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tert-Alcohol-functionalized imidazolium ionic liquid: catalyst for mild nucleophilic substitution reactions at room temperature

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ABSTRACT

Encouraged by a synergistic effect on nucleophilic fluorination, an imidazolium mesylate salt (**1a**) possessing two different solvent properties in one molecule—*tert*-alcohol and ionic liquid was utilized in various nucleophilic substitution reactions. By a comparison study with 1-*n*-butyl-3-methylimidazolium ionic liquids, **1a** has proved to be a better phase transfer catalyst even under room temperature conditions. It was successfully applied to other nucleophilic substitution reactions such as fluorination, chlorination, bromination, iodination, acetoxylation, azidation, and cyanation.

Phase transfer catalysts (PTCs)[1] have become a topic of great interest in organic chemistry in both industrial and academic research. Numerous soluble and insoluble PTCs are used in general organic transformations such as oxidation, reductions, transition metal co-catalyzed asymmetric synthesis, addition reactions, and widely in nucleophilic substitution reactions. In these reactions, they play a significant role in transporting the anion nucleophile from inorganic phase to the organic phase wherein the reaction can take place.[2] Quaternary salts[3] such as tetraalkylphosphonium and tetraalkylammonium salts are mainly used in nucleophilic substitution reactions because of their good solubilities and reactivities in most organic solvents. Macrocyclic and macrobicyclic polydentate ligands such as cryptands and crown ethers are also used in conventional solid–liquid phase nucleophilic substitution reactions since they have great ability not only to solubilize metal salts, but also to enhance nucleophilicity of the corresponding anion nucleophiles.[4] Insoluble supports such as polystyrene,[5] silica gel,[6] and alumina,[7] are utilized to immobilize these expensive and toxic PTCs to facilitate separation from reaction mixture and reuse. However, these solid PTCs are rarely used in industry because of low reactivity.[8]

Recently, special physical and chemical properties of imidazolium-based ionic liquids (ILs) offer broad applications in organic chemistry.[9] They have been recognized as a recoverable phase transfer catalyst in various organic reactions including nucleophilic fluorination,[10] dialkylation,[11] benzoin condensation,[12] and amination of aryl halides.[13] We have also used ILs as reaction media for efficient nucleophilic substitution reactions such as hydroxylation with water,[14] C-alkylation of pyrrole,[15] and O-alkylation of carbonate.[16] To maximize the benefits, ILs are often tailored to meet particular requirements through the introduction of diverse functional groups.[17] Recently, we demonstrated that the functionalized imidazolium-based IL, [mim-^{t}OH][OMs] (**1a**) having tertiary alcohol moiety provides remarkable enhancement of reactivity and selectivity in nucleophilic fluorination by increasing the solubility of metal salt and reducing the basicity of fluoride ion (Fig. 1).[18] In addition, polystyrene-supported **1a** showed a better phase transfer catalytic activity than other ionic resins for nucleophilic substitution fluorination under the heterogeneous conditions.[19] These results led us to expand the catalytic role of **1a** to a variety of nucleophilic substitution reactions.

Herein, we demonstrate the highly efficient phase transfer catalysis using **1a** in several nucleophilic substitution reactions such as halogenations, azidation, acetoxylation, and cyanation even under room temperature condition.

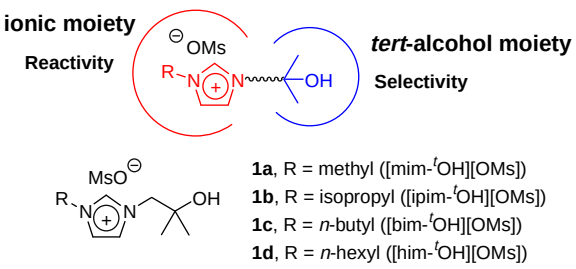

Figure 1. Hybridization of ionic liquid (IL) and *tert*-alcohol.

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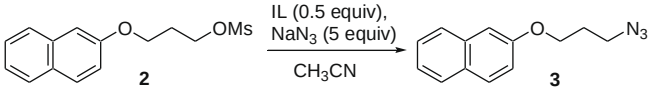
tert-Alcohol-functionalized imidazolium-based ILs: 1-(2-hydroxy-2-methyl-*n*-propyl)-3-methylimidazolium mesylate ([mim-^{t}OH][OMs] (**1a**), 1-(2-hydroxy-2-methyl-*n*-propyl)-3-isopropylimidazolium mesylate ([ipim-^{t}OH][OMs] (**1b**), 1-*n*-butyl-3-(2-hydroxy-2-methyl-*n*-propyl)imadazolium mesylate ([bmim-^{t}OH][OMs]) (**1c**), and 1-*n*-hexyl-3-(2-hydroxy-2-methyl-*n*-propyl) imadazolium mesylate ([him-^{t}OH][OMs]) (**1d**) were prepared according to a reported procedure.[18]

To compare the catalytic activity of ILs **1a–1d**, nucleophilic azidation was examined with an alkyl mesylate, 2-(3-methanesulfonyloxypropoxy)naphthalene (**2**) using 5.0 equiv of NaN_3 at two different temperatures. For this study, two 1-*n*-butyl-3-methylimidazolium ([bmim]) ILs were chosen as conventional ILs. As shown in Table 1, reactions were performed at 80 °C and room temperature in the absence or presence of 0.5 equiv of ILs until considerable conversion of **2** was observed on TLC. At 80 °C (entries 1–5), while the reaction did not proceed in the absence of any ILs (entry 1), the presence of ILs allowed the reaction to proceed. As a result of the first five experiments, **1a** was found to exhibit better catalytic activity than other [bmim] salts, affording 85% conversion after 1.5 h and 100% conversion after 2 h. The same reactions were then repeated at room temperature (entries 6–9). After 18 h at room temperature, two mesylate ILs, **1a** and [bmim][OMs] showed significant progress of reactions, 88% and 73%, respectively, whereas [bmim][BF_4] gave only 2% conversion. The slow reaction using [bmim][BF_4] could be explained by that hydrophobic BF_4 anion lowers the solvation of polar sodium azide salt.

In addition, **1a** displayed slightly higher activity than [bmim][OMs] due to polar hydroxyl group of **1a**. In the case of other *tert*-alcohol containing ILs **1b–1d**, reactions proceeded relatively slower than using **1a**. It is noteworthy that the longer alkyl chain ILs were less reactive for nucleophilic substitution reactions in order of **1a** > **1b** > **1c** > **1d**. This result is consistent with our previous report on nucleophilic fluorination.[19] Tertiary alcohol-containing ILs **1a–1d** displayed a superior phase transfer catalysis to [bmim] salts, ensuring mild reaction, and quantitative yield of azidation product. Obviously, increased nucleophilicity of azide anion is attributed to the synergism between the imidazolium salt and polar tertiary hydroxyl group of **1a**.

To find the best reaction media, nucleophilic cyanation of 3-*O*-(3-bromopropyl)estrone (**10**) using potassium cyanide was conducted in the presence of **1a** at room temperature in several solvents (Table 2). While aprotic polar organic solvents such as DMSO, DMF, acetone, and CH_3CN gave relatively fast conversion to afford 88–98% yields of cyanated compound **7** (entries 1–3 and 5), **1a** became much less active in non-polar aprotic solvents (THF and 1,4-dioxane, entries 6 and 7) and polar protic solvent (MeOH, entry 8), affording very slow reaction to give product **5** in a range from trace to 25% yield after 26 h. Although the reaction proceeded slightly faster in DMSO and DMF, acetone was chosen eventually as the optimal solvent for further nucleophilic substitution reactions because of easier work-up procedure.

Table 1
Azidation of mesylate **2** in the presence of IL[a]



2 **3**

Entry	IL	Time (h)	Temp (°C)	Yield[b] (%)
1	—[c]	1.5	80	Trace
2	[bmim][BF_4]	1.5	80	60
3	[bmim][OMs]	1.5	80	44
4	**1a**	1.5	80	85
5	**1a**	2.0	80	100 (97)[d]
6	[bmim][BF_4]	18	rt	2
7	[bmim][OMs]	18	rt	73
8	**1a**	18	rt	88
9	**1a**	24	rt	100 (98)[d]
10	**1b**	18	rt	72
11	**1c**	18	rt	60
12	**1d**	18	rt	45

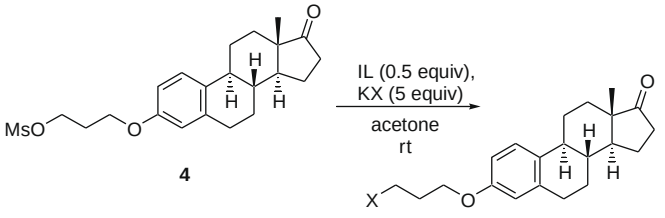
[a] Unless otherwise stated, the reactions were carried out on a 1.0 mmol scale of mesylate **2** in 3.0 mL of CH_3CN.
[b] Determined by ^{1}H NMR.
[c] In the absence of IL.
[d] Isolated yield in parenthesis.

Table 2
Solvent effect on **1a**-catalyzed nucleophilic cyanation of 3-*O*-(3-bromopropyl)estrone (**10**) using potassium cyanide at room temperature[a]

Entry	Solvent	Time (h)	Yield[b] (%)
1	DMSO	12	88
2	DMF	12	86
3	Acetone	20	98
4	Acetone[c]	20	8[d]
5	CH_3CN	26	98
6	THF	26	Trace[d]
7	1,4-Dioxane	26	10[d]
8	MeOH	26	25

[a] Unless otherwise stated, the reactions were carried out on a 1.0 mmol scale of **10** under the same condition as entry 7 in Table 1.
[b] Isolated yield.
[c] In the absence of **1a**.
[d] Determined by ^{1}H NMR.

Table 3
Nucleophilic substitution with KX in the presence of IL at room temperature[a]



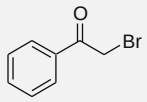
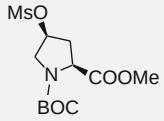
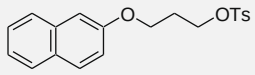
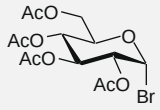
4

5, X = OAc
6, X = N_3
7, X = CN
8, X = F
9, X = Cl
10, X = Br
11, X = I

Entry	IL	KX	Time (h)	Product[b] (%)	Comments[b]
1	**1a**	OAc	24	**5** (98)	
	[bmim][BF_4]			**5** (74)	21% of **4**
2	**1a**	N_3	15	**6** (98)	
	[bmim][BF_4]			**6** (10)	87% of **4**
3	**1a**	CN	22	**7** (97)	
	[bmim][BF_4]			**7** (28)	70% of **4**
	[bmim][OMs][c]			**7** (0)[d]	
4	**1a**	F	48	**8** (63)	30% of **4**
	[bmim][BF_4]			**8** (0)	100% of **4**
	[bmim][OMs][c]			**8** (0)[d]	
5	**1a**	Cl	30	**9** (89)	
	[bmim][BF_4]			**9** (0)	100% of **4**
	[bmim][OMs][c]			**9** (45)[d]	
6	**1a**	Br	18	**10** (92)	
	[bmim][BF_4]			**10** (6)	91% of **4**
7	**1a**	I	16	**11** (92)	
	[bmim][BF_4]			**11** (61)	34% of **4**

[a] Unless otherwise stated, the reactions were carried out on a 1.0 mmol scale of mesylate **4** in 3.0 mL of acetone.
[b] Isolated yield.
[c] The reaction was carried out on a 0.2 mmol scale of mesylate **6**.
[d] Determined by ^{1}H NMR.

Table 4
Azidation of various substrates in the presence of ILs at room temperature[a]

Entry	Substrate	ILs	Time (h)	Yield[b] (%)
1		**1a**	5	98
		[bmim][BF_4]	5	80
2		**1a**	42	98
		[bmim][BF_4]	42	10
3		**1a**	12	97
		[bmim][BF_4]	12	Trace
		[bmim][OMs]	16	58
4		**1a**	20	89
		[bmim][BF_4]	20	34

[a] All reactions were carried out on a 1.0 mmol scale of substrate using 5.0 mmol of NaN_3, and 0.5 mmol of ILs in acetone (3 mL).
[b] Isolated yield.

To further demonstrate the different reactivity between **1a** and [bmim] salts, a series of nucleophilic substitution reactions were examined with 3-*O*-(3-methanesulfonyloxypropoxy)estrone (**4**) using 5 equiv of various potassium salts as nucleophilic sources. The reactions were performed under the same condition as entry 3 in Table 2, at room temperature in acetone solvent using 0.5 equiv of IL. As shown in Table 3, acetoxylation reaction in the presence of **1a** was completed within 24 h, but the same reaction using [bmim][BF_4] proceeded slowly, providing only 74% yield of **5** (entry 1). The azidation reactions with KN_3 in entry 2 showed significantly different result. Compared to fast conversion with **1a**, only 10% product was obtained after 15 h when using [bmim][BF_4]. Cyanation with KCN was completed within 22 h to yield 97% of 3-*O*-(3-cyanopropyl)estrone (**7**) in the presence of **1a**. However, the same reaction with [bmim][BF_4] gave only 28% yield (entry 3). Intriguingly, when using [bmim][OMs] as a PTC, the reaction did not proceed at all. It might be strong evidence that hydroxyl group of **1a** can provide extremely different outcome in certain nucleophilic substitution reactions.

As for nucleophilic halogenations (entries 4–7), the relative reactivities of four halide nucleophiles were found to follow the same order of reaction in aprotic polar solvents; I > Br > Cl > F.[20] In general, nucleophilic fluorination is carried out under heating condition for several hours, in which the fluoride ion should be highly activated. To our surprise, the specifically-designed ionic liquid **1a** allowed fluorination to proceed smoothly even at room temperature (entry 4), giving the fluorinated product in 63% yield after 48 h. It is no doubt that the fluorination is not possible under such ambient condition when using [bmim] salts. In addition, fluorination employing **1a** at room temperature did not produce any detectable side products such as terminal olefin, alcohol, and ether, which are the common byproducts in nucleophilic fluorination under conventional heating. In chlorination (entry 5), **1a** exhibited much better performance than [bmim] salts. Mesylate anion was found to play a key role in this chlorination compared to [BF_4] salt. Uneventfully, both nucleophilic bromination and iodination proceeded well under the same condition, giving the corresponding products in 92% after 18 and 16 h, respectively. Likewise, **1a** was found to be more effective PTC.

Further IL-catalyzed nucleophilic azidation was studied with various electrophile substrates having primary or secondary leaving group (Table 4). In entry 1, α-bromoacetophenone was reacted with NaN_3 using **1a** and [bmim][BF_4], in which **1a** gave better yield of azido product. A cyclic secondary mesylate in entry 2 was converted moderately to the corresponding azido compound in the presence of IL, in which **1a** catalyzed the reaction much faster than [bmim][BF_4] salt. In case of entry 3, [bmim][BF_4] did not give the product while mesylate ILs, **1a** and [bmim][OMs] produced the azido compound in 97% and 58% (after 16 h) yields, respectively. Compound **1a** also showed superior activity in azidation of a secondary α-bromoglucoside to [bmim][BF_4] as shown in entry 4.

Based on the results obtained above, previously reported synergistic effect of **1a** on nucleophilic fluorination[18] has proved to be widely applicable to other nucleophilic substitution reactions. The tertiary alcohol group of **1a** might assist ease dissociation of nucleophile from alkali metal salts (Fig. 2), consequently affording faster formation of the reactive nucleophile, [mim-^{t}OH][Nu]. The hydroxyl group can interact with the nucleophile by utilizing internal hydrogen bonding or additional ion-dipole force.

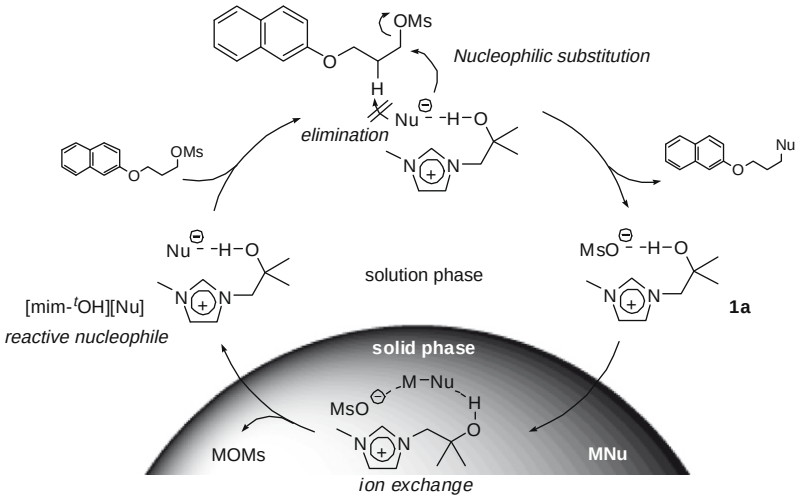


Figure 2. Catalytic cycle of **1a** in nucleophilic substitution reaction.

In conclusion, a specifically-designed IL **1a** having *tert*-alcohol moiety was employed in various nucleophilic substitution reactions as an efficient PTC. A comparison study with common [bmim] ILs revealed that **1a** has superior activity in most nucleophilic substitution reactions. In particular, **1a** allowed fluorination and cyanation to proceed moderately even at room temperature while [bmim] salts gave no product, indicating that hydroxyl group of **1a** may offer a great benefit on certain nucleophilic substitution reactions. It is also expected that **1a** can be applied to other phase transfer catalysis reactions.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.064.

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