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Synergistic Effect of Two Solvents, *tert*-Alcohol and Ionic Liquid, in One Molecule in Nucleophilic Fluorination

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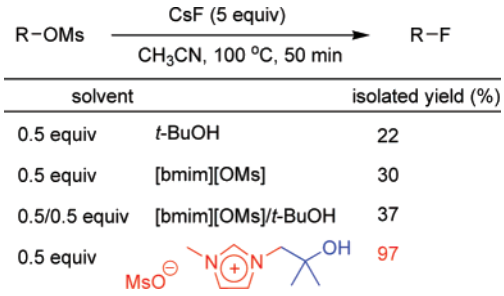
ABSTRACT



We have demonstrated the synergistic effect in nucleophilic fluorination when we combined two solvents—ionic liquid (IL) and *tert*-alcohol—into one molecule. Consequently, these functionalized ILs not only increase the nucleophilic reactivities of the fluoride anion but also remarkably reduce the olefin byproduct. Although the mechanism of this synergistic effect remains to be elucidated, we have illustrated the possibility of solvent engineering for a specific reaction.

Over the past decade, the intrinsic physical and chemical properties of ionic liquids (ILs) have been extensively investigated for numerous applications in most chemistry research areas because of their low melting point below room temperature, negligible vapor pressure, and high polarity.[1] They have been utilized as alternative reaction media instead of conventional volatile organic solvents for reaction acceleration and the recovery of expensive catalysts via multilayer extraction.[2] 1,3-Dialkylimidazolium-based salts are representative of tailor-made ILs. While anionic counterparts including BF_4, PF_6, SbF_6, NTf_2, and OTf play a critical role in determining different physical properties, such as melting point, polarity and solubility, few alkyl-derived anionic partners, including polymers, have been modified for task-specific ILs.[3]

Our continuing interest in the development of fluorination led us to use various ILs as both reaction media and phase-transfer catalysts, and we found that nucleophilic fluorination is accelerated in ILs.[4] More recently, we reported that *tert*-alcohol solvents show good performance in nucleophilic fluorination,[5] thereby allowing side reactions to be remark-

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ably suppressed via a weak F−H hydrogen bond, which maintains the inherent nucleophilicity and reduces the basicity of the fluoride anion.[6,7] However, an unresolved issue was whether or not the hybridization of ILs and *tert*-alcohol functionality would provide dual advantages of reaction acceleration and minimization of side reactions (Figure 1).

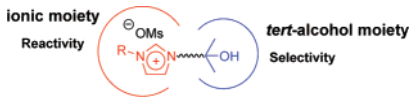
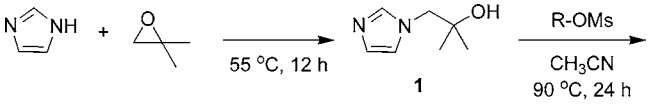


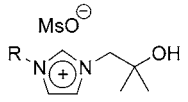
Figure 1. Hybridization of ionic liquid (IL) and *tert*-alcohol.

The results of this hybridization were, however, much greater than we expected. Herein, we describe the design and synthesis of novel, functionalized ILs with a *tert*-alcohol moiety and their application to nucleophilic fluorine substitution.

Four functionalized, imidazolium-based ILs **2a**−**d** having a *tert*-alcohol moiety and methanesulfonate as a counterion were prepared by modifying the procedure reported by Arnold et al. (Scheme 1).[8]

Scheme 1. Preparation of Novel Imidazolium Salts



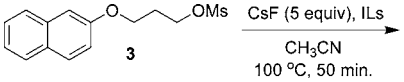


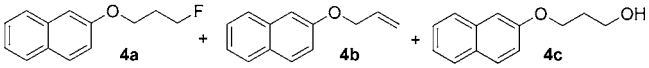
2a, R = methyl ([mim-^{t}OH][OMs])
2b, R = isopropyl ([ipmim-^{t}OH][OMs])
2c, R = *n*-butyl ([bim-^{t}OH][OMs])
2d, R = *n*-hexyl ([him-^{t}OH][OMs])

A solvent-free reaction of isobutylene oxide and imidazole provided *N*-*tert*-alcohol-substituted imidazole **1**,[8] quantitatively. Compound **1** was reacted with methyl, isopropyl, *n*-butyl, and *n*-hexyl methanesulfonate in CH_3CN at 90 °C for 24 h to yield quantitatively the corresponding N^1-alkyl-N^3-*tert*-alcohol substituted imidazolium salts: 1-(2-hydroxy-2-methyl-*n*-propyl)-3-methylimidazolium mesylate ([mim-^{t}OH][OMs] (**2a**), 1-(2-hydroxy-2-methyl-*n*-propyl)-3-isopropylimidazolium mesylate ([ipim-^{t}OH][OMs] (**2b**), 1-(2-hydroxy-2-methyl-*n*-propyl)-3-*n*-butylimadazolium mesylate ([bim-^{t}OH][OMs]) (**2c**), and 1-(2-hydroxy-2-methyl-*n*-propyl)-3-*n*-hexylimadazolium mesylate ([him-^{t}OH][OMs]) (**2d**). All of these imidazolium mesylate salts are liquids at 0 °C.

These ILs were then employed in the nucleophilic fluorination of an alkyl mesylate **3**, as both a solvent and a catalyst (under stoichiometric amount). Table 1 illustrates

Table 1. Fluorination of Mesylate **3** with CsF Using Various ILs[a]





			yield[b] (%)			
entry	imidazolium salt	equiv	**3**	**4a**	**4b**	**4c**
1	[bmim][OTf]	0.5	80	18	2	–[c]
2	[bmim][BF_4]	0.5	73	24	3	–
3	[bmim][OMs]	0.5	64	32 (30)[d]	4	–
4	**2a**	0.5	–	100 (97)[d]	–	–
5	**2b**	0.5	11	85	3	–
6	**2c**	0.5	28	70	2	–
7	**2d**	0.5	42	56	2	–
8[e]	**2a**	3.0	–	93	7	trace
9[f]	**2a**	3 mL	–	84	10	6
10[g]	*t*-BuOH	0.5	77	23 (22)[d]		–
11[h]	[bmim][OMs]/*t*-BuOH	0.5/0.5	58	40 (37)[d]	2	trace
12[i]	**2a**	0.5	–	83	5	12

[a] Unless otherwise noted, all reactions were carried out on a 1.0 mmol scale of **3** in CH_3CN (3.0 mL) for 50 min. [b] Determined by ^{1}H NMR integration. [c] –, not detected. [d] Isolated yield in parentheses. [e] Reaction was complete after 40 min. [f] In the absence of CH_3CN for 40 min. [g] 0.5 equiv of *t*-BuOH was used instead of ILs. [h] [bmim][OMs]/*t*-BuOH (0.5/0.5 equiv) were used in CH_3CN (2.5 mL). [i] In the presence of H_2O (100 μL).

the nucleophilic fluorination reaction with CsF (5 equiv) in the presence of a catalytic amount of various other ILs,[4c] including the newly synthesized imidazolium salts **2a**−**d**, in CH_3CN solvent under the same reaction conditions. The fastest fluorination was completed in 50 min based on TLC monitoring.

In entries 1−3, a quantity less than the stoichiometric amount (0.5 equiv) of commercially available ILs was used to give only 18, 24, and 30% of fluorinated compound **4a**,[4c] respectively, including 2−4% of olefin byproduct, while 80, 73, and 67% of the starting mesylate remained unreacted, respectively. Among these ILs, [bmim][OMs] showed better conversion than [bmim][OTf] or [bmim][BF_4]. The highest conversion and yield was obtained with [mim-^{t}OH][OMs] (**2a**, entry 4). Interestingly, no byproducts and no starting material were detected in the ^{1}H NMR spectrum. In the case of using the other *tert*-alcohol-containing ILs **2b**, **2c**, and **2d**, the reaction remained uncompleted at 50 min, and small amounts of olefin byproduct **4b** were formed. Thus, the longer alkyl chain ILs were less reactive for this transformation (**2d** > **2c** > **2b**). However, they did give better

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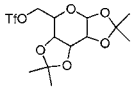
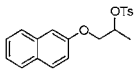
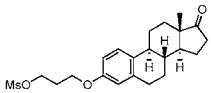
conversion and selectivity than conventional ILs (compare entries 5−7 with 1−3). These results (entries 1−7) indicated not only that *tert*-alcohol-containing ILs are superior in nucleophilic fluorination to conventional [bmim][X]s but also that *N*-methyl IL **2a** was the best among them. When the amount of **2a** was increased (entry 8), 7% of the olefin byproduct **4b** was detected. The reaction was complete in a slightly faster time. The use of **2a** as a solvent (entry 9) also afforded a faster reaction, but the amount of olefin byproduct was further increased, and significant quantities of a new byproduct **4c** were also observed.

The use of *t*-BuOH instead of ILs under the same conditions afforded a conversion of only 23% (entry 10). As mentioned above, *tert*-alcohol-containing ILs gain dual advantages of both ILs and *t*-BuOH. In entry 11, the same amount (0.5 equiv) of both *t*-BuOH and [bmim][OMs] was used instead of **2a** to compare the dual effect. Although the reaction was slightly better than that of each case in entries 3 and 10, this combination provided a conversion of only 40%, including 2% of olefin **4b**. We obtained the highly synergistic effect (100% conversion without byproducts) when the hybridized IL **2a** was used.

The fluorination of **3** was also performed using **2a** in the presence of water (entry 12), which is known to impede nucleophilic fluorination by the formation of an F−H hydrogen bond. However, no starting material remained after 50 min, yielding 83% of fluorinated product, 5% of olefin, and 12% of hydrolyzed compound by ^{1}H NMR. This result is consistent with our previous report that the hydroxylation of alkyl sulfonates and halides with water can proceed under neutral conditions in the presence of ILs, which are believed to enhance the nucleophilicity of water.[9]

We further validated our optimized IL **2a** by comparing with other nucleophilic fluorination methods using *t*-BuOH[5] and [bmim][BF_4].[4a] In entry 1 of Table 2, the reaction of the primary triflate of α-D-galactopyranose with 3 equiv of CsF in *t*-BuOH solvent (method A) proceeded smoothly at 100 °C to afford the corresponding fluorinated compound[10] in a yield of 94% after 5 h. The reaction of [bmim][BF_4] and CH_3CN as a cosolvent (entry 2, method B) gave 91% of fluorinated product and 4% alcohol in a shorter time. The same reaction using **2a** as a catalyst in CH_3CN (entry 3, method C) yielded the fluorinated product in almost quantitative yield (97%), with no byproducts, in 1 h. Reaction of the secondary mesylate (entries 4−6), which could easily be eliminated to the corresponding olefin, showed a similar trend. Such superior reactivity and selectivity was obviously due to the previously mentioned synergistic effect of *tert*-alcohol functionality and imidazolium salts. Entries 7 and 8 in Table 2 show additional nucleophilic fluorinations using method C. Even 0.1 equiv of **2a** produced a good result with high selectivity in entry 7. The primary estrone mesylate was converted to 3-*O*-(3-fluoro-*n*-propyl)estrone within 45 min in a yield of 94% (entry 8).

Table 2. Nucleophilic Fluorinations under Several Reaction Conditions[a]

entry	substrate	method[b]	time (min)	yield (%)[c]	comment
1		A	300	94	tracer ether
2		B	60	91	4% OH
3		C	60	97	-[d]
4		A	360	90	5% olefin, 4% ether
5		B	120	87	8% olefin, trace OH
6		C	150	95	trace olefin
7[e]	**3**	C	140	94	-
8		C	45	94	-

[a] All reactions were carried out on a 1.0 mmol scale of substrate with 3.0 equiv of CsF at 100 °C. [b] Method A: in *t*-BuOH (4 mL). Method B: in [bmim][BF_4] (1.6 mL) and CH_3CN (2 mL). Method C: **2a** (0.5 equiv) in CH_3CN (4 mL). [c] Isolated yield. [d] −, no byproduct was detected. [e] **2a** (0.1 equiv).

In this paper, we have demonstrated the synergistic effect of functionalized ILs having a *tert*-alcohol moiety, which affords high chemoselectivity to ILs in the fluorination reaction. Consequently, these functionalized ILs not only increase the nucleophilic reactivities of the fluoride anion but also remarkably reduce the amount of olefin byproduct. Although the mechanism of this synergistic effect remains to be elucidated, we have illustrated the possibility of solvent engineering for a specific reaction. We also expect that it can be used to prepare F-18-labeled radiotracers for positron emission tomography studies.

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Supporting Information Available: General methods, detailed experiments, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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