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Cooperative Catalysis

Bis-Terminal Hydroxy Polyethers as All-Purpose, Multifunctional Organic Promoters: A Mechanistic Investigation and Applications**

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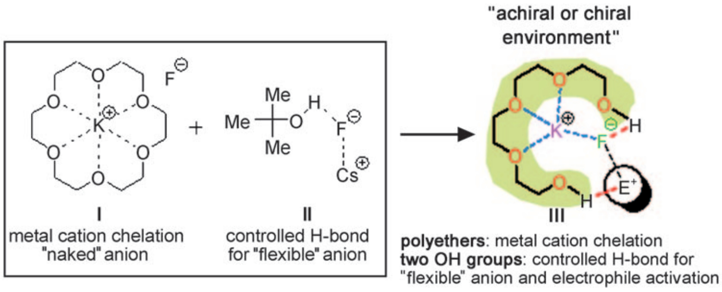

Figure 1. Bis-terminal hydroxy polyethers (**III**) as multifunctional promoters.

Catalysis is one of the central themes in chemical science. The promotion of physicochemical and biological processes, as demonstrated by enzymes in living cells, is an extremely important subject to be elucidated in all branches of science. Therefore, the design and application of new and efficient types of promoters for organic transformations are of fundamental importance.

A range of important classes of organic reactions can be conducted with fluoride anions as a catalyst or nucleophilic reagent.[1] Although alkali metal fluorides are a readily available source of the fluoride ion, their applications are limited because of their low solubility in organic solvents. To increase the solubility of alkali metal salts, crown ethers are frequently employed to generate a "naked" fluoride ion (Figure 1 **I**).[2] This simple but innovative concept of crown ethers helped lay the foundation for the important fields of ion and molecular recognition and has therefore had a profound impact on science.[3] However, their application to chemical reactions is often hampered by the strong basicity of fluoride, which causes it to induce the formation of by-products. During the course of our efforts to develop general catalyst (promoter) systems employing alkali metal salts as nucleophilic sources, it was observed that bulky protic solvents (e.g. *t*BuOH) can be suitable to generate a "flexible" fluoride ion from CsF through controlled hydrogen bonding to reduce the basicity of the nucleophile, fluoride (Figure 1 **II**).[4] However, owing to the strong Coulombic influence of K^+ on F^-, KF was observed to be inactive toward S_N2 reactions. Thus, the combination of these two concepts—"naked" and flexible systems together in one molecule (Figure 1 **I** and **II**)—became the focus of our study to design a much more versatile promoter system for a wide range of organic transformations. Herein, we describe the phenomenal efficiency of bis-terminal hydroxy polyethers as a new type of all-purpose promoter system (Figure 1 **III**), which act as extremely efficient catalytic reaction media for nucleophilic fluorination with alkali metal fluorides. Moreover, by using chiral bis-terminal hydroxy polyethers as catalysts, the catalytic desilylative kinetic resolution of the silyl ethers of racemic secondary alcohols with KF was successfully achieved for the first time.

Cooperative catalysis,[5] the simultaneous binding and activation of reacting partners resulting in both preorganization of the substrates and stabilization of the transition state structures, is a fundamental principle in modern catalysis. Recently, much efforts in this field have focused on the development of efficient multifunctional organocatalysts.[6] We anticipated that bis-terminal hydroxy polyethers might serve as a new type of multifunctional organic promoters in various organic reactions through a cooperative activation mechanism as depicted in Figure 1 **III**: The ether groups act as a Lewis base toward K^+, "freeing" the nucleophile, as well as "enhancing" the solubility of the potassium salts. On the other hand, one of the two OH groups forms controlled hydrogen bonding with the fluoride anion, thus decreasing the basicity of the nucleophile, whereas the other OH group may be able to simultaneously activate the electrophile by hydrogen bonding, thereby stabilizing the transition state (Figure 1 **III**). More importantly, this type of promoter can easily be modified to produce "chiral variants".

To prove the validity of this novel concept, we first examined bimolecular nucleophilic fluorination, which is considered to be one of the most difficult S_N2 reactions. We

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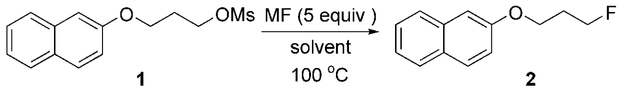
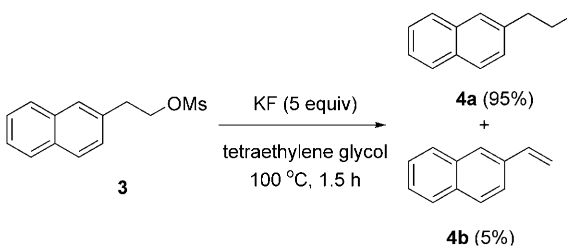
conducted the nucleophilic fluorination on the model substrate 2-(3-methanesulfonyloxypropoxy)naphthalene (**1**) with 5 equivalents of potassium fluoride in triethylene glycol or tetraethylene glycol as the solvent at 100°C. The results are summarized in Table 1, together with those obtained in other solvent systems reported previously by us[4,7] and other group.[8] Pleasingly, when using tri- or tetraethylene glycol as solvent, the substitution reactions proceeded at an unprecedented fast rate and were completed within 1.5 h to afford the fluorinated product **2** in excellent yields (92–93%) without forming any appreciable amount of by-products (Table 1, entries 6 and 7). Moreover, by applying microwave irradiation (700 W) to the same reaction, the fluorinated product **2** could be obtained in nearly quantitative yields within only 1 minute (Table 1, entries 8 and 9). In contrast to these results, the same fluorination reaction with KF in aprotic polar solvents such as acetonitrile in the presence or absence of [18]crown-6 proceeded sluggishly (Table 1, entries 1–3).[7,8] Bulky protic solvents such as *t*BuOH and *tert*-amyl alcohol, which are known to be excellent media for fluorination with CsF,[4] also showed no reactivity with KF (Table 1, entries 4 and 5). Interestingly, PEG 600 or PEG 1000 (containing ca. 13 and 22 ether units, respectively) showed low reactivity for the same reaction (Table 1, entries 10 and 12). Meanwhile the reaction of **1** with CsF in PEG 600 or PEG 1000 proceeded smoothly to give the desired fluorinated product **2** in nearly quantitative yields (Table 1, entries 11 and 13). This result strongly indicates that the effectiveness of alkali metal cation is determined by the chain length of the bis-terminal hydroxy polyethers, as would be expected. Moreover, as shown in Scheme 1, the fluorination of 2-(2-mesyloxyethyl)naphthalene (**3**) proceeded to give predominantly 2-(2-fluoroethyl)naphthalene (**4a**) in 95% yield, along with the alkene **4b** in 5% yield. It is well known that introducing fluorine into haloethyl or alkanesulfonyloxyethyl aromatic compounds is very difficult because of their tendency to undergo elimination reactions to produce styrenes.[9] All of the aforementioned results are certainly consistent with our hypothesis of a cooperative mechanism depicted in Figure 1 **III**.

Table 1: Nucleophilic fluorination with alkali metal fluoride in various solvent systems.[a]



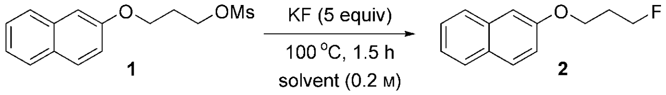
Entry	Solvent	Nucleophile (MF)	*t*	Yield [%][b]
1[c]	CH_3CN	KF	24 h	0
2[c]	[18]crown-6 in CH_3CN	KF	24 h	40
3[d]	[18]crown-6 in DMF	KF	1 h	4
4	*t*BuOH	KF	1.5 h	0
5	*tert*-amyl alcohol	KF	1.5 h	0
6	triethylene glycol	KF	1.5 h	93
7	tetraethylene glycol	KF	1.5 h	92
8[e]	triethylene glycol	KF	1 min	95
9[e]	tetraethylene glycol	KF	1 min	94
10	PEG 600	KF	1.5 h	70[f]
11	PEG 600	CsF	1.5 h	>98[f]
12	PEG 1000	KF	1.5 h	39[f]
13	PEG 1000	CsF	1.5 h	>98[f]

[a] Unless otherwise indicated, all reactions were carried out with **1** (0.1 mmol) and KF (5 equiv) at 100°C in 0.5 mL of solvent. [b] Yield of isolated product. [c] See Ref. [7]. [d] See Ref. [8]. [e] Reactions were carried out under microwave irradiation (700 W). [f] Yields were determined by ^{1}H NMR spectroscopy. DMF = *N*,*N*-dimethylformamide.



Scheme 1. Nucleophilic flourination of **3** with KF

To further verify the importance of the cooperative multifunctionality of the promoters, the fluorination of the mesylate **1** with KF (5 equiv) was carried out in various glycol derivatives as the solvent. As shown in Scheme 2, when triethylene glycol dimethyl ether (in which both terminal hydroxy groups are methylated) was used as the solvent, the reaction did not proceed at all. On the other hand, triethylene glycol monoethyl ether showed about half of the reactivity of triethylene glycol under the same reaction conditions. We also carried out the same reaction in a mixed solvent system consisting of triethylene glycol dimethyl ether and *t*BuOH (1:1, v/v) on the assumption that the ether units of the former can chelate the potassium cation and the latter can stabilize the fluoride anion by controlled hydrogen bonding. However, no conversion was observed. All of these experimental results strongly suggest that, in the case of bis-terminal hydroxy polyethers, the "intramolecular" cooperative activation mechanism is responsible for the rate acceleration in nucleophilic fluorinations.



Solvent	Conv. [%]
triethylene glycol dimethyl ether	0
triethylene glycohol monoethyl ether	42
triethylene glycohol	>99
triethylene glycol dimethyl ether/*t*BuOH (1:1, v/v)	0

Scheme 2. Nucleophilic fluorination with KF in triethylene glycol derivatives.

Support for the proposed cooperative mechanism was obtained from quantum chemical calculations carried out by employing the accurate DFT (MPW1K/6-31++G**) method.[10] Figure 2 depicts the reactions of C_3H_7OMs with K^+F^- in tetraethylene glycol. In Figure 2, five oxygen atoms in the tetraethylene glycol molecule act as a Lewis base toward K^+, thus drastically lowering its electrostatic effects and thereby "freeing" the nucleophile, F^-. The ion pair K^+F^- resides in the hollow "pocket" formed by the five oxygen atoms in the solvent (very much like an active site in an

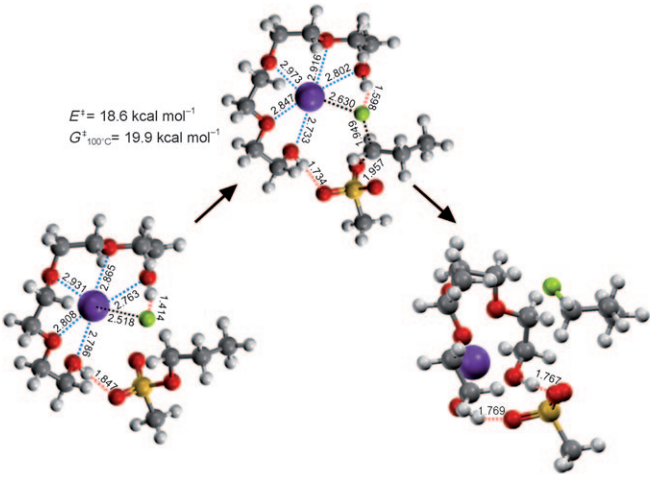
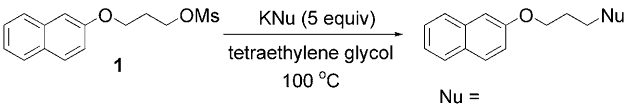


Figure 2. Calculated mechanism of the reaction [$K^+F^- + C_3H_7\text{-}OMs \rightarrow K^+OMs^- + C_3H_7\text{-}F$] in tetraethylene glycol by using DFT (MPW1K/6-31++G**) methods. Energy and Gibbs free energy in kcal mol^{-1} and bond lengths in Å.

enzyme). One of the two OH groups of tetraethylene glycol forms a hydrogen bond with the fluoride nucleophile. The other OH group interacts with the mesylate leaving group, thus helping it to detach from the reactant. The calculated energy barrier ($E^{\pm} = 18.6$ kcal mol^{-1}, $G^{\pm}(100\,°C) = 19.9$ kcal mol^{-1}) for the reaction with KF in tetraethylene glycol is much lower than even those calculated by similar methods for the same reaction with cesium and tetra-*n*-butylammonium fluoride in *tert*-butyl alcohol and ethylene glycol;[11] [$Cs^+F^- + C_3H_7OMs \rightarrow Cs^+OMs^- + C_3H_7F$] in *tert*-butyl alcohol ($E^{\pm} = 23.5$ kcal mol^{-1}, $G^{\pm}$ $(80\,°C) = 23.1$ kcal mol^{-1}), [$nBu_4N^+F^- + C_3H_7OMs \rightarrow nBu_4N^+OMs^- + C_3H_7F$] in *tert*-butyl alcohol ($E^{\pm} = 25.3$ kcal mol^{-1}, $G^{\pm}$ $(80\,°C) = 22.3$ kcal mol^{-1}),[12] and [$Cs^+F^- + C_3H_7OMs \rightarrow Cs^+OMs^- + C_3H_7F$] in ethylene glycol ($E^{\pm} = 20.0$ kcal mol^{-1}, $G^{\pm}$ $(80\,°C) = 21.5$ kcal mol^{-1}).[13] Replacing one hydroxy group of tetraethylene glycol by a methoxy group (see Figure S2) is calculated to increase the activation barrier significantly ($E^{\pm}$ and $G^{\pm}$ by 1.2 and 1.7 kcal mol^{-1}, respectively): this increase is due to the much lower acidity and tenuous interactions of OCH_3 with the leaving group compared with OH, which is in agreement with the experimental observation of a corresponding decrease in the reaction rate (see Scheme 2). In solvents containing two terminal OCH_3 groups, the reactant tends to separate away from the "loose" solvent molecule, with no prereaction complex being formed. These observations indicate that one of the terminal OH groups acts as an "anchor" to the nucleophile and the other acts as an "anchor" to the leaving group, thus supporting the mechanism depicted in Figure 2. A similar nucleophilic fluorination reaction with a metal fluoride was observed in an enzymatic reaction, where the controlled hydrogen bonding among the enzyme, fluoride, and substrate plays a crucial role in the formation of C–F bonds.[14] Notably, labeling organic compounds with [^{18}F] isotope ($t_{1/2} = 110$ min) is a particularly important process for the noninvasive imaging of molecular and biological processes in living subjects with positron emission tomography (PET).[15] However, the mass production of [^{18}F] labeled radiopharmaceuticals such as [^{18}F]FLT, [^{18}F]FP-CIT, and [^{18}F]BAY94-9172 by nucleophilic fluorination is still challenging, as this is one of the most difficult nucleophilic substitution reactions. Thus, we believe that our fluorination protocol will open up new perspectives for [^{18}F] labeling chemistry: because of its use of readily available alkali metal fluorides as nucleophilic sources, its fast reaction rates, and excellent product selectivity.

We also examined the scope of our protocol with a variety of different potassium salts. As shown in Scheme 3, a range of activated nucleophiles including carbon, nitrogen, oxygen, sulfur, and other halogen nucleophiles can be simply generated from the corresponding potassium salts in the presence of bis-terminal hydroxy polyethers. Thus, the substitution reactions proceed extremely well with a diverse set of nucleophiles to afford the corresponding substitution products in nearly quantitative yields. These results indicate that bis-terminal hydroxy polyethers can be used to generate the activated nucleophiles from potassium salts for diverse organic reactions.

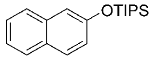
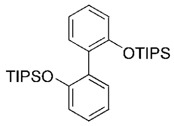
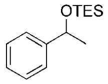
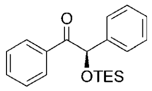


Nu =
Cl (1 h, 99%)
Br (0.5 h, 99%)
I (0.5 h, 99%)
CN (1.5 h, 98%)
OAc (1.5 h, 88%)
SCN (1.5 h, 99%)

Scheme 3. S_N2 reaction with various potassium salts.

To demonstrate that our concept is generally applicable to other organic reactions, we also examined the removal of various silyl ether protecting groups in **5**–**8** with KF in tetraethylene glycol at room temperature. As shown in Table 2, the silyl groups could be cleanly removed to give

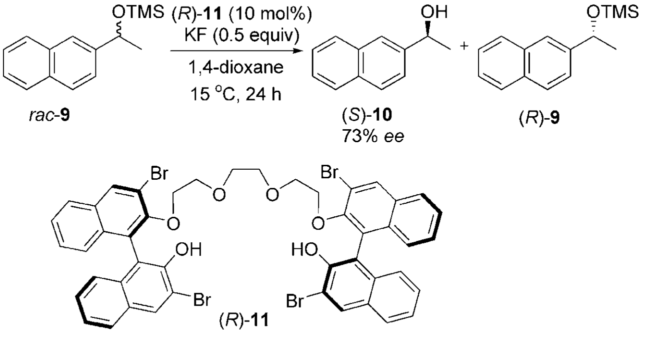
Table 2: Removal of silyl groups using KF in tetraethylene glycol.[a]

Entry	Substrate		KF [equiv]	*t*	Yield [%][b]
1	**5**	 OTIPS	1.5	15 min	98
2	**6**	 TIPSO, OTIPS	3	30 min	96
3	**7**	 OTES	1.5	3 h	99
4[c]	(*R*)-**8**	 O, OTES	1.5	2 h	93

[a] All reactions were carried out with 0.1 mmol of the substrate in tetraethylene glycol (1.0 mL) at room temperature. [b] Yield of isolated product. [c] Enantiopurity of the alcohol was determined by HPLC on a chiral stationary phase (see the Supporting Information). TIPS = triisopropylsilyl, TES = triethylsilyl.

the corresponding alcohols in nearly quantitative yields. Notably, the base-sensitive silyl ether (*R*)-**8** could also be selectively deprotected without racemization (Table 2, entry 4). It is well known that tetra-*n*-butylammonium fluoride (TBAF), the most common reagent for the cleavage of silyl ethers, is inappropriate for base sensitive substrates because of the strong basicity of the fluoride anion.[1a,16]

Finally, we are also in the process of developing asymmetric variants of the catalytic process using our multifunctional promoter. For example, treating the racemic silyl ether **9** with 0.5 equivalents of KF at 15 °C for 24 hours in the presence of the chiral variant (*R*)-**11** (10 mol %) of tetraethylene glycol as a catalyst furnished the resolved alcohol (*S*)-**10** with 73 % *ee* (Scheme 4 and the Supporting Information). To our knowledge, this is the first catalytic example of the desilylative kinetic resolution of the silyl ethers of racemic secondary alcohols.[17] This process can certainly open up a new avenue for asymmetric reactions catalyzed by chiral fluoride,[1b,c] which have vast synthetic potential but remain a relatively undeveloped field.



Scheme 4. Desilylative kinetic resolution of *rac*-**9** with KF. TMS = trimethylsilyl.

In conclusion, we have demonstrated that multifunctional bis-terminal hydroxy polyether derivatives can strongly promote a range of chemical reactions, in which alkali metal salts are used as nucleophilic sources. Achiral bis-terminal hydroxy polyether derivatives dramatically facilitated the most difficult process of nucleophilic fluorination, even with KF. We also described the first successful desilylative kinetic resolution of the silyl ethers of racemic secondary alcohols with KF by using the chiral variants of bis-terminal hydroxy polyether derivatives as catalysts. Quantum chemical calculations provide detailed insight into the modes of action of this type of organic promoter. On the basis of all these remarkable results, we believe that our new promoter system (bis-terminal hydroxy polyethers and their chiral variants) is a new development that constitutes a significant step forward in many important areas of science, e.g., solvent engineering, enantioselective organocatalysis, and diagnostic medicine. Our current work in the laboratory focuses on 1) expanding the scope of the applicability of bis-terminal hydroxy polyethers as multifunctional promoters for other organic reactions, 2) developing efficient asymmetric variants, and 3) PET applications.

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