Tetramethylammonium Fluoride Alcohol Adducts for S$_N$Ar Fluorination

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ABSTRACT: Nucleophilic aromatic fluorination (S$_N$Ar) is among the most common methods for the formation of C(sp^2)−F bonds. Despite many recent advances, a long-standing limitation of these transformations is the requirement for rigorously dry, aprotic conditions to maintain the nucleophilicity of fluoride and suppress the generation of side products. This report addresses this challenge by leveraging tetramethylammonium fluoride alcohol adducts (Me$_4$NF·ROH) as fluoride sources for S$_N$Ar fluorination. Through systematic tuning of the alcohol substituent (R), tetramethylammonium fluoride *tert*-amyl alcohol (Me$_4$NF·*t*-AmylOH) was identified as an inexpensive, practical, and bench-stable reagent for S$_N$Ar fluorination under mild and convenient conditions (80 °C in DMSO, without the requirement for drying of reagents or solvent). A substrate scope of more than 50 (hetero) aryl halides and nitroarene electrophiles is demonstrated.
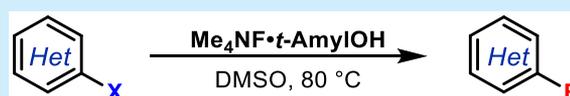
Over the past 20 years, (hetero)aryl fluorides have emerged as important structural features of numerous pharmaceuticals and agrochemicals.[1−5] The C(sp^2)−F bonds of these molecules are commonly formed via nucleophilic aromatic (S$_N$Ar) fluorination reactions of fluoride salts with aryl electrophiles.[6,7] Historically, S$_N$Ar fluorinations have employed anhydrous KF or CsF as the fluoride source (Figure 1A).

A. Classical S$_N$Ar fluorination.
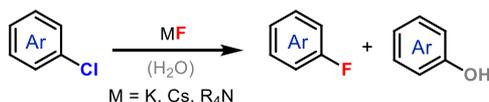
- Highly hygroscopic fluoride sources
- Formation of by-products

B. *Hypothesis:* ROH to modulate fluoride reactivity.

Reactivity for S$_N$Ar fluorination

Me$_4$NF·(H$_2$O)x — Me$_4$NF·ROH — Me$_4$NF (anh)

- Low reactivity
- Hygroscopic
- Competing hydrolysis

- Reactive for S$_N$Ar
- Less hygroscopic
- More practical

- High reactivity
- Hygroscopic
- Anhydrous conditions
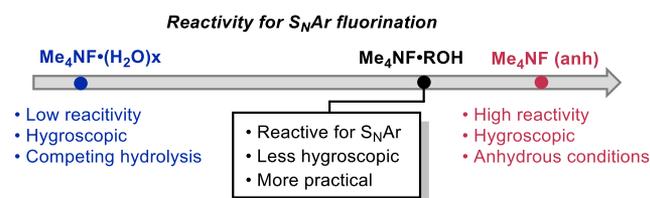
C. *This work:* Me$_4$NF·ROH for S$_N$Ar fluorination.
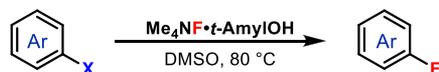
Figure 1. (A) Classical S$_N$Ar fluorination reactions are highly water sensitive. (B) Our hypothesis: complexation of fluoride to an alcohol (ROH) will reduce water sensitivity while maintaining reactivity. (C) Me$_4$NF·*t*-AmylOH as optimal fluoride reagent.

However, because of the low nucleophilicity of these reagents, the reactions require elevated temperatures (>130 °C) and long reaction times, which limit functional group compatibility and lead to side products.[6,8] Recently these challenges have been addressed through the identification of anhydrous fluoride salts with enhanced nucleophilicity.[9−11] For instance, our group has shown that anhydrous tetramethylammonium fluoride [Me$_4$NF (anh)][12−15] effectively promotes many S$_N$Ar fluorination reactions at room temperature. These mild conditions enable a wider substrate scope and minimize competing decomposition pathways.

Despite these advances, existing S$_N$Ar fluorination methods still suffer from a key limitation: the reactions are highly sensitive to water (Figure 1A).[16] Yields and selectivities typically plummet in the presence of even traces of moisture, and this adversely impacts both practicality and reproducibility.[17,18] As such, the substrates, solvents, and hygroscopic fluoride reagents must be rigorously dried, sometimes for days at elevated temperatures.[6,19] The water sensitivity of these reactions stems from strong hydrogen bonding between fluoride and water, which dramatically decreases the nucleophilicity of F$^-$.[8,20−22] In addition, water can serve as a competing nucleophile for S$_N$Ar, resulting in the formation of phenols and related side products (Figure 1A).

This Letter describes our approach to addressing this long-standing challenge by leveraging Me$_4$NF·alcohol adducts as fluoride sources for S$_N$Ar reactions (Figure 1B, C).[23] Our work was inspired by a report from Kim and co-workers,[24] who demonstrated that Bu$_4$NF·(t-BuOH)$_4$ is an effective fluoride reagent for S$_N$2 fluorination. Bu$_4$NF·(t-BuOH)$_4$ was found to be significantly less hygroscopic than anhydrous Bu$_4$NF; furthermore, it afforded comparable/higher yields and fewer E2 byproducts. However, translation of this precedent to S$_N$Ar fluorination presents two key challenges. First, alcohol complexation is well-known to attenuate the nucleophilicity of fluoride.[21,24,25] This is much more problematic for S$_N$Ar fluorinations, as these reactions are typically much slower and more sensitive to protic additives than their S$_N$2 analogues.[26] Second, while the alkyl fluoride products of S$_N$2 reactions are inert toward further substitution,[27] the aryl fluoride products of S$_N$Ar fluorination are highly reactive electrophiles.[28] As such, these can engage with alcohols to generate undesired aryl ether byproducts. Herein, we describe a detailed evaluation of Me$_4$NF·ROH adducts for S$_N$Ar fluorination (Figure 1C). We demonstrate that careful tuning of the alcohol results in a reagent *with high reactivity and selectivity for S$_N$Ar fluorination without the need for exclusion of ambient air/moisture.*

Our initial studies explored Me$_4$NF·MeOH as a fluoride source for S$_N$Ar. As shown in Scheme 1A, Me$_4$NF·MeOH (a key

Scheme 1. (A) Synthesis of Me$_4$NF·MeOH and (B) Reactivity of Me$_4$NF·MeOH for S$_N$Ar Fluorination under Ambient Conditions

A. Synthesis of Me$_4$NF·MeOH.

B. Initial studies for S$_N$Ar fluorination with Me$_4$NF·MeOH
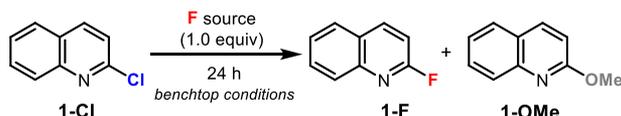
Entry[a]	F source	Solvent	1-F (%)	1-OMe (%)	Conv. (%)
1[b]	Me$_4$NF (anh)	DMF	99	–	100
2	Me$_4$NF·MeOH	DMF	0	0	0
3[c]	Me$_4$NF·MeOH	DMF	10	19	29
4[c]	Me$_4$NF·MeOH	DMA	12	27	39
5[c]	Me$_4$NF·MeOH	MeCN	9	10	19
6[c]	Me$_4$NF·MeOH	NMP	0	0	0
7[c]	Me$_4$NF·MeOH	DMSO	16	32	48
8[d]	**Me$_4$NF·MeOH**	**DMSO**	**25**	**30**	**55**

[a]Conditions: F source (1.0 equiv), 1-Cl (1.0 equiv), 25 °C. ^{1}H NMR yields determined by using nitromethane as standard. [b]Inside glovebox. [c]Reaction carried out at 60 °C. [d]Reaction carried out at 80 °C.

intermediate en route to anhydrous Me$_4$NF) is readily prepared on decagram scale via salt metathesis between KF and Me$_4$NCl in MeOH.[29] However, unlike anhydrous Me$_4$NF, Me$_4$NF·MeOH is a free-flowing powder that can be handled on the benchtop without significant deliquescence.[30]

Me$_4$NF·MeOH was first evaluated as a reagent for the S$_N$Ar fluorination of 2-chloroquinoline (1-Cl). For comparison, 1-Cl reacts with anhydrous Me$_4$NF in DMF at 25 °C in a N$_2$-

atmosphere glovebox to afford 2-fluoroquinoline (1-F) in 99% yield. Using Me$_4$NF·MeOH under analogous conditions but under ambient atmosphere (on the benchtop, without drying of reagents or solvents), the reaction afforded <1% of 1-F (Scheme 1B, entry 2). However, when the temperature was increased to 60 °C, product 1-F was formed in 10% yield, along with 19% of 2-methoxyquinoline (1-OMe) (Scheme 1B, entry 3). We next probed the yield/product distribution as a function of solvent and temperature. Improved reactivity was observed in DMSO at 80 °C (55% conversion, 25% yield of 1-F, Scheme 1B, entry 8); however, 1-OMe remained the major product (30% yield).

A series of competition experiments (see Figures S1 and S2)[31] indicate that 1-OMe derives primarily from the S$_N$Ar etherification of product 1-F under these reaction conditions. Literature studies suggest that such S$_N$Ar etherification reactions can be suppressed by increasing the size of the alcohol.[31] As such, a series of Me$_4$NF·ROH adducts were synthesized by first dissolving Me$_4$NF·MeOH in the appropriate ROH, followed by removal of the volatiles and drying at room temperature overnight under vacuum (Scheme 2A).[32] Me$_4$NF·(ROH)$_x$ (x =

Scheme 2. (A) Synthesis of Me$_4$NF·ROH and (B) Reactivity of Me$_4$NF·ROH for S$_N$Ar Fluorination under Ambient Conditions[a]

A. Synthesis of Me$_4$NF·ROH adducts.
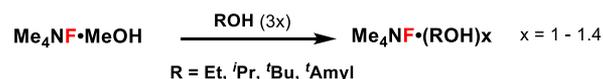
B. Reactivity of Me$_4$NF·ROH adducts.
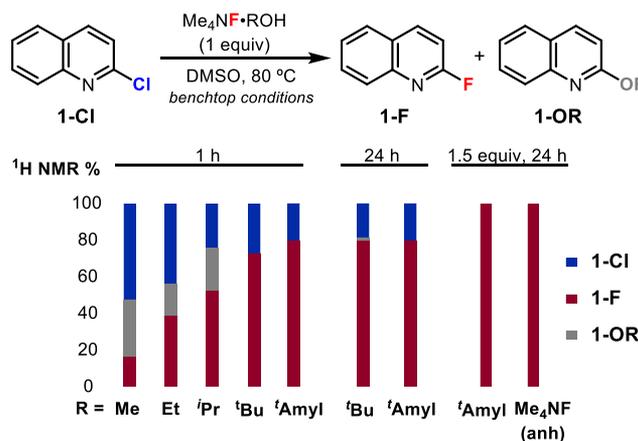
[a]^{1}H NMR yields determined by using nitromethane as standard.

1−1.4) were obtained as free-flowing white solids. Importantly, these syntheses are typically performed on the benchtop (without exclusion of ambient air/moisture) and have been scaled to >25 g.

A series Me$_4$NF·ROH adducts was evaluated for the S$_N$Ar fluorination of 1-Cl in DMSO at 80 °C (Scheme 2B). Both the conversion of 1-Cl and the yield of 1-F improved with increasing substitution on the R group of the alcohol, with MeOH < EtOH < i-PrOH < t-BuOH ~ t-AmylOH.[33,34] As predicted, the yield of the ether byproduct 1-OR decreased dramatically across this series, with <1% of 1-OR being detected with Me$_4$NF·t-AmylOH. Overall, Me$_4$NF·t-AmylOH exhibits the highest fluoride nucleophilicity (as indicated by the % conversion of 1-Cl after 1 h at 80 °C) and lowest alcohol nucleophilicity (as

Scheme 3. Substrate Scope for S$_N$Ar Fluorination with Me$_4$NF·t-AmylOH[h]

$$\text{Ar}-\text{X} \quad or \quad \text{Het}-\text{Cl} \xrightarrow[\text{DMSO, 80 °C, 24 h}]{\text{Me}_4\text{NF·t-AmylOH}} \text{Ar}-\text{F} \quad or \quad \text{Het}-\text{F}$$

Quinolines:

1
99%[b] (73%[b]), X=Cl
99%[b] (74%[b]), X=Br

2
74%[b], X=Cl

3
0%[c], X=Cl

4
99%[b] (84%[b]), X=Cl

5
70%[b] (44%[b]), X=Cl

6
86%[b] (77%[b]), X=Cl

7
96%[b] (84%[b]), X=I

8
33%[b], X=Cl

9
99%[b] (81%[b]), X=Cl

10
83%[b] (60%[b]), X=Cl
71% (76%[b]), X=Br
79%, X=I

11
87%[c] (41%[c]), X=Cl

12
99% (81%[a]), X=Cl

13
83%[b] (91%[a]), X=Cl

14
63%[d] (67%[e]), X=Cl

15
79% (74%[a]), X=Cl

16
82%[b] (76%[b]), X=Cl

Pyridines:

17
79%, X= Cl

18
95%[b], X=NO$_2$

19
65%, X=Cl

20
68%[b], X= Cl

21
99%[b], X= Cl

22
69%[b], X= Cl

23
86%[b], X= Cl

24
64%, X= Br

25
89%[b], X= Cl

26
50%, X=Cl

27
43%[b], X=I
60%[b], X=Cl
60%[b], X=Br
83%[b], X=NO$_2$

28
70%[f] (29%[f]), X=Cl

29
57% (42%), X=Cl

30
70% (43%), X=Cl

31
86% (72%), X=Cl

32
64%[c] (58%[c]), X=Cl

Arenes:

2-substituted

33
<5%[b], X=I
41%[b], X=Cl
52%[b], X=Br
81%[b], X=NO$_2$

4-substituted

34
18%[b], X=I
35%[b], X=Cl
39%[b], X=Br
53%[b], X=NO$_2$

3-substituted

35
0%[c], X=Br
0%[c], X=NO$_2$

36
38%[c] (28%[c]), X=NO$_2$

37
33%[b] (30%[b]), X=NO$_2$

38
35%[b] (31%[b]), X=NO$_2$

Diazines:

39
78%, X=Cl

40
92% (90%[a]), X=Cl

41
74%[b] (59%[a]), X=Cl

42
58%[b] (42%[b]), X=Cl

43
75%[b] (58%[b]), X=Cl

44
91%[b] (59%[b]), X=Cl

45
99%[b] (84%[b]), X=Cl

46
98% (90%[a]), X= Cl

47
91%[c] (77%[d]), X=Cl

48
99% (94%[a]), X=Cl

Fused Heterocycles:

49
53%[b] (44%[b]), X=Cl

50
82%[b] (52%[b]), X=Cl

51
32% (21%[b]), X=Cl

52
99% (63%[a]), X=Cl

53
91% (47%[a]), X=Cl

54
94% (74%[a]), X=Cl

55
95% (86%[a]), X=Cl

56
99%[g] (93%[a,g]), X=Cl

57 R = Bn, 84% (63%[a])
58 R = Me, 90% (69%[a])
X=Cl

[a]With 1.1 equiv of Me4$_N$F·t-AmylOH. [b]With 1.5 equiv of Me$_4$NF·t-AmylOH. [c]With 2.0 equiv of Me$_4$NF·t-AmylOH. [d]With 2.1 equiv of Me$_4$NF·t-AmylOH. [e]With 2.5 equiv of Me$_4$NF·t-AmylOH. [f]With 3.5 equiv of Me$_4$NF·t-AmylOH. [g]At 45 °C. [h]Conditions: Me$_4$NF·t-AmylOH (1.0 equiv) and substrate (1.0 equiv) were stirred in DMSO (0.2 M) at 80 °C for 24 h. Yields determined using ^{19}F NMR spectroscopy with 1,3,5-trifluorobenzene as standard. Isolated yields are given in parentheses.

indicated by the yield of **1-OR** after 1 or 24 h at 80 °C) among the alcohol adducts examined. Further optimization of the reaction time (moving from 1 to 24 h) and equivalents of Me$_4$NF·t-AmylOH (changing from 1.0 to 1.5 equiv) resulted in a quantitative yield of **1-F**.[35] Under these conditions, the reaction was highly reproducible (yields varied by ±5% over 12 runs). Furthermore, the yield showed minimal variance with different batches of DMSO or with changes in the ambient humidity.[36]

We next explored the scope of S$_N$Ar fluorination with Me$_4$NF·t-AmylOH for various commercially available halo- and nitro-(hetero)arene electrophiles. As summarized in Scheme 3, good to excellent yields were obtained for >50 different quinoline, pyridine, electron-deficient arene, diazine, and fused heterocyclic substrates.[37] Importantly, all of these transformations were conducted on the benchtop at 80 °C, without drying or purification of the electrophile substrates or DMSO solvent. These reactions provided comparable yields on scales ranging from 40 mg to 1 g (for instance **1-F** was obtained in 73% and 92% isolated yield, respectively, on these scales). Some other key trends and observations from these studies are summarized below.

(1) *Functional group compatibility.* Arene substituents including halogen (F, Cl, Br, I), nitrile (**21−23,33−35**), ether (**9**), ester (**16, 31, 32**), trifluoromethyl (**17**), nitro (**20, 25**), tertiary nitrogen (**45**), and N-Boc protecting groups (**48**) are all compatible with Me$_4$NF·t-AmylOH S$_N$Ar reactions. Many of these are valuable handles for downstream functionalization. In addition, various heterocycles found in biologically relevant scaffolds are tolerated (e.g., imidazole, pyrazole, indole, pyrrolidine, piperazine, benzimidazole).

(2) *Inherent reactivity.* In a series of isomeric chloroquinoline electrophiles, the 2-Cl derivative affords the highest yield (99% of **1-F**) followed by the **4-Cl** (74% of **2**), and then the **3-Cl** (0% of **3**). A similar trend was observed in the nitro benzonitrile series (**33** in 81% yield; **34** in 53% yield; **35** in 0% yield) and the bromo benzonitrile series (**33** in 52% yield; **34** in 39% yield; **35** in 0% yield). This reactivity reflects well-documented trends in S$_N$Ar reactions.[38]

(3) *Site selectivity of substitution.* In substrates containing multiple possible leaving groups, S$_N$Ar fluorination with Me$_4$NF·t-AmylOH reliably favors substitution at the more activated site, independent of the nature of the leaving group. This is exemplified by **4−7** and **24−27**, as well as **18** versus **20**.

(4) *Effect of leaving group.* The impact of the leaving group on reaction yield was examined in three different classes of substrates (that form products **27, 33,** and **34**).[39] In all cases, the yields trend as follows: NO$_2$ > Cl ∼ Br > I. This is generally consistent with observations in other S$_N$Ar fluorination systems.[12]

(5) *Biologically relevant scaffolds.* Substrate **16-Cl**, which forms the core of quinazoline based antibiotics, underwent S$_N$Ar fluorination to afford **16** in 76% isolated yield. In addition, 5-fluoropicolinate **32** was obtained using this method. This structural motif appears in numerous agrochemical candidates.[40]

In summary, this Letter describes the development of Me$_4$NF·ROH adducts as reactive and practical reagents for S$_N$Ar fluorination. We show that the alcohol substituent (R) can be tuned to enhance the nucleophilicity of fluoride as well as to mitigate competing S$_N$Ar of the alcohol. Me$_4$NF·t-AmylOH was ultimately identified as the optimal fluoride reagent. It can be synthesized, stored, and utilized on the benchtop without the rigorous exclusion of air/moisture. Furthermore, Me$_4$NF·t-AmylOH proved effective for the S$_N$Ar fluorination of a wide range of aryl and heteroaryl electrophiles under mild and convenient conditions (80 °C in DMSO, without drying of solvent or reagents). Overall, we anticipate that this reagent will find widespread application in the construction of C(sp^2)−F bonds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01490.

Experimental procedures, characterization data, and NMR spectra (PDF)

FAIR data, including the primary NMR FID files, for compounds **1, 4, 5−7, 9−16, 28−32, 36−38, 40−58**, Me$_4$NF·EtOH, Me$_4$NF·iPrOH, Me$_4$NF·MeOH, Me$_4$NF·t-AmylOH, and Me$_4$NF·t-BuOH (ZIP)

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Author Contributions

‡M.T.M.-C. and Y.Y.S. contributed equally. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(31) S_NAr etherification of **1-F** requires the presence of a base (in this case fluoride). Stirring **1-F** for 24 h at 80 °C in DMSO and in the presence of 1 equiv of MeOH did not afford **1-OMe**. In contrast, the analogous reaction in the presence of 1 equiv of Me4NF·MeOH afforded **1-OMe** in 83% yield (^{1}H NMR).

(32) Attempts to prepare the tertiary alcohol adducts Me4NF·*t*-BuOH and Me4NF·*t*-AmylOH directly from Me4NCl and KF via salt metathesis in the respective solvents were unsuccessful even at higher temperatures. We postulate that this is due to the low solubilities of KF and KCl in these alcohols.

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(35) Control reactions using anhydrous potassium fluoride (KF) or cesium fluoride (CsF) under these conditions afforded **1-F** in < 1% or 47% yield, respectively.

(36) The DMSO solvent used for all reactions in this work contains 28.7 ppm of water, as determined by Karl Fisher titration. However, as

shown in Table S5, similar reactivity was observed for **1-Cl** using a different batch of DMSO containing 2120 ppm of water. More detailed studies evaluating the effect of water on the reactions of both **1-Cl** and **32-Cl** are shown in Tables S3−S6.

(37) In some cases, isolated yields were lower than ^{19}F NMR yields due to the difficult separation from remaining starting material.

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