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Polymer-Supported Pentaethylene Glycol as a Facile Heterogeneous Catalyst for Nucleophilic Fluorination

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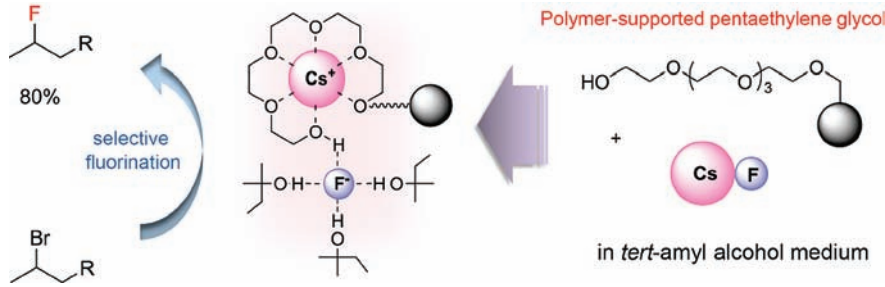
ABSTRACT



Polymer-supported pentaethylene glycols (PSpentaEG) as promising catalysts for nucleophilic fluorination with alkali metal fluoride (MF) could significantly enhance the nucleophilicity of MF and provide simple purification and recycling in the reaction. Furthermore, by their synergistic effect, the combination of PSpentaEG and a *tert*-alcohol media system showed tremendous efficiency in the fluorination of base-sensitive substrates such as *sec*-alkyl halide.

Organic molecules with fluorine content have received much attention in the field of life science, despite their rarity in nature.[1] Fluorine is often used as a substituent in pharmaceuticals and agrochemicals since it can often increase their bioavailability, potency, and metabolic stability compared to nonfluorinated analogues.[2,3] Furthermore, radiopharmaceuticals labeled with fluorine-18 are also widely used as in vivo probes for noninvasive imaging of biological processes in living subjects using positron emission tomography (PET).[4] It is well-known that the most common method for the introduction of fluorine into a specific aliphatic framework is by the nucleophilic substitution of various sulfonates and halides by fluoride in polar aprotic solvents employing alkali metal fluorides (MF), which have traditionally been used as a fluoride source; however, the low nucleophilicity and solubility of MF in organic media make this reaction require harsh conditions and restrict its wide applications.[5] Thus, over the past several decades, a large number of phase-transfer-type protocols, such as MF/crown ether complexation,[6] quaternary ammonium fluorides,[7] and MF/ionic liquid systems,[8] have been developed to generate soluble and reactive "naked" fluoride from MF.[5−8] However, these

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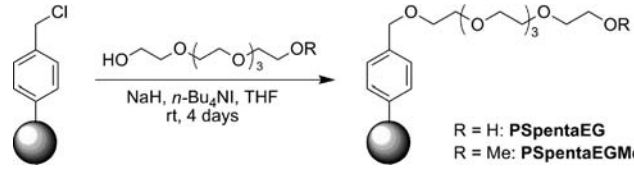
systems employing "naked" fluoride are generally strongly basic, which restricts their synthetic utility because it promotes various side reactions such as eliminations and hydroxylations.[9]

In a recent significant advance, it was reported that bulky protic *tert*-alcohol solvents can be excellent media for the fluorination of various sulfonate substrates with CsF through the formation of "flexible" fluoride by controlled hydrogen bonding between MF and these *tert*-alcohol media. However, this *tert*-alcohol media protocol has these synthetic limitations: (i) the *tert*-alcohol media fluorination of a substrate with halide-leaving group showed poor performance because of its requiring harsh conditions; (ii) *tert*-alcohol media could not reduce enough the formation of side products in the reaction of base-sensitive substrates using a "naked" fluoride source such as tetrabutylammonium fluoride (TBAF), compared with CsF; and (iii) tight-ion pair alkali metal fluorides (e.g., KF, RbF) were observed to be inactive in the reactions.[10] More recently, it was reported that oligoethylene glycols, such as triethylene or tetraethylene glycols, act as highly efficient reaction solvents for nucleophilic fluorination with KF.[11] However, the high boiling point of these oligoethylene glycols might cause purification problems or, frequently, inconvenience in the chemical processes.[12,13]

The immobilization of a catalyst or reagent on various polymeric supports is attracting considerable attention in chemical processes, including the green chemistry field due to its ease of recycling, easy handling, and the unique microenvironment caused by the reactants within the polymeric support.[12] Herein, we introduce polymer-supported pentaethylene glycol (PSpentaEG) as a promising catalyst for nucleophilic fluorination with MF. We found that this PSpentaEG has the advantage of significantly enhancing the nucleophilicity of the metal fluoride as well as the ease of purification in the reaction. Moreover, the combination of PSpentaEG catalyst and *tert*-alcohol media system showed very good performance in the fluorination of base-sensitive substrates.

The PSpentaEG were prepared by a simple one-step reaction, as shown in Scheme 1. We prepared various

Scheme 1. Preparation of Polymer-Supported Pentaethylene Glycol- PSpentaEG and Methylated PSpentaEG



PSoligoEGs with different lengths of oligoEGs (EG = ethylene glycol). The physical and chemical properties of the PSoligoEGs depend on the length of oligoEGs. In this report, the most efficient polymer-supported pentaethylene glycol system is described. The treatment of Merrifield resin[14] (1% divinylbenzene, 3.7 mmol Cl/g) with pentaEG in dried THF for 4 days afforded PSpentaEG (1.9 mmol of pentaEG per gram of polymer-supported product obtained). The PSpentaEG was characterized by ^{13}C NMR (solid state) spectroscopy and by elemental analysis.

Figure 1 illustrated the influence of the hydrogen bond between the terminal hydroxyl group of PSpentaEG and

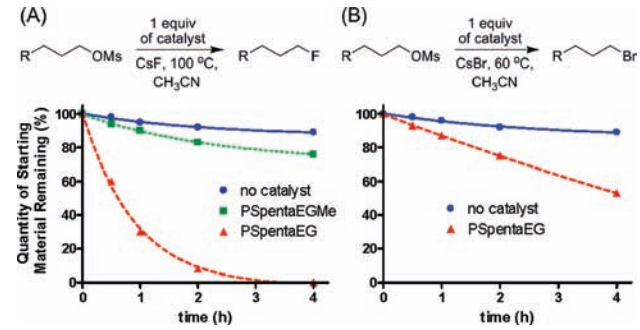


Figure 1. (A) Nucleophilic fluorination using CsF with PSpentaEG, PSpentaEGMe, or no catalyst. (B) Nucleophilic bromination using CsBr with PSpentaEG or no catalyst. The quantity of starting material remaining was determined by ^1H NMR. R = naphthyloxy.

nucleophiles on the nucleophilic substitution reaction. PSpentaEGMe, which is methylated at the terminal OH group to prevent hydrogen bonding with the fluoride of CsF, showed very low catalytic activity in nucleophilic fluorination using CsF, and thus the fluorination reaction with PSpentaEGMe proceeded very sluggishly compared with the same reaction with PSpentaEG (Figure 1A). Furthermore, comparison with parts A and B of Figure 1 shows that PSpentaEG has much higher activity in the fluorination reaction with CsF, which can form a much stronger hydrogen bond with PSpentaEG than CsBr than in

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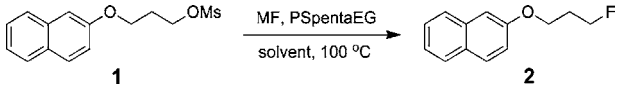
the bromination with CsBr. These results suggest that it is not only that the controlled hydrogen bonding of the terminal hydroxyl group of PSpentaEG with the fluoride of MF may allow its nucleophilicity to increase by a "flexible" fluoride effect[10] but also that the recognition of CsF by PSpentaEG through the hydrogen bonding may also make the formation of the CsF/ether complex more effective; this hydrogen bonding may play an important role in the initial interaction between PSpentaEG and CsF to form the complex.

Table 1 presents the nucleophilic fluorination of 2-(3-methanesulfonyloxypropyl)naphthalene (**1**), as a model compound, with various alkali-metal fluorides in the presence of the PSpentaEG under various reaction conditions. Whereas the fluorination reaction of mesylate **1** using 3 equiv of CsF at 100 °C in a polar aprotic solvent such as acetonitrile barely proceeded after 4 h (entry 4), the same reaction in the presence of 2 or 1 equiv of PSpentaEG was complete within 2.5 h, providing the fluorinated product **2** in excellent yields (93 and 95%, entries 1 and 2). Moreover, the fact that the use of less than 1 equiv (0.5 equiv) of PSpentaEG also greatly accelerated the reaction rate demonstrates that PSpentaEG is likely to be a good catalyst for this reaction (entry 3). In addition, the same fluorination using 18-crown-6 as a nonimmobilized catalyst (entry 5), for which a hydrogen bonding effect with CsF cannot be expected, proceeds much slower than that using the same amount of PSpentaEG (entry 1). Bulky protic solvent *tert*-amyl alcohol, which is known to be an excellent medium for fluorination using CsF, also showed a greatly enhanced rate of fluorination with PSpentaEG (entry 6). The combination system of PSoligoEG and *tert*-amyl alcohol media could enhance the nucleophilicity of RbF, which has stronger coulombic influence than CsF, significantly with affording the product in high yield (94%, entry 7), compared with a *tert*-amyl alcohol media system in the absence of PSoligoEG (entry 8). However, this combination system still did not show good performance in the reaction using KF (entry 9). To investigate how many times PSpentaEG could be reused, we performed the fluorination repeatedly under the conditions given in entry 2 in Table 1. PSpentaEG was observed to be able to indeed be reused repeatedly without the loss of its catalytic activity; in each cycle, the fluoro product **2** was obtained in high yield (92−95%).

To investigate the influence of the synergistic effect between PSpentaEG catalyst and *tert*-alcohol media on the selectivity of the fluorination reactions, we conducted nucleophilic fluorination on various base-sensitive substrates with CsF in the presence of PSpentaEG in *tert*-amyl alcohol. The results are summarized in Table 2, together with those obtained in other systems reported previously. It is well-known that the fluorination of secondary alkyl bromide to

Table 1. Fluorination of Mesylate **1** with Alkali-Metal Fluorides (MF) Using PSpentaEG or the Stated Alternative Reagents[a]

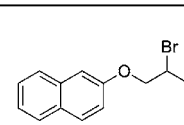
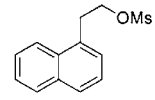
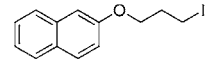
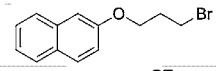
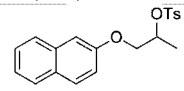
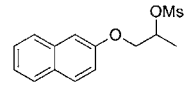
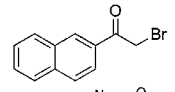
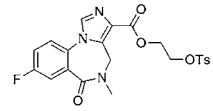
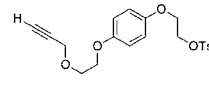


1 **2**

entry	PSpentaEG (equiv[b])	MF	time (h)	solvent	yield[c] (%)
1	2.0	CsF	2.5	CH_3CN	93
2	1.0	CsF	2.5	CH_3CN	95
3	0.5	CsF	4	CH_3CN	92
4		CsF	4	CH_3CN	10
5	18-crown-6[d]	CsF	6	CH_3CN	88
6	1.0	CsF	1	*tert*-amyl alcohol	97
7	1.0	RbF	3	*tert*-amyl alcohol	94
8		RbF	3	*tert*-amyl alcohol	24
9	1.0	KF	24	*tert*-amyl alcohol	29

[a] All reactions were carried out on a 1.0 mmol reaction scale of mesylate **1** using 3 mmol of CsF in 4.0 mL of solvent at 100 °C. [b] Equivalent amount of the pentaethylene glycol portion, not PSpentaEG. [c] Yields were determined by ^{1}H NMR spectroscopy. [d] 2 equiv of 18-crown-6 was used.

Table 2. Selective Nucleophilic Fluorinations Using PSpentaEG in *tert*-Alcohol Medium

entry	substrate	method[a]	time (h)	temp (°C)	yield (%)[b] product	yield (%)[b] alkene
1		A	3	100	80	17
2		B	3	100	8	92
3		C	3	100	19	81
4		D	12[e]	100	28	16
5		E	4	100	59	23[d]
6		A	1	90	94	trace
7[e]		B	1	80	33	61
8[c]		C	1	80	87	9
9		D	2.5	90	92	trace
10		A	2	100	86	13
11[f]		B	1	70	38	57
12[g]		D	12	reflux	72	22
13		E	2	100	73	24
14		A	3	100	92	6
15[g]		D	18	reflux	88	6
16		A	1	100	91	9
17		A	1	100	92	8
18		A in CH_3CN	2.5	100	85	-
19		A in CH_3CN	3	100	87	-
20		A in CH_3CN	3	100	96	-

[a] Method A: reactions were carried out on a 1.0 mmol scale of substrate with 3.0 equiv of CsF and 1.0 equiv of PSpentaEG in 4.0 mL of *tert*-amyl alcohol. Method B: with TBAF in CH_3CN. Method C: with TBAF in *tert*-amyl alcohol. Method D: with CsF in *tert*-amyl alcohol. Method E: with 5.0 equiv of KF in triethylene glycol. [b] Yields were determined by ^{1}H NMR spectroscopy. [c] 56% of starting material was remained. [d] With 18% alcohol byproduct. [e] Reference 10b. [f] Reference 10d. [g] Reference 10a.

the corresponding fluoride using TBAF as a "naked" fluoride source is very difficult because of the competing elimination to predominantly give the alkene byproduct, as shown in entry 2 (method B; only 8% of the secondary fluoride product was obtained). Despite the use of *tert*-amyl alcohol as a bulky protic solvent to reduce the basicity of TBAF, the same reaction also predominantly produced alkenes (81%), with the desired *sec*-fluoroalkane product being formed in only 19% yield. Surprisingly, the combination of PSpentaEG catalyst and *tert*-alcohol media system allowed the selectivity of the fluorination to be enhanced dramatically, providing the desired *sec*-fluoroalkane in excellent yield (80%, entry 1, method A) compared with the previous "naked" fluoride systems. Moreover, a comparison of entries 1 and 4 (method D) showed that the fluorination reaction using this combination system could proceed significantly fast as well as more selectively compared with the *tert*-alcohol media fluorination in the absence of PSpentaEG. Interestingly, this heterogeneous catalysis system which immobilized oligoethylene glycols on polymeric supports showed much better performance in this fluorination reaction than the nonimmobilized triethylene glycol reaction medium system[11] with KF as shown in a comparison of entries 1 and 5 (method E). The examples with other base-sensitive substrates such as 1-(2-mesyloxyethy)naphthalene (entries 6−9) and primary haloalkane substrates such as 2-(3-iodopropoxy)naphthalene (entries 10−13) and 2-(3-bromopropoxy)naphthalene (entries 14 and 15) showed similar trends. A secondary alkyl fluoride was produced by fluorination using this combination system with the corresponding tosylate or mesylate substrate in excellent yield (91 and 92%, entries 16 and 17, respectively). In this reaction, we anticipated that this combination system of PSpentaEG and *tert*-amyl alcohol media might generate a polymer-supported activated "flexible" fluoride during the reaction processing as depicted in Figure 2, and this polymer-supported activated "flexible" fluoride might have good nucleophilicity with low basicity, and that the *tert*-alcohol medium might afford protic atmosphere in the reaction condition, of which favorable properties might not only greatly suppress the competing elimination side reaction but also accelerate the reaction rate. Entries 18−20 show the fluorination of various substrates using PSpentaEG in CH_3CN. The fluorination reaction of α-bromoacetophenone afforded α-fluoroacetophenone in good yield (entry 18). A fluoroflumazenile, which can be a radiopharmaceutical for PET,[15] was synthesized in good yield through the fluorination of the tosylate precursor (entry 19). In the final example, a fluoroacetylene derivative, which is known to be useful in the field of click chemistry,[16] was produced in excellent yield by the reaction with the corresponding tosylate (entry 20).

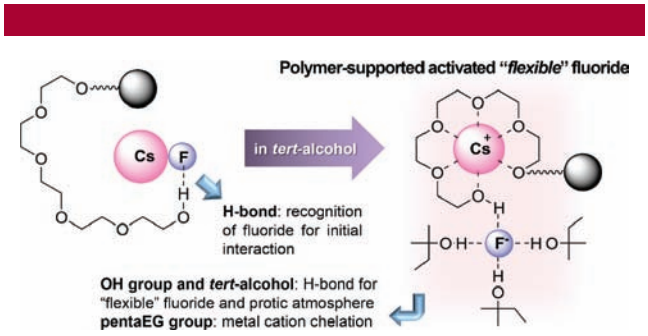


Figure 2. Proposed polymer-supported "flexible" fluoride.

In summary, we report a polymer-supported pentaethylene glycol as a highly effective catalyst for nucleophilic fluorination of various haloalkanes and sulfonyloxyalkanes to their corresponding fluorinated products with alkali metal fluorides. This PSpentaEG itself has many synthetic and practical merits: it can significantly enhance the nucleophilicity of the metal fluoride in the reaction and provide simple purification of the product and ease of recycling, of which factors are technically attractive for considering the use of this material in industrial chemical processes. Furthermore, the combination of PSpentaEG and *tert*-alcohol media system showed the tremendous efficiency in the fluorination of base-sensitive substrates. In this method, this combination system could make the fluorination reaction proceed much more selectively at a remarkably fast rate by the synergistic effect of a polymer-supported activated "flexible" fluoride and protic atmosphere. In particular, this heterogeneous catalysis system prepared by tethering pentaethylene glycol on the polymeric support shows much higher efficiency in the fluorination than the free triethylene glycol solvent system. Further studies on the development of more efficient PSoligoEGs through structural modifications and the application of these unusual catalysts to the rapid ^{18}F labeling for radiopharmaceuticals with PET are currently underway.

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Supporting Information Available: Experimental procedures and characterization data of all compounds and PSpentaEG. This material is available free of charge via the Internet at http://pubs.acs.org.

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