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Nucleophilic fluorine substitution reaction of α -carbonyl benzyl bromide, phenylthiofluoroalkyl bromide, and 2-bromo-2-phenoxyacetonitrile†

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We herein describe a new method for nucleophilic fluorine substitution of alkylbromides using $\text{Et}_3\text{N}\cdot 3\text{HF}$. The process is characterized by a broad substrate scope, good functional-group compatibility, and mild conditions and provides a variety of alkylfluorides including tertiary alkylfluorides that are versatile and structurally attractive.

The development of methods for $\text{C}(\text{sp}^3)\text{-F}$ bond formation has been in great demand in medicinal and biological chemistry because organofluorine compounds are attractive structural motifs as agrochemicals, pharmaceuticals, and ^{18}F -labeled radiotracers for positron emission tomography imaging.^{1–4} The nucleophilic substitution reaction involving $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ reactions is one of the most basic and substantial transformations in organic chemistry. Traditionally, various methods for preparing alkylfluorides from alkyl halides or sulfonates using nucleophilic fluorination reagents such as silver fluoride (AgF), potassium fluoride (KF), cesium fluoride (CsF), tetrabutyl ammonium fluoride (TBAF), anhydrous HF, and amine/HF reagents [e.g. triethylamine tris(hydrogen fluoride) ($\text{Et}_3\text{N}\cdot 3\text{HF}$) and Olah's reagent (pyridine $\cdot 9\text{HF}$)] have been developed extensively.^{5–8} Among the most applied was the halogen exchange fluorination with metal fluoride in an $\text{S}_{\text{N}}2$ reaction that is generally amenable to primary and secondary alkyl halides including benzylic halides, α -halo ketones, and related electrophiles. Meanwhile, for alkyl $\text{C}(\text{sp}^3)\text{-F}$ bond formation, C–H fluorination,⁹ hydrofluorination,¹⁰ and decarboxylative fluorination¹¹ using nucleophilic fluorine sources have been developed. Despite these advances, only a few examples have been reported on nucleophilic substitution reactions of alkylhalide access to alkylfluorides including tertiary alkylfluorides which limit its potential reaction window.^{12–14}

Although it is generally preferable to use neutral nucleophiles for the $\text{S}_{\text{N}}1$ reaction, the highly toxic HF gas causes undesirable reactions due to its acidity. In 1980, Franz prepared

weakly corrosive $\text{Et}_3\text{N}\cdot 3\text{HF}$ which is a colorless liquid with its pH close to neutral.¹⁵ Since that time, $\text{Et}_3\text{N}\cdot 3\text{HF}$ as a fluoride source for nucleophilic monofluorination in organic molecules has been used frequently.¹⁶ In particular, $\text{Et}_3\text{N}\cdot 3\text{HF}$ has frequently been used in electrochemical fluorination of thioethers and O,S -acetal derivatives bearing α -electron-withdrawing groups in the last decades.^{6,17} However, due to its weak nucleophilicity, the fluorination reactions of alkylhalides with $\text{Et}_3\text{N}\cdot 3\text{HF}$ usually require harsh reaction conditions, particularly high temperatures. Thus, it is of interest to find mild conditions and a class of alkylbromides forming carbocation intermediates that allow fluorine–bromine exchanges.

Recently, Doyle and co-workers developed a method for nucleophilic fluorination of *N*-hydroxyphthalimide esters using $\text{Et}_3\text{N}\cdot 3\text{HF}$ as a fluorine source *via* the carbocation generation under photocatalysis (Fig. 1A).¹⁸ Recent advances in this area: the direct replacement of bromide or chloride at tertiary carbon centers using AgF under phosphine catalysis have been

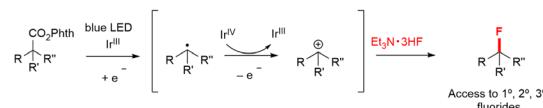
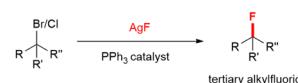
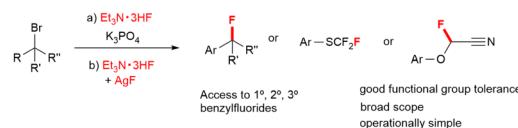
A. Photochemical approach to $\text{S}_{\text{N}}1$ mechanism (Doyle)B. Nucleophilic fluorination of unactivated tertiary alkylbromides and chlorides with AgF under phospholysis (Fu)C. This work: Nucleophilic fluorination of a variety of alkylbromides with $\text{Et}_3\text{N}\cdot 3\text{HF}$ and AgF 

Fig. 1 Nucleophilic substitution reactions with nucleophilic fluorinating reagents.

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reported by Fu (Fig. 1B).¹⁹ From prior arts, we envisaged that $\text{Et}_3\text{N}\cdot 3\text{HF}$ and AgF reagents would be potential for employing as fluorine sources in the halogen exchange of alkylhalides *via* the $\text{S}_{\text{N}}1$ process. In this paper, we describe the development of methods for the nucleophilic fluorine substitution to α -carbonyl benzyl bromides, phenylthiofluoroalkyl bromides, and 2-bromo-2-phenoxyacetonitriles with $\text{Et}_3\text{N}\cdot 3\text{HF}$, leading to the desired alkylfluorides (Fig. 1C). Notably, a combination of AgF and $\text{Et}_3\text{N}\cdot 3\text{HF}$ enhanced the reactivity compared with the single use of AgF , exhibiting an increase yield for monofluorinated products.

Our initial efforts focused on the halogen exchange reactions of α -bromo phenylacetate (**1a**) as a model substrate in a variety of fluorine sources for optimal conditions (Table 1). The reaction of the substrate **1a** using 8.0 equivalent of $\text{Et}_3\text{N}\cdot 3\text{HF}$ in ethylene glycol dimethyl ether (DME) at 80 °C obtained the desired fluorinated product **2a** in 18% yield (entry 1). The yield of **2a** was increased by the addition of K_3PO_4 as the base up to 62% (entry 2). Then, it was found that solvent significantly affects the reactivity of fluorination (entries 3–5): acetonitrile was superior to other solvents, giving the product **2a** in 68% isolated yield. Further screening of the nucleophilic fluorinating reagents such as Olar's reagent, KF, and CsF (entries 6–9), in which use of them provided a loss yield. In contrast, AgF as a fluorine source successfully employed the nucleophilic fluorination of benzylbromide **1a** without a base at room temperature under mild conditions, providing the desired fluorinated product **2a** in 40% yield, regardless of the heterogeneous reaction (entry 9). Interestingly, the addition of $\text{Et}_3\text{N}\cdot 3\text{HF}$ aids in dissolving AgF salt in acetonitrile. Then, the combination of $\text{Et}_3\text{N}\cdot 3\text{HF}$ and AgF as fluorine sources improved the fluorine–bromine exchange, furnishing the product with high yield (entry 10).

The fluorination reactions of benzylbromides **1b–t** were carried out using 8 equiv. of $\text{Et}_3\text{N}\cdot 3\text{HF}$, and 1.2 equiv. of K_3PO_4

in MeCN at 80 °C (Method A). On the other hand, as in Method B: reaction conditions with benzyl bromides **1b–t**, a combination of AgF (2.0 equiv.) and $\text{Et}_3\text{N}\cdot 3\text{HF}$ (3.0 equiv.) in MeCN at room temperature was also used. With these optimized

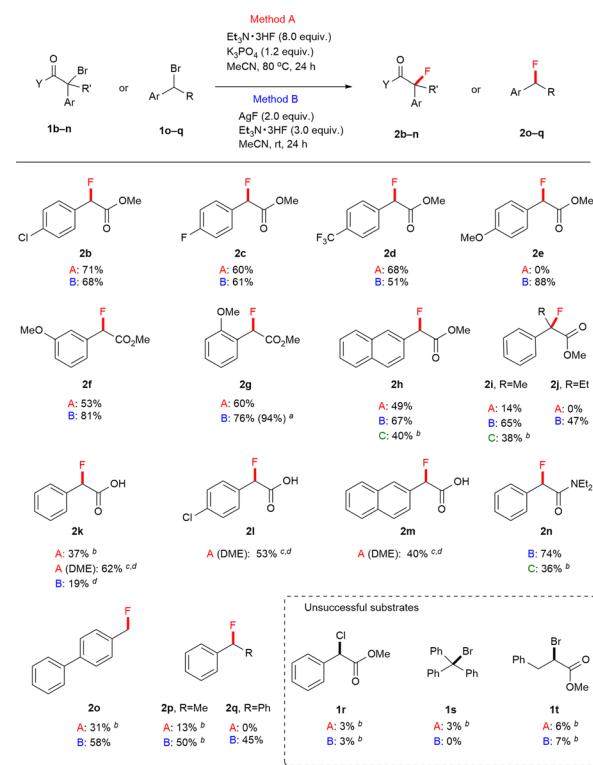


Fig. 2 Scope of benzylic fluorination (0.15 mmol). ^aPerformed on a 4.0 mmol scale, affording 748 mg of product **2g** (94% isolated yield). ^b¹⁹F NMR yields was determined using fluorobenzene as an internal standard. ^cDME was used as a solvent. ^dYield of isolated methyl ester with esterification using H_2SO_4 as a catalyst in MeOH.

Table 1 Optimization of conditions for the nucleophilic fluorination of **1a**

Entry	Fluorine sources (equiv.)	K_3PO_4 (equiv.)	Solvent	Temp. (°C)	Yield ^a (%)	Fluorine sources		
						K_3PO_4		
1	$\text{Et}_3\text{N}\cdot 3\text{HF}$ (8)	None	DME	80	18			
2	$\text{Et}_3\text{N}\cdot 3\text{HF}$ (8)	1.2	DME	80	62			
3	$\text{Et}_3\text{N}\cdot 3\text{HF}$ (8)	1.2	THF	80	63			
4	$\text{Et}_3\text{N}\cdot 3\text{HF}$ (8)	1.2	MeCN	80	78 (68) ^b			
5	$\text{Et}_3\text{N}\cdot 3\text{HF}$ (8)	1.2	DMF	80	38			
6	Py·HF (8)	1.2	MeCN	80	0			
7	KF (8)	1.2	MeCN	80	0			
8	CsF (8)	1.2	MeCN	80	30			
9	AgF (2)	None	MeCN	r.t.	40			
10	AgF (2), $\text{Et}_3\text{N}\cdot 3\text{HF}$ (3)	None	MeCN	r.t.	83 (74) ^b			

^a Yields determined by ¹⁹F NMR spectroscopy using fluorobenzene as an internal standard. ^b Isolated yield in parentheses.



conditions in hand, we examined the scope and limitations of this method for the fluorine substitution of alkyl halides. As shown in Fig. 2, α -bromo benzylacetates **1b–j** bearing substituents including halogen and electron-withdrawing group and electron-donating group underwent fluorine–bromine exchange to afford the desired products **2b–h** in satisfactory yields as well as tertiary benzyl fluorides (**2i**, and **2j**). In a gram scale reaction of methyl 2-bromo 2-(2-methoxyphenyl)acetate **1g**, the fluorinated product **2g** could be obtained in a higher yield (92%) than that of a 0.15 mmol scale reaction (76%). Furthermore, we found that DME was a suitable solvent for the fluorination reactions of α -bromo benzylacetic acid under reaction conditions of Method A (see, Table S1†). A class of α -bromo benzylacetic acid substrates **1k–m** was subject to the fluorination reaction followed by esterification to isolate the corresponding methyl ester. When Method B was used, the substitution reaction of α -bromo benzylamide **1n** afforded alkylfluoride **2n** in 74% yield. The primary and secondary benzylfluorides **2o–q** were obtained with moderate yield under the optimization conditions. Still, this new method is not applied to substrates such as α -chloro benzylacetate (**1r**), trityl bromide (**1s**), and α -bromo phenyl propanoate (**1t**). For **1r** and **1s**, their poor reactivity resulted in the recovered starting material, and for **1t** the elimination reaction occurred rapidly.

The thio carbenium and oxocarbenium ions can be stabilized by the interaction between the lone-pair electron of sulfur and oxygen atom with the unoccupied p-orbital of the carbocation, those reported in the literature.²⁰ The phenylthiofluoroalkyl bromide, and 2-bromo-2-phenoxyacetonitrile are precursors to form thio carbenium and oxocarbenium ions, respectively. We demonstrated the introduction of fluorine to phenylthiofluoroalkyl bromide **3a–c**, and 2-bromo-2-phenoxyacetonitrile **4a–c** bearing neighbouring groups such as fluorine, sulfur, and oxygen atoms, as illustrated in Fig. 3. When

Method B was used, the substitution reaction of phenylthiofluoroalkyl bromide **3a–c** provided a good yield of aryl trifluoromethyl sulfide to be a biologically effective functional group.²¹ Additionally, 2-fluoro-2-phenoxyacetonitrile compounds **6a–c** were readily obtained from alkylbromide substrates **4a–c** in better yields *via* fluorine–bromine exchange when both Method A and B were used, compared to when the substitution using AgF as a fluorine source.

To gain insight into the reaction mechanism, a stereochemical study was conducted. At first, the substitution reactions of α -racemic α -bromo phenyllactate (**7**) afforded the corresponding product **8** without stereoselectivity under reaction conditions of Methods A and B. Subsequently, we synthesized a highly diastereoenriched (α R)- α -bromo phenyllactate (**9**) through crystallization induced dynamic resolution (CIDR) following the previous work reported by Park.²² The fluorine substitution of (α R)- α -bromo arylacetate (**9**) *via* the S_N1 process should occur epimerization of the α -carbon because it forms a carbocation intermediate. Virtually, the substitution reaction of (α R)-**9** under standard conditions of Method A observed the epimerization in the fluorinated product (**10**). In contrast, the stereochemistry in the reaction with AgF showed the predominate inversion with dr of 92 : 8 and 59% yield. The substitution reaction in the presence of Et₃N·3HF and AgF revealed the stereochemistry with dr of 83 : 17 and a high yield of 92%. These results indicate that two pathways including S_N1 and S_N2 processes exist in fluorination reactions of Method B (Scheme 1).

To investigate the stability of Et₃N·3HF under standard conditions, ¹⁹F NMR studies were performed. Et₃N·3HF complex consists of N–H···F hydrogen bond and the central fluoride coordinated with an H₂F₃[–] or [F(HF)₂][–] ion according to an equilibrium.²³ However, Et₃N·3HF in acetonitrile converts to Et₃N·2HF, Et₃N·HF, and HF after 12 h at 80 °C. This was confirmed by ¹⁹F NMR spectroscopy, of which spectra showed that the chemical shift of Et₃N·3HF (–166 ppm) completely disappeared, and three additional signals appeared at –127, –151, and –152 ppm as same as those reported in the literature (Fig. S2†).²⁴ Further studies found that the presence of K₃PO₄ decreased the signal for acidic HF. Previously reported literature indicates the nucleophilicity varies in the order Et₃N·2HF > Et₃N·3HF >

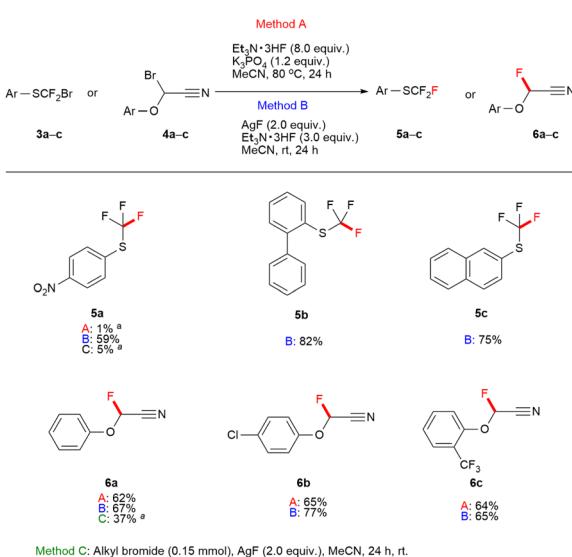
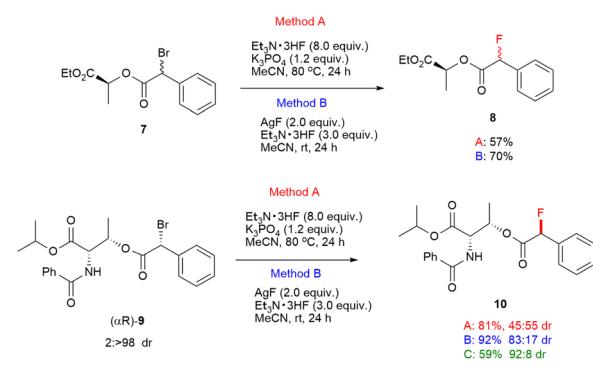


Fig. 3 Scope of phenylthiofluoroalkyl bromides, and 2-bromo-2-phenoxyacetonitriles (0.15 mmol scale). ¹⁹F NMR yields were determined using fluorobenzene as an internal standard.



Scheme 1 Asymmetric fluorination with α -bromo phenyllactate **7** and (α R)- α -bromo phenyllactate (α R)-**9**.



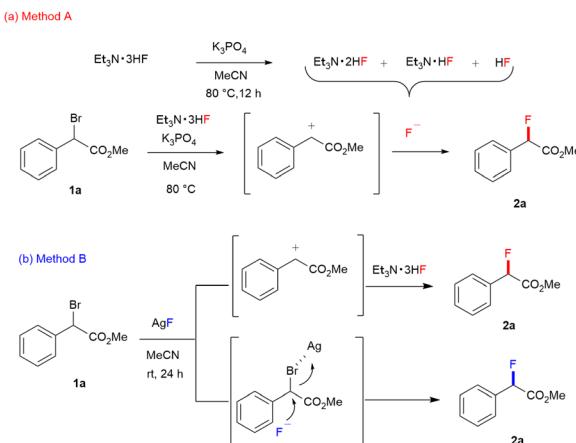


Fig. 4 (a) The plausible reaction pathway of Method A with Et₃N·3HF in the presence of K₃PO₄. (b) The plausible reaction pathway of Method B using a combination of Et₃N·3HF and AgF.

Et₃N·HF.²⁵ Therefore, *in situ* generated Et₃N·2HF may act as a part of active species for fluorine substitution to putative carbocation intermediate when Method A is used. Whereas, Et₃N·3HF assists in solubilizing AgF in acetonitrile and the resulting solution seems to stabilize Et₃N·3HF after 16 h at room temperature. In the obtained ¹⁹F NMR spectra, the most was a signal of Et₃N·3HF (162 ppm) and weak signals of HF and HF₂[–] (–128 and –145 ppm) were observed without signals of Et₃N·2HF, Et₃N·HF (Fig. S3†). Based on these results, the reaction pathway of Method A might proceed through the generation of a carbocation intermediate from α -bromo phenylacetate (**1a**) followed by the nucleophilic attack of *in situ* generated Et₃N·2HF, Et₃N·HF, or HF (Fig. 4a). Concerning the mechanism for Method B, we speculate that while the S_N2 reaction pathway mediated by AgF is proceeding, the S_N1 type reaction is also proceeding through Ag-assisted dissociation of bromide to form carbocation intermediate followed by the fluorine substitution with Et₃N·3HF (Fig. 4b).

Conclusions

We demonstrated that Et₃N·3HF is an efficient reagent to accomplish bromine–fluorine exchange on α -carbonyl benzyl bromides, phenylthiofluoroalkyl bromides, and 2-bromo-2-phenoxyacetonitriles. One strategy for the fluorine substitution with Et₃N·3HF in the presence of K₃PO₄ has been developed. Another strategy for fluorine substitution using a combination of Et₃N·3HF and AgF has also been developed. These methods showed good advantages such as a broad scope of substrates involving tertiary alkylbromides, functional group tolerance, mild conditions, and operationally simple. Further investigation on the ability of Et₃N·3HF for the nucleophilic fluorination reactions is undergoing.

Author contributions

The synthesis of alkylfluorides was carried out by SM and TY. The characterization and data curation were made by SM and

TI. SM and TI were responsible for financial resource. The manuscript was written through contributions of ESI.† All authors have given approval to the final version of the manuscript.

Conflicts of interest

There is no conflict of interest to declare.

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