Tetrahedron Letters 49 (2008) 4245–4248

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: http://www.elsevier.com/locate/tetlet

Polymer-supported protic functionalized ionic liquids for nucleophilic substitution reactions: superior catalytic activity compared to other ionic resins

Sandip S. Shinde[a], Byoung Se Lee[a,b], Dae Yoon Chi[a,b,*]

[a] Department of Chemistry, Inha University, 253 Yonghyundong Namgu, Inchon 402-751, Republic of Korea
[b] Labeling Research Laboratory, FutureChem Co., Ltd, Inchon 402-751, Republic of Korea

ARTICLE INFO

Article history:
Received 9 April 2008
Revised 25 April 2008
Accepted 28 April 2008
Available online 1 May 2008

Keywords:
Phase transfer catalysts
Polymer-supported ionic liquids
Nucleophilic substitution

ABSTRACT

Three polymer-supported quaternary ammonium mesylates were synthesized for recyclable polymeric phase transfer catalysts (PTCs). Through comparison study using nucleophilic fluorination, tertiary alcohol containing polymer **3c** proved to be the best catalyst with high catalytic activity and chemoselectivity. It also exhibited not only superior activity in other nucleophilic substitution reactions, such as chlorination, bromination, iodination, acetoxylation, and azidation, but also good recyclability without any loss of catalytic activity or product yield.

© 2008 Elsevier Ltd. All rights reserved.

From economic and environmental points of view, the heterogenization of homogeneous catalytic reactions has attracted great attention from a wide range of organic chemists over the last two decades.[1] Immobilization into insoluble polymeric supports by covalent bonding or complexation enables the easy recovery and reuse of expensive/toxic catalysts. Among numerous catalysts, phase transfer catalysts (PTCs) occupy a specific class of organic chemistry when using immiscible materials in reaction media.[2] PTC facilitates the interphase migration of a reactant or another catalyst in heterogeneous liquid–liquid and solid–liquid systems from one phase into another where reaction can take place. PTCs also increase the solubility and reactivity of insoluble inorganic salt reactants in organic solution by continuous ion exchange. Tetraalkylammonium, tetraalkylphosphonium salts, and crown ether derivatives are conventionally used as PTCs due to their ability to accelerate the reaction progress in numerous nucleophilic substitution reactions by enhancing the nucleophilicity of the anion reactant.[3]

Imidazolium-based ionic liquids (ILs) were reported to exhibit catalytic activity when used as a PTC or reaction media in several nucleophilic substitution reactions[4] such as fluorination with metal fluorides,[5] hydroxylation with water,[6] C-alkylation of pyrrole,[7] and O-alkylation of carbonate.[8] However, ILs can cause problems in product separation and recovery of ILs, especially when the product is polar or somewhat soluble in water. To overcome this limitation, we immobilized ILs into polystyrene-based, insoluble polymer for ease of separation, thereby providing a family of polymer-supported ILs (PSILs).[9] These PSILs showed sufficient catalytic activity in several nucleophilic substitution reactions and facilitated the isolation of product. Recently, we reported a functionalized, imidazolium-based IL [mim-^{t}OH][OMs] (Fig. 1) possessing tertiary alcohol moiety, which provided remarkable reactivity and selectivity in nucleophilic fluorination by reducing the basicity of the fluoride ion.[10] In addition, the polar hydroxyl group of [mim-^{t}OH][OMs] is believed to elevate the solubility and reactivity of anion nucleophiles such as halides, acetate, cyanide, and azide (data not reported).

Herein, we describe a comprehensive study on the catalytic activity of polymer-supported quaternary ammonium salts prepared by solid phase quaternization of mesylate polymer with triethylamine, *N*-methylimidazole, and *N*-(2-hydroxy-2-methylpropyl)imidazole.

In our previous report, the hexyl chain between the polystyrene backbone and IL portion was proved to improve the reactivity and selectivity in nucleophilic substitution reactions compared to methyl, propyl, and dodecyl.[11] For this study, therefore, a hexanol-branched polystyrene was synthesized as spherical beads by aqueous suspension radical polymerization with styrene (0.5 equiv), 6-(4-vinylbenzyloxy)hexanol (0.5 equiv), and 2 mol %

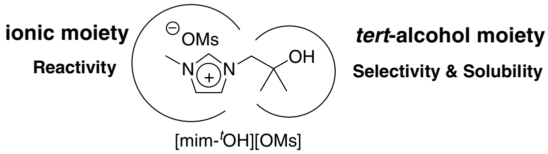
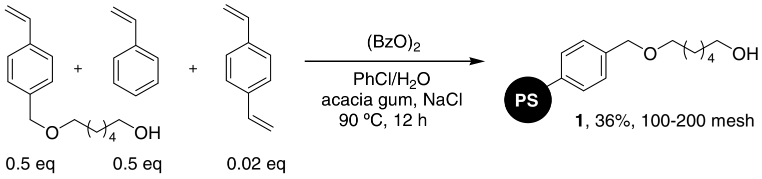


Figure 1. Hybridized ionic liquid with tertiary alcohol.

---

[*] Corresponding author. Tel.: +82 32 860 7686; fax: +82 32 867 0340.
E-mail address: dychi@inha.ac.kr (D. Y. Chi).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.04.151



Scheme 1. Preparation of hexanol-branched polystyrene.

divinylbenzene initiated by benzoyl peroxide (Scheme 1). After Soxhlet extraction and drying, the resulting resin was narrowed using sieves to give 36% of polymer beads in a range of 100–200 mesh size. 6-(4-Vinylbenzyloxy)hexanol was synthesized by reaction of 4-chloromethylstyrene and excess 1,6-hexanediol in the presence of NaOH at 50 °C for 6 h in 58% yield with 30% of the undesired dimer, 1,6-di(4-vinylbenzyloxy)hexane.

Hexanol-branched polystyrene resin (**1**) was treated with methanesulfonyl chloride in the presence of triethylamine in CH_2Cl_2 using a shaker to obtain mesylate polymer **2** (Scheme 2). Subsequently, a series of quaternizations of mesylate polymer **2** were performed by shaking with triethylamine, *N*-methylimidazole, or 1-(2-hydroxy-2-methylpropyl)imidazole at 100 °C for 7 days to afford the corresponding ionic polymers, that is, PS[hNEt$_3$][OMs] (**3a**), PS[hmim][OMs] (**3b**), and PS[him-^{t}OH][OMs] (**3c**), respectively. These were analyzed by elemental analysis to quantify the percentage loading of the ammonium moieties by measuring the nitrogen content, giving 1.68 mmol/g for **3a**, 1.63 mmol/g for **3b**, and 1.21 mmol/g for **3c**. All dried resins were slightly brown in color and free flowing. They exhibited good swelling properties in polar solvents such as CH_3CN, acetone, DMSO, *t*-BuOH, and DMF for sufficient access to the inside of the resin, considering that most nucleophilic substitution reactions were carried out in such polar solvents (Table 1).[12]

Table 1
Swollen volumes (mL/g) of ionic polymers **3a–c** in various solvents[a]

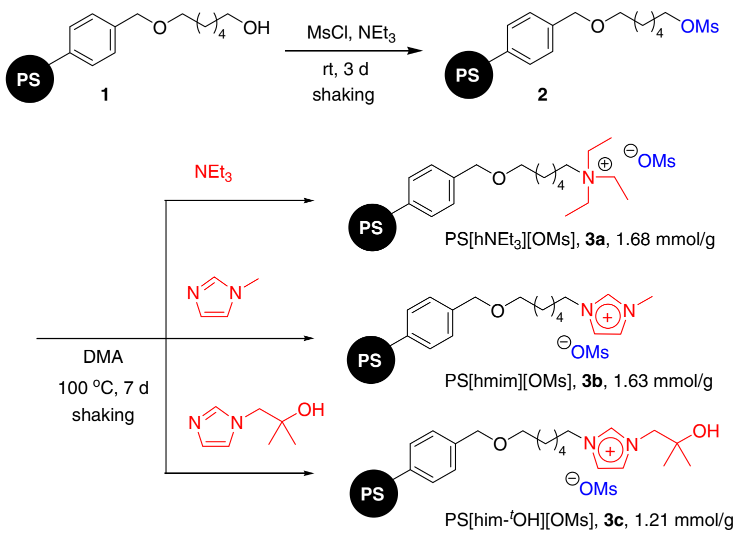
Solvent	3a	3b	3c
CH_3CN	4.2	4.2	4.0
Acetone	3.2	3.0	3.0
DMSO	6.2	7.8	5.6
t-BuOH	3.0	4.0	3.8
DMF	6.0	5.6	5.0

[a] Swollen volumes were determined by a syringe method using 50 mg of resin.

To evaluate and compare the catalytic abilities of ionic resins **3a–c**, heterogeneous fluorination was examined with alkyl mesylate, 2-(3-methanesulfonyloxypropoxy)-naphthalene (**4**) using 3 equiv of CsF. The reactions were performed at 100 °C in CH_3CN using 0.5 equiv of catalyst resins until the starting mesylate **4** disappeared on TLC. As shown in Table 2, the polymer-supported triethylammonium salt (**3a**) showed relatively slow transformation and afforded 6% of the undesired, eliminated byproduct. Our previously reported PSIL **3b** completed the reaction within 2 h.[9] However, a small amount of byproduct was also obtained with 96% of fluorinated product. Tertiary alcohol containing PSIL, **3c**, displayed superior reactivity and chemoselectivity to the above two entries, ensuring fast reaction completion within 1.3 h and a nearly quantitative yield of fluorinated product with no byproducts. This result was almost consistent with that of the solution phase,[10] homogeneous reaction (50 min, 97% yield, no byproducts). Of note, the heterogeneous reaction was generally much slower than the homogeneous reaction. However, the reactivity of solid catalyst **3c** approximately reached the inherent reactivity of the IL [mim-^{t}OH][OMs].

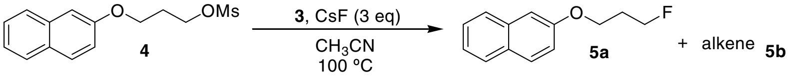
We further studied the relationship between reactivity and the amount of catalyst **3c**, which was varied from 0.1 equiv to 2.1 equiv (entries 4–6). In entries 5 (1.5 equiv) and 6 (2.1 equiv), the reaction volume was increased because the resins used were swollen over 3 mL. Interestingly, 0.1 equiv of **3c** also catalyzed the fluorination reaction sufficiently with high chemoselectivity (entry 4). With more catalyst, the fluorination reaction was quickly completed. However, in entries 5 and 6, a very small amount of alkene byproduct was formed and diminished the product yield slightly, despite the faster reaction completion. The same reaction did not proceed in the absence of catalysts (entry 7).

These results demonstrated that the synergism between the imidazolium salt and the tertiary hydroxyl group was the key factor supporting the high catalytic activity and chemoselectivity. The tertiary hydroxyl group was thought to have led to the dissociation



Scheme 2. Preparation of quaternary ammonium salt resins.

Table 2
Nucleophilic fluorinations with CsF in the presence of polymer catalysts **3a–c**[a]



Entry	3 (equiv)	CH$_3$CN (mL)	Time (h)	Yield[b] (%)	Comments
1	**3a** (0.5)	3.0	5.0	89	6% of **5b**
2	**3b** (0.5)	3.0	2.0	96	Trace of **5b**
3	**3c** (0.5)	3.0	1.3	98	—
4	**3c** (0.1)	3.0	4.2	98	—
5	**3c** (1.5)	3.5	1.1	96	Trace of **5b**
6	**3c** (2.1)	4.0	0.9	94	Trace of **5b**
7	—[c]	3.0	5.0	Trace	94% of **4**

[a] All reactions were carried out on a 1.0 mmol scale of mesylate **4**.
[b] Isolated yield.
[c] In the absence of catalyst.

of fluoride ions from CsF (complex **I** in Scheme 3), thereby affording faster formation of the reactive fluoride, PS[him-^{t}OH][F] (complex **II** in Scheme 3) than PS[hmim][OMs] (**3b**). In addition, the tertiary hydroxyl group can interact with the fluoride ion of PS[him-^{t}OH][F] by utilizing internal hydrogen bonding, which is known to reduce the basicity of the fluoride ion. As shown in complex **III** in Scheme 3, the fluoride ion, therefore, attacks only α-carbon with no abstract of β-proton.

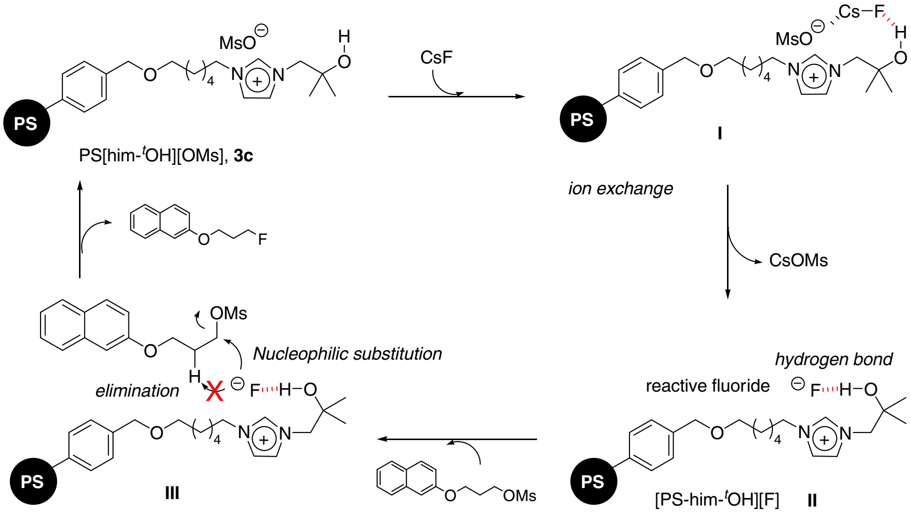
We conducted the nucleophilic fluorination reactions in several solvents to determine the best solvent. The reaction volume depended on the different swelling properties of **3c** in each solvent. While the polar solvents, including IL [bmim][BF$_4$], gave fast transformations, the fluorination in benzene proceeded much slower, affording a produce yield of 82% with a recovery of 17% of the starting molecule after 9 h (entry 6 in Table 3). In entries 1 and 2, fluorination in the aprotic polar solvents, DMF and DMSO, gave good yields along with alkene side-product in a short time. The same reaction in conventional IL [bmim][BF$_4$] afforded fluorinated product at a yield of 89% and 6% of alkene byproduct (entry 4). The fluorination in protic *t*-BuOH afforded product at a yield of 95% and a considerable amount of *t*-butyl 3-naphthoxypropyl ether by etherification with *t*-BuOH. It should be noted that although tertiary alcohol solvents such as *t*-BuOH and *t*-amyl alcohol offer the great advantage of remarkably reducing the eliminated byproduct, especially in nucleophilic fluorination reactions, the other byproducts *t*-butyl or *t*-amyl ethers were usually synthesized. Consequently, CH$_3$CN was chosen as the best solvent for further nucleophilic substitution reactions because only it gave no byproducts.

Other nucleophilic substitutions such as chlorination, bromination, iodination, and acetoxylation were also investigated in the presence of 0.5 equiv of polymer catalysts **3a–c**, as shown in Table 4. Additional comparison studies were performed using three polymer catalysts in chlorination and bromination (entries 1–3). Unlike fluoride ion, chloride and bromide ions are known to form few hydrogen bonds with protic proton, and possess only nucleophilicity. However, **3c** offered better conversion than **3a** and **3b**. In particular, while the bromination with NaBr (entry 2) using **3a** afforded no product, the use of **3c** resulted in 66% conversion within the same period of time, probably because the polar hydroxyl group contributed to the solvation and ion exchange of the

Table 3
3c-Catalyzed nucleophilic fluorination of mesylate **4** in various solvents[a]

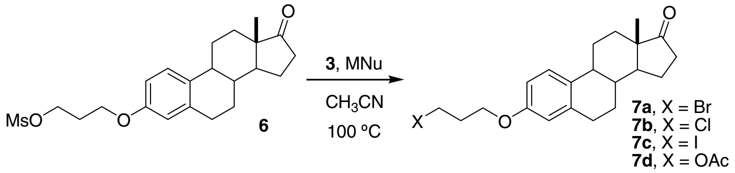
Entry	Solvent (mL)	Time (h)	Yield[b] (%)	Comments[c]
1[d]	CH$_3$CN (3)	1.3	98	—
2	DMF (4)	1.0	90	7% of **5b**
3	DMSO (4)	2.0	87	10% of **5b**
4	[bmim][BF$_4$] (3)	1.0	89	6% of **5b**
5	*t*-BuOH (4)	1.1	93	4% ether[e]
6	Benzene (3)	9.0	82	17% of **4**

[a] Unless otherwise noted, all reactions were carried out using 0.5 equiv of **3c** under the same condition as entry 3 in Table 2.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Taken from entry 3 in Table 2.
[e] *t*-Butyl 3-(2-naphthoxypropyl) ether was detected.



Scheme 3. Catalytic cycle of **3c** in fluorination.

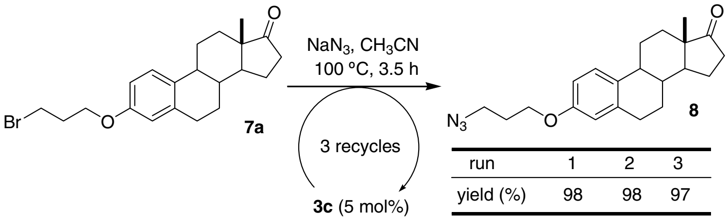
Table 4
Nucleophilic substitution reactions of mesylate **6**[a]



Entry	3	MNu	Time (h)	Yield[b] (%)
1	**3a**/**3b**/**3c**	KCl	2.0	16/25/52
2	**3a**/**3b**/**3c**	NaBr	2.0	–/18/66
3	**3a**/**3b**/**3c**	KBr	0.5	17/32/73
4	**3c**	KCl	5.0	96
5	**3c**	NaBr	6.0	90
6	**3c**	KBr	1.1	98
7	**3c**	CsBr	0.8	99
8	**3c**	KI	0.5	98
9	**3c**	KOAc	0.8	99

[a] All reactions were carried out on a 0.5 mmol scale of mesylate **6** using 1.5 mmol MNu and 0.5 equiv of **3** in CH_3CN (3 mL) at 100 °C.

[b] Conversion determined by ^1H NMR in entries 1–3, and isolated yield in entries 4–9.



Scheme 4. Recycle of **3c** in azidation reaction.

insoluble NaBr in CH_3CN, despite the absence of any hydrogen bonding interaction. Based on our experimental finding that polymer catalyst **3c** has a superior activity as a PTC to the others, several nucleophilic substitutions were attempted under the same condition for different reaction times, depending on the reactant reactivities. Chlorination with KCl was completed within 5.0 h with a product yield of 96%. Bromination was carried out using three alkali metal bromides (entries 5–7) to afford good to excellent yields. Iodinated compound was readily synthesized by using KI with a yield of 98%. Acetoxylation with KOAc was completed in 0.8 h and provided a product yield of 99%.

Nucleophilic azidation of bromo compound **7a** was also performed under the same condition as the other reactions listed in Table 4 using polymer catalyst **3c** (Scheme 4). The polymer catalyst **3c** catalyzed that reaction well, affording a 98% yield for azido compound **8**, and was recovered by simple filtration and was reused twice more without any loss of activity and product yield.

In conclusion, three polymer-supported, quaternary ammonium mesylates, **3a**–**c**, were synthesized and used as recyclable, polymeric PTCs in various nucleophilic substitution reactions. PS[him-^{t}OH][OMs] (**3c**), having a tertiary alcohol group-containing IL [mim-^{t}OH][OMs], showed an excellent and superior catalytic activity compared to that of the other two polymer catalysts, **3a** and **3b**. This catalyst is therefore expected to be generally applicable to various phase transfer catalysis.

Acknowledgments

This work was supported by a Korea Science and Engineering Foundation (KOSEF) grant funded by the Korea government (MOST) (2007-02236) and a Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (A062254). High resolution mass spectra were carried out at the Korea Basic Science Institute (Daegu, Korea).

Supplementary data

Experimental procedures and spectral data for all compounds are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.151.

References and notes

1. (a) Tomoi, M.; Nakamura, E.; Hosokawa, Y.; Kakjuchi, H. *J. Polym. Sci. Polym. Chem. Ed.* **1985**, *23*, 49–61; (b) Desikan, S.; Doraiswamy, L. K. *Ind. Eng. Chem. Res.* **1995**, *34*, 3524–3537; (c) McMorn, P.; Hutchings, G. J. *Chem. Soc. Rev.* **2004**, *33*, 108–122.
2. (a) Regen, S. L. *J. Am. Chem. Soc.* **1975**, *97*, 5956–5957; (b) Montanari, F.; Quici, S.; Tundo, P. *J. Org. Chem.* **1981**, *46*, 2125–2130; (c) Arrad, O.; Sasson, Y. *J. Org. Chem.* **1989**, *54*, 4993–4998; (d) Tundo, P.; Venturello, P. *J. Am. Chem. Soc.* **1981**, *103*, 856–861.
3. (a) Starks, C. M. *J. Am. Chem. Soc.* **1971**, *93*, 195–199; (b) Naik, S. D.; Doraiswamy, L. K. *AIChE J.* **1998**, *44*, 612–646.
4. For recent reviews on ionic liquids, see: (a) Sheldon, R. *Chem. Commun.* **2001**, 2399–2407; (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772–3789; (c) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2083; (d) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667–3692; (e) Dupont, J.; Suarez, P. A. Z. *Phys. Chem. Chem. Phys.* **2006**, *8*, 2442–2452.
5. (a) Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Am. Chem. Soc.* **2002**, *124*, 10278–10279; (b) Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Org. Chem.* **2003**, *68*, 4281–4285; (c) Kim, D. W.; Choe, Y. S.; Chi, D. Y. *Nucl. Med. Biol.* **2003**, *30*, 345–350.
6. Kim, D. W.; Hong, D. J.; Seo, J. W.; Kim, H. S.; Kim, H. K.; Song, C. E.; Chi, D. Y. *J. Org. Chem.* **2004**, *69*, 3186–3189.
7. Jorapur, Y. R.; Lee, C.-H.; Chi, D. Y. *Org. Lett.* **2005**, *7*, 1231–1234.
8. Jorapur, Y. R.; Chi, D. Y. *J. Org. Chem.* **2005**, *70*, 10774–10777.
9. Kim, D. W.; Chi, D. Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 483–485.
10. Shinde, S. S.; Lee, B. S.; Chi, D. Y. *Org. Lett.* **2008**, *10*, 733–735.
11. Kim, D. W.; Hong, D. J.; Jang, K. S.; Chi, D. Y. *Adv. Synth. Catal.* **2006**, *348*, 1719–1727.
12. Lee, B. S.; Mahajan, S.; Clapham, B.; Janda, K. D. *J. Org. Chem.* **2004**, *69*, 3319–3329.