Unbalanced Ion Pairs-Catalyzed Nucleophilic Fluorination Using Potassium Fluoride

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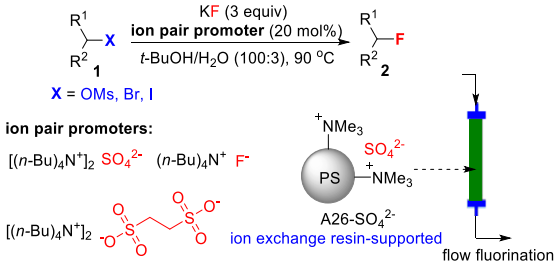


ABSTRACT: An unbalanced ion pair promoter (e.g., tetrabutylammonium sulfate), consisting of a bulky and charge delocalized cation and a small and charge-localized anion, greatly accelerates nucleophilic fluorinations using easy handling KF. We also successfully converted an inexpensive and commercially available ion exchange resin to the polymer-supported ion pair promoter (A26-SO_4^{2-}), which could be reused after filtration. Moreover, A26-SO_4^{2-} can be used in continuous flow conditions. In our conditions, water is well-tolerated.

Because of fluorine's unique properties, such as its small size and the metabolically resistant C-F bond, fluorine substitution has become the go-to strategy in drug and material development.[1-9] Fluorination reagents can be categorized as nucleophilic fluorination reagents (e.g., KF, HF-pyridine) and electrophilic fluorination reagents (e.g., Selectfluor and NFSI). In general, nucleophilic fluorination reagents are less expensive and more atom-economic than their electrophilic counterparts. Among the most common nucleophilic fluorination reagents, KF is inexpensive and easy to handle. Therefore, fluorination methods based on KF, such as Gouverneur and coworkers' hydrogen bonding phase-transfer catalysis with KF, [10] are highly desired. However, KF itself is not a good nucleophile; one of the major reasons is the high affinity between K^+ and F^-. KF is only soluble and dissociable in a high dielectric constant protic solvent such as water. However, the strong hydrogen bond between water and fluoride significantly reduces the nucleophilicity of fluoride. KF is not very soluble in most organic solvents and exists mainly as an ion pair rather than dissociated free ions in a solution.[11,12] Even in highly polar aprotic solvents such as DMF, the solubility and degree of dissociation are small.[13]

To increase the reactivity of K^+F^- and to lessen the twisted transition state (**TS-2** in Figure 1a), the counterion K^+ was replaced with a highly bulky cation (e.g., Bu_4N^+),[14] but this substitution increased the cost and led to side reactions, such as eliminations, because of the higher basicity.[15] Chelators with high affinity to K^+ such as cryptands (e.g., K_{222}), crown ethers (e.g., 18-crown-6, BTC5A[16]), bis-terminal hydroxy polyethers[17] have been utilized (Figure 1a). Also, transition metal complexes with fluoride-affinity, such as [IPrCuOTf], have been reported in the fluorination of alkyl triflate.[18]

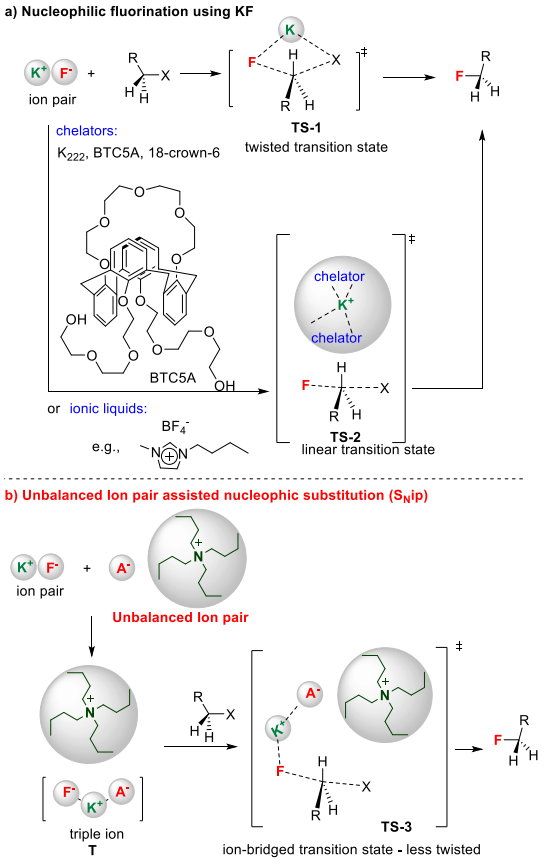


Figure 1. Nucleophilic fluorinations using potassium fluoride.

Most of the above mediators are expensive or must be used in relatively large amounts. Nucleophilic fluorinations have also

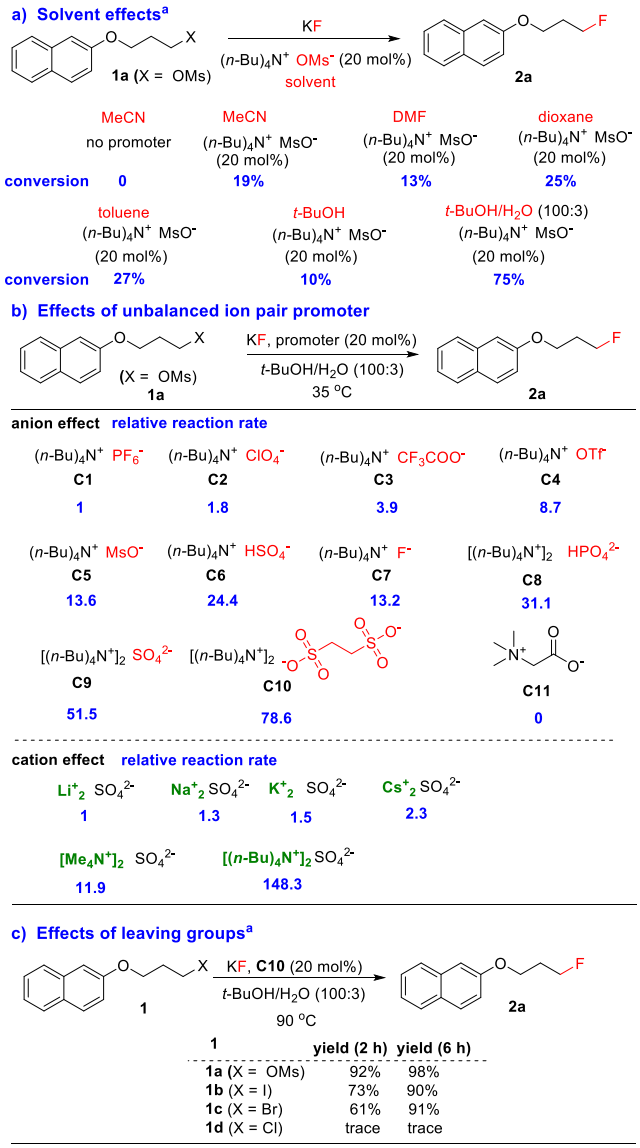
been promoted by ionic liquids (Figure 1a), as reported by the group of Song and Chi.[19-22] These authors suggested that ion-pairing might have played a critical role in ionic liquid promoted nucleophilic fluorination.

Recently, we introduced a general and quantitative model, namely Transition State Expansion (TSE), that describes how the size of a counterion affects the transition state structure and the kinetics of an ionic reaction.[14] According to our model, in an S_N2 reaction, in the presence of a paired counterion, the K^+F^- ion pair has to adopt a highly twisted transition state (Figure 1, TS-1).[23,24] As a result, the reactivity of the paired K^+F^- in an S_N2 reaction will be very low because of the small size of K^+.[14] Based on our model, we are now proposing a new concept for nucleophilic fluorination: an unbalanced ion pair promoter-assisted nucleophilic substitution pathway (Figure 1b). In our definition of "unbalanced" ion pair, the cation part is highly bulky, and the positive charge is delocalized or embedded; the anion counterpart though, is relatively small, and the negative charge is localized and can be accessed easily. A typical example of the former is the ammonium cation (n-Bu_4N^+), whereas a representative example of the latter is the mesylate anion (OMs^-). In an unbalanced ion pair, the affinity between the cation and the anion is relatively small because of the large size of the cation. In a low dielectric constant solvent,[11,25] the anion A^- of the unbalanced ion pair could interact with the K^+F^- ion pair to form a triple ion (**T** in Figure 1b).[26-29] We speculated that the electrophile RCH_2-X could react with the triple anion **T** ($F^-K^+A^-$) *via* a macrocyclic transition state **TS-3**. The directing effect of the ion pair promoter may play a crucial role in the stabilization of the transition state. Because of the formation of a macrocyclic transition state (vs. the 4-membered ring in **TS-1**), the F-C-X's geometry is much more linear (less twisted) than the geometry that it would have had in **TS-1**. In the transition state, anion **A** could also help to detach K^+ from the F^-. It should be noted that our proposal is conceptually different from commonly used phase transfer catalysis[30] because there is only one phase in most of our model reactions.

We chose the nucleophilic fluorination of alkyl electrophile **1** as our model system (Scheme 1). First, we investigated the solvent effect (Scheme 1, part a) using tetrabutylammonium methanesulfonate as the ion pair promoter. Without the promoter, the reaction only gave a trace amount of the fluorinated product **2a**, but in the presence of catalytic amounts of the promoter, the reaction sped up considerably. Furthermore, in polar aprotic and high dielectric constant solvents such as MeCN (ε = 37.5) or DMF (ε = 36.7)--the solvents of choice for nucleophilic substitutions--the reactions were slow compared to when low dielectric constant solvents such as dioxane (ε = 2.3) or toluene (ε = 2.4) were used. Of even more interest is that we found that a mixture of *t*-BuOH (ε = 10.9) and a small amount of water gave the best conversion. This could be explained by the improved solubility of KF when water was present. The tolerance to water is a significant advantage compared to most nucleophilic fluorination protocols.[15] The beneficial properties of *t*BuOH solvent are consistent with the literature reports on the bulk alcohol effect.[31-35] Moreover, the water effect is consistent with Song and Chi's observation of fluorination using aqueous ionic liquids.[20]

We proceeded to investigate the effect of other ionic promoters. To get a clearer picture of the kinetic effects of promoters, we measured the initial reaction rate and then calculated the relative reaction rate for each promoter (Scheme 1, part b). As expected, unbalanced ion pair promoters, consisting of a bulky and charge delocalized cation part and a small and charge-localized anion, led to faster reactions. Salts (**C5-c10**) proved to be excellent ion pair promoters. Finally, we studied the effect of leaving groups (Scheme 1, part c): whereas alkyl iodide **1b** and alkyl bromide **1c** were suitable leaving groups, albeit needing longer reaction times, the reaction of chloride **1d** was sluggish, under the same conditions.

Scheme 1. Optimization of Fluorinations of Alkyl Electrophiles.

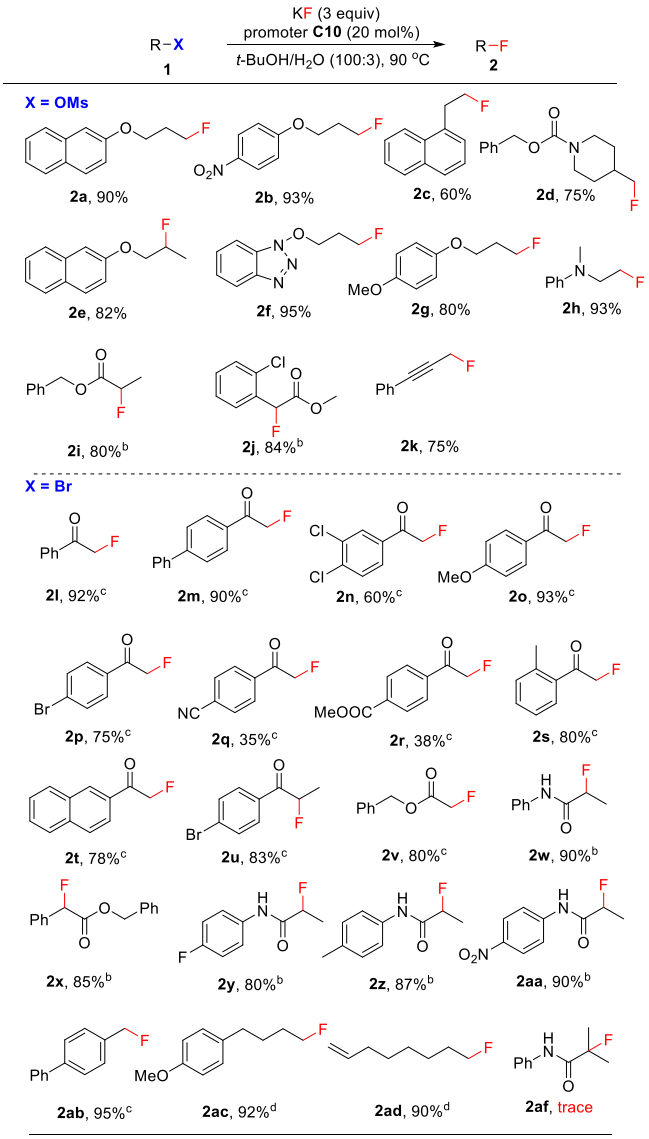


[a]Condtions: **1a** (0.1 mmol), promoter (0.02 mmol, 20 mol%) and KF (0.3 mmol, 3 equiv), solvent (1.0 mL), 90 °C for 2 h. Yields were determined by GC-MS.

With the optimized fluorinating conditions in hand, we explored the substrate scope and functional group tolerance (Scheme 2). First, we tested the reactivity of alkyl methanesulfonates (Scheme 2, top). Both primary and secondary substrates (**2e**, **2i**) worked very well, and unreactive (e.g., alkyl) or reactive substrates (benzyl and propargyl) were suitable starting materials. In addition, the formation of alkene side products, commonly observed during nucleophilic fluorinations, was minimal in most cases. Diverse functional groups such as

ether, nitro, amide, amine, and ester were well tolerated. We also assessed the reactivity of the more readily available and less expensive alkyl bromides (Scheme 2, bottom). Because α-bromo ketones, α-bromo esters, α-bromo amides are inexpensive and widely commercially available, we attempted the synthesis of synthetically important α-fluoro carbonyl compounds and obtained good to excellent yields of these products. Our protocol also worked for both reactive benzyl bromides (**2ab**) and unactivated long-chain aliphatic bromides (**2ac**, **2ad** but failed to work for tertiary substrates (**2af**).

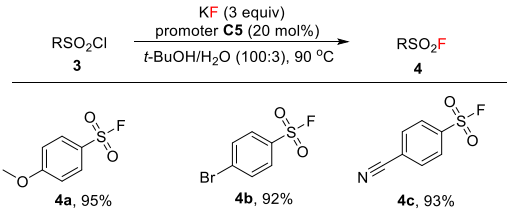
Scheme 2. Substrate Scope of Nucleophilic Fluorinations.[a]



[a]Reaction Conditions: **1** (0.5 mmol, 1 equiv), promoter **C10** (0.1 mmol, 20 mol%) and KF (1.5 mmol, 3 equiv) in *t*-BuOH/H_2O (100:3) (2.0 mL) at 90 °C for 4 h. [b]Promoter (40 mol%). [c] Reaction time was 2 h. [d] Promoter **C10** (0.240 mol%) and KF (1.5 mmol, 3 equiv) in 2.0 mL mixed solvent (*t*-BuOH/H_2O =100:3) at 90 °C for 8 h.

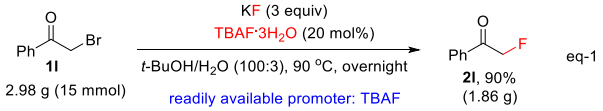
When our reaction conditions were applied to the nucleophilic fluorination of sulfonyl chlorides, they led to the facile synthesis of sulfonyl fluorides (Scheme 3). Both electron-rich and electron-deficient aryl sulfonyl chlorides furnished excellent yields of products. It should be pointed out that the literature synthesis of sulfonyl fluorides via nucleophilic fluorination of sulfonyl chlorides relies on the use of corrosive potassium bifluoride (KHF_2).[36]

Scheme 3. Nucleophilic Fluorinations of Sulfonyl Chloride.[a]



[a]Reaction Conditions: **3** (0.5 mmol, 1 equiv), promoter **C10** (0.1 mmol, 20 mol%) and KF (1.5 mmol, 3 equiv) in *t*-BuOH/H_2O (100:3) (2.0 mL) at 90 °C for 4 h.

Many unbalanced ion pair promoters (i.e., **C5** – **C10**) in Figure 1 worked equally well under our reaction conditions, differing only in their reaction rates. As a result, we can choose a readily available and inexpensive promoter for larger-scale synthesis. To demonstrate the synthetic usefulness of our method, we conducted a larger-scale transformation (15 mmol) using the readily available promoter TBAF. The larger reaction scale had little impact on the yield of the protocol (eq 1).



The ion-pair promoters reported thus far are water and organic solvent-soluble, so they can not be easily recycled or reused. To make the ion pair promoter recyclable, we converted an inexpensive and commercially available anionic resin possessing a quaternary ammonium functional group, Amberlyst A-26, into a polymer-supported promoter that could be separated easily at the end of the reaction--usually through filtration--from the soluble reaction mixture. The preparation of this polymer-supported promoter was straightforward: Amberlyst A-26 (OH^- form) was treated with a K_2SO_4 solution to exchange the OH^- with SO_4^{2-} After washing with water and drying, the polymer-supported ion pair promotor A26-SO_4^{2-} was obtained (Figure 2).

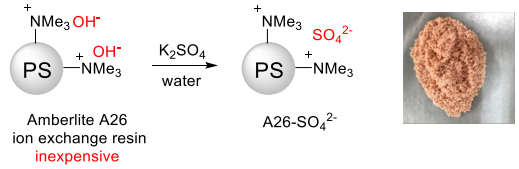


Figure 2. Preparation of polymer-supported ion pair promotor A26-SO_4^{2-}.

To demonstrate the recyclability potential of the polymer-supported A26-SO_4^{2-} promoter, we conducted four runs using the same catalyst (Figure 3). When the reaction was complete, the resin promoter was easily recycled through filtration or liquid decantation. This promoter was reused without a significant loss of catalytic activity and selectivity.

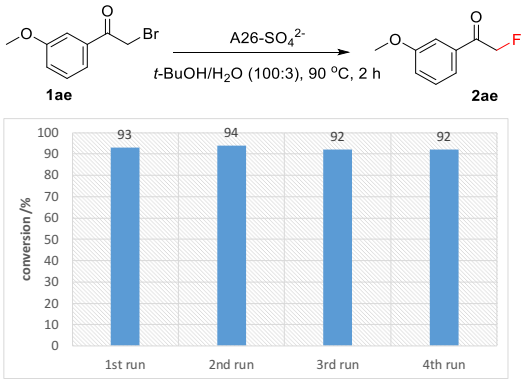


Figure 3. Recyclability of A26-SO_4^{2-} resin promoter. Conditions: **1ae** (0.5 mmol), A26-SO_4^{2-} (1.0 mL) and KF (1.5 mmol) in *t*-BuOH/H_2O (100:3) (2.0 mL) at 90 °C for 2 h.

To the best of our knowledge, nucleophilic fluorination of alkyl electrophiles using KF under continuous flow conditions has not been achieved. Our ionic exchange resin-supported ion pair promoter A26-SO_4^{2-} was easily packed into a glass column suitable for flow reactions (Figure 4, see supporting information for more details). A solution of bromide **1ae** and KF in *t*-BuOH/H_2O (100:3) was pumped into the A26-SO_4^{2-} resin-packed glass reactor at a 100 µL/min flow rate (Figure 4). The high conversion was maintained over a long period of time (24 h).

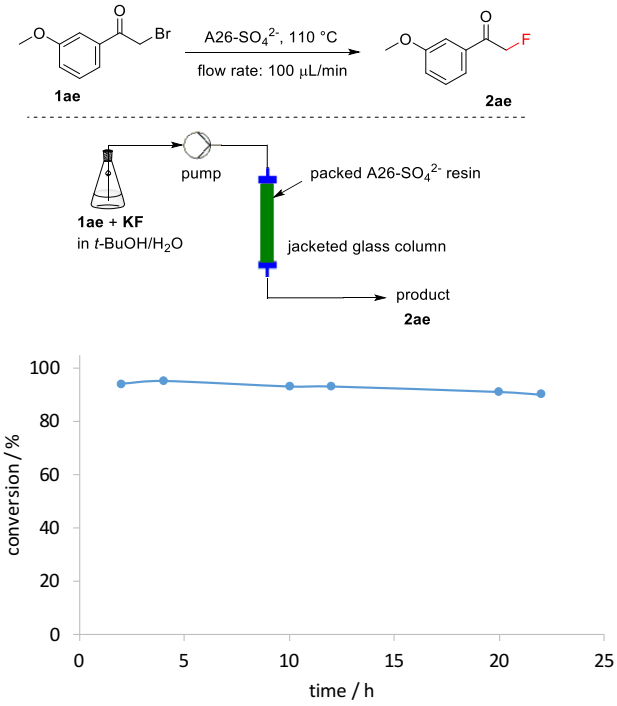


Figure 4. Flow-fluorination using KF. Conditions: A26-SO42- resin (2.5 g) was packed into an empty jacketed Omni-fit column (8 mm diameter × 88 mm length). A solution of 1ae (1 equiv, 0.1 M) and KF (3 equiv, 0.3 M) in *t*-BuOH/H2O (100:3) were pumped at the rate of 100 µL/min.

In summary, an unbalanced ion pair promoter, consisting of a bulky and charge delocalized cation and a small and charge-localized anion, greatly accelerates nucleophilic fluorinations using easy handling KF as the fluorination agent. Other unbalanced ion pair promoter-catalyzed reactions are currently under investigation in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental details and copies of NMR spectra (PDF). The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

The manuscript was written through the contributions of all authors. All authors have approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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