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Facile Nucleophilic Fluorination Reactions Using *tert*-Alcohols as a Reaction Medium: Significantly Enhanced Reactivity of Alkali Metal Fluorides and Improved Selectivity

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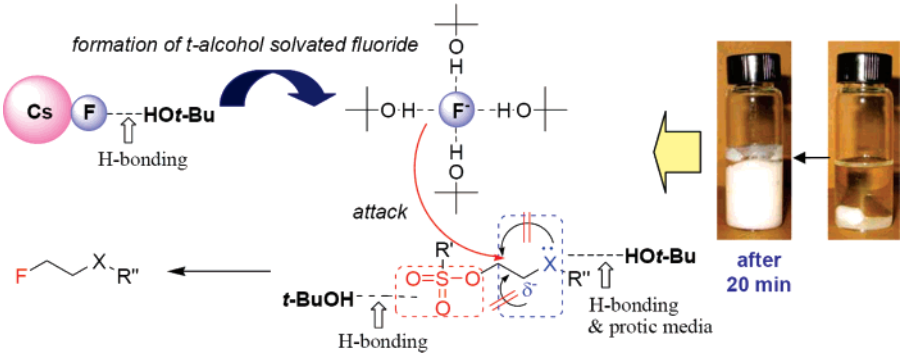

Although protic solvents are generally not preferred for nucleophilic displacement reactions because of their partial positive charge and hydrogen-bonding capacity that solvate the nucleophile and reduce its reactivity, we recently reported a remarkably beneficial effect of using tertiary alcohols as a reaction media for nucleophilic fluorination with alkali metal fluorides, as well as fluorine-18 radiolabeling with [^{18}F]fluoride ion for the preparation of PET radiopharmaceuticals. In this work, we investigate further the influence of the *tert*-alcohol reaction medium for nucleophilic fluorination with alkali metal fluorides by studying various interactions among *tert*-alcohols, the alkali metal fluoride (CsF), and the sulfonyloxy substrate. Factors such as hydrogen bonding between CsF and the *tert*-alcohol solvent, the formation of a *tert*-alcohol solvated fluoride, and hydrogen bonding between the sulfonate leaving group and the *tert*-alcohol appear to contribute to the dramatic increase in the rate of the nucleophilic fluorination reaction in the absence of any kind of catalyst. We found that fluorination of 1-(2-mesyloxyethyl)naphthalene (**5**) and *N*-5-bromopentanoyl-3,4-dimethoxyaniline (**8**) with $Bu_4N^+F^-$ in a *tert*-alcohol afforded the corresponding fluoro products in much higher yield than obtained by the conventional methods using dipolar aprotic solvents. The protic medium also suppresses formation of byproducts, such as alkenes, ethers, and cyclic adducts.

1. Introduction

Methods for introducing a fluorine atom at a specific molecular site have received much attention because of the generally favorable pharmaceutical properties of many fluorine-containing organic compounds.[1] This is especially true for radiopharmaceuticals labeled with fluorine-18 that are used as in vivo probes for the noninvasive imaging of molecular and biological processes in living subjects using positron emission tomography (PET). For this application, in particular, fluorine-18 has many desirable characteristics: small steric size, stable bonding to carbon, suitable decay rate and properties ($t_{1/2}$ = 110 min), low positron energy, and ease of production.[2]

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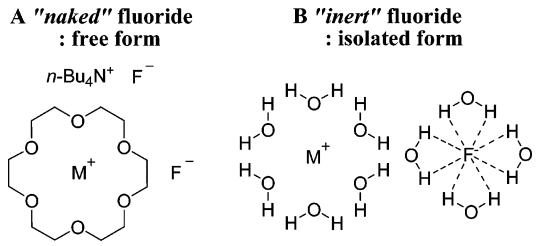

FIGURE 1. Various fluoride sources. (A) Phase-transfer-type protocols: "naked" (free) fluoride from TBAF or MF/crown ethers—strong nucleophiles as well as strong bases. (B) Hydrated fluoride in water: "inert" (isolated) fluoride—neither nucleophilic nor basic.

The nucleophilic displacement of various sulfonates and halides by fluoride ion is the method typically used for the introduction of a single fluorine atom at a specific aliphatic molecular site.[3] While alkali metal fluorides are the reagents traditionally used for this purpose, their limited solubility in organic solvents and their generally low nucleophilicity means that vigorous reaction conditions are required for this sort of substitution. Curiously, in their desolvated state, fluoride ions are, in fact, potent nucleophiles,[3] but in water they are tightly hydrated and become chemically inert ("*inert*" fluoride, Figure 1B). Perhaps the sole exception of this is enzymatic fluorination in water catalyzed by a fluorinase enzyme, but here, specific hydrogen bonding of the enzyme with the fluoride and the substrate appears to facilitate formation of C−F bonds.[4]

To facilitate nucleophilic aliphatic fluorinations, various "*naked*" fluoride ion systems have been developed. Fluoride ion solubility and nucleophilicity are improved by the use of bulky countercations, often generated by phase-transfer type protocols,[5] such as tetrabutylammonium fluoride (TBAF), or by alkali metal fluoride/crown ether complexation (Figure 1A). While the enhanced nucleophilicity of these naked fluoride ions generally accelerates the rate of nucleophilic fluorination,[6] these systems are generally strongly basic, which restricts their synthetic utility because it engenders various side reactions, such as eliminations of alkyl halides or sulfonates to form alkenes.[7] In addition, because it is difficult to get naked fluoride that is completely anhydrous, naked hydroxide typically completes with fluoride in nucleophilic substitutions, leading to hydroxylations that form alcohols.[7]

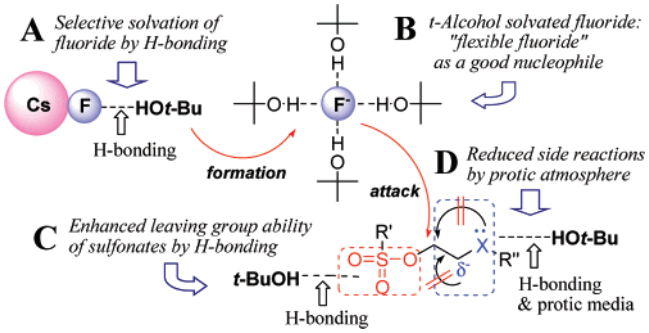

FIGURE 2. Four proposed reactivity-enhancing effects of a *tert*-alcohol medium on nucleophilic aliphatic fluorination reactions.

It is well-known that protic solvents do not provide the proper medium for most nucleophilic displacement reactions. Despite of their good solvating ability for salts, protic solvents reduce the nucleophilicity of the anion by extensive hydrogen bonding and interaction with the partial positive charge of these solvents. Consequently, dipolar aprotic solvents, such as *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and acetonitrile, have been widely used as a medium for these substitution reactions. Anions in this latter medium usually show enhanced nucleophilicity that results from the selective solvation of their counter cations by the negative end of the dipolar aprotic solvent dipole and the lack of a proton for hydrogen bonding, which leave the anions free or "naked". In dipolar aprotic solvents, the halide ions are all of comparable nucleophilicity, whereas their nucleophilicity in protic solvents is much different, following the order $I^- > Br^- > Cl^- > F^-$, the progressive reduction in reactivity reflecting the increasing solvation of the smaller anions by the protic solvent.[8]

Recently, we reported a highly efficient aliphatic nucleophilic fluorination method with alkali metal fluorides using nonpolar protic *tert*-alcohols as a reaction medium. In this method, the *tert*-alcohol media not only greatly enhanced the reactivity of alkali metal fluorides, it also reduced the formation of typical byproducts (namely, alkenes, alcohols, or ethers) compared to those obtained with conventional dipolar aprotic solvents.[3,7,9] The attributes of this novel fluorination method were particularly important for the efficient preparation of [^{18}F]fluorine-substituted radiopharmaceuticals for PET imaging studies. Since our findings are in marked contrast with the expectations from the conventional S_N2 mechanism, we wanted to elucidate further the mechanism of the S_N2 fluorination reaction in *tert*-alcohol solvent. In the present work, we have examined the influence of the *tert*-alcohol medium on S_N2 fluorination reactions with cesium fluoride and other fluorides through a variety of experiments.[10]

As shown Figure 2, we imagined that the *tert*-alcohol solvent system might have four influences on the mechanism of this

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(11) See the Supporting Information of ref 9a.

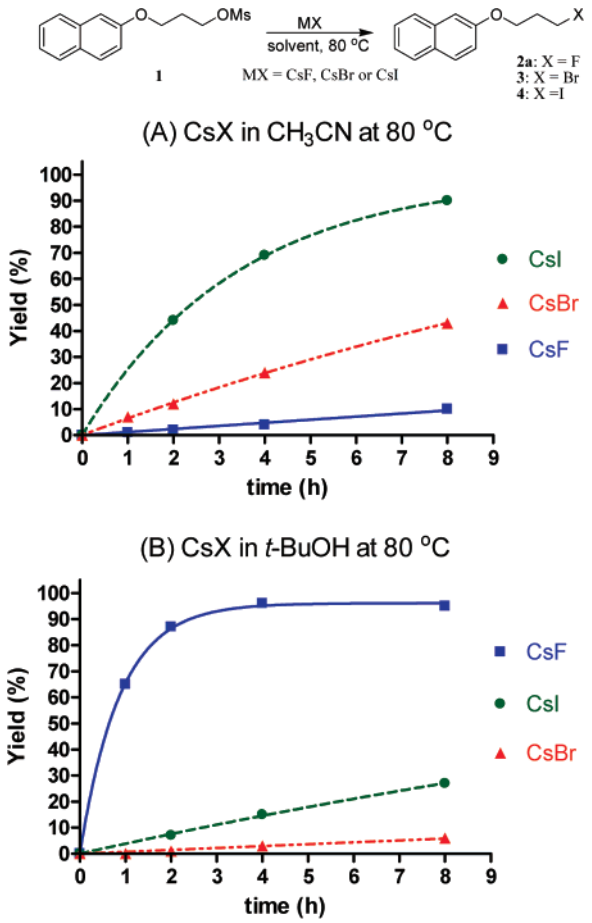


FIGURE 3. Solvent dependence of the reactivity of CsF, CsBr, and CsI in a nucleophilic substitution reaction. All reactions were carried out on a 0.12 mmol reaction scale of mesylate **1**, using 3 equiv of cesium halide in 0.5 mL of solvent at 80 °C; product yields were determined by ^{1}H NMR.

fluorination process, all of which we have studied. Part A: The strength of the CsF ionic bond might be reduced by hydrogen bonding of the *tert*-alcohol solvent with the fluoride in the CsF lattice, resulting in selective solvation of the fluoride into *tert*-alcohol reaction media. Part B: The limited solvation of fluoride coordinated with bulky *tert*-alcohols, which we term a *"flexible"* fluoride, might make the fluoride an especially good nucleophile in this medium. Part C: Hydrogen bonding of the *tert*-alcohol solvent with oxygen atoms of a sulfonate leaving group might enhance leaving group ability. Part D: The protic environment of the reaction medium, as well as hydrogen bonding between the *tert*-alcohol and reactive heteroatoms in the substrate, might reduce side reactions such as eliminations, hydroxylations and intramolecular alkylations.

2. Results and Discussion

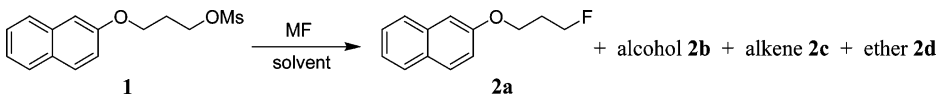
2. A. Selective Solvation of Fluoride Ion by H-Bonding in *tert*-Alcohol Solvents. Figure 3 illustrates the dependence of the reactivity of three cesium halides—CsF, CsBr, and CsI—on two different solvent systems, nonpolar protic (*t*-BuOH) and dipolar aprotic (acetonitrile), to elucidate the first proposed effect of the *tert*-alcohol medium on a nucleophilic fluorination reaction. For an S_N2 reaction using metal salts to proceed, their ion pairs need to be separated during the reaction. Figure 3A shows that the reactivity of the three cesium salts, CsF, CsBr, and CsI, in the reaction of alkyl mesylate **1** to the corresponding alkyl halides (**2a**, **3**, and **4**, respectively) in acetonitrile. In this representative dipolar aprotic solvent at 80 °C, the reaction rate is inversely dependent on the strength of their ionic bonding: the weaker the ionic bonding of the cesium halide, the higher the reactivity. Thus, in acetonitrile, the order of reactivity is CsI > CsBr > CsF. By contrast, at 80 °C with *t*-BuOH, a nonpolar protic solvent, the reactivity of CsF, which can form the strongest hydrogen bonding, shows a greatly enhanced rate of substitution with 2-(3-fluoroproproxy)naphthalene (**2a**) (Figure 3B), with the other cesium halides following the reverse order of reactivity: CsF ≫ CsI > CsBr. These results suggest that effective hydrogen bonding can occur between the *tert*-alcohol solvent and fluoride ion in the CsF lattice that weakens the ionic bonding of the salt, and that by selective—and presumably moderate—solvation of the fluoride ion, it makes it a potent nucleophile. We believe that this effect (part A in Figure 2) may be the most important factor in the reactivity-enhancing effect of *tert*-alcohols on this reaction pathway.

2. B. Formation of *"Flexible"* Fluoride as a Good Nucleophile. Table 1 presents the results of the same fluorination reaction using CsF or TBAF, using different solvents. We carried out the reaction of mesylate **1** with CsF to fluoroalkane **2a** at 80 °C for 6 h in MeOH, EtOH, *n*-PrOH, *t*-BuOH, *tert*-amyl alcohol, and 3-methyl-3-pentanol to examine the influence of steric hindrance of the alcohol solvent on the reaction rate and product purity (entries 1−7, Table 1). The rate of fluorination increased with increasing bulk of the alcohol (reaction rates follow the order *tert*-alcohol > i-PrOH > EtOH > MeOH); the selectivity against formation of the ether byproduct **2d** also increased. Comparison with entries 8 and 9 in Table 1 shows that "*naked*" fluoride from TBAF in *t*-BuOH shows similar (slightly lower) nucleophilicity than TBAF in CH_3CN, while water-solvated fluoride (fluoride ion has a high hydration energy, 117 kcal/mol) is not reactive, regardless of whether CsF or TBAF is used (entries 10 and 11).

These results suggest that because of its bulk, the *tert*-alcohol does not coordinate to fluoride too tightly and thus affords some flexibility between the alcohol and fluoride. Thus, *tert*-alcohol-solvated fluoride, which we have termed "*flexible*" fluoride, generated from the cesium fluoride lattice by hydrogen bonding with the *tert*-alcohol, can be a good nucleophile for nucleophilic fluorination.

2. C. Leaving Group Ability in *tert*-Alcohol Solvents. Mesylates, iodides, and bromides are widely used as leaving groups in nucleophilic substitution reactions, and in most S_N2 reactions, the order of leaving group ability is mesylates > iodides > bromides.[8] Figure 4 shows a comparison of the leaving group ability of mesylate, bromide, and iodide in the fluorination reaction as a function of solvent. The rate of consumption of alkyl mesylate **1**, bromoalkane **3**, and iodoalkane **4** under the conventional fluorination reaction conditions using TBAF in acetonitrile as a dipolar aprotic solvent at 60 °C, or under the fluorination reaction conditions using CsF in *tert*-amyl alcohol as a nonpolar protic solvent 90 °C, show pronounced differences in reactivity. The rate of loss of mesylate **1** is slightly slower than that of halides **3** and **4** under conventional fluorination conditions (Figure 4A), the leaving group reactivity order being iodide ≥ bromide ≥ mesylate. By contrast, the rate of loss mesylate **1** is enhanced dramatically relative to that of the halides in the *tert*-alcohol medium (Figure 4B), the leaving group reactivity order being mesylate ≫ iodide

TABLE 1. Fluorinations of Mesylate 1 with CsF in Different Solvents[a]



1 2a

entry	solvent	MF	reaction temp (°C)	reaction time (h)	yield of product[b] (%) 1	2a	2b	2c	2d
1	MeOH	CsF	80	6	35	20			43
2	EtOH	CsF	80	6	19	47			31
3	*n*-PrOH	CsF	80	6	10[c]	58			29
4	*i*-PrOH	CsF	80	6	6c	78			14
5[d]	*t*-BuOH	CsF	80	6	trace	92			7
6[d]	*t*-amyl alcohol	CsF	80	6		93			5[c]
7	3-methyl-3-pentanol	CsF	80	6		94			3[c]
8	CH_3CN	TBAF	60	1.5		92	5[c]	trace	
9	*t*-BuOH	TBAF	60	1.5	trace	91	3[c]		trace
10	H_2O/toluene (1:1)	CsF	80	6	96				
11	H_2O/CH_3CN (1:1)	TBAF	60	1.5	95				

[a] All reactions were carried out on a 1.0 mmol reaction scale of mesylate **1**, using 3 mmol of metal fluoride in 4.0 mL of solvent. [b] Isolated yield. [c] NMR determined yield. [d] Reference 10.

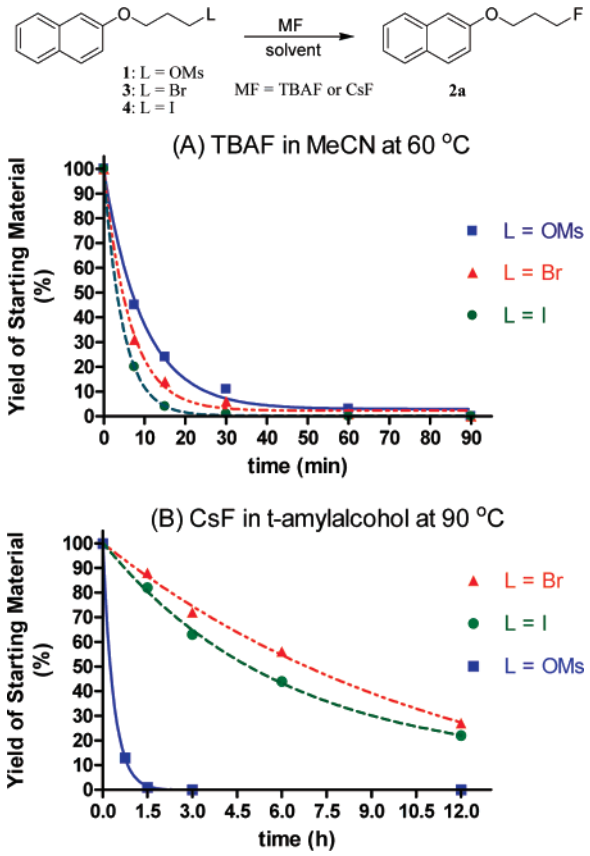


FIGURE 4. Dependence of leaving-group reactivity of bromoalkane **3**, iodoalkane **4**, and mesylate **1** on the reaction medium. All reactions were carried out on a 0.12 mmol reaction scale of starting material, using 3 equiv of metal fluoride in 0.5 mL of solvent. The quantity of starting material remaining was determined by ^{1}H NMR.

> bromide. This result suggests that effective hydrogen bonding between the oxygen atoms in the mesylate substrate and the *tert*-alcohol solvent may enhance its leaving group activity compared to that of the halides which are less effective in forming hydrogen bonds in alcohol media.

We could observe a unique phase change in the reaction medium during the progress of the reaction. Parts a and b of Figure 5a and b show that the reaction medium of the

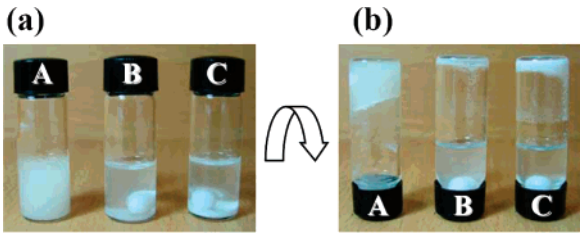
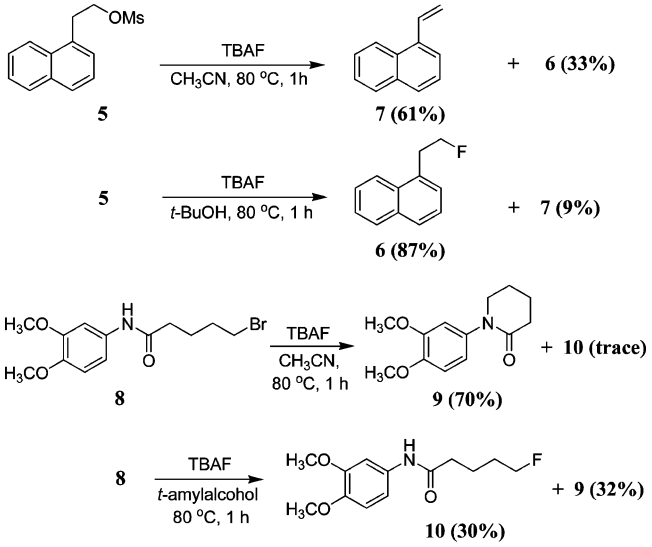


FIGURE 5. (a) Picture of formation of a gel-like solid during the fluorination reaction using CsF in *t*-BuOH: (vial A) 0.5 mmol reaction scale of mesylate **1** using CsF in 2 mL of *t*-BuOH after 30 min at 90 °C; (vial B) the same reaction condition as that of vial A except for the use of bromoalkane **3** instead of mesylate **1** after 6 h; (vial C) the same reaction condition as that of vial A except for the use of CsBr instead of CsF after 6 h. (b) The result of inverting the reaction vials: (vial A) gel-like solid remains adhered to the vial bottom; (vials B and C) gel-like solid does not form.

fluorination of mesylate **1** using CsF in *t*-BuOH at 90 °C (vial A) starts to turn into a heterogeneous liquid phase that becomes a gel-like solid after approximately 20 min. After the reaction was complete, the reaction medium of the gel-like solid phase again returned to a heterogeneous liquid phase.[2] By contrast, with bromoalkane **3** as a substrate instead of mesylate **1** in the same reaction media (vial B) or using CsBr as a nucleophile source instead of CsF in the same reaction media (vial C), no change in the reaction medium was observed during the progess of the reaction. This result suggests that the interaction between the *tert*-alcohol solvent, CsF ("*flexible fluoride*") and the sulfonyloxy group of substrate as a leaving group—by extensive hydrogen bonding—results in formation of a gel-like solid phase in the reaction medium. This gel, in fact, might be contributing to acceleration of the reaction rate.

2. D. Selective Fluorination in Protic Media. To investigate the influence of the *tert*-alcohol solvent system on the selectivity of fluorination reactions, we carried out the fluorination on two model compounds that have some potential for side reactions under the basic reaction conditions associated with "*naked*" fluoride. Fuorination using TBAF in the *tert*-alcohol was compared to the reaction under conventional conditions using acetonitrile as a solvent (Scheme 1). It is known that fluorination of haloethyl or alkanesulfonylethyl aromatic compounds using "*naked*" fluoride is often compromised by competing β-elimination of these systems to the corresponding styrenes, a side

SCHEME 1. Selectivity of Fluorination Using TBAF in *tert*-Alcohol Medium vs Acetonitrile



reaction that can become dominant. Nevertheless, fluorination of 1-(2-mesylethyl)naphthalene (**5**) to 1-(2-fluoroethyl)naphthalene (**6**) using TBAF in *t*-BuOH proceeded efficiently and provided the corresponding fluoride in 87% yield, with the alkene byproduct **7** being formed in only 9% yield. By contrast, the same reaction in acetonitrile provided alkene **7** as the major product (61%), with the desired fluoroalkane substitution product (**6**) being formed in only 33% yield. Similarly, nucleophilic fluorination of *N*-5-bromopentanoyl-3,4-dimethoxyaniline (**8**) to *N*-5-fluoropentanoyl-3,4-dimethoxyaniline (**10**) using TBAF in acetonitrile at 80 °C gave only trace quantities of the desired fluoro product **10**, forming instead the intramolecular cyclization product 1-(3,4-dimethoxyphenyl)piperidin-2-one (**9**) in 70% yield. The same transformation in *tert*-amyl alcohol, however, furnished the desired fluoroalkane (**10**) in 30% yield. Thus, the protic environment of the *tert*-alcohol, which reduces the basicity of the "*naked*" fluoride by forming "*flexible*" fluoride, also appears to hydrogen bond with the reactive heteroatom in the substrate, effectively inhibiting side reactions such as elimination and intramolecular alkylation, and consequently enhancing the selectivity of the fluorination reaction.

3. Conclusion

In summary, we present a mechanistic study of the effect of the *tert*-alcohol medium in nucleophilic fluorination of some halo- and alkanesulfonyloxy alkane systems to the corresponding fluoroalkanes. According to our findings, the *tert*-alcohol solvents appear to reduce the strength of the ionic bonding of alkali metal fluorides by hydrogen bonding to the fluoride, thereby generating a *tert*-alcohol solvated "*flexible*" fluoride ion species that has very favorable properties as a strong nucleophile yet moderate base, highly suitable for the synthesis of organofluorine compounds with minimal side reactions that are base catalyzed. In addition, the *tert*-alcohols appear to form strong hydrogen bonds with the leaving group of sulfonylated substrates, and they accelerate the rate of substitution, making this reaction more valuable in various fluoride ion synthetic and [^{18}F]-fluoride ion radiosynthetic applications.

Further studies on the development of even more efficient protocols (greater selectivity, shorter reaction time, etc.) for nucleophilic substitution using *tert*-alcohol media are in progress in our laboratories. Further applications of this *tert*-alcohol medium fluorination method for the prepration of fluorine-18 labeled molecular imaging probes for PET studies are also under investigation.

4. Experimental Section

1-(2-Methanesulfonylethyl)naphthalene (5). To 1-(2-hydroxyethyl)naphthalene (4.6 g, 26.8 mmol) in methylene chloride (150 mL) were added triethylamine (4.5 mL, 32.2 mmol) and methanesulfonyl chloride (2.5 mL, 32.2 mmol) at 0 °C. The mixture was stirred at 25 °C for 6 h and evaporated under reduced pressure to remove methylene chloride. The residue was dissolved in water (200 mL) and extracted from the aqueous phase with EtOAc (200 mL × 3). The organic layer was dried (sodium sulfate) and evaporated under reduced pressure. The residue was purified by flash column chromatography (30% EtOAc/hexane) to give 5.7 g (22.8 mmol, 85%) of **5** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.79 (s, 3H), 3.55 (t, J = 7.2 Hz, 2H), 4.54 (t, J = 7.2 Hz, 2H), 7.40−7.59 (m, 4H), 7.79−8.03 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.7, 37.2, 69.6, 123.0, 125.5, 125.8, 126.5, 127.5, 127.9, 128.9, 131.6, 132.0, 133.8; MS (EI) m/z 250 (M^+); HRMS (EI) m/z calcd for $C_{13}H_{14}O_3S$ (M^+) 250.0664, found 250.0700.

***N*-5-Bromopentanoyl-3,4-dimethoxyaniline (8).** To a well-stirred solution of 5-bromopentanoic acid (1.3 g, 7.18 mmol) in anhydrous THF (50 mL) were added triethylamine (0.5 mL, 7.18 mmol), *p*-toluenesulfonyl chloride (1.37 g, 7.18 mmol), and 4-(dimethylamino)pyridine (880 mg, 7.18 mmol) at 25 °C. After 30 min at 25 °C, 3,4-dimethoxyaniline (1.0 g, 6.52 mmol) was added to the reaction mixture at 25 °C. The mixture was stirred for additional 12 h at 25 °C. The residue was dissolved in water (100 mL) and extracted from the aqueous phase with EtOAc (100 mL × 3). The organic layer was dried (sodium sulfate) and evaporated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/hexane) to give 1.43 g (4.55 mmol, 70%) of **8** as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.89−1.95 (m, 4H), 2.38 (t, J = 7.2 Hz, 2H), 3.44 (t, J = 6.5 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 6.79 (d, J = 8.9 Hz, 1H), 6.85−6.86 (m, 1H), 7.36 (s, 2H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.0, 32.0, 33.2, 36.3, 55.8, 56.0, 104.9, 111.2, 111.8, 131.4, 145.8, 148.9, 170.5; MS (EI) m/z 315 (M^+), 317 (M^+), 153 (100), 138; HRMS (EI) m/z calcd for $C_{13}H_{18}O_3N^{79}Br$ (M^+) 315.0469, found 315.0470.

Typical Procedure of Fluorination in Table 1. CsF (456 mg, 3.0 mmol) was added to the mixture of 2-(3-methanesulfonyloxypropoxy)naphthalene (**1**, 280 mg, 1.0 mmol) in alcohol (4.0 mL). The mixture was stirred over 6 h at 80 °C. The reaction mixture was triturated with ethyl ether to remove most of ionic salts. The filtrate was evaporated under reduced pressure. The residue was purified by flash column chromatography (20% CH_2Cl_2/hexanes) to obtain 41−192 mg (20−94%) of 2-(3-fluoropropoxy)naphthalene (**2a**) as a colorless oil with ether byproduct (**2d**).

2-(3-Fluoropropoxy)naphthalene (2a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14−2.39 (m, 2H), 4.24 (t, J = 6.2 Hz, 2H), 4.72 (dt, J = 46.8, 5.8 Hz, 2H), 7.16−7.22 (m, 2H), 7.34−7.53 (m, 2H), 7.76−7.83 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.4 (d, J = 20.1 Hz), 63.6 (d, J = 5.3 Hz), 80.8 (d, J = 163.9 Hz), 106.8, 118.8, 123.6, 126.4, 126.7, 127.6, 129.1, 129.4, 134.6, 156.7; MS (EI) m/z 204 (M^+); HRMS (EI) m/z calcd for $C_{13}H_{13}FO$ (M^+) 204.0950, found 204.0932.

2-(3-Methoxypropoxy)naphthalene (2d in entry 1): ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.08−2.13 (m, 2H), 3.36 (s, 3H), 3.59 (t, J = 6.2 Hz, 2H), 4.16 (t, J = 6.2 Hz, 2H), 7.13−7.14 (m, 2H), 7.30−7.32 (m, 1H), 7.41−7.42 (m, 1H), 7.71−7.74 (m, 3H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.6, 58.7, 64.8, 69.3, 106.6, 118.9, 123.5, 126.3, 126.7, 127.6, 128.9, 129.3, 134.5, 156.9; MS (EI) m/z 204 (M^+), 144 (100); HRMS (EI) m/z calcd for $C_{14}H_{16}O_2$ (M^+) 216.1150, found 216.1148.

2-(3-Ethoxypropoxy)naphthalene (2d in entry 2): ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.21 (t, J = 6.9 Hz, 3H), 2.09−2.13 (m, 2H), 3.51 (q, J = 6.9 Hz, 2H), 3.63 (t, J = 6.2 Hz, 2H), 4.18 (t, J = 6.5 Hz, 2H), 7.12−7.18 (m, 2H), 7.31−7.32 (m, 1H), 7.41−7.43 (m, 1H), 7.71−7.76 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.2, 29.7, 64.9, 66.3, 67.1, 106.6, 118.9, 123.5, 126.3, 126.7, 127.6, 128.9, 129.3, 134.6, 156.9; MS (EI) *m*/*z* 230 (M^+), 144 (100); HRMS (EI) *m*/*z* calcd for $C_{15}H_{18}O_2$ (M^+) 230.1307, found 230.1312.

2-(3-*n*-Propoxypropoxy)naphthalene (2d in entry 3): ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.92 (t, J = 7.5 Hz, 3H), 1.57−1.63 (m, 2H), 2.09−2.13 (m, 2H), 3.41 (t, J = 6.8 Hz, 2H), 3.63 (t, J = 6.3 Hz, 2H), 4.18 (t, J = 6.3 Hz, 2H), 7.13−7.15 (m, 2H), 7.30−7.33 (m, 1H), 7.41−7.44 (m, 1H), 7.71−7.76 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.6, 22.9, 29.7, 64.9, 67.2, 72.7, 106.6, 118.9, 123.5, 126.3, 126.7, 127.6, 128.9, 129.3, 134.6, 157.0; MS (EI) *m*/*z* 244 (M^+), 144 (100); HRMS (EI) *m*/*z* calcd for $C_{16}H_{20}O_2$ (M^+) 244.1463, found 244.1463.

2-(3-Isopropoxypropoxy)naphthalene (2d in entry 4): ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.16 (d, J = 6.2 Hz, 6H), 2.07−2.11 (m, 2H), 3.57−3.59 (m, 1H), 3.63 (t, J = 6.3 Hz, 2H), 4.18 (t, J = 6.2 Hz, 2H), 7.14−7.15 (m, 2H), 7.30−7.33 (m, 1H), 7.41−7.44 (m, 1H), 7.71−7.76 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.1, 30.0, 64.5, 64.9, 71.6, 106.6, 118.9, 123.5, 126.3, 126.7, 127.6, 128.8, 129.3, 134.6, 157.0; MS (EI) *m*/*z* 244 (M^+), 144 (100); HRMS (EI) *m*/*z* calcd for $C_{16}H_{20}O_2$ (M^+) 244.1463, found 244.1465.

2-(3-*t*-Butoxypropoxy)naphthalene (2d in entry 5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 9H), 2.04−2.11 (m, 2H), 3.60 (t, J = 6.0 Hz, 2H), 4.19 (t, J = 6.0 Hz, 2H), 7.15−7.18 (m, 2H), 7.31−7.46 (m, 2H), 7.73−7.78 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 30.4, 58.0, 64.8, 72.8, 106.6, 119.0, 123.4, 126.24, 127.7, 127.6, 128.8, 129.2, 134.6, 157.0; MS (EI) *m*/*z* 258 (M^+), 210, 144 (100); HRMS (EI) *m*/*z* calcd for $C_{17}H_{22}O_2$ (M^+) 258.1620 Found 258.1624

1-(2-Fluoroethyl)naphthalene (6). According to the typical procedure for fluorination with **5** (250 mg, 1.0 mmol) and TBAF (783 mg, 3.0 mmol) in *t*-BuOH, **6** (151 mg, 87%) was obtained as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.49 (dt, J = 13.7, 6.9 Hz, 2H), 4.75 (dt, J = 47.4, 6.9 Hz, 2H), 7.37−7.54 (m, 4H), 7.75−8.02 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 33.8 (d, J = 20.1 Hz), 83.5 (d, J = 168.0 Hz), 123.3, 125.5, 125.6, 126.2, 127.1, 127.5, 128.9, 132.0, 132.8 (d, J = 8.5 Hz), 133.8; MS (EI) *m*/*z* 174 (M^+), 141 (100). Anal. Calcd: C, 82.73; H, 6.36. Found: C, 82.63; H, 6.34. CAS Registry No. provided by the author: 693785-25-0.

1-Vinylnaphthalene (7). Compound **7** (14 mg, 9%) as a byproduct above reaction was obtained as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.47 (dd, J = 10.7, 1.7 Hz, 1H), 5.79 (dd, J = 17.5, 8.8 Hz, 1H), 7.43−7.52 (m, 4H), 7.61−7.62 (m, 1H), 7.77−7.85 (m, 2H), 8.10−8.12 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 117.1, 123.6, 123.7, 125.6, 125.7, 126.0, 128.1, 128.5, 131.1, 133.6, 134.4, 135.6; MS (EI) *m*/*z* 154 (M^+), 153 (100), 76; HRMS (EI) *m*/*z* calcd for $C_{12}H_{10}$ (M^+) 154.0783, found 154.0784. CAS Registry No. provided by the author: 826-74-4.

***N*-5-Fluoropentanoyl-3,4-dimethoxyaniline (10).** According to the typical procedure for fluorination with **8** (315 mg, 1.0 mmol) and TBAF (783 mg, 3.0 mmol) in *tert*-amyl alcohol, **10** (76 mg, 30%) was obtained as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.74−1.88 (m, 4H), 2.40 (t, J = 7.2 Hz, 2H), 3.85 (s, 6H), 4.49 (dt, J = 47.2, 5.8 Hz, 2H), 6.79 (d, J = 8.2 Hz, 1H), 6.86 (dd, J = 8.6, 2.4 Hz, 1H), 7.36 (d, J = 2.7 Hz, 1H), 7.45 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5 (d, J = 5.7 Hz), 29.7 (d, J = 18.6 Hz), 36.8, 55.8, 56.0, 83.9 (d, J = 163.8 Hz), 104.8, 111.2, 111.7, 131.5, 145.7, 148.9, 170.7; MS (EI) *m*/*z* 255 (M^+), 153 (100), 138; HRMS (EI) *m*/*z* calcd for $C_{13}H_{18}O_3NF$ (M^+) 255.1271, found 255.1270.

1-(3,4-Dimethoxyphenyl)piperidin-2-one (9). Compound **9** (76 mg, 32%) as a byproduct above reaction was obtained as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.92−1.95 (m, 4H), 2.55 (t, J = 6.2 Hz, 2H), 3.61 (t, J = 5.5 Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 6.77−6.78 (m, 2H), 6.86−6.88 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3, 23.4, 32.7, 52.0, 55.7, 55.8, 110.0, 111.2, 118.0, 136.4, 147.6, 149.0, 170.0; MS (EI) *m*/*z* 235 (M^+, 100), 220, 166; HRMS (EI) *m*/*z* calcd for $C_{13}H_{17}O_3N$ (M^+) 235.1208, found 235.1208.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **1**, **2a**, **2d**, and **3**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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