Fluorination Catalysts

Polymer-Supported Ionic Liquids: Imidazolium Salts as Catalysts for Nucleophilic Substitution Reactions Including Fluorinations**

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Although nucleophilic substitutions that use metal salts as nucleophiles are crucial synthetic transformations, these reactions, especially fluorinations,[1] often proceed sluggishly because of the limited solubility and low nucleophilicity of metal salts in organic solvents.[2] Phase-transfer catalysts such as crown ethers[3] and quaternary ammonium or phosphonium salts[4] have been used to enhance the solubility and nucleophilicity of the metal salt in organic solvent systems, consequently accelerating the reaction rate.[3,4] However, phase-transfer catalysts are ineffective when the metal and nuclelophile form a tight ion pair, and some quaternary ammonium salt catalysts are thermally unstable.[5] There are many reports in which catalysts of this nature are immobilized (so-called triphase catalysts) to facilitate product isolation and enable catalyst recovery by simple filtration.[5,6] However, nucleophilic displacements using such solid-supported phase-transfer catalysts generally proceed at slower rates than those using the corresponding nonimmobilized catalysts.[5]

Due to their unique physical and chemical properties, ionic liquids containing imidazolium cations and their counteranions have currently received much attention as alternative reaction media for conducting various chemical processes.[7] Recently, we reported highly efficient nucleophilic fluorination and other substitution reactions[8] using alkali-metal salts in the presence of ionic liquids. In these transformations, the ionic liquid not only significantly enhanced the reactivity of the alkali-metal salts, but they also reduced by-product formation compared to the use of conventional protocols.[1,8a] However, we encountered problems when the product was polar and contained many heteroatoms, because it became difficult to extract it from the ionic liquid.

To overcome this drawback of ionic liquids, we have designed a polymer-supported ionic liquid (Figure 1) that can be used for nucleophilic displacements. There have been some recent efforts to prepare immobilized ionic liquids. Mehnert et al. reported an ionic liquid supported on the surface of silica gel.[9] However, they used a nonimmobilized ionic liquid to carry out their reaction, and the silica framework is also unstable against fluoride ions, water, and acids. In this report, we introduce a new polystyrene-based polymer-supported ionic-liquid system, which we term a "polymer-supported imidazolium salt" (PSIS), as a highly efficient catalyst for nucleophilic fluorination and for other nucleophilic substitution reactions. These PSISs have the advantage of significantly enhancing the nucleophilicity of the metal salts compared with conventional methods. Furthermore, PSISs can be reused many times without decomposition and loss of activity.

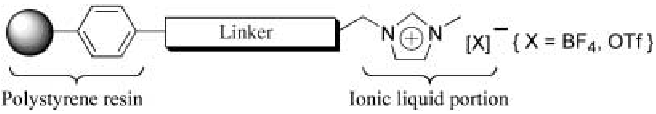
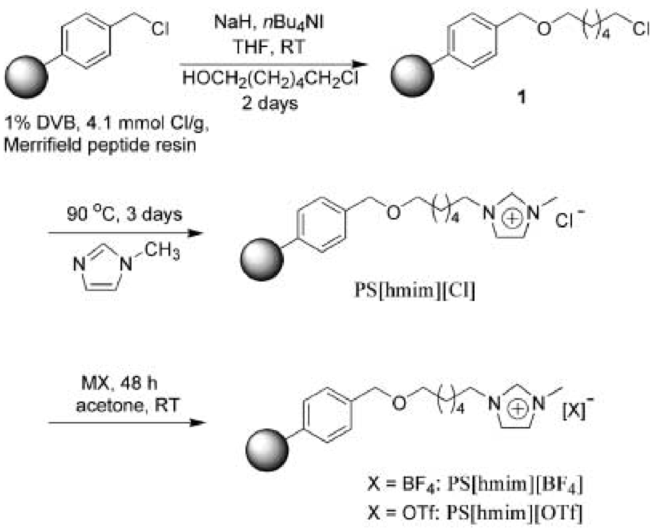


Figure 1. Polystyrene-supported ionic liquids: polymer-supported imidazolium salts.

The PSISs PS[hmim][X] (PS = polymer support; hmim = 1-*n*-hexyl-3-methylimidazolium cation; X = BF_4, OTf) were prepared by the procedure shown in Scheme 1. We have prepared many PSISs with different linkers. The physical and chemical properties of the PSISs depend on the length as well as type of linker employed. In this report, the most promising polymer-supported imidazolium system are described. Merrifield resin[10] (divinylbenzene (1%), Cl (4.5 mmol g^{-1})) was reacted with 6-chloro-1-hexanol in the presence of NaH in THF to obtain resin **1**. PS[hmim][Cl] was prepared by the direct reaction of resin **1** and 1-methylimidazole at 90 °C for 3 days. Further treatment of PS[hmim][Cl] with either $NaBF_4$ or KOTf in acetone for 48 h provides PS[hmim][BF_4] (2.2 mmol of ionic liquid per gram of polymer-supported product obtained) or PS[hmim][OTf] (2.1 mmol of ionic



Scheme 1. Preparation of the polymer-supported imidazolium salts PS[hmim][BF_4] and PS[hmim][OTf]. DVB = divinylbenzene; hmim = 1-*n*-hexyl-3-methylimidazolium cation; MX = $NaBF_4$, KOTf; PS = polymer support.

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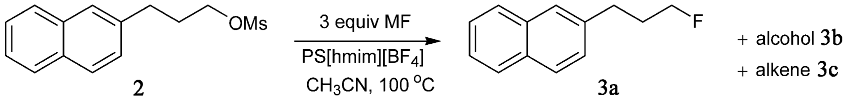
liquid). The PSISs were characterized by ^{1}H, ^{13}C, and ^{19}F NMR (solid-state) spectroscopy, and by elemental analysis.

Table 1 concerns the nucleophilic fluorination of the model compound 2-(3-methanesulfonyloxypropyl)naphthalene (**2**) with various alkali-metal fluorides in the presence of the PSISs under various reaction conditions. Whereas the fluorination of mesylate **2** with 3 equiv of CsF in CH_3CN at 100 °C barely proceeded after 2 h (entry 5), the same reaction in the presence of 2.2 or 1.1 equiv of PSIS PS[hmim][BF_4] was complete within 2 h, affording the fluoroalkane **3a** (97 and 98 %, entries 1 and 2). Moreover, the fact that the use of less than one equiv (0.55 or 0.28 equiv in entries 3[11] and 4) of PS[hmim][BF_4] also greatly accelerated the fluorination demonstrates that PS[hmim][BF_4] is likely to be a good catalyst for this reaction. Interestingly, fluorination using PS[hmim][BF_4] as an immobilized catalyst (entry 3) proceeds much faster than that using the same amount of ionic liquid as the phase-transfer catalytic system (entry 6),[5] or by using [18]crown-6 (entry 7). An alternative PSIS (PS[hmim][OTf]; entry 8) with a different anion shows slightly lower catalytic activity compared with PS[hmim][BF_4] in affording the fluoroalkane **3a** (91 %). The results of entries 3, 9, and 10 indicate that even with the PSIS, the rate of fluorination still depends on the nature of the metal cation.

Table 1: Fluorinations of mesylate **2** with alkali-metal fluorides (MF) using PS[hmim][BF_4] or the stated alternative reagents.[a]



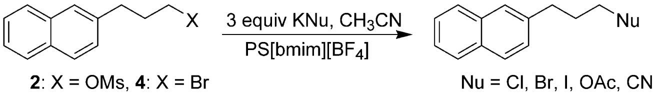
2 → **3a**

Entry	PS[hmim][BF_4] [mg] (equiv[b])	MF	CH_3CN [mL]	*t* [h]	Yield of product [%]			
					2	**3a**	**3b**	**3c**
1	1000 (2.2)	CsF	12	1.5	–	97	–	trace
2	500 (1.1)	CsF	6	2	–	98	–	–
3	250 (0.55)	CsF	3	2.5	–	98	–	–
4	125 (0.28)	CsF	3	4	trace	95	trace	–
5	–	CsF	3	2	91	trace	–	–
6	[bmim][BF_4] (0.55)	CsF	3	3	27	68	–	–
7	[18]crown-6 (2)	CsF	6	5	trace	88	–	7[c]
8	PS[hmim][OTf] (0.55)	CsF	3	5	trace	91	6[c]	–
9	250 (0.55)	RbF	3	9	–	94	5[c]	–
10	250 (0.55)	KF[d]	3[e]	24	–	66	31	–

[a] All reactions were carried out on a 1.0 mmol reaction scale of mesylate **2** using 3 mmol of CsF at 100 °C. [b] Equivalent amount of the ionic liquid portion, not PS[hmim][BF_4]. [c] Determined by NMR spectroscopy (see Supporting Information). [d] 5 equiv of KF was used. [e] CH_3CN containing 5 % H_2O.

To investigate how many times PS[hmim][BF_4] could be reused, we carried out the fluorination repeatedly under the conditions given in entry 2 in Table 1. It was observed that PS[hmim][BF_4] could indeed be reused repeatedly without the loss of its catalytic activity; in each cycle, product **3a** was obtained in high yield (96–99 %).

Table 2: Nucleophilic substitutions with various potassium salts using 0.5 equiv of PS[hmim][BF_4] as a catalyst.[a]

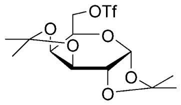
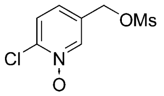
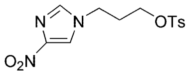
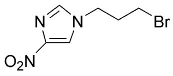


Entry	Substrate	KNu	*T* [°C]	*t* [h]	Yield [%]
1	**2**	KCl	100	6	97
2	**2**	KBr	100	0.8	99
3	**2**	KI	100	0.5	99
4	**4**	KOAc	90	1	99
5	**4**	KCN	100	3	97

[a] Mesylate **2** or bromoalkane **4** (1.0 mmol), KNu (3 mmol), and 0.5 equiv of the ionic liquid portion of PS[bmim][BF_4] were used in 3 mL of CH_3CN.

Nucleophilic substitutions with various potassium salts in the presence of 0.5 equiv of PS[hmim][BF_4] were also attempted (Table 2). Entries 1, 2, and 3 show that the halogenation of mesylate **2** proceeds nearly quantitatively (in 97, 99, and 99 % yield, respectively). In entries 4 and 5, the acetoxylation and nitrile substitution of bromoalkane **4** also proceeded in high yield (99 and 97 %, respectively).

Table 3: Fluorination or acetoxylation of various substrates in the presence of PS[bmim][BF_4].[a]

Entry	Compound	Metal salt	Reaction time [min]	*T* [°C]	Yield [%]
1		CsF	90	80	94
2		CsF	60	80	63
3		CsF	60	90	80
4		KOAc	50	90	96

[a] 1.0 mmol of each compound with 3 mmol of the metal salt and 0.5 equiv of the ionic liquid portion of PS[hmim][BF_4] in 3 mL of CH_3CN.

Table 3 illustrates the fluorination of polar substrates, which can only be extracted from ionic liquids with great difficulty because of their high solubility in the liquid salts. Reaction of these substrates with 0.5 equiv of PS[hmim][BF_4] not only proceeded in high yield, but also allowed products to be isolated and purified easily. A fluorosugar was synthesized under mild conditions in

94 % yield in 1.5 h by fluorination of the corresponding sugar triflate (entry 1). The fluorination of 6-chloro-α-mesyloxy-3-picoline *N*-oxide afforded the corresponding fluorinated product in relatively good yield compared with that from an earlier method (entry 2).[12] 1-(3-Fluoropropyl)-4-nitroimidazole was produced in good yield by the fluorination of the corresponding tosylate (entry 3). In the final example, acetoxylation of 1-(3-bromopropyl)-4-nitroimidazole afforded the acetoxy product in 96 % (entry 4).

In summary, we have prepared new polymer-supported imidazolium salts (PSIS) that act as highly efficient catalysts for nucleophilic fluorination and other substitutions, which convert various haloalkanes and sulfonyloxyalkanes to their corresponding fluorinated products. The PSIS itself has many practical merits: product recovery and purification is simple and catalyst recovery and reuse is practical. These factors are technically attractive for considering the use of these materials in industrial chemical processes. Furthermore, these PSISs enhance the reactivity of the alkali-metal salts significantly. In particular, PS[hmim][BF_4] shows much higher catalytic activity than the free ionic liquid. Further studies on the development of more efficient PSISs through structural modifications and the application of these unusual catalysts to other reactions, such as the rapid labeling of radiopharmaceuticals with the short-lived positron-emitting radionuclide fluorine-18, are in progress in our laboratories.

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[1] For reviews on nucleophilic fluorination, see: a) M. R. C. Gerstenberger, A. Haas, *Angew. Chem.* **1981**, *93*, 659–681; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 647–667; b) O. A. Mascaretti, *Aldrichimica Acta* **1993**, *26*, 47–58.

[2] See: M. D. Smith, J. March, *Advanced Organic Chemistry*, 5th ed., Wiley InterScience, New York, **2001**, pp. 389–674.

[3] a) G. W. Gokel, *Crown Ethers and Cryptands.* Royal Society of Chemistry, Cambridge, **1991**; b) C. J. Pedersen, *J. Am. Chem. Soc.* **1967**, *89*, 7017–7036; c) C. L. Liotta, H. P. Harris, *J. Am. Chem. Soc.* **1974**, *96*, 2250–2252; d) D. J. Sam, H. E. Simmons, *J. Am. Chem. Soc.* **1974**, *96*, 2252–2253.

[4] a) E. V. Dehmlow, S. S. Dehmlow, *Phase Transfer Catalysis*, 3rd ed., VCH, New York, **1993**; b) E. V. Dehmlow, *Angew. Chem.* **1977**, *89*, 521–533; *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 493–505; c) C. M. Starks, *J. Am. Chem. Soc.* **1971**, *93*, 195–199; d) C. M. Starks, R. M. Owens, *J. Am. Chem. Soc.* **1973**, *95*, 3613–3617.

[5] a) M. Cinquini, S. Colonna, H. Molinari, F. Montanari, P. Tundo, *J. Chem. Soc. Chem. Commun.* **1976**, 394–396; b) H. Molinari, F. Montanari, P. Tundo, *J. Chem. Soc. Chem. Commun.* **1977**, 639–641.

[6] a) S. L. Regen, D. P. Lee, *J. Am. Chem. Soc.* **1974**, *96*, 294–296; b) S. L. Regen, *J. Am. Chem. Soc.* **1975**, *97*, 5956–5957.

[7] For recent reviews on ionic liquids, see: a) H. Zhao, S. V. Malhotra, *Aldrichimica Acta* **2002**, *35*, 75–83; b) R. Sheldon, *Chem. Commun.* **2001**, 2399–2407; c) P. Wasserscheid, W. Kein, *Angew. Chem.* **2000**, *112*, 3926–3945; *Angew. Chem. Int. Ed.* **2000**, *39*, 3772–3789; d) T. Welton, *Chem. Rev.* **1999**, *99*, 2071–2083; e) C. C. Tzschucke, C. Markert, W. Bannwarth, S. Roller, A. Hebel, R. Haag, *Angew. Chem.* **2002**, *114*, 4136–4173; *Angew. Chem. Int. Ed.* **2002**, *41*, 3964–4000.

[8] a) D. W. Kim, C. E. Song, D. Y. Chi, *J. Am. Chem. Soc.* **2002**, *124*, 10278–10279; b) D. W. Kim, C. E. Song, D. Y. Chi, *J. Org. Chem.* **2003**, *68*, 4281–4285; c) D. W. Kim, Y. S. Choe, D. Y. Chi, *Nucl. Med. Biol.* **2003**, *30*, 345–350.

[9] C. P. Mehnert, R. A. Cook, N. C. Dispenziere, M. Afeworki, *J. Am. Chem. Soc.* **2002**, *124*, 12932–12933.

[10] R. B. Merrifield, *J. Am. Chem. Soc.* **1963**, *85*, 2149–2154.

[11] In a typical experiment, CsF (454 mg, 3 mmol) was added to a mixture of mesylate **2** (264 mg, 1.0 mmol) and PS[hmim][BF_4] (250 mg, 0.55 mmol) in acetonitrile (3 mL). This mixture was stirred for 2.5 h at 100 °C and then filtered through a short flash-chromatography column (20 % EtOAc/hexanes). The filtrate afforded 184 mg (98 %) of 2-(3-fluoropropoxy)naphthalene (**3a**).

[12] K. C. Lee, D. Y. Chi, *J. Org. Chem.* **1999**, *64*, 8576–8581.