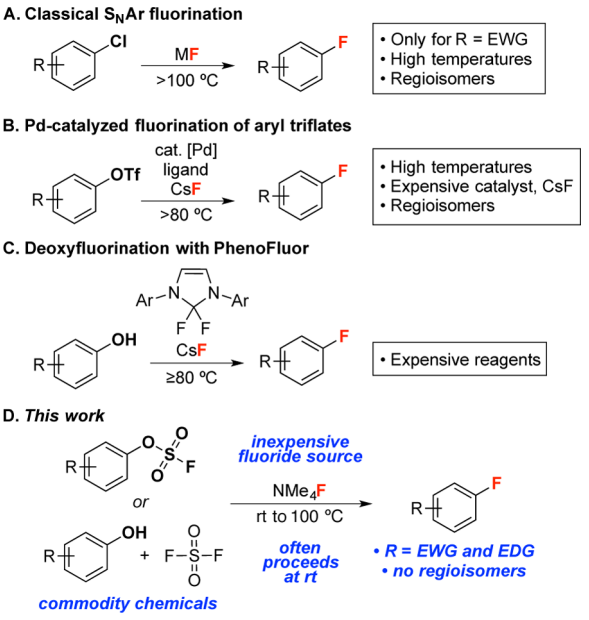

Figure 1. (A−C) Major synthetic methods for nucleophilic fluorination of aryl electrophiles; (D) this work.

are readily available from biomass.[13] This transformation is accomplished by the initial conversion of ArOH to an aryl fluorosulfonate (ArOFs) via reaction with sulfuryl fluoride (SO_2F_2), an inexpensive commodity chemical that is widely used as an insecticide. The nucleophilic fluorination of ArOFs with tetramethylammonium fluoride (NMe_4F) then affords an aryl fluoride product without the requirement for a transition metal catalyst or an expensive stoichiometric reagent (Figure 1D).[14−17] These transformations proceed under milder conditions and with a dramatically enhanced substrate scope relative to traditional S_NAr fluorinations. Ultimately, we demonstrate a scalable one-pot deoxyfluorination of phenols that can be applied to a variety of biologically active substrates. Ab initio calculations implicate a low energy concerted transition state for C(sp^2)−F bond formation, rather than the formation of a discrete Meisenheimer intermediate.

Aryl fluorosulfonates are readily available aryl electrophiles that can be prepared in a single step by the reaction of phenol

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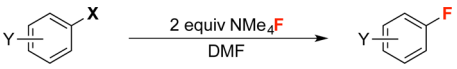
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

derivatives with SO_2F_2.[18−21] We initially examined the reactivity of aryl fluorosulfonates toward nucleophilic fluorination with NMe_4F in order to benchmark their reactivity relative to more traditional aryl electrophiles. 4-Cyanophenyl sulfofluoridate (**1-OFs**) was selected as a test case, because *para*-CN substituents are strongly activating for S_NAr fluorination reactions.[22] These initial studies revealed that **1-OFs** reacts with 2 equiv of NMe_4F within 24 h at room temperature to afford the aryl fluoride **1-F** in 92% yield (Table 1, entry 1).[23,24] This result compares very

Table 1. Fluorination of Different Aryl Electrophiles with NMe_4F.[a]



entry	Y	X (substrate #)	% yield (prod #)
1	*p*-CN	OFs (**1-OFs**)	92 (**1-F**)
2	*p*-CN	Cl (**1-Cl**)	35 (**1-F**)
3	*p*-CN	NO_2 (**1-NO_2**)	88 (**1-F**)
4	*p*-CN	OTf (**1-OTf**)	10 (**1-F**)
5	*p*-CN	OMs (**1-OMs**)	<1 (**1-F**)
6	*p*-CN	OTs (**1-OTs**)	<1 (**1-F**)
7	*p*-CN	OH (**1-OH**)	<1 (**1-F**)
8	*m*-Cl[b]	OFs (**2-OFs**)	67 (**2-F**)
9	*m*-Cl[b]	Cl (**2-Cl**)	2 (**2-F**)
10	*m*-Cl[b]	NO_2 (**2-NO_2**)	15 (**2-F**)
11	*p*-Ph[c]	OFs (**3-OFs**)	85 (**3-F**)
12	*p*-Ph[c]	Cl (**3-Cl**)	<1 (**3-F**)
13	*p*-Ph[c]	NO_2 (**3-NO_2**)	6 (**3-F**)

[a]Conditions: Substrate (0.1 mmol) and NMe_4F (0.2 mmol) stirred in DMF (0.2 M) at 25 °C for 24 h. Yields were determined by ^{19}F NMR spectroscopy. [b]80 °C. [c]100 °C.

favorably to analogous reactions involving other common electrophiles, such as aryl chloride **1-Cl**, nitroarene **1-NO_2**, aryl triflate **1-OTf**, aryl mesylate **1-OMs**, and aryl tosylate **1-OTs** (entries 2−6). These electrophiles universally afforded lower yields than **1-OFs**. Furthermore, times studies (Figure 2) show

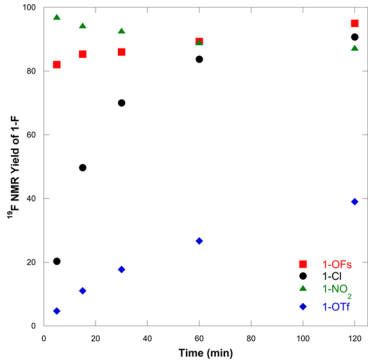


Figure 2. Reaction profiles for the conversion of **1-X** to **1-F** at 80 °C. Yields at each time point were determined by ^{19}F NMR spectroscopy using 1,3,5-trifluorobenzene as a standard.

that the reaction of **1-OFs** with NMe_4F proceeds significantly faster than that of the corresponding aryl chloride **1-Cl** and triflate **1-OTf** at 80 °C. Furthermore, while the nitroarene **1-NO_2** reacts faster than **1-OFs**, the product yield erodes with time due to side reactions involving the NO_2^- leaving group.[25−27] Overall, these results demonstrate that **1-OFs** is a superior electrophile for this transformation.

We next examined the significantly less activated 3-chlorophenyl-substituted electrophiles **2-OFs**, **2-Cl** and **2-NO_2**. As expected based on the extensive literature on classical S_NAr fluorination reactions,[5,26,22,28] **2-Cl** and **2-NO_2** exhibited very low reactivity, affording 2% and 15% yield of **2-F**, respectively, after 24 h at 80 °C (entries 9 and 10). In contrast, **2-OFs** afforded 67% yield of the fluoroarene product under analogous conditions. Remarkably, even the electron-neutral substrate (1,1′-biphenyl)-4-yl sulfofluoridate (**3-OFs**) reacted with NMe_4F to afford **3-F** in 85% yield over 24 h at 100 °C. In contrast, minimal reactivity was observed with **3-Cl** or **3-NO_2** (<1% and 6% yield, respectively). Overall, these results demonstrate the feasibility of the high yielding nucleophilic fluorination of electronically diverse aryl fluorosulfonates. These results stand in marked contrast to those obtained with analogous traditional aryl chloride and nitroarene electrophiles.[29]

We next investigated the scope and limitations of the fluorination of aryl fluorosulfonates with NMe_4F. As shown in Figure 3, aryl fluorosulfonates bearing *para*- or *ortho*-electron-withdrawing substituents reacted with NMe_4F under mild conditions (typically room temperature) to afford **1-F** and **4−10-F** in moderate to high yields. These substrates highlight the compatibility of this method with aryl halides as well as nonenolizable esters, amides, and ketones. Notably, the FsO reacts selectively in the presence of other potential leaving groups such as NO_2 (to form **8-F**) and Cl (to form **9-F**).[30] Aryl fluorosulfonates bearing electron-withdrawing substituents at the less activating *meta*-position also reacted with NMe_4F at 60−80 °C to afford **2-F** and **11−14-F** in good yields. Notably, no isomeric fluorinated products were detected by ^{19}F NMR spectroscopy. This indicates that competing benzyne formation (a common side reaction in S_NAr reactions of less activated aryl electrophiles)[31,32] does not occur under these conditions.

Remarkably, this transformation could also be applied to a variety of electron-neutral and moderately electron-rich arene substrates (Figure 3). For example, the *p*-H, *p*-Ph, and naphthyl fluorosulfonates reacted with 2−5 equiv of NMe_4F over 24 h at 100 °C to afford fluoroarene products **3-F** and **15−18-F**. In addition, aryl fluorosulfonates bearing electron-donating methyl, methoxy, and phenoxy substituents underwent fluorination at 100 °C to afford **19−24-F** in low to moderate yields.[33] Heterocyclic fluorosulfonates, including pyridines, quinolines, carbazoles, and indoles were also viable substrates, affording **25−30-F**.[28] In all of these cases, the only fluorinated product detected was derived from substitution at the *ipso* carbon. Overall, these results demonstrate that the nucleophilic fluorination of ArOFs proceeds with high selectivity to afford a wide range of aryl fluoride products that are not accessible via classical S_NAr reactions.[22,26,28]

We next sought to directly convert phenols to aryl fluorides without the isolation of ArOFs intermediates. Aryl fluorosulfonates are typically synthesized by the reaction of phenols with SO_2F_2 in the presence of a base.[18,34] We reasoned that NMe_4F could act as the base for this reaction, and thus pursued the one-pot combination of ArOH, NMe_4F, and SO_2F_2 to access aryl fluorides.[14] As shown in Figure 4, this one-pot deoxyfluorination of phenols proved highly effective for a variety of phenol substrates.[14,35] The yields from this one-pot procedure were comparable to those obtained from the fluorination of isolated aryl fluorosulfonate intermediates (compare data in Figure 3 to that in Figure 4). Furthermore, the one-pot deoxyfluorination was readily scalable, and comparable yields of **3-F** were obtained

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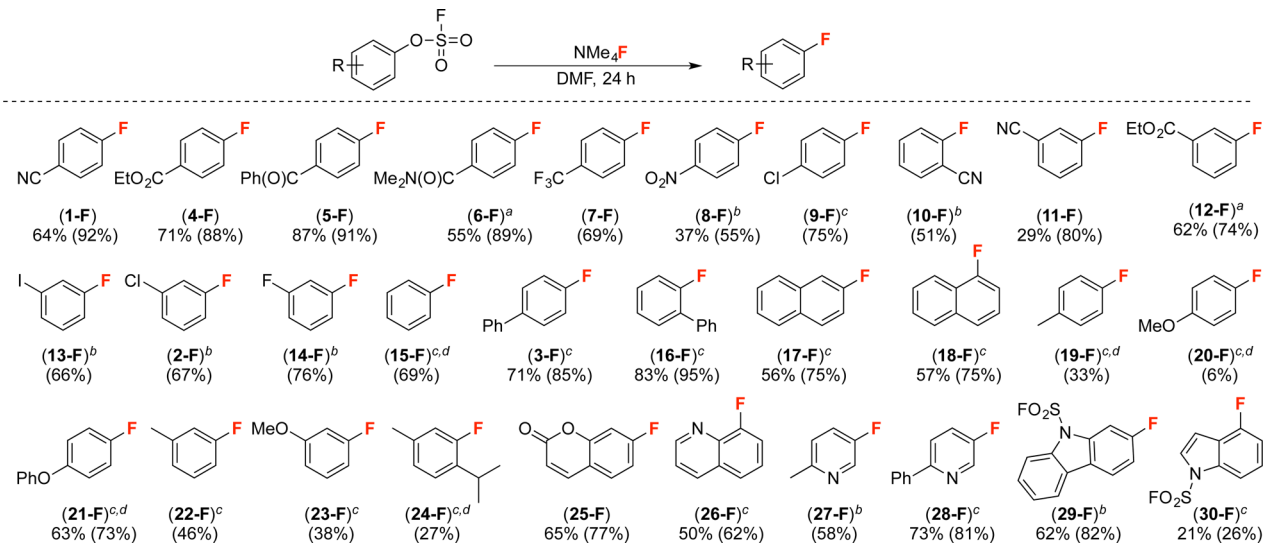

Figure 3. Reactions of ArOFs with NMe_4F. Conditions: 2 equiv of NMe_4F in DMF at 25 °C for 24 h. Isolated yields are reported, with ^{19}F NMR yields in parentheses. [a]60 °C; [b]80 °C; [c]100 °C; [d]5 equiv of NMe_4F.

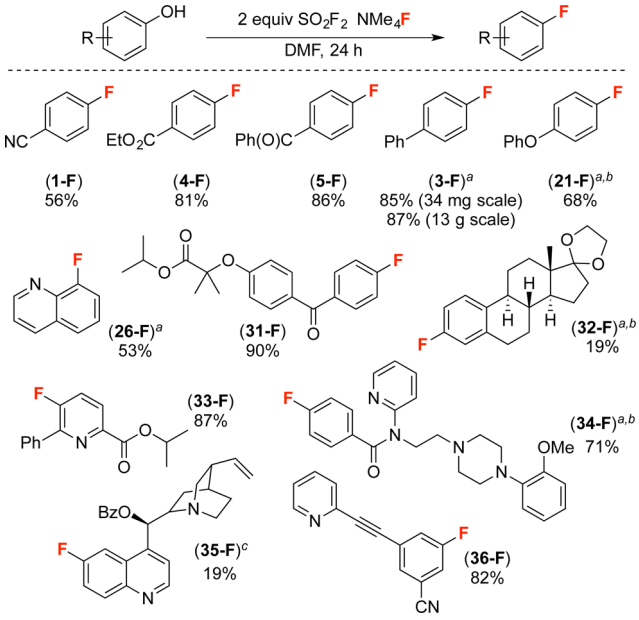

Figure 4. Direct conversion of ArOH to ArF. Conditions: 3 equiv of NMe_4F in DMF at 25 °C for 24 h. Isolated yields are reported. [a]Run at 100 °C; [b]6 equiv of NMe_4F; [c]4.5 equiv of NMe_4F.

on scales ranging from 34 mg to 13 g (85% and 87%, respectively).

This method was next applied to the deoxyfluorination of a series of bioactive molecules. For example, fluorine-containing analogues of the hypercholesterolemia drug fenofibrate,[36] the steroid estrone, and the cinchona alkaloid quinine were prepared (**31-F**, **32-F**, and **35-F**, respectively). Notably, in the latter two cases, the enolizable ketone and the alcohol functional group required protection to avoid side reactions under the basic reaction conditions. The 6-arylpicolinate ester **33-F**, a motif that appears in several herbicides,[37] was synthesized in 87% yield from the corresponding phenol. Finally, 2′-methoxyphenyl-(*N*-2′-pyridinyl)-*p*-fluorobenzamido-ethylpiperazine (MPPF, **34-F**), a serotonin 1A receptor ligand, as well as 3-fluoro-5-(pyridine-2-ylethynyl)benzonitrile (PEB, **36-F**), a metabotropic glutamate receptor subtype 5 ligand, were accessed in good yields from the corresponding phenols. These examples highlight the compatibility of this method with common functional groups including alkenes, esters, aromatic ketones, pyridines, amides, and amines.

To gain preliminary insights into the mechanism of this transformation, we conducted ab initio calculations on the reaction of **1-OFs** with fluoride (F^-).[38] As shown in Figure 5,

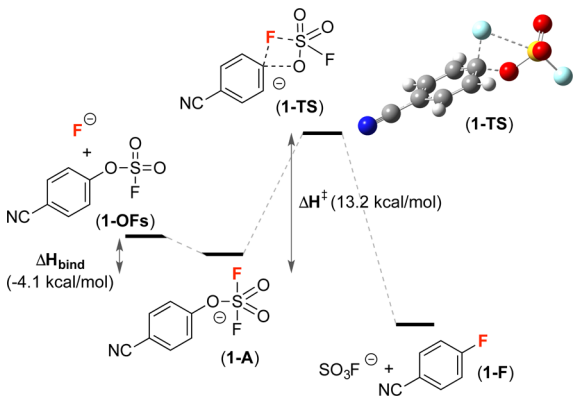

Figure 5. Energy diagram for the reaction of **1-OFs** with fluoride.

these calculations reveal that the binding of fluoride to sulfur to form the pentacoordinate intermediate **1-A** is enthalpically favorable (ΔH_{bind} = −4.1 kcal/mol for **1-OFs** → **1-A**).[39] The conversion of **1-A** to the transition state **1-TS** then proceeds with an activation enthalpy ($\Delta H^{\ddagger}$) of 13.2 kcal/mol, consistent with the fast rate measured experimentally. Importantly, the transition state for this reaction (**1-TS**) is concerted, involving concomitant cleavage of the C(sp^2)−O bond and formation of the C(sp^2)−F bond, without the generation of a Meisenheimer-type intermediate. All computational efforts to identify a stable Meisenheimer complex led to dissociation of the fluorosulfonyl moiety.[40] We note that a similar transition state was implicated as a key feature of the PhenoFluor-mediated deoxyfluorination of phenols.[12]

In summary, this report describes the nucleophilic deoxyfluorination of electronically diverse aromatic and heteroaromatic phenols via aryl fluorosulfonate intermediates. The combination of a wide substrate scope, relatively mild conditions,

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and inexpensive reagents represents a major advance relative to existing aryl fluorination processes. Ab initio calculations implicate a mechanism involving concerted C−O cleavage and C−F bond formation in this transformation. Overall, we anticipate that this method will find extensive application in the synthesis of pharmaceutical and agrochemical target molecules in both discovery and process development applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b12911.

Experimental and spectral data for all new compounds and all reactions reported as well as computational details (PDF)

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Notes

The authors declare the following competing financial interest(s): The Dow Chemical Company has filed a patent application on this chemistry.

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(40) Analogous mechanisms were calculated for electronically diverse *p*-XC_6H_4OFs (X = CN, CF_3, H, Me, OMe). In general, ΔH_{bind} decreases as the substituents become more electron-donating, but this is off-set by an increase in $\Delta H^{\ddagger}$ over the same series. The calculated $\Delta H^{\ddagger}$ values remain relatively low (between 20.8 and 24.0 kcal/mol), consistent with the experimental results with these substrates. For comparison, we also calculated $\Delta H^{\ddagger}$ for the classical S_NAr fluorination of an analogous series of aryl chlorides. These calculations show a $\Delta H^{\ddagger}$ of 16.2 kcal/mol for **1-Cl**, consistent with its significantly lower reactivity relative to **1-OFs**. In addition, $\Delta H^{\ddagger}$ is calculated to be >26 kcal/mol for aryl chlorides bearing electron-neutral and -donating substituents. These high barriers are consistent with the extensive literature showing that these (and related) aryl chlorides are unreactive in S_NAr fluorination reactions. See Scheme S1 for details.

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